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Endocrine and Metabolic Aspects of Various Sleep Disorders

Endokrinní a metabolické aspekty vybraných spánkových poruch

Disertační práce

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Abstract:
Recent epidemiological and experimental data suggest a negative influence of shortened or disturbed night sleep on glucose tolerance. However, no comparative studies of glucose metabolism have been conducted in clinical sleep disorders. Dysfunction of the HPA axis may play a causative role in some sleep disorders and in other sleep disorders it may be secondary to the sleep disorder. Moreover, dysfunction of the HPA axis is regarded as a possible causative factor for the impaired glucose sensitivity associated with disturbed sleep. However, data on HPA system activity in sleep disorders are sparse and conflicting.

We studied 25 obstructive sleep apnea (OSA) patients, 18 restless legs syndrome (RLS) patients, 21 patients with primary insomnia and compared them to 33 healthy controls. We performed oral glucose tolerance test and assessed additional parameters of glucose metabolism. The dynamic response of the HPA system was assessed by the DEX-CRH-test which combines suppression (dexamethasone) and stimulation (CRH) of the stress hormone system.

Compared to controls, increased rates of impaired glucose tolerance were found in OSA (OR: 4.9) and RLS (OR: 4.7), but not in primary insomnia. In addition, HbA1c values were significantly increased in the same two patient groups. Significant positive correlations were found between 2-h plasma glucose values and the apnea-arousal-index in OSA ($r = 0.56$; $p,0.05$) and the periodic leg movement-arousal-index in RLS ($r = 0.56$, $p,0.05$). Sleep duration and other quantitative aspects of sleep were similar among patient groups.
After HPA axis suppression the number of non-suppressors did not differ among groups. Following CRH stimulation we did not detect differences in ACTH or cortisol levels and adrenocortical responsivity to ACTH was comparable among groups. These results for the first time document normal HPA system feedback sensitivity in various sleep disorders.

Keywords: Sleep, Insomnia, Obstructive sleep apnea, Restless legs syndrome, Glucose metabolism, Oral glucose tolerance test, Hypothalamus-pituitary-adrenal axis, Negative feedback sensitivity, Dexamethasone suppression corticotropin releasing hormone stimulating test

Abstrakt:
Výsledky epidemiologických a experimentálních studií naznačují negativní vliv krátké doby trvání spánku nebo přerušovaného spánku na glukózovou toleranci. Doposud však nebyly provedeny žádné srovnávací studie glukózového metabolismu u klinických spánkových poruch. Dysfunkce HPA osy může hrát stěžejní roli v patofysiologii některých spánkových poruch, u jiných poruch spánku může být sekundární k narušenému spánku. Dysfunkce HPA osy je také považována za možnou příčinu poruch glukózové tolerance spojených s poruchami spánku. Nicméně údaje o funkci HPA osy u spánkových poruch jsou skrovné a konfliktní.

Vyšetřili jsme celkem 25 pacientů s obstrukční spánkovou apnoe (OSA), 18 pacientů se syndromem neklidných nohou (RLS), 21 pacientů s primární insomnií a porovnali je s 33 zdravými kontrolami. Provedli jsme orální glukózový toleranční test (OGTT) a hodnotili další parametry metabolismu sacharidů. Dynamická odezva HPA systému byla hodnocena DEX-CRH-testem, který spojuje supresi (dexametazon) a stimulaci (CRH) HPA osy.

Zaznamenali jsme vyšší výskyt poruch glukózové tolerance u pacientů s OSA (OR: 4.9) a RLS (OR: 4.7) ve srovnání s kontrolní skupinou, nikoli však u primárních insomniaků. Kromě toho byly u těchto dvou skupin pacientů výrazně vyšší hodnoty HbA1c. Statisticky významné positivní korelace jsme nalezli mezi plasmatickou hladinou glukózy 2h po zátěži a indexem počtu probouzecích reakcí vázaných na respirační událost za 1h spánku u OSA (r = 0.56; p,0.05) a indexem počtu probuzení souvisejících s periodickými pohyby končetin za 1h u RLS (r = 0.56, p,0.05). Doba trvání spánku a obdobné polysomnografické parametry se mezi skupinami pacientů nelišily. Po supresi HPA osy se také skupiny neodlišovaly v počtu non-supresorů. Po stimulaci HPA osy jsme nezjistili rozdíly v hladinách ACTH a kortizolu, stejně jako v adrenokortikální responsivitě k ACTH. Výsledky poprvé dokumentují normální sensitivitu zpětné vazby v HPA systému u vybraných spánkových poruch.

Klíčová slova: spánek, insomnie, obstrukční spánková apnoe, syndrom neklidných nohou, glukózový metabolismus, orální glukózový toleranční test, hypotalamo-hypofyzární-nadledvinová osa, negativní zpětná vazba, dexametazonový supresní kortikotropin uvolňující hormon stimulační test

Table of contents:

List of commonly used abbreviations:

ACTH	Adrenocorticotropin hormone
AVP	Arginine vasopressin
BMI	Body mass index
CBT	Cognitive behavioral therapy
CRH	Corticotropin releasing hormone
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
GH	Growth hormone
GR	Glucocorticoid receptors
HbA1c	Glycated hemoglobin
HPA	Hypothalamo-pituitary-adrenal (axis)
MR	Mineralocorticoid receptors
MSLT	Multiple sleep latency test
OSA	Obstructive sleep apnea
OGTT	Oral glucose tolerance test
PLMS	Periodic limb movements
PVN	Nucleus paraventricularis
REM	Rapid eye movements (sleep)
RLS	Restless legs syndrome
SCN	Nucleus suprachiasmaticus
SWA	Slow wave activity
SWS	Slow wave sleep
TST	Total sleep time
WASO	Wake after sleep onset
2h-PG	2h-Postload glucose
2h-PI	2h-Postload insulin

INTRODUCTION

The study aims to highlight the important role of sleep in glucose homeostasis and HPA axis function. It also considers the impact of common sleep disorders on glucose metabolism and HPA axis.

1. Changes in sleep duration

Sleep is among the most basic of human needs. Sleep is commonly viewed as a restorative process that influences the homeostatic regulation of the autonomic, neuroendocrine, and immune system (Krueger and Toth, 1994). It is well known that “getting a good night of sleep” is associated with good health. This is supported by increasing epidemiological a laboratory evidence. A person’s sleep can be disrupted not only by pathological processes but also by a personal lifestyle and by societal demands on the sleep – wake schedule. Sleep disruption, regardless of reason, may lead to serious consequences for the individual and in some circumstances for society.

A good night sleep equates to between 7 to 8 hours of continuous sleep for most individuals. Morbidity outcomes such as cardiovascular disease, metabolic syndrome, diabetes mellitus and obesity, have been described in people with short and long sleep durations relative to those with intermediate sleep durations (Patel, 2007). This U-shaped association between sleep duration and growing number of diseases has been confirmed (Cappucio et al., 2010a). The presence of a U-shaped association has been also generally confirmed between sleep duration and mortality (Kripke et al., 2002). In other words, individuals with both short and long sleep durations have a greater mortality risk than those with intermediate sleep durations.

During the last century the duration and habits influencing the sleep – wake muster have dramatically changed. Sleep patterns have been altered by the industrial revolution. The transition to industrialization involves elimination of daytime siesta and implementation of shift-work. Until the close of the early modern era, Western Europeans experienced, on most evenings, two major intervals of sleep, bridged by up to an hour or more of quiet wakefulness (Ekirch, 2001). Artificial light enabled the delay of bedtime. We are not forced to go to the bed after dark as our great grandparents did. Unfortunately, technological advances aimed at improving life have been accompanied by a parallel reduction in societal priority for adequate sleep.

In an influential paper from 1975 „Are we chronically sleep deprived?“, Webb and Agnew indicated that there was a reduction of about 1.5 h in the average sleep duration in children from the years 1910–11 to 1963 (Webb and Agnew, 1975). Although this study was criticized for methodological reasons, these results were confirmed by further research. In 1913, eight to twelve years old children slept an average of 10,5 hours per night (Terman and Hocking, 1913) by 1964, the average had dropped to 9,2 hours per night (Kryger et al., 2005). In 1994, thirteen to fourteen years old slept an average 7,7 hours on school nights and 9,5 hours on weekends (Wolfson and Carskadon, 1998).

Epidemiological studies in western society show that sleep duration in adults and adolescent has declined by up to 2 hours per day in the last decades (Van Cauter et al., 2008). Despite sleep professionals and the American National Sleep Foundation recommending 8 hours of sleep per night, American young adults sleep only in average 6,7 hours per night and older adults 7,0 hours per night (National Sleep Foundation, 2002). Over the past several years, there has been a downward trend in the proportion of individuals who report sleeping eight or more hours a night on weekdays (from 38% in 2001 to 30% in 2002 and 26% in 2005) (National Sleep Foundation, 2005).

A study examining the sleep duration from time diaries (records of sleep time and wake time) of full time workers from 1975 to 2006 (Knutson et al., 2010b) found a significant increase in the number of individuals who were sleeping less than 6 hours per night. A study from the National Health Interview Survey which examined the sleep duration of individuals across several occupations ranging from manufacturing to public administration found that the percent of workers who reported sleep duration of 6 hours or less per night increased from 24% to 30% in the last 20 years (Luckhaupt et al., 2010).

2. Consequences of short sleep duration

Even a modest amounts of daily sleep loss accumulate as a sleep debt that is manifest as an increasing tendency to fall asleep and reduced levels of neurobehavioral functioning. Although most people can resist this tendency under normal circumstances, when physical activity is low and circadian alerting effects are minimal, the likelihood of a lapse in vigilance, a microsleep or even longer sleep episode, can become high (Kryger et al., 2005). Neural processes controlling alertness and sleep produce an increased sleep tendency and diminished capacity to function during certain early morning hours (circa 2–7 a.m.) and, to a lesser degree, during a period in the midafternoon (circa 2–5 p.m.) whether or not we have slept (Mitler et al., 1988).

Therefore consequences of sleep curtailment involve not only impact of individual's heath status, but also vehicular accidents, performance errors and industrial and engineering disasters. These public health consequences of sleep loss and sleep-related disorders are far from benign. The most visible consequences are errors in judgment contributing to disastrous events such as the space shuttle Challenger, where the key managers had obtained <2 h sleep the night before and had been on duty since 1:00 a.m. that morning. The most serious United States incident in a commercial nuclear power plant at the Three Mile Island plant unit 2 reactor in Pennsylvania is attributed to fatigue and insufficient sleep due to shift work (Mitler et al., 1988).

Less visible consequences of sleep conditions are far more prevalent: mortality and morbidity connected with sleep loss/sleep disorders, performance, accidents and injuries, functioning and quality of life, family well-being, and health care utilization. Some of these consequences, such as automobile crashes, are relatively easy to link to sleep problems. Others—for example, obesity and hypertension—develop more insidiously over months and years of chronic sleep problems. After decades of research, the case can be confidently made that sleep loss and sleep disorders have profound and widespread effects on human health.

Too little or too much sleep are associated with adverse health outcomes, including type 2 diabetes (Cappuccio et al., 2010b), hypertension (Gangwisch et al., 2006), obesity in both children and adults (Cappuccio et al., 2008), poor self-rated health (Steptoe et al., 2006) or total mortality (Cappuccio et al., 2010a).

Cappuccio's meta-analysis (2010b) concerning relationship between habitual sleep disturbances and the incidence of type 2 diabetes showed that quantity and quality of sleep predicted the risk of development of type 2 diabetes. For short duration of sleep (≤5–6 h/night), the RR was 1.28 (95% CI 1.03–1.60); for long duration of sleep (>8–9 h/night), the RR was 1.48 (1.13–1.96); for difficulty in initiating sleep, the RR was 1.57 (1.25–1.97); and for difficulty in maintaining sleep, the RR was 1.84 (1.39 –2.43).

Obesity, the most important risk factor for type 2 diabetes, is also significantly associated with short sleep duration. Short sleep duration plays an important role in the regulation of leptin and ghrelin levels in humans, two hormones that have a major influence on energy balance and their abnormalities contribute to the development of obesity. Above that, subjects with sleep problems report a significant reduction in their levels of physical activity, which impacts their activity related energy expenditure (Weaver et al., 1997). Activity related

energy expenditure plays a major role in the homeostatic control of body weight (Rising et al., 1994).

As the causes of worldwide increase in prevalence of obesity and type 2 diabetes are not fully explained by changes in traditional factors such as diet and physical activity, a theory for a link between short sleep and increased risk of obesity and diabetes has been postulated (Knutson et al., 2007). Although obesity is the major risk factor for type 2 diabetes, recent data indicate that short sleep duration may impair glucose metabolism and increase the risk of diabetes independently of changes of the body mass index.

3. Experimental studies

Laboratory findings in sleep restriction paradigm support results from epidemiologic surveys. Spiegel et al. (1999) published data from 11 young men who underwent sleep restriction of 4h per night for 6 consecutive nights. Glucose clearance (measured as glucose utilization divided by plasma glucose) was 40% slower in sleep debt condition than in the sleep recovery condition. Glucose effectiveness (quantifies the ability of glucose to mediate its own disposal independently of insulin) was 30% lower in sleep debt compare to sleep recovery conditions. The acute insulin response to glucose was also 30% lower in the sleep debt condition. The glucose response after breakfast was higher in the sleep debt condition despite similar insulin secretory responses. The 24-hour cortisol profile was altered too. There were a shorter quiescent period and raised concentrations in the afternoon and early evening. The decrease of free cortisol concentrations in the afternoon and in the evening was about six times slower in the sleep debt condition. This might reflect decreased efficiency of the negative feedback loop.

4. Possible causative mechanisms

Potential causative mechanisms relating sleep problems/short sleep duration to adverse health outcomes include changes in circulating levels of leptin and ghrelin. Sleep duration plays an important role in the regulation of leptin and ghrelin levels in humans. Several studies have shown that recurrent partial sleep deprivation and chronic short are associated with a significant decrease in levels of leptin and increase of levels of ghrelin (Taheri, 2004). These in turn would increase appetite and caloric intake, reduce energy expenditure, facilitate the development of obesity, impair glycemic control (Spiegel et al., 2009) and increase cardiovascular risk.

Increased cortisol secretion and altered growth hormone metabolism have also been implicated (Copinschi, 2005). Cortisol, a stress hormone released by the adrenal axis,

induces gluconeogenesis, reduces peripheral glucose utilization, induces insulin resistance and raises blood glucose concentrations (Khani and Tayek, 2001). Effect of sleep loss on the adrenal axis, potentially as a stress response, is one hormonal mechanism by which altered sleep could cause changes in glucose metabolism, either directly acting on the adrenal gland or indirectly through changes in pituitary hormones such as adrenocorticotropic hormone (ACTH).

Low-grade inflammation is activated during short sleep, with possible implications not only for cardiovascular disease (Miller and Cappuccio, 2007) but also for other chronic conditions including cancer. The association of difficulty of initiating or maintaining sleep could be related to these mechanisms, as an expression of reduced total sleep duration.

Conversely, there is a less clear indication of possible mechanisms mediating the effect of long duration of sleep (U shape) as a cause of type 2 diabetes. It has been hypothesized that psychiatric comorbidity, particularly depressive symptoms might contribute to this association. In the only published investigation on correlates of long sleep duration in a large sample of middle-aged women, an investigation of women participating in Nurses' Health Study II, depression and low socioeconomic status were the strongest possible explanations for the association between long sleep duration and mortality (Patel et al., 2006). Furthermore, the associations of long sleep duration with morbidity may be driven by lack of physical activity as an outcome or effect of infirmity and disease, whereas behavioral short sleep duration may be part of an unhealthy lifestyle, which in turn may impair general health status and predispose to morbidity (Stranges et al., 2008). It is therefore possible that long duration of sleep might be a consequence of, rather than a causative risk factor for, unrecognized chronic comorbidity, which in turn could explain the higher risk of mortality observed in many studies (Kripke et al., 2002).

6. Sleep disorders and their consequences

Most research focuses on sleep loss consequences resulting from a behavioral sleep restriction rather than from presence of a sleep disorder. Although the total sleep time per night may be equal in duration, behavioral bedtime curtailment differs significantly from insomnia or other sleep disorders. For example insomnia is a clinically defined syndrome of physiological and cognitive hyperarousal and therefore metabolic and endocrine consequences may differ from those of sleep loss attributable to sleep curtailment.

Prevalence of sleep disorders is high. At least 10% of the population suffers from a sleep disorder that is clinically significant and of public health importance. Insomnia is the most

common sleep disorder, followed by the sleep apnea and then the restless legs syndrome (Kryger et al., 2005).

Primary insomnia is a sleep disorder per se, from intrinsic reasons. In two other major sleep disorders – the obstructive sleep apnea and the restless legs syndrome - sleep is disturbed due to other reasons. Obstructive sleep apnea is associated with repeated episodes of upper airway obstruction connected with breathing cessations and followed by hypoxia and sleep fragmentation. RLS syndrome is a sensorimotor disorder characterized by an urge to move the legs accompanied by unpleasant sensations in the legs occurring in the rest or inactivity periods especially in the evening. RLS symptoms typically disturb sleep.

It is well-documented that obstructive sleep apnea is, independently of BMI and other confounders, associated with glucose intolerance, insulin resistance, and diabetes (Tasali et al., 2008a). On the other hand, there is only one study assessing glucose metabolism in restless legs syndrome and there is not even one study in insomniacs.

There is also paucity of studies assessing HPA activity in insomnia. Insomnia patients with objectively fragmented nighttime sleep show elevated 24-h plasma ACTH and cortisol levels (Rodenbeck and Hajak, 2002) with greatest elevations in the evening and the first half of the night (Vgontzas et al., 2001a). However, insomnia patients showing only minor alterations of sleep exhibited normal cortisol secretion levels (Riemann et al., 2002). Results obtained from studies in sleep disordered breathing are quite inconsistent. In patients with an obstructive sleep apnea syndrome some studies reported enhanced cortisol secretion (Bratel et al., 1999) while other studies did not find alterations in HPA system activity (Dadoun et al., 2007). Noteworthy, several of these studies were limited in that cortisol was measured at a single time point. Finally, four studies assessed HPA axis activity in patients with a restless legs syndrome. Three of them reported normal cortisol profiles and no differences in feedback inhibition (Hornyak et al., 2008) (Garcia-Borreguero et al., 2004) (Wetter et al., 2002) whereas the most recent study focusing on HPA system activity in RLS patients reported enhanced nocturnal cortisol secretion levels (Schilling et al., 2010).

7. Hypothesis and objectives

The aim of our study was to assess glucose metabolism by oral glucose tolerance test in three most common sleep disorders – primary insomnia, obstructive sleep apnea and restless legs syndrome. We hypothesized based on abovementioned studies that there is an impaired glucose sensitivity measured with an oral glucose tolerance test in all three sleep disorders due to disturbed sleep from different reasons. We assumed that disturbed sleep

per se in primary insomnia as well as fragmented sleep due to upper airway obstruction with concomitant hypoxia in OSA and due to unpleasant sensations in legs and concomitant periodic leg movements in RLS would equally contribute to the supposed impaired glucose sensitivity. We also hypothesized that all three sleep disorders would demonstrate a HPA axis dysfunction, which might be expected to significantly contribute to the disturbed glucose metabolism. We assumed that the putative HPA axis dysfunction might play an important role in primary insomnia and might be interpreted as one the physiological markers of the hyperarousal state, directly contributing to the pathophysiology of insomnia (Vgontzas et al., 2001b). In two other major sleep disorders – obstructive sleep apnea and restless legs syndrome, the potential dysfunction of HPA axis may be secondary due to disturbed sleep due to the sleep fragmentation.

PRIMARY INSOMNIA

Insomnia is by far the most common sleep compliant. Insomnia is a symptom that often arises from primary medical illness, mental disorder or other sleep disorders. It may also arise from use of certain substances. Whether a sleep disorder in a given individual is an independent condition or simply one of the features of another disorder should be determined on the basis of its clinical presentation and course. When the insomnia that occurs in these conditions is prominent, then is classified as a separate diagnosis, secondary insomnia. There are also several forms of insomnia that persist as primary, independent sleep disorder (AASM 2005).

1. Definition, classification

Currently, the three most widely used insomnia classification systems are the International Classification of Sleep Disorders, second edition (AASM 2005), the text revised fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual (APA 2000) and the World Health Organization's International Classification of Diseases (WHO 1992).

1.1 The International Classification of Sleep Disorders, second edition: definition of the general criteria for insomnia:

A) A complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early or sleep that is chronically nonrestorative or poor in quality. In children, the sleep difficulty is often reported by the caretaker and may consist of observed bedtime resistance or inability to sleep independently.

B) The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.

C) At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the patient:

- fatigue or malaise
- attention, concentration, or memory impairment
- social or vocational dysfunction or poor school performance
- mood disturbance or irritability
- daytime sleepiness
- motivation, energy, or initiative reduction
- proneness for errors or accidents at work or while driving
- tension, headaches, or gastrointestinal symptoms in response to sleep loss
- concerns or worries about sleep

Specific diagnostic criteria for psychophysiological (primary) insomnia are:
A The patients symptoms meet the criteria for insomnia
B The insomnia is present for at least one month
C the patient has evidence of conditioned sleep difficulty and/or heightened arousal in bed as indicated by one or more of the following criteria:
- excessive focus on and heightened anxiety about sleep
- difficulty falling asleep in bed at the desired bedtime during planned naps, but no difficulty falling asleep during other monotonous activities when not intending to sleep
- ability to sleep better away from home better than at home
- mental arousal in bed characterized either by intrusive thoughts or a perceived inability to volitionally cease sleep-preventing mental activity
- heightened somatic tension in bed reflected by a perceived inability to relax the body sufficiently to allow the onset of sleep
D the sleep disturbance is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

The International Classification of Sleep Disorders specifies 11 types of insomnia. Adjustment (acute, transient, stress-related) insomnia is characterized by presence of insomnia in association with an identifiable stressor (psychological, environmental, interpersonal, physical). Adjustment insomnia has a short duration, less than 3 month and resolves when the specific stressor resolves or when the subject adapts to the stressor (AASM 2005).

Paradoxical insomnia (sleep misperception, pseudo-insomnia) occurs without evidence of objective sleep disturbance, while patients complain little or no sleep as well as daytime symptoms (AASM 2005).

Idiopathic insomnia (childhood-onset) is typical with onset during infancy or early childhood and longstanding complaint without periods of sustained remission. The hallmark of idiopathic insomnia is the absence of any factors associated with the onset or persistence of the condition (AASM 2005).

Insomnia due to mental disorder is vied as a symptom of the identified mental disorder and shares course with this disorder. However insomnia could appear few days or weeks before the mental condition develops (AASM 2005).

Inadequate sleep hygiene is associated with daily living activities that are inconsistent with the maintenance of good quality of sleep and full daytime alertness. The specific behaviours can be classified into two categories: practice that produce increased arousal and practice that are inconsistent with the principles of good sleep organization (AASM 2005).

Behavioural insomnia of childhood is related to identified behavioural etiology. Sleep difficulties are results of inappropriate sleep associations or inadequate limit setting; there are therefore two types of behavioural insomnia in childhood: sleep-onset association type and limit-setting type. Sleep-onset association type is characterized by dependency on inappropriate sleep associations (bottle, parents´ bed etc.), in absence of these conditions sleep onset is delayed. Usually presents as frequent nighttime awaking. Limit-setting type is characterized by bedtime stalling or bedtime refusal that is the result of inadequate limit setting by caregivers (AASM 2005).

Insomnia due to drug or substance is caused by consumption of medication, drugs, caffeine, alcohol, food items or environmental toxins that are known to have sleep-disrupting properties. Sleep disturbance may occur during periods of use, exposure or discontinuation of the substance (AASM 2005).

Insomnia due to medical condition (organic insomnia) is caused by a coexisting medical disorders or other physiologic factor. Although the sleep difficulty may be viewed as a common symptom of the identified medical disorder, the diagnosis of insomnia should be assigned when the insomnia causes marked distress or warrant separate clinical attention (AASM 2005).

Insomnia not due to substance or known physiologic condition, unspecified (nonorganic insomnia) is a form of insomnia that cannot be classified elsewhere but is suspected to be related to an underlying mental disorder, psychological factors or sleep-disruptive practice. Physiologic (organic) insomnia, unspecified is a form of insomnia that cannot be classified elsewhere but is suspected to be related to an underlying medical condition, physiological state or substance use exposure (AASM 2005).

1.2 The American Psychiatric Association's Diagnostic and Statistical Manual requires for primary insomnia these diagnostic criteria:

- The predominant complaint is difficulty in initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month.

- The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing related sleep disorder, circadian rhythm sleep disorder or a parasomnia.
- The disturbance does not occur exclusively during the course of another mental disorder (e.g. major depressive disorder, generalized anxiety disorder, a delirium)
- The disturbance is not due to direct physiological effect of a substance (e.g. a drug of abuse, a medication) or a general medical condition

DMS-IV-TR classifies other insomnia into following categories.
Insomnia related to another mental disorder is judged to be related to another Axis I. or Axis II. disorder, but is sufficiently severe to warrant independent clinical attention. Substance-induced sleep disorder, insomnia type is a prominent disturbance in sleep that is sufficiently severe to warrant independent clinical attention. The symptoms develop during, or within a month of substance intoxication or withdrawal; or medication use is etiologically related to the sleep disturbance. The disorder is specific for alcohol, amphetamine, caffeine, cocaine, opioids, sedatives, hypnotics, anxiolytics, or other (unknown) substance. Sleep disorder due to a general medical condition, insomnia type is a prominent disturbance in sleep that is severe enough to warrant independent clinical attention. There must be evidence from the history, physical examination, or laboratory findings that the sleep disturbance is the direct physiological consequence of a general medical condition (APA 2000).

1.3 International Classification of Diseases (ICD 10) divides insomnias into two categories: organic and nonorganic in which emotional causes are considered to be a primary factor.
Diagnostic guidelines of primary (nonorganic) insomnia:
- the complaint is either of difficulty falling asleep or maintaining sleep, or of poor quality of sleep;
- the sleep disturbance has occurred at least three times per week for at least 1 month;
- there is preoccupation with the sleeplessness and excessive concern over its consequences at night and during the day;
- the unsatisfactory quantity and/or quality of sleep either causes marked distress or interferes with ordinary activities in daily living.

Organic insomnias are coded under diseases of the nervous system as disorders of initiating and maintaining sleep. Inadequate sleep hygiene is coded in the chapter Factor

influencing health status and contact with health services as Personal history of unhealthy sleep-wake schedule (Z91.3). Children sleep problems are in reality often difficulties in the management of bedtime routines rather than of sleep per se, thus they are coded in chapter Factor influencing health status and contact with health services as Inadequate parental supervision and control (Z62.0).

2. Epidemiology

95% of randomly selected adults reported having experienced insomnia at some time during their lives. For most, however, insomnia represented a transient problem (Gallup Organization, 1979). In Ohayon's (2002) review prevalence of chronic insomnia ranged from 4,4% to 48%. Epidemiologic surveys provide estimates of the prevalence of insomnia according to four definitions: presence of insomnia symptoms, presence of insomnia symptoms with daytime consequences, dissatisfaction with sleep quality and quantity and insomnia diagnosis. The presence of insomnia symptoms without restrictive criteria is reported in 30% of general population. By using frequency quantifiers, the prevalence of insomnia drops to around 16% - 21%. By using severity quantifiers, the prevalence of insomnia ranges between 10% and 28%. When daytime consequences of insomnia are taken in account, the prevalence is between 9% - 15%. When indices of sleep dissatisfaction are counted, the prevalence estimates of insomnia range between 8% - 18%. 6% of insomnias fulfilled DSM diagnostic criteria (Ohayon et al., 1997) (Quera-Salva et al., 1991).

In Drake´s summaries of epidemiologic studies is concluded that 10% - 13% of the adult population suffers from chronic insomnia and additional 25% - 35% has transient or occasional insomnia (Drake et al., 2003). It is estimated that 75% of population based chronic insomnia is associated with psychiatric and medical diseases or with sleep disorders and primary insomnia accounts for approximately 25% of all chronic insomnias (Krystal, 2003).

Insomnia is more prevalent in women than men in all ages, occurring approximately 1,5 times more often in women than in men. This is especially true in menopausal and postmenopausal women compared with middle-aged men (Foley et al., 2004) (Ohayon et al., 2002).

Insomnia complaints are generally reported with age (Anticoli Israel and Roth 1999), but in some studies after controlling for medical illness and other confounders, it appears that healthy elderly sleep about as well as do younger people (Chevalier et al., 1999). In younger age group, the most common manifestation of insomnia is the trouble falling asleep, whereas

trouble staying asleep is the most frequent form of insomnia in middle-aged and elderly people (Kryger et al., 2005).

A higher prevalence of insomnia symptoms is found in people who are separated or divorced or who are widowed. This association is stronger in women (Chevalier et al., 1999). There are also reports that insomnia complaints are more likely to be reported in individuals with lower incomes and lower education, after controlling for age (Newman et al., 1997).

Seasonal differences may also influence incidence of insomnia. This relationship was reported from Nordic countries, probably due to light exposure. Interestingly, insomnia in the "dark period" (midwinter insomnia) was reported by 17.6% of women and 9.0% of men, whereas insomnia in the midnight-sun period was much less common (Hugsby and Lingjaerde, 1990).

Other risks reported for insomnia include medical illnesses, sleep apnea, depression and other psychiatric disorders (Foley et al., 2004) (Krakow et al., 2001).

3. Pathophysiology

Many theoretical models of insomnia have been developed. The most influential are the neurocognitive and the psychobiological models.

3.1 Psychobiological model

This model was proposed by Colin Espie (2002). According to this theory, normal cognitive processes are deregulated and the automaticity of normal unattended sleep initiation is breached. Inhibition of arousal – the ability to de-arouse - might be absent or deficient.

The literature provides so far much empirical support to another theory, to the neurocognitive model.

3.2 Neurocognitive model/Hyperarousal theory

Hyperarousal has been suggested as being the core feature in insomnia. The hyperarousal theory has gained widespread attention as an integrative approach to the pathophysiology of insomnia, assuming an interplay between psychological and physiological factors in etiology of chronic insomnia (Riemann et al., 2010).

Neurocognitive model

This model proposes that insomniacs develop conditioned cortical arousal from the association of sleep related stimuli and encountered sleep difficulties. This conditioned arousal may lead to enhanced sensory and informational processing around sleep onset and in sleep-wake transitions during the night.

Insomnia is frequently triggered by acute stressor. In healthy individuals, with cessation of the stressor the insomnia resolves. Only a subpopulation of afflicted patients tends to develop persistent, chronic insomnia, independent of the initial stressor. The concept says that individuals who tend to focus cognitively on the insomnia and start to ruminate about their sleep problems are prone to developed learned sleep-preventing associations. This may explain the transition to chronic insomnia. Maladaptive behaviour contributes to perpetuation of the disorder (perpetuating factors). Maladaptive behaviour strategies result in conditioned arousal (Perlis et al., 1997).

Arousal is expressed in terms of somatic, cognitive and cortical activation. The cortical arousal occurs as a result of classical conditioning and promotes abnormal levels of sensory and information processing, and of long-term memory formation. Enhanced sensory processing around sleep onset and during sleep is thought to do the insomniacs especially vulnerable to perturbation by different stimuli. Enhanced information processing during sleep may distort the distinction between sleep and wakefulness. Enhanced memory formation for events around sleep onset and arousal during sleep may interfere with subjective experience of sound, uninterrupted sleep (Riemann et al., 2010).

Perlis and colleagues (1997) and Espie and colleagues (2006) proposed that insomnia may result from top-down process, in which dysfunctional cognitive process results in physiological arousal. A bottom-up approach is also discussed. A genetically determined dysfunction in sleep –wake regulating neural circuits originating from the brainstem may lead to sleep disruption and cognitive and emotional disturbances (Riemann et al., 2010).

3.2.1 Genetic studies

35% of patients with insomnia at a sleep clinic had a positive family history for sleep disorders (Bastien and Morin, 2000). In another study 72,7% of insomniacs reported familiar insomnia compared to 24,1% of controls (Dauvilliers et al., 2005). A twin study showed a heritability estimate of 57% for insomnia in monozygotic twins (Watson et al., 2006).

First-line candidate genes of specific relevance for insomnia may include adenosine and GABA receptor genes and cyclic AMP-response element binding protein (CREB) gene.

A genetic variant of adenosine deaminase is coupled with enhanced slow wave activity (Retey et al., 2005). Polymorphisms of the adenosine A2 receptor gene is associated with interindividual differences in anxiety reaction to caffeine and with an increased frequency of subjectively experienced sleep problems and less slow wave sleep measured by PSG (Retey et al., 2007). Therefore adenosine gene may be a good candidate gene.

The cyclic AMP-response element binding protein (CREB) is an activity-dependent transcription factor. Levels of phosphorylated CREB within the cortex are higher in waking than in sleep, suggesting that CREB plays a role in sleep/wake regulation in mammals. In a mice lacking the alpha and Delta isoforms of CREB the amount of time spent awake was significantly decreased and time spent in nonrapid eye movement sleep (NREM) sleep was increased (Graves et al., 2003).

So-called clock genes (clock, Bmal, Per1, Per2, Cry1, Cry2) are involved in regulation of circadian rhythms in humans and their mutation in circadian rhythm disorders. In a subgroup of insomnia patients, there is a evidence for circadian contribution (Lack and Wright, 2007).

3.2.2 Autonomic system

Cardiac measures

Significantly higher heart rates in insomnia patients compare to controls have been reported, both in sleep and wake periods (Haynes et al., 1981). However, not all studies have replicated this finding (Varkevisser et al., 2005). Using heart rate variability, nocturnal sympathetic activity was enhanced and parasympathetic activity was reduced in insomniacs (Bonnet and Arand, 1998) but another study did not replicate the finding (Fang et al., 2008).

Body temperature

In a review of literature concerning insomnia and elevated body temperature the authors come to the conclusion that sleep maintenance insomnia has been associated not with a circadian rhythm timing abnormality, but with nocturnally elevated core body temperature, even in a constant routine protocol. Combination of sleep onset and maintenance insomnia has been associated with a 24-h elevation of core body temperature supporting the chronic hyper-arousal model of insomnia (Lack et al., 2008).

In contrast, sleep onset insomnia was associated with a circadian core temperature that is delayed. Early awaking insomnia has been associated with a circadian temperature rhythm timed much earlier than normal (Lack et al., 2008).

Metabolic measures

Two studies measured whole-body metabolic rate across night in insomnia patients and healthy controls. Both found significantly elevated VO2 consistently at all measurement points across the day and throughout one night of sleep in the insomniacs as compared to the normal controls (Bonnet and Arand, 1995). In patients with sleep state misperception insomnia the overall increase in whole body oxygen use was less than that seen in psychophysiological insomniacs (Bonnet and Arand, 1997).

Elevated global brain metabolism in insomnia patients both asleep and awake has been shown (Nofzinger et al., 2004). Insomnia patients had a smaller decline in metabolism during sleep in the reticular system, hypothalamus, thalamus, insular cortex, amygdala and hippocampus. Both subjective and objective WASO positively correlated with NREM sleep-related cerebral glucose metabolism (Nofzinger et al., 2006). These studies provide a possible measure for physiological hyperarousal (Riemann et al., 2010).

Galvanic skin response

Both patients with psychophysiological insomnia and insomnia associated with psychiatric disorders had higher electrodermal activity than the controls, and electrodermal activity was also significantly related to sleep in both groups (Broman and Hetta, 1994). In contrast, another older study found no differences between groups (Freedman and Sattler, 1982).

3.2.3 Endocrinology

HPA axis – for details see the chapter HPA axis and sleep

There is also evidence for decreased melatonin secretion at night in insomnia patients. Plasma melatonin levels in insomnia patients tended to begin to increase earlier in the evening and were significantly lower during the middle of the night. The most severely reduced nocturnal plasma melatonin levels were found in those patients with a history of sleep disturbance lasting for longer than five years (Hajak et al., 1995). Significantly diminished nocturnal melatonin production in insomniac patients found also Riemann et al. (2002).

Nocturnal increases of average levels of circulating norepinephrine were shown in a study of insomniacs, depressed patients and healthy controls by Irwin et al. (2003). Impairments of sleep efficiency correlated with nocturnal elevations of norepinephrine in the insomniacs but not in the depressives or controls. These data indicate that insomnia is associated with nocturnal sympathetic arousal.

3.2.4 Immune functions

Results of studies on total and partial sleep deprivation indicate that changes in sleep are connected with proinflammatory state. Moreover, cytokines are involved in regulation of spontaneous sleep. Although the experimental data are fairly consistent in demonstrating an effect of sleep deprivation on immunity, experimental sleep deprivation may not generalize to clinical insomnia. Data regarding insomnia are sparse and conflicting.

Insomnia is linked with changes in innate immunity. Chronic insomnia has been shown to be associated with significant decreases in the numbers of CD3, CD4 and CD8 T cells and with reduced NK cells response (Irwin et al., 2003). Similar results found Savard et al. (2003). In their study, chronic insomnia was significantly associated with lower counts of lymphocyte subpopulations (ie, CD3+, CD4+, and CD8+ cells) and was marginally associated with lower total lymphocyte count. No differences were found in NK cell activity or cytokine production. Sakami et al. (2002) found in otherwise healthy insomniacs low levels of INF γ and low INF γ to IL 4 ratio indicating a shift in the Th1/Th2 cell balance toward Th2 dominance. However, NK cell activity was independent of insomnia in this study.

Changes in cytokine levels were studied too. Chronic insomnia was found to be associated with a shift of IL-6 and TNF secretion from nighttime to daytime (Vgontzas et al., 2002). Authors hypothesized that this may explain daytime fatigue in chronic insomnia. Other study demonstrated significantly increased nocturnal IL-6 secretion in insomniacs with polysomnographically documented sleep impairments (Burgos et al., 2006). In contrast, in a community dwelling sample of older adults revealed no significant differences in interleukin 6 and tumor necrosis factor alpha in insomniacs and good sleepers (Okun et al., 2011).

It is not clear if these findings relate directly to hyperarousal. It is most likely that the interaction between immunological parameters and sleep is bidirectional (Riemann et al., 2010).

3.2.5 Electrophysiology

Polysomnography

Sleep continuity in primary insomnia is compromised. Sleep latency is prolonged, wake time after sleep onset increased and sleep efficiency reduced in insomniacs compare to normal sleepers. Absolute differences are not large. Indeed, differences are of much lesser magnitude than subjectively estimated differences. There is also a marked night-to-night variability in some insomniacs. Many studies described changes of sleep architecture – the SWS or REM sleep reductions (Reite et al., 1995) (Hudson et al., 1992).

Multiple Sleep Latency Test (MSLT).

Although insomnia patients have reduced sleep time, non study reported reduced sleep latencies in the MSLT. In contrast many studies reported increased sleep latencies in the MSLT compared to healthy controls. Numerous studies have also shown a positive correlation of physiological activation and sleep variables, usually measured by heart rate and sleep latency (Bonnet and Arand, 2010). It was also shown that insomnia patients had significantly longer sleep latencies after a brief walk to produce state arousal compare to controls and obviously to their own resting baseline (Bonnet and Arand, 2000). MSLT findings in insomnia patients strongly support the hyperarousal theory.

On the other hand, it was also discussed that the demand characteristics of the MSLT ("try to sleep") are involved in this prolongation of sleep latencies (Espie et al., 2006). The demand to "do something" that the patient with insomnia has difficulty doing would elicit performance anxiety, interfering with sleep initiation. This mechanism would therefore rather detect the specific fears regarding sleep than a general physiological hyperarousal.

Sleep microstructure

Microarousals

Feige et al. (2008) focused on the discrepancy between subjective and PSG determined total sleep time in patients with primary insomnia, comparing subjective sleep ratings and polysomnographic data from drug-free patients with primary insomnia and good sleepers. A significant relationship between subjective wake time and the amount of REM sleep was found in insomnia patients. Furthermore, the frequency of micro-arousals was significantly enhanced during both REM and NREM sleep in primary insomnia compared to good sleepers, the REM sleep effect being more pronounced, approximately 2-3 times larger.

Sleep spindles, K complexes

In sleep maintenance insomnia subjects the sleep spindle index was significantly lower than in controls and did not decrease during slow-wave sleep. Moreover during recovery night the sleep spindle index decreased significantly during the first sleep cycle in controls and not in insomniacs (Besset et al., 1998). Bastien et al. (2009) did not replicate these findings. Forget et al. (2011) examined both spontaneous and evoked K-complexes in primary insomnia patients and good sleepers. While the rate of evoked K-complexes was comparable, primary insomnia patients had more spontaneous K-complexes.

Spectral analysis

There some studies performed to highlight differences in the spectral sleep EEG composition between primary insomnia and good sleeper controls. Freedman (1986) first investigated drug-free patients with sleep onset insomnia compared to good sleepers. He found that insomniacs had significantly more beta activity during wake, stage 1 and REM sleep and less alpha activity than normals. There were no differences during stages 2, 3, or 4. Merica et al. (1998) described increased beta power throughout the night with maximum in REM sleep, in addition to reductions in slower EEG frequencies in both REM and NREM sleep in chronic sleep maintenance insomnia. Perlis et al. (2001a) showed that beta and gamma power were increased in the patients with insomnia relative to good sleepers for several stages of NREM sleep, and that only Beta-2 was increased during REM sleep. In a second analysis of the same data set, Perlis et al. (2001b) evaluated the temporal and stage-wise distribution of high frequency EEG activity in primary and secondary insomnia to major depressive disorder and in good sleepers. High frequency EEG activity tended to increase across NREM cycles, occurred maximally during stage 1 and during REM sleep, and both of these effects were exaggerated in patients with primary insomnia compared to both other groups.

Krystal et al. (2002) compared EEG frequency spectra from REM and NREM sleep in primary insomnia subjects subtyped as subjective insomnia sufferers (those with relatively long total sleep time and relative underestimation of sleep time compared with PSG), and objective insomnia sufferers (those with relatively short PSG total sleep time) with EEG frequency spectra in normals. They reported reduced relative delta and increased relative alpha, sigma and beta power during NREM sleep in the patients with "subjective" insomnia but not in the "objective" insomnia group. No differences were found for REM sleep.

Cerebral asymmetry is used to describe the differences in electroencephalographic activity between regions of the brain. St Jean et al. (2012) focused on hemispheric asymmetry in patients with psychophysiological insomnia, with paradoxical insomnia and good sleepers.

Patients with paradoxical insomnia showed a trend for increased left frontal omega (60-125Hz)-band activity while good sleepers had more omega-band power over right frontal sites. The psychophysiological insomnia group had more right parietal beta power than the paradoxical insomnia group but none differed from good sleepers in this measure.

Almost all studies have found increased fast frequencies (in the sigma and beta range) as characteristics of the sleep EEG of patients with primary insomnia. Cortical electrophysiological signals in the beta and especially gamma band have been assumed to reflect coherent cortical processing of sensory information and possibly of all cognitive activity. Thus, an EEG power increase in these frequency bands during sleep can be interpreted as a marker of cortical hyperactivity or hyperarousal (Feige et al., 2013).

Event related potentials

Event related potentials offers a mean for a direct evaluation of cortical activation to an experimental stimulus.

Bastien et al. (2008) compared chronic psychophysiological insomnia and good sleepers on N1, P2 and N350 components in a multi-assessment protocol. They reported greater P2 amplitude on the sleep onset and larger N1 in the morning and in the evening in primary insomnia compared to good sleepers. They also recorded a smaller P350 in insomniacs at sleep onset. Yang and Lo (2007) examined auditory ERPs of primary insomnia patients and good sleepers across the whole night. They found a larger N1 and a smaller P2 amplitude to rare tones and a smaller N350 to standard tones during the first 5 minutes of continuous stage 2. No differences across the whole night were found. The results were interpreted as an enhancement of attention and a reduction in the inhibitory process at sleep onset in insomnia.

Milner et al. (2009) explored sensory information processing in poor and normal sleepers using paired-click stimuli during pre-sleep wakefulness, stage 2 and REM sleep. The poor sleepers were not diagnosed with insomnia but similar criteria of subjectively poor sleep and related daytime complaints were used. Lower P50 amplitudes were observed in poor sleepers during wake but neither during REM (where both groups showed clear gating) nor during stage 2 (where both groups did not show significant gating). This result is interpreted as showing heightened sensory processing in the pre-sleep period in poor sleepers.

Turcotte and Bastien (2009) investigated the relation between objective sleep parameters and the amplitudes and latencies of ERPs components N1 and P2 in a multi-assessment

protocol. As the amplitude of N1 and P2 increased before going to sleep in insomniacs, the sleep quality of the following night decreased. Furthermore, the sleep quality of the previous night also appeared to have an impact on morning (daily) arousal levels. Authors concluded that that the hyperactivation and inhibition deficits in insomnia sufferers are directly associated with a poorer sleep quality.

The existing studies appear to show an increased sensitivity to auditory stimuli in primary insomnia patients during both wake and sleep onset. Increased amplitude to N1 and decreased amplitude for N350 in insomniacs during night compared to controls have been shown. An increased N100 amplitude is also observed intra-individually when slow negative potentials such as the contingent negative variation are modulated, reflecting increased expectation and lowered response threshold (i.e., increased cortical excitability). Alternatively, the described results may also be viewed as a consequence of a compromised ability of patients with insomnia to inhibit alerting sensory inputs when trying to fall asleep (Feige et al., 2013).

Cyclic alternating pattern

The cyclic alternating pattern first described by Terzano et al. (1985) is a NREM sleep phenomenon based on the observation that certain EEG elements, distinct from background EEG, recur with a periodicity of 20-40s (Terzano et al., 2001). The cyclic alternating pattern is a long-lasting periodic activity consisting of two alternate electroencephalogram patterns. It marks an arousal fluctuation, containing a succession of unstable or aroused (phase A) and electrophysiologically quiet sleep (phase B). This variation in EEG is closely related to fluctuations in the level of arousal that characterize two different functional states in the arousal control mechanism. A large CAP rate marks disturbed sleep with poor sleep quality (Terzano et al., 1990). There is also a strict relationship between ASDA arousals and the CAP phase A subtypes A2 and A3 (de Carli et al., 2004).

Terzano et al. (2003) compared primary insomniacs and good sleepers. Untreated primary insomniacs showed an increased number of arousals and an increased CAP rate, as well as increased nocturnal wake time. After treatment, active medication significantly reduced CAP rate compared to placebo. Parrino et al. (2004) also showed that hypnotic medication reduced CAP rate in patients with insomnia and concluded that CAP rate is a measure of the instability of sleep with increased CAP rates indicating a "destabilization" of sleep in insomnia. Chouvarda et al. (2011) defined new methodologies for the quantitative characterization of insomnia using CAP. Comparing primary insomnia patients to good sleepers, they confirmed the increased CAP rate in primary insomnia and added that CAP

cycles were more irregular and desynchronisation phases more extended in primary insomnia.

3.2.6 Neuroimaging

Neuroimaging methods in insomnia research did not arise a clear-cut picture yet.

Manually derived morphometric analysis of structural magnetic resonance images revealed significantly reduced hippocampal volumes bilaterally in patients with chronic primary insomnia compared to healthy good sleeper controls (Riemann et al., 2007). This finding is in line with the data on cognitive deficits in insomnia. However, a study by Winkelman et al. (2010) failed to show reduced hippocampus gray matter volumes using manual tracing in patients with primary insomnia in comparison with healthy good sleepers. In the third morphometric study in insomnia patients, Altena et al. (2010) used voxel-based morphometry without a priori definition of regions of interest investigating an elderly sample. In this sample, the authors reported reduced orbitofrontal and precuneus gray matter volumes but no between-group differences in the hippocampal region. In the largest study so far, significant between-group differences were observed in any of the investigated brain morphometry variables (Spiegelhalder et al., 2013).

In a functional magnetic resonance imaging study, insomniacs and carefully matched controls underwent scanning during the performance of a category and a letter fluency task. Compared to controls, insomnia patients showed hypoactivation of the medial and inferior prefrontal cortical areas (Brodmann Area 9, 44-45), which recovered after sleep therapy. Prefrontal hypoactivation in the absence of behavioral differences (no performance deficits) may be related to individually differential recruitment of other brain regions for successful task completion (Altena et al., 2008).

A SPECT study conducted around the first NREM episode has found that insomnia showed a consistent pattern of hypoperfusion across all 8 pre-selected regions of interest, with particular deactivation in the basal ganglia. The frontal medial, occipital, and parietal cortices also showed significant decreases in blood flow compared to good sleepers. Subjects with insomnia had decreased activity in the basal ganglia relative to the frontal lateral cortex, frontal medial cortex, thalamus, occipital and parietal cortices (Smith et al., 2002). This finding is rather in contradiction to the hyperarousal theory of insomnia. Therefore authors have speculated that the enhanced cerebral deactivation that occurred during SWS mighty serve a recuperative function for daytime hyperactivity. Or, since they only sampled a two-

minute windows of perfusion during the first NREM cycle, it might be a relatively short-lived or sporadic phenomena.

A PET study suggested that the inability of patients with insomnia to fall asleep may be caused by arousal mechanisms failing to decline in activity from waking to sleep states. Although sleep EEGs did not differentiate the two groups, patients with insomnia showed a greater global cerebral metabolism and a smaller decline in relative metabolism from waking to sleep in the wake-promoting areas of the ascending reticular formation and hypothalamus, compared to healthy subjects. Similar effect was observed in areas associated with cognition and emotions. In the daytime, however, patients with insomnia had reduced relative metabolism in the prefrontal cortex (Nofzinger et al., 2004). The reduced prefrontal cortex activity while awake was later associated with daytime fatigue due to sleep deprivation.

The first evidence of a neurochemical difference in the brains of those with primary insomnia compared to normal sleeping controls was demonstrated by Winkelman et al. (2008b). They found a global reduction of GABA in insomniacs compare to good sleepers by using proton magnetic resonance spectroscopy. There was also a strong association between PSG measures of sleep continuity and GABA levels.

3.2.7 Neuropsychological studies

Many patients suffering from chronic insomnia subjectively report deficits in various neuropsychological domains, including alertness and memory. However, neuropsychological studies often failed to detect robust impairments. According to review articles on this topic the significant group differences to controls are reported in only 20% - 25% of studies (Fulda and Schultz 2001).

This could be explained by the fact that insomniacs´ expectations toward their performance increase when they perceive that have not slept well (Broman et al., 1992). Or, it is possible that the neuropsychological tests are not sensitive enough to detect differences between insomniacs and controls.

Hyperarousal during sleep may interfere with the strengthening of labile memory traces acquired during preceding wakefulness. There is evidence that newly acquired memories are replayed and processed during sleep (Ribeiro and Nicolelis 2004). Chronic sleep disruption may lead to persistent alterations in brain circuits critical for memory functioning. Ongoing hyperarousal may disrupt basic mechanisms of brain plasticity and synaptic homeostasis. The synaptic homeostasis hypothesis proposes that plastic processes occurring during

wakefulness result in a net increase in synaptic strength in many brain circuits. The role of sleep is to downscale synaptic strength to a baseline level that is energetically sustainable, makes efficient use of gray matter space, and is beneficial for learning and memory (Tononi and Girelli, 2006).

For more clinical details see the subchapter Consequences of insomnia, Psychological symptoms

4. Diagnosis and clinical course

Insomnia follows a chronic clinical course. In Morin´s et al. study (2009) 74% of subjects reported insomnia for at least 1 year and 46% reported insomnia persisting over 3 years. The course of insomnia was more likely to be persistent in those with more severe insomnia. Remission rate was 54%; however, 27% of those with remission of insomnia experienced a relapse.

In epidemiological studies, sleep maintenance symptoms are most prevalent among individuals with insomnia (50% - 70%), followed by difficulty initiating sleep (35% - 60%). and nonrestorative sleep (20% - 25%) (Morin et al., 2011). However, multiple sleep symptoms are more common than any single symptom.

The evaluation of insomnia centers on the clinical interview but can be enhanced by a number of complementary examinations.

4.1 Clinical interview

The clinical interview is the most important component of an insomnia assessment. Key elements of assessment include sleep history with the nature of complaint (onset, course, pattern, duration, severity), predisposing, precipitating and perpetuating factors, as well as relieving factors, sleep – wake pattern, daytime symptoms and consequences, symptoms of other sleep disorders, sleep hygiene practice, sleep and bed environment, lifestyle, eventual treatment history and also believes about sleep and cause of insomnia.
Family sleep history concerns sleep disorders in the family and sleep – wake pattern by relatives.

Medical history should include a review of systems most commonly associated with sleep problems such as cardiac system (e.g. congestive heart failure, angina pectoris), pulmonary system (e.g. chronic obstructive pulmonary disease, bronchial asthma), rheumatologic system (e.g. rheumatoid arthritis, fibromyalgia), neurological system (e.g. neurodegenerative

disorders, stroke), gastrointestinal system (e.g. peptic ulcer, gastroesophageal reflux) and endocrine system (e.g. hyperthyroidism, diabetes). The presence of chronic pain, pruritus, dyspnea of any cause and oncologic diseases should be evaluated. Prostate disease in middle-aged men and menopausal status in middle-aged women should be assessed (Kryger et al., 2005) (Thase, 2005).

Psychiatric history is indispensable part of insomnia evaluation. Mood disorders, anxiety, alcoholism or substance abuse are most commonly met in patients with insomnia complaint. The clinician should ask about the perceived level of stress and psychosocial factors. A brief psychological/psychiatric screening is generally sufficient, in some cases a profound psychiatric or/and psychological examination is needed (Kryger et al., 2005).

Insomnia could be caused by medication use. Commonly prescribed drugs associated with insomnia are: beta blockers, calcium channel blockers, some diuretics, bronchodilators, decongestants, stimulants, monoamine oxidase inhibitors, stimulating antidepressants, thyroid preparations, adrenocorticoid hormone, corticosteroids, oral contraceptives, dopaminergic medication, diphenylhydantoin, alpha-methyldopa (Thase, 2005). Therefore current medication use must be evaluated. Some medication can exacerbate periodic limb movements or even restless legs syndrome with associated insomnia. Sudden discontinuation of hypnotics use may cause rebound insomnia. Over-the-counter medication, supplements or herbal remedies may also interfere with sleep. Use of caffeine, nicotine, alcohol as well as of illicit substances should be evaluated.

4.2 Self reported questionnaires for insomnia

Self reported questionnaires typically address estimates of sleep quality, specific sleep characteristics and behaviors, insomnia severity, functional impairment, and attitudes pertaining to sleep. Self reported questionnaires demonstrate high global test-retest correlations in validation studies. They can distinguish insomniacs/poor sleepers and normal sleepers (Zammit, 1988). Some of them demonstrate significant correlation with polysomnographic findings (Buysse et al., 1989). These instruments are not immune to subjective biases. Combining of self reported questionnaires with other methods maximizes their utility.

Most frequently used are the Pittsburgh Sleep Quality Index and Insomnia Severity Index.
The Pittsburgh Sleep Quality Index has been applied in a variety of settings to measure sleep quality (Buysse et al., 1989). A 19-item questionnaire is used to measure sleep quality and disturbances within previous months. Seven component scores assess habitual duration

of sleep, nocturnal sleep disturbances, sleep latency, sleep quality, daytime dysfunction, sleep medication usage, and sleep efficiency. These 7 components are summed to yield a measure of global sleep quality with a range of 0 (good sleep quality) to 21 (poor sleep quality). A cut-off score > 5 to identify those with poor sleep quality in depressed and normal sleepers, and a cut-off score > 10 to identify poor sleep quality among people with insomnia.

Insomnia Severity Index (ISI) (Bastien et al., 2001) consists of seven sections: the first assesses the severity of insomnia (divided into three items), while the rest are used to measure the satisfaction of sleep, interference in daytime functioning, the perception of the sleep problem by others and the patient's level of concern.

Other frequently used scales associated with adult insomnia are: (listed in alphabetical order, a selection of commonly used scales, not an exhaustive review):
Athens Insomnia Scale (Soldatos et al., 2000) assesses the severity of insomnia using diagnostic criteria by the International Classification of Diseases (ICD-10). Eight-item questionnaire evaluates sleep onset, night and early-morning waking, sleep time, sleep quality, frequency and duration of complaints, distress caused by the experience of insomnia, and interference with daily functioning. A shorter version of the questionnaire, consisting of the first five items alone, may also be used.

Bergen Insomnia Scale (BIS) (Pallesen et al., 2008) was constructed on the basis of the inclusion criteria for insomnia in the DSM-IV-TR. Six items assess pertain to sleep onset, maintenance, and early morning wakening insomnia, not feeling adequately rested , experiencing daytime impairment , and being dissatisfied with current sleep.

Dysfunctional believes and attitudes about sleep (Morin 1993), a 28 item scale assess believes, attitudes, expectations, and attributions about sleep and insomnia. Questions reflect five themes: misattributions and amplifications of the consequences of insomnia, diminished perception of control and predictability of sleep, unrealistic sleep expectations, misconceptions about the causes of insomnia, and faulty believes about sleep-promoting practices.

Insomnia impact scale (Hoelscher et al., 1993) is a 40 item self reporting measure of the impact of insomnia on the quality of live spanning the cognitive, emotional, physical, occupational, and social domains of the general functioning.

Insomnia Diurnal Impact Scale (IDIS) (Ruiz et al., 2011) is a similar scale comprising six items designed to evaluate the daytime effects of insomnia. It evaluates daytime sleepiness, irritability, difficulties in concentration, tiredness, difficulties in management of daily tasks and in socialization due to sleepiness.

Insomnia Symptom Questionnaire (ISQ) (Okun et al., 2009) is a 13-item self-report instrument designed to identify insomnia based on the Diagnostic and Statistical Manual criteria for primary insomnia. It determines the presence, frequency and duration of sleep symptom criteria and identifies significant daytime consequences of the sleep complaint.

Medical Outcomes Study (MOS) Sleep Measure (Hays et al., 2005) measures 6 sleep dimensions: initiation (time to fall asleep)., quantity (hours of sleep each night)., sleep maintenance, respiratory problems, perceived adequacy and somnolence.

Leeds sleep evaluation questionnaire (Parrott and Hindmarch, 1978) is10 item questionnaire providing subjective ratings of medication effects on aspects of sleep and early morning behavior. Scales are grouped chronologically and include ease of falling asleep, quality of sleep, ease of waking, and integrity of early morning behavior after wakefulness.

Short Insomnia Questionnaire (SDQ) (Violani et al., 2004) is a rapid evaluation of insomnia based on the DSM-IV and ICSD criteria.

St Mary's hospital sleep questionnaire (Ellis et al., 1981) is a 14 item measure assessing an individual's previous night sleep, including sleep quantity, sleep quality, sleep latency, and early morning awaking. The scale was designed for repeated use with a particular focus on the needs of hospital patients.

Women's Health Initiative Insomnia Rating Scale (WHIIRS) (Levine et al., 2003) is a five item scale developed to insomnia symptoms. It provides information on sleep latency, sleep maintenance, early morning awaking, and sleep quality.

4.3 Sleep diary

Sleep diary provides a subjective record of an individual's sleep. Sleep diary typically include entries for bedtime, rising time, sleep latency, number and duration of awakenings, sleep duration, naps, use of sleep aids, and various indices of sleep quality and daytime functioning. Sleep diary should be completed for a minimum one to two weeks (Lacks and Morin, 1992). Sateia reported modest to poor correlation between subjective reports and

objective findings. There is a tendency to underestimate total sleep time and overestimate sleep latency. Sleep logs may be therefore better indicators of patient perception of sleep disturbance than they are reflective of true, quantitative sleep abnormalities (Sateia et al., 2000).

4.4 Actigraphy

Actigraphy estimates sleep based on measurements of body movements. Actigraph device is an accelerometer which monitors rest/activity cycles. Its main advantage except of price is comfortable collecting data in home environment. Coupling the actigraph with a sleep diary is important. Actigraph information can help diagnose, document severity, guide the proper treatment and monitor compliance to treatment in insomnia. Actigraphy is also very useful to assess night-to night variability (Anticoli-Israel et al., 2003). However, for routine diagnostic of insomnia is actigraphy, like PSG, not recommended (Standards of Practice Committee of the American Academy of Sleep medicine, Littner et al., 2002).

4.5 Polysomnography

Polysomnography provides a complex measurement of sleep and is essential in diagnosis of many sleep disorders, but it is not necessary in the assessment of insomnia (Kryger et al., 2005). Insomnia diagnosis requires the subjective component of perception of poor sleep which may not be always supported by objective measurements. However in patients with pathologic levels of daytime sleepiness, not responding to usual insomnia treatment, uncertain initial diagnosis or with suspicion for comorbid other sleep pathology the PSG should be considered.

5. Differential diagnosis

Differential diagnosis includes other sleep disorders that could present clinically as insomnia complaint. Up to 50% of adults with obstructive sleep also report insomnia (Buysse, 2013). Patients with periodic leg movement disorder and restless legs syndrome complain sleep onset difficulties and nocturnal awakenings. Insomnia is a prominent symptom of most circadian rhythm disorders.

There is very high prevalence of insomnia in psychiatric disorders. Insomnia is a part of the symptom profile of many psychiatric disorders (e.g. mood disorders, anxiety disorders). Moreover, insomnia often appears as a prodromal symptom before the appearance of mental disorder.

Insomnia could be caused by many other factors and is often secondary to other diseases. A separate diagnosis of insomnia is not needed for all patients who have insomnia complaints. Only if the symptoms are severe or require an independent focus of clinical attention, a separate insomnia diagnosis should be made. Considering the differential diagnosis is crucial for successful treatment. Nevertheless insomnia is often complex and multifactorial (Kryger et al., 2005).

6. Consequences of insomnia

6.1 Mental disorders

6.1.1 Depression

There is a large body of evidence suggesting that insomnia is a risk factor for new onset and recurrent major depressive disorder. More than twenty years ago the longitudinal work of Ford and Kamerow (1989) highlighted the role of insomnia as a predictor of depression. Over a dozen studies have since then replicated their findings in different cohorts and over various periods of assessment.

Epidemiological and clinical data in those in the community reporting symptoms of insomnia finds comorbidity rates between insomnia and psychiatric disorders around 50% (Kryger et al., 2005). Sleep disorder is among the most prevalent symptoms of current depression, with insomnia symptom rates according to some studies of around 80%. The rate was nearly 90% when anxiety disorder was present concomitantly (Ohayon et al., 2000). In other trail, it was estimated that 60% of adults meeting criteria for major depressive disorders complain of clinical relevant insomnia (Ohayon 2007).

In individuals with insomnia, 40–60% have features of concomitant mental disorder, mainly depression (Ohayon and Roth 2003). In another study, approximately 10%–20% of individuals diagnosed with insomnia met criteria for major depressive disorder (Ohayon 2007). Stewart et al. (2006) applied in his epidemiological study more stringent diagnostic criteria then most other studies. Prevalence rate estimates were 5% for insomnia and 3% for depression. Among those with insomnia 21% were depressed, whereas among individuals with depression 40% had insomnia.

Insomnia is also one of the most common and most prominent prodromal features of depression. Insomnia appeared first in more than 40% of cases of depression; when it was a relapse of the depression, insomnia appeared first in 56% of cases and usually reach its zenith at the week of recurrence of depressive disorder (Ohayon and Roth 2003).

Moreover, comorbid insomnia is a risk factor for unremitting depression. Patients with persisting insomnia had a diminished treatment response at six month and yearly follow up compared with patients without persistent insomnia (Pigeon et al., 2008). Indeed, a history of persistent insomnia is associated with a significantly increased risk of developing a new episode of depression.

The current findings may lend support to the hypothesis that depression is secondary to insomnia and that insomnia may be considered a risk factor of depression (Isaac and Greenwood, 2011) (Pigeon, 2010)..

6.1.2 Other mental disorders

Anxiety disorders are even equally or more prevalent than depression among insomniacs. 24% of responders with insomnia had anxiety disorder and insomniacs were 6 times more likely to have an anxiety disorder than those without insomnia (Taylor et al., 2005) (Ford and Kamerow, 1989). In another study, 36% of insomniacs had at least one anxiety disorder compared with 19% of those with no insomnia. In insomnia group, 8% of patients had generalized anxiety disorder, 6% had panic disorder, 5% had obsessive compulsive disorder and 25% had a phobia (Breslau et al., 1996).

Generalized anxiety disorder is frequently associated with difficulty initiating or maintaining sleep or restless unsatisfying sleep. Positive correlations have been reported between anxiety ratings and number of awakenings, latency to stage 1 NREM sleep, and percentage of stage 2 NREM sleep. A significant negative relationship was found between anxiety and percentage of deep sleep (Rosa et al., 1983).

Nocturnal panic episodes, occurring in 44% to 71% of patients with panic disorder, are associated with sudden awakening with the onset of typical panic symptoms and lead to disturbed night sleep and insomnia. Interestingly, Cervena et al. (2005) have shown that reduced anxiety after successful treatment of panic disorder was not necessarily followed by improved sleep parameters.

Sleep disturbances, particularly insomnia and nightmares, are common features of post-traumatic stress disorder. Rates of insomnia in trauma population range from 60% to 90% (Pigeon, 2010). Moreover, it was shown that 72% of individuals experiencing insomnia within one month of their trauma developed post-traumatic stress disorder.

It has been shown that alcohol abuse occurs at double the rate in individuals with insomnia compared to those without insomnia (Breslau et al., 1996). Insomnia and fragmented sleep have been found to predict relapse in alcohol dependence (Brower et al., 2001). During alcohol withdrawal, sleep is grossly disturbed with extremely disrupted sleep continuity, increased wakefulness after sleep onset, REM sleep rebound with vivid dreaming. After acute withdrawal, subjects with chronic alcohol use may complain of light fragmented sleep lasting for months to years, and the EEG shows persistent deficit in slow wave sleep and persistent sleep continuity disturbances.

A decrease in sleep duration has been correlated with the onset or exacerbation of manic or hypomanic symptoms. In most patients, the mood change occurred on the day following the change in sleep and/or bed rest. Sleep changes from a previous pattern, especially those of more than 3 h, may indicate that a large mood change is imminent (Bauer et al., 2006).

In clinical practice, insomnia is a common feature in schizophrenia, including difficulty falling asleep, maintaining sleep or achieving a restful sleep. Sleeping disorders occur as early signs of the first manifestation of illness as well as early signs of relapse. They bear a relation to positive symptoms and disorganization of thought (Staedt et al., 2010). Although some sleep impairments improve with antipsychotic treatment, in many cases, even during the remission of the disease, sleep continues fragmented , suggesting that there are pathofysiologic mechanisms involved in sleep disturbance in these patients.

A recent meta-analysis supports earlier reported association between sleep disturbance and suicidal thoughts and behaviors. Sleep disturbances in general, as well as insomnia individually, appear to represent a risk factor for suicidal thoughts and behavior (Pigeon et al., 2012).

6.2 Psychological symptoms

Patients with insomnia reported increased psychological stress and decreased ability to cope with stress (Kim et al., 2000). Moreover, almost 80% of insomniacs had significant increases on one or more clinical scales of the Minnesota Multiphasic Personality Inventory. These increases were found even in patients with insomnia due to identified medical factors, suggesting a possible causal relationship between insomnia and psychological symptomatology (Kalogjera-Sackellares and Cartwright, 1997).

Individuals with insomnia consistently report difficulties pertaining to their cognitive functioning. A recent meta-analysis (Fotier-Brochu et al., 2012) have revealed that

individuals with insomnia exhibit performance impairments for several cognitive functions, including working memory, episodic memory and some aspects of executive functioning. These impairments are of small to moderate magnitude. No significant group differences were observed for tasks assessing general cognitive function, perceptual and psychomotor processes, procedural learning, verbal functions, different dimensions of attention and some aspects of executive functioning, such as verbal fluency and cognitive flexibility.

People with insomnia have also higher rates of absenteeism, more traffic accidents and poorer quality of life (Zammit et al., 1999).

6.3 Medical disorders

Subjects with insomnia have often recurrent, persistent or multiple health problems. Mellinger et al. (1985) found that 53% of patients with severe insomnia had two or more health problems, in contrast to 24% of those without insomnia. Insomniacs have also higher rates of general medical services utilization (Ford and Kamerow, 1989).

An epidemiologic longitudinal study showed that the incidence of insomnia was higher in subjects with heart disease, stroke, incident hip fracture and respiratory symptoms. The persistence of insomnia over a 3-years period was associated with heart disease, incident diabetes, respiratory symptoms and stroke (Foley et al., 1999). A higher occurrence of rheumatic disease and untreated hypertension was reported in individuals who had difficulty in initiating and maintaining sleep (Gislason and Almqvist, 1987). Insomniacs are also more likely to have a painful physical condition. Insomnia increases the risk of developing hypertension and cardiovascular disease (Phillips and Mannino, 2007).

There is a link between insomnia and immunity. Insomnia is associated with changes in innate immunity including decreased natural killer cells activity, higher levels of interleukine-6 and shift in circadian distribution of interleukine-6 and tumor necrosis factor from the night to the daytime (Vgontzas et al., 2002) (Irwin et al., 1996).

For more details from the pathophysiological perspective see please the subchapter Pathophysiology of insomnia, Immune functions

7, Treatment of primary insomnia

7.1. Non-pharmacological treatments

7.1.1 Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) comprises a group of techniques that address the factors that help perpetuate chronic insomnia, regardless of the cause. Individual CBT interventions

may be delivered as monotherapy, but it is widely accepted that multicomponent CBT is the best approach to treatment. Such combined strategy addresses the multiple putative causes and perpetuators of insomnia.

Sleep hygiene

Many patients presenting for treatment of insomnia have inadequate sleep hygiene. Sleep hygiene addresses conditions and practices that promote sleep. Evaluation of sleep hygiene is recommended in all patients with insomnia. Behaviors that foster poor sleep quality and result in perpetual sleep complains can be classified into two categories: those that produce hyperarousal and those that foster poor sleep organization.

Sleep hygiene rules were first proposed by Hauri (1977) and include a wide range of recommendations to address presumed behavioral and cognitive contributions to insomnia. “Original” sleep hygiene rules proposed by Hauri were adapted and there are many versions of sleep hygiene rules by now. Most of them include instructions that the patient should avoid caffeine, alcohol, large meals and exercise for several hours prior to bed, maintain regular bed and waking times, keep an environment conductive to sleep. Hauri´s rules included also recommendations to limit time in bed and go to bed only when sleepy. These recommendations overlap with stimulus control therapy.

Data showing efficacy of sleep hygiene as stand-alone therapy are sparse (Stepanski and Wyatt, 2003). Sleep hygiene rules are useful, but should not be provided as monotherapy.

Stimulus control therapy

Stimulus control therapy is a specific type of cognitive behavioral therapy that is based on the assumption that insomnia is a maladaptive response to factors such as bedtime and the bedroom environment. This conditioned response to the sleep environment requires a learning process to re-associate the bed with sleep. Stimulus control therapy is considered to be the first line behavioral treatment for chronic insomnia (Chesson et al., 1999).

Stimulus control therapy limits the amount of time spends awake in bed. Spending time in bed, while awake, strengthens the association between wakefulness and the bedroom. Therefore the primary goal is to have patient in bed only when drowsy or asleep. Patients are advised to keep a fixed wake time during the whole week, including weekend, irrespective of how much sleep they get during the night, not nap during the day, sleep in the bedroom only and avoid any behavior in the bed other than sleep, leave the bedroom when awake for

approximately 10 to 15 minutes, and return to bed only when sleepy and when they cannot fall asleep again, they leave the bedroom once more.

Stimulus control therapy has been found to be the most effective single treatment and is recommended as a standard treatment for chronic insomnia (Morgenthaler et al., 2006).

Sleep restriction

Sleep restriction therapy is a behavioral treatment based on manipulation time in bed according to systematic rules. The therapy is in fact controlled, partial form of sleep deprivation. Sleep restriction was developed by Spielman et al. (1987) and there are several adapted versions nowadays. It begins by calculating average total sleep time, which is accomplished by completing sleep logs that record the duration of time in bed and the total duration of time spent sleeping. Afterwards, arising time is fixed and bedtime is delayed and manipulated based on sleep efficiency. Total time in bed is reduced to an amount equal to patient's actual average total sleep time (but not less than 4,5-5 hours) in order to increase homeostatic sleep drive and thereby improve sleep propensity. As sleep improves - the sleep efficiency for the prior 5 days is greater than 90%-85% - the patients are allowed to increase time in bed by 15-20 minutes. If sleep efficiency is less the 85%-80%, the bedtime is pushed back later to equal the mean sleep total time of the prior 5 days. A decrease in time in bed is not made for at least 10 days from the beginning of the treatment, or within 10 days of any schedule change.

Patients may suffer from excessive daytime drowsiness, especially in the initial phases of the treatment. Since patients perceive daytime sleepiness, some of them become reluctant to reduce their time in bed. Adherence to treatment may be reduced from these reasons. Sleep restriction is contraindicated in patients with history of bipolar disorder, seizures or untreated hypersomnolence.

Sleep restriction therapy is also found to be efficacious (Morin et al., 1994). Sleep restriction therapy has effect sizes equal to that with stimulus control therapy (Morgenthaler et al., 2006).

Cognitive therapy

Cognitive therapy is aimed at addressing the cognitive changes that accompany insomnia and contribute to the problem. Cognitive features of insomnia include sleep-disruptive cognitions such as irrational fears, unrealistic expectations, faulty causal attributions, excessive worries regarding sleep, as well as maladaptive cognitive processes such as

excessive self-monitoring. Common fears about insomnia center around catastrophizing and amplification of consequences of daytime impairment associated with poor sleep. These fears place additional pressure on the individual to fall asleep quickly, and this pressure raises tension and arousal and exacerbates insomnia. Cognitive therapy challenges these beliefs and fears through Socratic questioning and behavioral experiments and reframe them into more adaptive substitutes to short-circuit the self-fulfilling nature of this vicious cycle.

Cognitive restructuring is a type of cognitive therapy that modifies dysfunctional cognitive processes. This is accomplished first by systematically identifying cognitive problems. Then misattribution, exaggeration, unrealistic expectations, or other inappropriate cognition is challenged and replaced with a more rational interpretation of the situation.

Paradoxical intention is a special form of cognitive therapy that involves specific instructions to the patient to engage willingly in the most feared behavior (i.e., staying awake). The rationale is that trying to stay awake at bedtime or upon awakening at night will produce a paradoxical effect and override the performance anxiety associated with the attempt to fall asleep. There is some evidence supporting the efficacy of this treatment for initial insomnia (Broomfield and Espie, 2003). Paradoxical intention is rarely recommended over more empirically supported methods or methods included in multimodal therapy, but may be useful when patients do not benefit from other methods (Morgenthaler et al., 2006).

Relaxation based interventions

Relaxation therapy is based on observations that insomnia patients often display high levels of physiologic, cognitive, and/or emotional arousal, both at night and during the daytime and is the most commonly used nondrug therapy for insomnia. Of the different relaxation-based interventions, some methods, such as progressive-muscle relaxation, autogenic training, and biofeedback, focus primarily on reducing physiologic arousal, whereas attention-focusing procedures, such as imagery training and meditation, target mental arousal in the form of worries, intrusive thoughts, or a racing mind. Abdominal breathing is often a component of various relaxation techniques, or it may be used alone (Morin, 2006). Most research evidence favours progressive-muscle relaxation as a treatment for insomnia (Sharma and Andrade, 2012).

The most critical issue is to practice regularly. Professional guidance often is necessary in the initial phase of training. Some individuals may have a paradoxical response to relaxation and became more anxious.

Cognitive behavioral therapy combines treatments described above. It is usually conducted as weekly sessions over period of 6-8 weeks, and may be used to treat patients with insomnia individually or in a group format.

The efficacy and effectiveness research provides strong support for cognitive behavioral therapy (Babson et al., 2010). More than 50 randomized controlled clinical trials have shown that cognitive behavioral therapy results in reliable and robust improvements across different subjective and objective measures of sleep disturbance (Malaffo and Espie, 2007). While the individual components of cognitive behavioral therapy (behavioral strategies, cognitive therapy, and relaxation training) can be delivered as monotherapies, multicomponent cognitive behavioral therapy is the preferred approach (Morgenthaler et al., 2006). Additionally, cognitive behavioral interventions are as effective as pharmacological treatments and its effects may be more durable than medication (Mitchell et al., 2012).

7.2 Pharmacotherapy

Hypnotics are recommended when immediate symptom response is desired, when insomnia produces serious impairment or when non-pharmacological measures do not produce the desired improvement.

7.2.1 Benzodiazepine receptor agonists

Benzodiazepine receptor agonists are recommended as first line pharmacologic treatment for insomnia. The name of the group is derived from their mechanism of action, which involves occupation of benzodiazepine receptor on the gamma-aminobutyric acid, type A, receptor complex, resulting in the opening of chloride ion channels and facilitation of GABA inhibition. Benzodiazepine receptor agonists have either a benzodiazepine chemical structure (“classical” benziodiazepines) or do not (non-benzodiazepines: eszopiclone, zopiclon, zaleplon, zolpidem). Binding affinities of benzodiazepines for most GABA A receptor subtypes are similar, whereas binding affinities of non-benzodiazepines are much higher for GABA A receptor alpha 1 subtype. Most benzodiazepine receptor agonists have rapid absorption and rapid onset of action.

Hypnotic agents with short half-lives (eg, triazolam, zolpidem) mainly reduce sleep latency. Zaleplon, with its ultra-short half-life, can even be used after awakening during the night without substantial risk of daytime effects (Zammit et al., 2006). Drugs with intermediate half-life (temazepam) are less effective for inducing sleep and more indicated for sleep maintenance and decreasing nocturnal awakenings. Agents with long half-lives (flurazepam) are best indicated for people with insomnia plus concomitant daytime anxiety, but can lead to

hangover and daytime impairment, especially with regular nightly use. They are less highly associated with risk for addiction. Accumulation of active metabolites is most problematic in elderly patients or in those with impaired liver function.

Adverse effects include morning sedation, anterograde amnesia, cognitive impairment and impaired balance. Benzodiazepine receptor agonists may elicit parasomnia. Most of adverse effects are dose related. Long-term use can lead to dependence or misuse in some individuals. Abrupt discontinuation of particularly short-acting agent can lead to transient rebound insomnia, which can be more severe than the initial insomnia disorder.

Relative contraindications include dependence, severe pulmonary disease or untreated sleep apnea, myastenia gravis and severe hepatic disease. The risks are greater in the elderly, who are more sensitive to the adverse effects such as cognitive impairment, and to an increased risk of hip fractures.

They are usually recommended for short-term use only; this standard of care minimizes dependency. Many reliable patients however, responsibly use these drugs for years without abuses, while maintaining efficacy. Clinical discretion is required; monitoring should continue during all prescribing.

7.2.2 Chronobiotic agents

Chronobiotic agents for insomnia are melatonin, the hormone secreted by the pineal gland, and ramelteon. Because of its short half life, melatonin slow release preparations were introduced for treatment of insomnia. Prolonged-release melatonin is indicated for poor quality sleep in adults aged 55 years or older. In patients with primary insomnia aged ≥55 years melatonin was associated with significant improvements relative to placebo in many sleep and daytime parameters, including sleep quality, sleep latency and morning alertness (Lyseng-Williamson, 2012).

Ramelteon, a selective melatonin receptors agonist, reduces subjective and polysomnographic sleep latency and total sleep time, but did not influence the percentage of REM. Moreover, subjective sleep latency was reduced in patients in the age group between 18-64 years old, without change in the patients over 65 years (Liu and Wang, 2012). Ramelteon was approved for sleep onset insomnia. Ramelteon might help to promote circadian rhythm entrainment at lower doses (Richardson et al., 2006) although it is not specifically indicated for this aim.

Melatonergic agents have no demonstrable misuse potential, do not seem to cause next-day impairment and do not lead to rebound insomnia. There is no effect on psychomotor functions, memory recall or driving skills during the night or the next morning. They might cause dizziness, somnolence and fatigue.

7.2.3 Off-label prescription for insomnia

The off-label prescription for insomnia includes antidepressants, antipsychotics and anticonvulsants. In fact, certain off-label medications have been described more commonly than approved medication for insomnia (Walsh, 2004). Reasons for prescribing off-label medication for insomnia include the benefit of using single medication to manage both, psychiatric disorder and insomnia and avoiding the use of hypnotics due to concerns about dependence and side effects.

Antidepressants

Antidepressants prescribed for insomnia include trazodone, mirtazapine, tricyclic antidepressants such as doxepin, and agomelatine. Doxepin is the only one antidepressant FDA approved for insomnia at doses 3 to 6 mg. The doses should be as low as possible and significantly lower than those used to treat depression. Drugs blocking serotonin 5-HT2A or 5-HT2C receptors should be preferred over those whose sedative property is caused by histamine receptor blockade only. These agents can improve sleep in patients with comorbid depression and can have sleep-promoting effects in individuals with primary insomnia (Wiegand, 2008). In a meta-analysis of Buscemi and colleagues (2007), both self-reported and objectively measured sleep latency were reduced with antidepressants, although the improvements were smaller than with hypnotic agents.

Antidepressants do not have misuse potential. They can lead to pronounced side-effects such as weight gain, increased suicidal ideation, hypomania or mania in patients with bipolar disorder, and orthostatic hypotension. Side effects of tricyclics include anticholinergic activity, adrenergic blockade, and cardiac conduction prolongations. Their use is problematic in geriatric patients. Withdrawal effects from rapid eye movement sleep-suppressing drugs (e.g., tricyclics) include REM sleep rebound with excessive dreaming and possible rebound insomnia. Other effects on sleep include possible exacerbation of restless legs syndrome or appearance of REM sleep behaviour disorder (Wilson and Argyropoulos, 2005).

Antipsychotics

Mainly atypical antipsychotics are used for chronic insomnia, most of these agents tend to increase total sleep time or sleep efficiency, or both. Their sleep-inducing effects might be

related to blockade of histamine and 5-HT2C receptors (Cohrs, 2008). Some observational studies found promising improvements in sleep quality and sleep onset. However, recently, one small trial of quetiapine did not report a statistical difference from placebo in sleep outcomes (Tassniyom et al., 2010).

Side effects can be serious and include substantial weight gain, abnormal lipid and glucose regulation, and increased mortality, particularly in elderly people. They can exacerbate restless leg syndrome and, possibly, increase rates of parasomnia (Morin and Benca, 2012).

Antiepileptics

Some anticonvulsants are used for potential sleep promoting effects, particularly those with effects on GABA neurotransmission. Gabapentin, tiagabine and pregabalin, which increase slow wave sleep in dose-dependent manner, might be helpful for insomnia since the disorder is often associated with a deficit in slow wave sleep (Welsh et al., 2006). They are often used to treat chronic pain conditions with comorbid insomnia. Because gabapentin is not metabolized in the liver, it is safe even in patients with hepatic impairment. Side-effects can include weight gain, daytime sedation, dizziness, and cognitive impairment.

Antihistamines are commonly used to treat insomnia. Hydroxyzine and diphenhydramine are most widely used. There are some empirical data supporting their efficacy, but they are still less effective than benzodiazepines (Glass et al., 2008). Psychomotor impairment with sedation and anticholinergic manifestations are common adverse effects.

OBSTRUCTIVE SLEEP APNEA

1. Definition

Obstructive sleep apnea syndrome is characterized by repetitive episodes of partial or complete upper airway collapse during sleep. The collapse of the airways impairs ventilation and often results in intermittent hypoxemia and hypercapnia. The termination of obstructive respiratory events is typically associated with arousal from sleep leading to sleep fragmentation. The sleep fragmentation and the accompanying hypoxemia lead to many negative consequences such as excessive daytime sleepiness, cardiac arrhythmias, nocturnal hypertension, cognitive impairment and depressive symptoms.

2. Epidemiology

Prevalence of obstructive sleep apnea differs based on definition. When defined based on polysomnographic measurement as apnea hypopnea index (AHI). ≥ 5 per hour, the prevalence is 9% in women and 24% in men (Young et al., 1993). When defined as a clinical syndrome including in addition to AHI ≥ 5 per hour also excessive daytime sleepiness, the prevalence is around 2% in women and 4% in men (Bixler et al., 2001). Other studies in diverse populations have reported similar prevalence.

Most population based studies have found a 3-fold higher prevalence of sleep apnea in males then in females (Punjabi, 2008). The ratio of men to women diagnosed in sleep center is even more skewed toward men, with reported ratios 8 : 1 and higher (Ye et al., 2009). In a cross-sectional prevalence study, a four –fold higher prevalence of moderate and severe OSA in post-menopausal women as compared with pre-menopausal women was found. And, in post-menopausal women taking hormonal replacement therapy, the prevalence of OSA was similar to pre-menopausal women (Bixler et al., 2001). Also sex differences in clinical manifestation are described; women in general suffer from less severe disease and report more frequent non-specific symptoms.

The frequency of obstructive sleep apnea increases with aging, with a remarkable prevalence in older individuals. However, the increase in prevalence appears to plateau after 65 years (Bixler et al., 1998). When the prevalence is controlled by body mass index, the severity appears to decrease with age (Young et al., 1993). Mechanism proposed for increased prevalence of sleep apnea in the elderly includes increased deposition of fat in the parapharyngeal area, lengthening of the soft palate, and changes in body structures surrounding the pharynx (Eikermann et al., 2007).

3. Risk factors

3.1 Obesity

Obesity is a key risk factor for development of sleep apnea. It is thought to be associated with anatomic alterations that predispose to upper airway obstruction during sleep. In the Sleep Heart Heath Study the prevalence of moderate to severe OSA was 3-fold higher in the highest quartile of BMI, relative to the lowest (Young et al., 2002). The Wisconsin Sleep Cohort found an approximately 3% change in OSA severity for every 1% change in weight over a 4-year period (Peppard et al., 2000b). In addition, in subjects with severe obesity (BMI > 40) the prevalence of sleep apnea was markedly increase to 40% - 90% (Frey and Pilcher 2003). It was also demonstrated that a 10% body weight reduction is associated with a parallel 26% decrement in AHI (Peppard et al., 2000b).
For details about the role of obesity in pathophysiology of OSA see please subchapter Pathophysiology of OSA, Fat depositions

3.2 Family history, genetic predisposition

First degree relatives of those with OSA increase the relative risk compared to those without OSA by 1,5 – 2,0. Familiar susceptibility to OSA increases directly with the number of affected relatives (Schwab, 2005). Heritability estimates for the AHI from both pedigree and twin studies are approximately 35% to 40%, with the recurrent risk factors of approximately 2 (Redline and Tishler, 2000).

Varvarigou et al. (2011) using meta-analysis of allele frequency contrasts identified a statistically significant association for the TNFA rs1800629 variant. 4 polymorphism-disease associations that have been investigated by at least 3 population studies were identified: TNFA rs1800629, ACE I/D, and the APOE *ε2* and *ε4* alleles. Only TNFA rs1800629 was significantly associated with OSA. TNFA variants have been associated with disease phenotypes such as ischemic heart disease, heart failure, and chronic obstructive pulmonary disease. The association of TNFA rs1800629 with OSA suggests the potential existence of common genetic pathways between OSA and these disorders.

A recent study evaluated a large number of genetic loci identified as relevant to heart, lung, blood, and sleep phenotypes in relationship to sleep apnea. A polymorphism in PTGER3, a prostaglandin E2 receptor, was significantly associated with OSA in Americans of European ascends. The PTGER3 gene is expressed in neuronal tissue and modulates neurotransmitter release in both central and peripheral neurons. A haplotype analysis of PTGER3 suggested this gene may represent a risk factor for hypertension. Among African Americans, the lysophosphatidic acid receptor 1 (LPAR1) gene was identified as a potential susceptibility

locus. The rs7030789 SNP in an intronic region of LPAR1 was significantly associated with AHI in the discovery sample. The other loci identified included one in plekstrin (PLEK), which is a substrate for protein kinase C in platelets and a wide range of leukocytes including monocytes and macrophages. The identified SNPs all lie in genes associated with inflammation suggesting inflammation may play a role in OSA pathogenesis (Patel et al., 2012).

Obesity is associated with OSA and itself aggregates in families. It is possible that familiar aggregation of OSA is at least partly related to the genetics of obesity. Craniofacial morphology represents another mechanism by which genetics may influence the development of OSA. This includes also specific craniofacial disorders (e.g. Pierre Robin syndrome). It is likely that genetic factors are also associated with neural control of the upper airway and central regulation of breathing. Genetics of sleep-wake control may play a role too.

3.3 Craniofacial abnormalities

Morphology features associated with OSA include cranial base dimension being more obtuse, inferior displacement of the hyoid bone, macroglossia, adenotonsillar hypertrophy, increase in lower facial height, a retroposed maxilla and a short mandible (Riha et al., 2005).

The growth of the craniofacial complex comprises a number of independent grown patterns. Growth of the craniofacial skeleton continues throughout adulthood. Environmental mechanisms play a strong role in determining craniofacial skeleton growth. These include for example thumb sucking, nasopharyngeal disease, disturbed respiratory function, loss of teeth, endocrinopathy (Lavie and Rubin, 1984).

There are at least 50 syndromes with congenital craniofacial malformations associated with upper airway obstruction. The most common complex congenital conditions associated with a number of craniofacial abnormalities are Down syndrome (brachycephaly, microgenia, macroglossia), Pierre Robin syndrome (micrognathia, glossoptosis), Treacher Collins syndrome (micrognathia, undeveloped zygoma), Marfan syndrome (micrognathia, abnormality of connective tissues).

3.4 Smoking, alcohol consumption

Smoking is associated with a higher prevalence of snoring and sleep disordered breathing (Lin et al., 2012). Alcohol relaxes upper airway dilator muscles, increases upper airway resistance and may induce OSA in susceptible subjects.

For more details see please the subchapter Treatment of OSA, Non-pharmacological treatment of OSA

3.5 Endocrine disorders

3.5.1 Acromegaly

Acromegaly is characterized by excess growth hormone production after epiphyseal plate closure. A number of disorders may increase the pituitary's growth hormone output, although most commonly it involves a pituitary adenoma. OSA, assessed by polysomnography, was found in an average of 69% of patients with active disease in prospective or retrospective studies (Attal and Chason, 2010).

Acromegaly is associated with facial skeletal, pharyngeal, and tongue modifications. Generalized soft-tissue thickening is a feature of acromegaly and is related to glycosaminoglycan deposition and increased collagen production by connective tissue, but also to tissue edema. Tissue edema is due to increased renal sodium reabsorption by the distal kidney tubules, owing to direct stimulation of epithelial sodium channel by growth hormone and insulin like growth factor I (Kamenicky et al., 2008).

Anatomical disorders may predispose acromegalic patients to OSA, but they are not in themselves sufficient to cause OSA. Soft tissue thickening plays a major role in the onset of OSA in acromegaly (Dostalova et al., 2001). Effective treatment of acromegaly, whether surgical or medical, has been shown to improve OSA in a substantial number of patients.

3.5.2 Polycystic ovary syndrome

Polycystic ovary syndrome is the most common endocrine disorder of premenopausal women, characterized by chronic hyperandrogenism, oligo/anovulation, and insulin resistance. Women with polycystic ovary syndrome are more likely to have OSA and were found to have higher AHI values than age- and BMI-matched controls. AHI correlated with the waist-hip ratio and with the serum testosterone level (Fogel et al., 2001).

In Vgontzas et al. (2001c) study polycystic ovary syndrome patients were 30 times more likely to suffer from sleep disordered breathing than controls. Insulin resistance was stronger risk factor than was body mass index or testosterone for sleep disordered breathing in polycystic ovary syndrome women.

3.5.3 Hypothyroidism

An increased prevalence of OSA (between 25 and 35%) has been reported in patients with hypothyroidism studied prospectively or retrospectively (Attal and Chanson, 2010). The main pathophysiological determinant of OSA in hypothyroidism seems to be pharynx narrowing due to soft tissue infiltration by mucopolysaccharides and protein, in the context of the generalized infiltration of skin and soft tissue, which is a well-known feature of hypothyroidism. However, altered regulatory control of pharyngeal dilator muscles due to the neuropathy frequently observed in hypothyroidism may also be involved. Replacement therapy for hypothyroidism was reported to reduce OSA significantly in patients with hypothyroidism (Attal and Chanson, 2010).

The other way around, obstructive sleep apnea has long been suggested to increase the risk of development of autoimmune diseases. A study investigating the prevalence of Hashimoto thyroiditis in sleep apnea patients found that female patients with severe OSA had the highest Hashimoto thyroiditis prevalence, while male control subjects had the lowest. Isthmus thickness was significantly correlated to AHI (Bozkurt et al., 2012). Bahamman et al. (2011) reported that subclinical hypothyroidism was common among patients with severe OSA.

3.5.4 Other

In **hypogonadism** the results are conflicting. In one study, lower testosterone levels were associated with more severe sleep-disordered breathing, as evidenced by a higher AHI and more frequent hypoxemia. However, higher levels of adiposity were associated with both increased sleep-disordered breathing and low testosterone levels and adjustment for BMI in attenuated all the observed associations (Barrett-Connor et al., 2008). In contrast, in a cross-sectional study of men with sleep apnea, more severe hypoxia was associated with lower free and total testosterone levels, independently of age and obesity (Grundstein et al., 1989).

The relation between OSA and **growth hormone deficiency** is also not clear. Growth hormone replacement therapy was associated with a shift from obstructive to central apnea and hypopnea in one study (Nolte et al., 2002). Various effects of growth hormone treatment on OSA were documented: two patients had no longer OSA after treatment, whereas two patients developed OSA during treatment (Perker et al., 2006).

4. Pathophysiology of OSA

Due to the evolution of human speech, the upper airway, from the posterior end of the nasal septum to the epiglottis, has relatively little bonny or rigid support. The upper airways are therefore vulnerable to collapse.

4.1 Control of upper airways

4.1.1 Biomechanics of the pharynx

The human pharynx can be modeled as a collapsible tube, the patency of which can be described using a ‘‘balance of pressures’’ concept (Remmers et al., 1978). The size of the upper airway depends on the balance between those forces that would collapse the airway, such as negative intraluminal pressure and increased tissue (extraluminal) pressure, and those that maintain airway patency (contraction of pharyngeal dilator muscles). The airway pressure required to collapse the pharyngeal airway has been best described by the critical closing pressure (Pcrit). A number of studies generally report a higher (less negative or even positive) closing pressure in those with OSA (Fogel et al., 2004). Schwartz and colleagues (1988) measured the critical closing pressure (Pcrit, pressure at zero flow) during sleep in patients with OSA and controls. Normal subjects typically had Pcrit values below -8 cm H2O while those with mild OSA/snoring had a slightly negative Pcrit value and those with severe disease had a Pcrit of >0. This suggests an anatomically smaller airway in patients with apnea that is more collapsible during sleep when muscle activity may be low.

4.1.2 Anatomy of the pharynx

First studies comparing anatomic structures in sleep apneics and healthy controls used mainly X-ray cephalometry. They found that patients with OSA have a reduction in the length of the mandible, an inferiorly positioned hyoid bone, and a retroposition of the maxilla (Lowe et al., 1995).

Sophisticated imagine techniques revealed that the upper airway is smaller in patients with sleep apnea syndrome compared with normal subjects (Schwab et al., 1995). The airway narrowing is due to an increase in the volume of the tongue, soft palate, parapharyngeal fat pads, and the lateral walls surrounding the pharynx. Most of anatomical studies were performed during wakefulness, when the dilatator muscle is active. However, these results were validated by Isono et al. (1997) using endoscopic techniques to assess pharyngeal airway size in both patients with apnea and healthy controls under general anesthesia with full muscle paralysis.

There is also a difference in airway shape, with apneic subjects having an airway with its long axis directed anterior-posterior rather than laterally. Leiter et al. (1995) have suggested that this airway orientation in patients with apnea may place pharyngeal dilator muscles at a relative mechanical disadvantage, decreasing their ability to maintain pharyngeal patency.

The observed variability in airway size is probably determined by genetic influences on bony structure, tongue size, and tonsillar tissue as well as acquired factors such as obesity. Obesity may affect pharyngeal size by direct deposition of fat around the airway or by altering muscle orientation and function (Fogel et al., 2004).

4.1.3 Muscles of pharynx and reflexes

There are three important groups of muscles: the muscles influencing hyoid bone position (geniohyoid, sternohyoid), the muscle of the tongue (genioglossus), and the muscles of the palate (tensor palatini, levator palatini). The activity of many of these muscles is increased during inspiration, thus stiffening and dilating the upper airway and acting to counteract the collapsing influence of negative airway pressure (Van Lunteren, 1993). There are two types of muscles: inspiratory phasic upper airway muscles, with the genioglossus being the one best studied and tonic (postural) muscles such as the tensor palatini. The activity of inspiratory phasic muscles is substantially reduced during expiration when pressure inside the airway becomes positive and there is less tendency for collapse. Tonic muscles maintain a relatively constant level of activity throughout the respiratory cycle and play a role in the maintenance of airway patency. These two types of pharyngeal muscles are probably controlled by groups of neurons within the brainstem that have different firing patterns relative to the respiratory cycle (Fogel et al., 2004).(Tangel et al., 1991).

The transition from wake to sleep is associated with an initial small fall in the inspiratory phasic activity of muscles which then recovers to waking, or slightly greater levels within a few breaths (Wornsnop et al., 1998). However, muscles with a primarily tonic activation pattern lose activity at sleep onset which continues to fall as sleep deepens, reaching levels of 20–30% of waking values during slow wave sleep (Tangel et al., 1991).

The differential effect of sleep on the activity of these two types of muscles (phasic versus tonic) relates to differential effects on the brainstem neurons controlling their activity. By recording brainstem neurons across sleep-wake states in cats, Orem et al. (1985) have shown that neurons with activity closely related to the respiratory cycle (phasic neurons) largely maintained their activity during sleep, while neurons whose activity pattern is not clearly related to the respiratory cycle (tonic neurons) have large decrements in activity.

Sleep is associated with a significant rise in upper airway resistance, even in normal subjects (Kay et al., 1996). This may be due to a decrement in the activity of tonic muscles.
During wakefulness both rapid pulses of negative pressure and slow phasic increases in negative pressure lead to marked activation of the genioglossal muscle. Many studies have suggested that, during NREM sleep, this negative pressure reflex is substantially diminished or lost completely (Wheatley et al., 1993).

4.2 Arousals from sleep

Most respiratory events, but not all, are associated with a cortical arousal. Younes et al. (2004) challenged the notion that arousal is not essential for the restoration of airway. Obstructive apneas-hypopneas were induced by dial-down of continuous positive airway pressure in OSA patients. Inspiratory flow increased in 22% of events prior to arousal and was restored in 17% of trails in the absence of EEG arousal. Younes concluded that arousals are incidental events that occur when thresholds for arousal and for arousal-independent opening are close. They are not needed to initiate opening or to obtain adequate flow and they likely increase the severity of the disorder by promoting greater ventilatory instability. Jordan et al. (2007) observed that genioglossus activity and changes in respiratory duty cycle (inspiratory time prolonged relative to expiratory time) restored ventilation without cortical arousal. These compensatory responses had similar magnitude in OSA and healthy control; however OSA patients were less able to restore ventilation without cortical arousals.

The level of the pleural pressure, generated by respiratory effort regardless of the stimulus, is likely to be the key trigger for inducing arousals from NREM sleep (Berry and Gleeson, 1997). Patients with OSA tend to have an impaired arousal response to airway occlusion (more negative pressure required or a higher arousal threshold) than controls. Treating with CPAP tends to lower arousal threshold (Haba-Rubio et al., 2005). This suggests that an elevated arousal threshold in OSA may be at least in part acquired from the disease.

4.3 Functional residual capacity

Changes in lung volume influence upper airway size and resistance during sleep and wakefulness. This upper airway dependence on lung volume appears to be even more pronounced in sleep apnea patients versus healthy controls. During sleep, upper airway resistance increases as lung volume falls. This sleep induced decrease in lung volume results in increased upper airway collapsibility and contributes to inspiratory flow limitation, although the exact mechanisms have not been delineated (Campana et al., 2010).

Animal data using mongrel dogs have suggested that thoracic inflation increases upper airway pharyngeal size and stiffness through caudal traction on the trachea independently of upper airway muscle activity. When lung volume is reduced, there is a displacement of the diaphragm and thorax toward the head. This movement results in a loss of caudal traction on the upper airway, yielding a more collapsible airway (Van de Graaff, 1991). Heinzer et al. (2006) have shown that an increase in lung volume decreases upper airway collapsibility and improves respiratory mechanics, causes a decrease in sleep disordered breathing and improves sleep architecture in patients with sleep apnea during NREM sleep.

4.5 Ventilatory control stability

The quantity and pattern of ventilation in humans is tightly regulated to maintain oxygen and carbon dioxide levels within narrow limits. There are several feedback loops within this system – chemoreceptors, intrapulmonary receptors and respiratory muscle afferents.

Any system regulated by feedback loops has potential to become unstable. Ventilatory control stability can be described using the engineering term loop gain. Loop gain is used to describe stability or instability in a negative feedback control system. In context of ventilatory control, loop gain can be considered as the propensity for the ventilatory control system to develop cyclical fluctuations in ventilatory output (periodic breathing). There are three major principal components to loop gain: controller gain, plant gain and mixing gain. Controller gain refers to the chemoresponsiveness of the system. Plant gain reflects the efficiency of CO2 excretion. Mixing gain is a function of circulatory delay as well as hemoglobin binding of O2 and CO2. Mixing gain appears to be less crucial and tends to be constant. A high loop gain system is present if periodic breathing develops in the setting of minimal perturbation whereas a low loop gain system remains stable despite major perturbation (Eckert and Malhotra, 2008).

Younes (1992) has developed a technique using the proportional assist ventilation to measure gain loop. Sleep apneics have elevated gain loop. There are two major possibilities how elevated loop gain may affects propensity for apnea. Elevated loop gain may increase oscillations from the brainstem central pattern generator. In this case, pharyngeal obstruction occurs when central motor output is at its nadir. Or, elevated loop gain may increase the ventilatory response to arousal which would drive PaCO2 below the apnea threshold during sleep.

4.6 Fat depositions

Obesity is a key risk factor for development of sleep apnea. Depositions of fat around pharyngeal walls increase the collapsibility of the pharyngeal airway. The volume of this adipose tissue correlates with the number of apneas plus hypopneas per hour of sleep. If patients lose weight, there is a marked decrease in the pharyngeal adipose tissue volume (Shelton et al., 1993). Fat deposition around abdomen leads to reductions in lung volumes (Salome et al., 2009). Low lung volumes have an effect on resistance of the upper airways, moreover low lung volumes are also associated with diminished oxygen stores, which could contribute to ventilatory control instability – a high loop gain.

4.7 Gender

Sleep apnea is considerably more common in men then in women. Men have increased length of the pharyngeal airway compared to women. There is also an increased cross-sectional area of the soft palate and an increased airway volume in men compared to women. A representative male and female finite element airway models (finite element method is a numerical technique for finding approximate solutions to biomedical problems) demonstrated the male airway to be substantially more collapsible than the female airway, solely on the basis of anatomic differences (Malhotra et al., 2002). In addition, the pharyngeal airway is longer in postmenopausal as compared with premenopausal women. Lengthening of pharyngeal airway with aging was observed in association with aging in women but not in men (Malhotra et al., 2006).

Hormonal differences between men and women contribute to the increased male prevalence in OSA and to the propensity for women to develop OSA after menopause. Bixler and coworkers studied the relationship between menopause and OSA and after adjusting for several potential cofactors, determined that in comparison to premenopausal women, postmenopausal women with hormonal replacement therapy were not at increased risk of OSA but postmenopausal women without hormone replacement therapy had an almost four-fold risk (Bixler et al., 2001).

Several different mechanisms have been proposed to explain how male/female specific hormones would affect the propensity of one gender towards OSA. One hypothesis is that the different hormones affect the distribution of body fat. The proportion of android fat also increases with both age and years of onset after menopause. Acquiring a “male/android” body fat distribution is a risk factor for the development of OSA (Lin et al., 2008).

Hormone levels have also been hypothesized to affect central and neural respiratory control mechanisms. In a cohort of patients with surgically-induced menopause, combined estrogen/progesterone treatment led to a decrease in the number of apneas and hypopneas during sleep (Pickett et al., 1989). Indeed, the ventilatory response to arousal from sleep is greater men then in women (Jordan et al., 2003).

4.8 Aging

Anatomic susceptibility to OSA appears to worsen with aging. In both sexes, the parapharyngeal fat pad size increased independent of body mass index. Moreover, the genioglossus negative pressure reflex deteriorates with aging. The negative pressure reflex allows the upper airway dilator muscles to compensate for a collapsing perturbation. This reflex is a primary mechanism to maintain pharyngeal patency and the loss of this protective reflex with aging may therefore be a critical mechanism predisposing older persons to pharyngeal collapse (Malhotra et al., 2006).

4.9 REM sleep

The reported prevalence of REM-related OSA is quite variable, ranging from as little as 10% to as much as 36% of the patient population with OSA undergoing PSG. Despite the wide variation in prevalence, studies have consistently shown that REM-related OSA occurs more commonly in younger individuals, women, children, and in patients with mild or moderate OSA (Conwell et al., 2012).

Hypopneas and apneas increase in duration and are associated with more pronounced hypoxemia during REM compared with non-REM sleep in OSA (Findley et al., 1985) well as with higher levels of sympathetic activity compared to events in NREM sleep (Somers et al., 1995). Some patients with less pronounced disease have sleep apneas during REM sleep only.

REM sleep is associated with decreased upper airway muscle tone, impaired genioglossus reflex responsiveness to negative pressure and reduced chemosensitivity (Kryger et al., 2005). These factors contribute to emergence of sleep disordered breathing.

5. Diagnosis

A definitive diagnosis of OSA requires objective recording and measurement of sleep and breathing during night. In addition, levels of daytime sleepiness and other symptoms are evaluated.

The gold standard diagnostic test for OSA is the **overnight in-laboratory polysomnography**. Nasal airflow, thoracoabdominal movements and oxygen saturation are necessary for identification of different types of apneas and hypopneas during sleep. Split-night protocols are also used, in which the first half of the study night is used for diagnosis and the second half to monitor treatment response.

Portable ambulatory monitoring systems are used as an alternative diagnostic test for OSA in patients with a high pre-test probability of OSA. American Academy of Sleep Medicine (AASM) defined the different types of sleep studies and polysomnographs based on the technology available at that time. Type I is a conventional, attended sleep-laboratory polysomnography that includes cardiorespiratory and sleep stage/neurophysiologic measurements. All the other types of polysomnography are unattended and conducted with portable polysomnographs. Only type II includes sleep-stage/neurophysiologic assessment. Type III has at least 4 recorded parameters, including air flow and 2 respiratory-effort channels. Type IV requires only 2 parameters, one of which must be air flow or chest wall movement measurement and the other is oximetry. Type IV is not appropriate for OSA evaluation (Standards of Practice Committee of the American Sleep Disorders Association 1994).

An apnea is defined as the complete cessation of airflow for at least 10 s regardless of whether or not is associated with oxygen desaturation or arousal. There are three types of apneas: central, obstructive and mixed. In obstructive sleep apnea, the respiratory effort is maintained but ventilation disappears because of total obstruction in the upper airways. Central sleep apnea is defined as reduced respiratory effort resulting in absent ventilation. Mixed apnea starts with central apnea and ends with obstructive event.

There is a “recommended” and an “alternative” hypopnea definition according the Manual for the Scoring of Sleep and Associated Events (Iber, 2007) published by American Academy of Sleep Medicine. Hypopnea scoring requires ≥ 30% reduction in nasal pressure signal excursions from baseline and associated ≥ 4% desaturation from pre-event baseline. The alternative definition requires ≥ 50% reduction in nasal pressure signal excursions and associated ≥ 3% desaturation or arousal.

Obstructive sleep apnea is defined with apnea-hypopnea index (AHI) ≥ 5/h. It is classified as mild with AHI of 5 to 15; moderate with AHI of 16 to 30 and severe with AHI > 30.

5.1 Other examinations

Measurement of height and weight and the calculation of BMI, as well as measurement of neck circumference should be obtained in every patient. A BMI greater then 28kg/m² both in men and women reflect a risk factor and should increase a suspicion for OSA (Kripke et al., 1997). Neck circumference has been reported to correlate better with presence of obstructive apnea than the BMI does and circumference greater than 40 cm should lead to questions related to presence of sleep disordered breathing (Davies and Stradling, 1990).

Upper airway examination allows identify abnormalities that potentially narrow the airway. This examination is important to indicate need of specific treatments. Retrognatia carries the risk of narrow upper airway behind the base of the tongue. Dental malocclusion and overlapping teeth are indicators of small dental cavity leading to tongue malposition, and dislocation of the temporomandibular joint during mouth opening. The oropharyngx should be examined for the presence of macroglossia. Uvula and soft palate are addressed for size, length, and height. A low-lying soft palate and uvula are commonly seen in patients with OSA. Edema or erythema of uvula may indicate repetitive vibration trauma from snoring. Tonsillar hypertrophy and the size of tonsillar pillars should be noted (Kryger et al., 2005).

Standardized scales for oropharyngeal clinical evaluation have been developed. Mallampati scale is most commonly used (Mallampati et al., 1985) (For schema see please Appendices). A modified technique is performed with the open mouth without protrusion of tongue (Friedman et al., 1999). The degree of oropharyngeal obstruction is scored between 1 and 4:

1 unobstructed, wide oropharynx with uvula clearly above the tongue
2 visible pillars and part of the inferior segment of the uvula
3 much more limited visualization of the oropharynx and the base of uvula barely visible
4 very crowded oropharynx with only the hard palate visible because the uvula is entirely masked by the tongue

Nose should be aspect (by otorhinolaryngologist) for septal deviation, evidence of trauma, or enlarge inferior nasal turbinate.

5.2 Screening questionnaires for obstructive sleep apnea

The Berlin questionnaire is the most commonly used. The Berlin questionnaire was validated in differing populations. It has 11 questions organized into three categories. It incorporates questions about risk factors for sleep apnea, such as snoring behavior, wake-time sleepiness or fatigue, and the presence of obesity or hypertension. When two of three categories are classified as positive for a patient, the patient is rated as being at high risk of having OSA

(Netzer et al., 1999). The Berlin questionnaire was an outcome of the Conference on Sleep in Primary Care, held in April 1996 in Berlin, Germany, but was validated two years later.

STOP and STOP-Bang questionnaires were developed by Chung et al. (2008a). The STOP questionnaire is a self-administered screening tool that includes four yes/no questions regarding Snoring, Tiredness, Observation of sleep apneas and Being treated for high pressure. Incorporating BMI, age, neck circumference, and gender into the STOP scoring (STOP-Bang), the sensitivity increased especially for patients with moderate to severe OSA. When two or more questions in STOP questionnaire are classified as positive, the patient is rated as being at high risk of having OSA. In STOP-Bang questionnaire, the positive answer to three or more questions reveals a high risk patient.

The American Society of Anesthesiologists Task Force on the Perioperative Management of Patients with Obstructive Sleep Apnea published practice guidelines. These guidelines recommend the routine screening of surgical patients with a three-category checklist with 12 items for adults. Chung et al. (2008b) have transformed these guidelines into a questionnaire. The questionnaire has twelve questions (fourteen in pediatrics version) divided into three categories - predisposing physical characteristics, history of apparent airway obstruction during sleep and somnolence. When two or more categories are classified as positive for a patient, the patient is rated as being at high risk of having OSA.

5.3 Other diagnostic tools

Static charge sensitive bed (SCSB) is a sensitive movement sensor. It consists from a mattress with two electrically active layers and enables polygraphic recordings of the movements in the head, trunk and extremities, as well as respiratory movements and ballistocardiogram (BCG), reflecting the mechanical activity of the heart. No electrodes or strain devices need to be attached to the subject. The low frequency band represents respiratory movements, whereas the high frequency band reflects cardiac activity (the ballistocardiogram). Prolonged episodes of SCSB spiking (high amplitude, high frequency deflections) are common in patients with sleep-disordered breathing. The static charge sensitive bed has been widely used in Finland and Sweden (Polo et al., 1988).

Watch-PAT 100 is a portable monitoring device that uses peripheral arterial tone (PAT), pulse rate, actigraphy and oximetry for sleep apnea diagnosis. Identification of respiratory events is based on the well documented intensive sympathetic activation accompanying respiratory events termination. Sympathetic activation causes attenuation of the PAT signal, a measure of arterial pulsatile volume changes in the fingertip, indicative of vasoconstriction,

coupled with pulse rate acceleration in addition to the typical changes in oximetry (Bar et al., 2003).

Stein et al. (2003) used heart rate tachogram patterns derived from the ambulatory electrocardiography for identifying sleep apnea syndrome and other sleep disturbances in patients without major autonomic dysfunction. They reported that all predictions from Holter-only data were concordant with clinical diagnoses.

5.4 Daytime sleepiness evaluation

Sleepiness can be defined as being an awake-state in which an individual has an increased propensity to fall asleep (Dement, 1993). Excessive sleepiness can be conceptually defined as the desire or tendency to fall asleep at an inappropriate time, reflecting the ratio of the total sleep-drive to the total wake-drive (Johns, 1993). Although excessive daytime sleepiness has many possible etiologies, this complaint increases the suspicion for OSA.

Subjective sleepiness can be assessed by subjective rating scales. The most widely used and best-validated scale is the Epworth Sleepiness Scale (ESS) (Johns, 1991). It is based on retrospective reports of dozing behavior in eight different situations that are commonly experienced in daily life. The questionnaire asks the respondent to rate the likelihood of falling asleep on a scale from 0 to 3, were 0 indicates no chance and 3 represents a great chance of dozing. It assesses the global level of sleepiness and is independent of short-term variations in sleepiness with the time of day and also of inter-day variations. The ESS is able to discriminate between normal and pathological sleepiness; score grater then 10 suggest significant excessive daytime sleepiness.

The Karolinska sleepiness scale (KSS) (Akerstedt and Gillberg, 1990) is frequently used for evaluating subjective sleepiness, particularly for describing changes over time within subjects. It measures the subjective level of situational sleepiness at a particular time during the day. KSS is a 9-point Likert scale based on a self-reported of drowsiness at the time. The scale varies from 1= “very alert” to 9=“very sleepy, fighting sleep, an effort to keep awake.

The Stanford Sleepiness Scale (SSS) (Hoddes et al., 1973) is also a Likert scale based on a series of statements, numbered 1 to 7, that range from “feeling active, vital, alert, wide awake” to “almost in reverie, cannot stay awake, sleep onset appears imminent”. Respondents are asked to choose which statement most accurately describes how they feel at the time. The SSS is mainly used to measure changes in sleepiness within subjects over time, particularly over periods of hours and days.

Reaction-time tests are used to investigate the effects of sleep deprivation/sleepiness. The Psychomotor Vigilance Test (PVT) (Dinges and Powell, 1985) is one of most commonly used. PVT is sustained-attention, reaction-timed task that measures the speed with which subjects respond to a visual stimulus. At random intervals of a few seconds, the light will turn on until the subject pushes a button. The main measurement of this task is not to assess the reaction time, but to see how many times the button is not pressed when the light is on (lapses).

A computer based version of the Quatember Maly clocktest (originally published by Macworth, 1948) measures sustained attention and vigilance. A bright dot moves slowly along a circular path/clock. Sometimes the dot jumps two positions at once. The subject must respond to these events as quick as possible. The duration of the test can be varied. The recommendations are minimum 30 minutes but longer test runs will lead to better results (up to 70 minutes). The following variables are calculated: number of correct, number of incorrect, mean value of reaction time correct in seconds, gradient of correct and gradient of reaction time correct together with the associated measures of exactitude.

Multiple sleep latency test (MSLT) (Carskadon and Dement, 1977). is performed in a sleep laboratory, in a darkened, and quiet bedroom in which the subject is asked to lie down and try to fall asleep while their EEG/EOG/EMG are monitored. The sleep latency after the lights have been switched off in the room is measured. If the subject does not fall asleep within 20 minutes the attempt is interrupted. Each subject has 4 or 5 such nap opportunities two hours apart during the day, starting at 10 am. The sleep latency for each nap in the MSLT gives an objective measure of the subject's individual sleep propensity at the time.

Maintenance of wakefulness test (MWT) (Mitler et al., 1982) quantifies wake tendency by measuring the ability to remain awake during soporific circumstances. The sleep latency is also measured. It is also performed in a sleep laboratory, in a similar environment and with the same electrodes attached as in the MSLT. The main difference is that the subject sits up in bed with their back and head partially supported by pillows, and they are asked to stay awake rather than fall asleep during four periods of 40 minutes, two hours apart during the day.

6. Clinical features

Typical clinical presentation of OSA is signs of the upper airway obstruction during sleep, including laud snoring, snorting, gasping and chocking. Episodes of breathing cessation during sleep are witnessed by bed partner. A characteristic pattern in OSA is loud snoring or

brief gasping that alternate with episodes of silence. Apneic episodes are usually terminated by gasps, chokes, snorts, vocalization or brief awakenings. Some patients may report abrupt awakenings accompanied by shortness of breath, most are unaware of the apneas. Some patients, especially elderly, are aware of frequent intermittent awakenings and present with a complaint of insomnia. Nocturia is frequently reported. Increased intra-abdominal pressure due to increased breathing effort during apneas/hypopneas and an elevation in plasma levels of atrial natriuretic factor secondary to hypoxia have been proposed contributors to nocturia (Oztura et al., 2006). Esophageal reflux is another commonly reported symptom among patients with OSA. Increased breathing effort during apneas/hypopneas increases intra-abdominal pressure while making the intrathoracic pressure more negative. This increased gradient between intra-abdominal and intrathoracic pressure leads to gastroesophageal reflux.

Fatigue and daytime sleepiness, secondary to sleep fragmentation, are the most significant daytime complaints of patients suffering from OSA. Other common daytime symptoms include morning headache, dry mouth and sore throat at waking up time. Morning headache is often described as dull and generalized and lasts 1 to 2 hours. Erectile dysfunctions are common in sleep apnea patients, particularly those with severe disease. Erectile dysfunction in OSA is at least partially reversible with CPAP treatment (Budweisder et al., 2013). Obstructive sleep apnea is also connected with problems with vision, such as floppy eyelids, dry eyes, and normotension glaucoma (Hirunwiwatkul et al., 2010). Neurocognitive sequelae are discussed later.

7. Consequences of OSA

Untreated OSA can contribute to development or progression of other diseases.

7.1 Cardiovascular system

OSA is an independent, dose-dependent risk factor for systemic hypertension. No evidence of a threshold of the apnea–hypopnea index below which hypertension was not related to sleep-disordered breathing was found. Even persons with minimal sleep-disordered breathing have higher odds of hypertension than those with no episodes of sleep-disordered breathing (Peppard et al., 2000a). Effects of OSA on blood pressure appear to be more relevant in middle-aged compare with older subjects (Haas et al., 2005). Indeed, OSA is most common condition associated with resistant hypertension with an estimated prevalence of 64% among subjects with resistant hypertension (Pedrosa et al., 2011). The use of CPAP therapy is accompanied by a reduction in daytime blood pressure in patients with resistant

hypertension and CPAP therapy also permitted de-escalation of antihypertensive drug therapy in a significant proportion of patients with resistant hypertension.

Sleep-disordered breathing is among the causes of secondary pulmonary hypertension. Several studies have shown pulmonary hypertension in 20% to 40% of patients with OSA in the absence of other known cardiopulmonary disorders. CPAP treatment leads to reductions in pulmonary artery pressure in patients with OSA. The pulmonary hypertension associated with OSA appears to be mild and may be due to a combination of precapillary and postcapillary factors including pulmonary arteriolar remodeling and hyperreactivity to hypoxia and left ventricular diastolic dysfunction and left atrial enlargement (Sajkov and McEvoy, 2009).

In the Sleep Heart Healthy Study cohort, OSA predicted incident heart failure in men in a graded fashion - 13% increase per 10 event/hour increase in AHI. In analyses adjusted for multiple confounders, men with severe OSA were nearly 60% more likely to develop heart failure compared to those without OSA (Gottlieb et al., 2010). OSA might induce deterioration of left ventricular function mostly by raising blood pressure levels. Moreover, the left ventricular hypertrophy is more closely linked to blood pressure levels during sleep than during wakefulness (Verdecchia et al., 1990). Patients with heart failure and OSA have significantly greater mortality than patients without OSA (Wang et al., 2007).

Recent articles have highlighted the role of OSA in patients with hypertrophic cardiomyopathy. The prevalence of OSA in individuals with echocardiographically-defined hypertrophic cardiomyopathy was estimated to be 70% (Eleid et al., 2009). Indeed, an increased prevalence of atrial fibrillation in hypertrophic cardiomyopathy patients with OSA compared to those without OSA was also reported (Konecny at al 2010a).

The prevalence of OSA in individuals with coronary heart disease is 30–60%, considerably higher than the prevalence in the general population (Bradley and Floras, 2009). Among men hospitalized for acute myocardial infarction, the prevalence of OSA has been reported to be nearly 70% (Konecny et al., 2010b). There is compelling evidence for OSA as a risk factor for incident coronary heart disease and for coronary heart disease related mortality. Observational data suggest that CPAP treatment in those with severe OSA reduces the risk of coronary heart disease fatal and non-fatal events (Marin et al., 2005). The association between OSA and coronary heart disease may be bi-directional. Chami et al. (2011) found in participants that developed incident coronary heart disease, that AHI worsened modestly (< 3

events/hour) on follow-up evaluation relative to baseline. The effect was most pronounced in those that were neither obese nor overweight.

A wide spectrum of conduction disturbances have been described in sleep apneics, including clinically relevant arrhythmias such as ventricular tachycardia or fibrillation, complex ventricular ectopy, supraventricular tachycardia and second- or third-degree heart block (Haribson et al., 2000). The likelihood of atrial fibrillation is increased 4-fold in patients with OSA even after adjusting for confounders (Mehra et al., 2006). There is a strong temporal relationship between OSA-related respiratory events and the occurrence of these arrhythmias. A paroxysm of atrial fibrillation or an episode of non-sustained ventricular tachycardia were 18-times more likely to occur within 90 seconds of an apnea or hypopnea than during normal breathing (Mohanan et al., 2009). Patients with untreated sleep disordered breathing and atrial fibrillation have a higher recurrence of atrial fibrillation after cardioversion than patients without a known sleep apnea diagnosis (Kanagala et al., 2003). Significant rhythm disturbances often occur only during the nighttime and a positive correlation between OSA severity and the severity of rhythm disturbance has been observed (Olmetti et al., 2008).

Sleep apnea seems to be a risk factor for stroke. Analysis of prospective data from the Sleep Heart health Study suggests that sleep apnea patients with moderate to severe disease had a nearly 3-fold higher risk of having an incident ischemic stroke relative to those without OSA, even after adjusting for confounders (Redline et al., 2010). The mechanisms implicated in increased stroke risk likely include adverse effects of OSA on cerebral blood pressure regulation and tissue oxygenation. An increase in intracranial pressure has been reported during obstructive apneas and a reduction of up 20% in the middle cerebral artery blood flow has been observed (Jennum and Borgesen, 1989). Recent data also have highlighted the potential adverse effect of snoring, which causes neck tissue vibration leading to carotid endothelial dysfunction (Cho et al., 2011).

The pathogenesis of cardiovascular complications in OSA in not fully understood. Proposed mechanisms include increased sympathetic activity, endothelial dysfunction, metabolic dysregulation, oxidative stress and inflammation.

7.2 Neurocognitive sequelae

OSA is associated with impaired neurocognitive functions. Many cognitive domains have been shown to be affected, including attention, concentration, visuospatial and verbal memory, learning, executive function and constructional abilities (Aloia et al., 2004).

However, OSA does not appear to result in deficits in language ability or psychomotor functions.

There are several mechanisms that could promote the cognitive impairment in OSA. Sleep fragmentation and sleep deprivation, and the associated excessive daytime sleepiness, have been proposed as mechanisms underlying cognitive impairment in OSA via their impact on attention. Sleep-deprived individuals show increased daytime sleepiness and reduced activity in the prefrontal and posterior parietal cortices and in the thalamus. Sleep fragmentation might also mediate the cognitive deficits seen in OSA via dysfunction in neural networks, especially in the frontal lobes. The basis of this hypothesis is that sleep disruption reduces the efficacy of restorative processes in the prefrontal cortex leading to cellular and biochemical stress. These stresses, in turn, disrupt functional homeostasis, altering glial and neuronal viability. Intermittent hypoxia could also be an important contributor to cognitive dysfunction in OSA. In individuals with OSA, hypoxia changes have been attributed to reduced cell neurogenesis and density of the hippocampus, the frontal cortex and generalized grey matter (Bucks et al., 2013).

It remains unclear whether more severe OSA is associated with poorer cognition. By separating those with OSA into a ‘mild/moderate’ group and a ‘severe’ group based on apnoea-hypopnoea index, reported deficits in cognitive function in OSA were irrespective of disease severity (Beebe et al., 2003). On the other hand, some studies reported a significant correlation between hypoxemia severity and neuropsychological impairment (Naegele et al., 1995).

The effect of OSA on attention/vigilance was found to be more strongly influenced by sleep fragmentation than hypoxemia. This finding was based on the proposition that apnea-hypopnea index, respiratory disturbance index or apnea index can be considered measures of sleep fragmentation, whereas nadir of blood oxygen saturation or time blood oxygen saturation ≤ 80% represent measures of hypoxemia (Aloia et al., 2004). In the same way, typical frontal lobe-related abnormalities seemed to be related rather to the level of nocturnal hypoxemia (Naegele et al., 1995).

7.3 Depression

There are high rates of depression in people with obstructive sleep apnea in both community and clinical populations. Chen et al. (2013) found in a recent cohort study that women with sleep breathing disorder have nearly 3-fold increased risk of developing depression, in men with OSA the risk was increased nearly 2-fold.

Several possible causal mechanisms linking OSA and depression have been proposed. Sleep fragmentation and hypoxemia are likely to play a role. Ishman et al. (2010) reported that patients with OSA and excessive daytime sleepiness are more likely to be depressed than patients with OSA without excessive daytime sleepiness. The principal cause of EDS in OSA is sleep fragmentation. Another study compared the effects of oxygen, CPAP, and placebo in patients with OSA. In this trial, oxygen treatment was associated with a significant reduction in psychological symptoms of depression (Bradwell et al., 2007). Nightly, recurrent, intermittent hypoxemia has been studied in animal models. It has been associated with dose-dependent cell loss in the areas rich in noradrenergic and dopaminergic pathways important for both sleep/wake and mood regulation (Gozal et al., 2001).

Abnormalities in central and peripheral neurotransmission of serotonin have been implicated as a potential factor in depression. Serotonin also influences upper airway dilator motor neurons through the hypoglossal nucleus, which is further reduced in sleep stages (Canessa et al., 2011). Therefore serotonin might play role in both, depression and sleep apnea. Obstructive sleep apnea and depression are also associated with elevated levels of various pro-inflammatory substances and cytokines. Interleukin 6 and tumor necrosis factor are thought to be responsible for increased daytime sleepiness. These pro-inflammatory markers seem to be significant mediators between depression as well as OSA.

7.4 Endocrine system

Insulin resistance, diabetes – for details see please chapter Glucose metabolism

7.5 Epilepsy

OSA appears to be more prevalent in patients with epilepsy than in the general population and untreated OSA may theoretically worsen seizure control by increasing seizure burden through sleep disruption/deprivation. The association between sleep apnea and epilepsy appears to be stronger among older men who present with new onset epilepsy. Seizure control can be improved with an adequate treatment of coexisting OSA (Malow et al., 2000).

7.6 Traffic

Drivers with OSA are at significantly increased risk of having a traffic accident. The severity of OSA and the magnitude of excessive daytime sleepiness were correlated with crash risk in about a half of studies. Treatment of sleep apnea consistently improved driver performance including crashes (Ellen et al., 2006).

8. Treatment

Management of OSA requires a long-term multidisciplinary approach. Behavioral, medical and surgical options are available for the treatment.

8.1 Behavioral interventions

8.1.1 Weight loss

The most effective behavioral measure is weight loss. Peppard et al. (2000b) have demonstrated in a prospective cohort study that a 10% weight reduction predicted a 26% reduction in the AHI. Low energy diet was followed by 67% reduction of the AHI in patients with moderate to severe OSA. Patients with severe OSA benefited most from the intervention (Johansson et al., 2009). Unfortunately, weight loss through diet, exercise, and/or medications has been hard to achieve and maintain for some patients. Bariatric surgery may be an alternative treatment of severe or complicated obesity. There is also a population of non-obese patients with OSA who do not obtain benefit from weight loss.

8.1.2 Smoking cessation

Smokers have increased risk of having sleep apnea. In a large population-based epidemiologic study carried out by Wetter et al. (1994) heavy smokers (more than 40 cigarettes per day) had an odds ratio of 40 compared with nonsmokers for having moderate to severe sleep disordered breathing. Smoking may contribute to upper airway dysfunction during sleep by inducing chronic mucosal inflammation such as cellular hyperplasia, mucosal edema, thicker epithelium, and impaired cilia function and increased nasal resistance.

Effects to respiratory systems attributable to smoking are not limited to the upper airways. Smoking has been reported to be associated with decreased lung function. The efficiency of the diaphragm is enhanced in patients with low lung volumes, which might generate more negative inspiratory pressure in the thorax and upper airway, predisposing the pharynx to collapse. Above that, in chronic bronchitis, increased sputum production may contribute to increased upper airway resistance resulting in snoring and OSA (Lin et al., 2012).

8.1.3 Alcohol

Alcohol evokes obstructive sleep apnea in individuals who otherwise only snore and increases apnea frequency and duration of sleep disordered breathing events in patients with preexisting disease (Issa and Sullivan, 1982). Alcohol also has an adverse impact on daytime alertness in patients with OSA. Patients with OSA should therefore limit the alcohol intake to small quantity and not consume alcohol for a time before bedtime.

8.1.4 Body position

In many patients, the frequency of sleep disordered breathing is greater during sleep in the supine position. In a number of studies, around 50 % of patients with OSA had a difference of 50 % or more in the apnea index between the supine and non-supine positions (Richard et al., 2006). Sleeping in the supine position increases the probability of upper airway occlusion because of the effect of gravity on the tongue, which tends to relapse posteriorly and come into apposition with the posterior pharyngeal wall (Kryger et al., 2005).

Various techniques are described to prevent patients from assuming the supine position such as positional alarms, verbal instructions, tennis balls, vests, “shark fins,” or special pillows. Also manipulation with body position to promote sleeping with a 30 to 60 degree head elevation is recommended. In general, a positive effect of positional therapy on the AHI with a good compliance is reported (Ravesloot et al., 2012).

8.1.5 Nasal dilators

Products that may effectively dilate the nasal airway in the region of the nasal valves are commercially available. One is an elastic plastic nasal strip, which is applied externally and pulls the nares open. Other product consists of an elastic plastic bar with two tabs at each end that are fitted inside the nostrils and dilate the nasal valves by pushing outwards. Some studies found that improving nasal patency by external nasal dilators has some beneficial effects on subjective snoring, and improved slightly sleep architecture in OSA and desaturation time (product with tabs)., but does not decrease the frequency of apneas or improve daytime sleepiness (Kohler et al., 2007). Therefore nasal dilators cannot be recommended in treatment of OSA.

8.2. Medical therapies

8.2.1 Pharmacotherapy

The treatment of choice for moderate to severe obstructive sleep apnea is continuous positive airways pressure (CPAP). However this is not tolerated by all patients. Drug therapy has been proposed as an alternative to CPAP in some patients with mild to moderate sleep apnea and could be of value in patients intolerant of CPAP. A number of mechanisms have been proposed by which drugs could reduce the severity of OSA. These include an increase in tone in the upper airway dilator muscles (tricyclic antidepressants, serotonergic drugs), an increase in ventilatory drive (methylxanthine derivatives, opioid antagonists), a reduction in the proportion of REM sleep, an increase in cholinergic tone during sleep (antidepressants), a reduction in airway resistance (oximethazoline) and a reduction in surface tension in the upper airway (soft tissue lubricants) (Smith et al., 2006).

Intranasal fluticasone, topical nasal lubricant, physostigmine, mirtazipine 15 mg and paroxetine have been shown to reduce the AHI in largely unselected populations with OSA by between 24 and 45%. Protriptyline led to a symptomatic improvement but there was no change in the apnea frequency. However, most of the studies were small and many trials had methodological limitations (Smith et al., 2006).

8.2.3 Continuous positive airway pressure (CPAP)

CPAP is the treatment of choice for most patients with OSA because of it remarkable effectiveness in reducing symptoms and also consequences of the disease. Nasal CPAP therapy for sleep apnea was first described in 1981 by Sullivan.

CPAP acts as physical pressure splint to prevent partial or complete collapse of the upper airways. It does this by elevating pressure in the oropharyngeal airway and reversing the transmural pressure gradient across the pharyngeal airway. It effectively reduces the apnea hypopnea index, normalizes oxyhemoglobin saturation, and reduces cortical arousals associated with apneic/hypopneic events (Gay et al., 2006).

A typical CPAP device consists of a flow generator which provides the constant airflow lined with sound-absorbing material for quieter operation. A hose carries the pressurized air to a face mask or nasal pillow.

Titration of CPAP level can be effected manually by a sleep technician attending an overnight polysomnography (the accepted standard), automatically by an auto- titrating device (APAP), calculated with formulas based upon OSA severity and neck circumference, or even self-titrated by the patient.

The level of therapeutic pressure that is identified being most therapeutically effective is sufficient to prevent not only apnea and hypopnea and oxyhemoglobin desaturation but also respiratory related arousals in all sleep stages and all sleep postures. When the correct pressure is reached there is often rebound SWS and REM sleep. This rebound phase lasts about a week, the duration and intensity of rebound sleep episodes decrease quickly after the first night of treatment (Issa and Sullivan 1986).

Side effects reported by patients are usually related to pressure or airflow or the mask – nose interface. Side effects may be attributable to mask interface-related skin changes (abrasions, pressure sores, contact dermatitis, etc), aerophagia, sinus pain, oral and nasal dryness, conjunctivitis and even tooth decay. A nonspecific sense of claustrophobia may be

reported by patients. In some patients, the administration of CPAP may eliminate CO_2 and reduce arterial P_{CO2} below the apnea threshold, and consequently leads to ventilatory instability characterized by central apneas and periodic breathing.

Dangerous complications of CPAP therapy (pulmonary barotrauma, pneumocephalus, increased intraocular pressure, tympanic membrane rupture, massive epistaxis, subcutaneous emphysema after facial trauma) are extremely rare and represent isolated case reports in the literature (Strollo et al., 1998).

A ramp function of the CPAP is useful in some patients who complain of initial increased resistance to exhalation or the sensations of too much pressure in the nose. The ramp allows the pressure to increase to optimal CPAP pressure gradually over a time interval.

APAP, auto-adjustable positive pressure devices, are a treatment alternative to CPAP. APAP delivers optimized pressure throughout sleep. APAP may also assist in the initial diagnosis of OSA and help determine an effective level of fixed pressure for treatment with CPAP.

Bi-level positive pressure devices (BiPAP) adjust independently inspiratory and expiratory positive pressures. This approach is used to lower mean airway pressure and resistance to expiration.

C-flex is a technological option to CPAP in which the positive airway pressure is reduced in the initial phase of expiration on the breath by breath basis in proportion to the patient's expiratory flow rate.

A-flex is a further modification of C-flex that matches pressure delivery through the patient's entire breathing cycle. Initially, pressure is significantly reduced at the start of exhalation, with the pressure approximately 2 cm H_2O less than inspiratory pressure by the end of exhalation; the pressure returns to the therapeutic level at the start of the next inspiratory phase. A-Flex softens the pressure transition from inhalation to exhalation to enhance breathing comfort and it mirrors the normal breathing rhythm.

Although CPAP is highly effective therapy, its efficacy is dependent on regular usage and therefore adherence to therapy is of major importance. Average usage is about 5 – 6 hours per night in most compliant patients. Empiric studies have suggested that rates for CPAP use range from 30–60%. Patients who become non-adherent in the first few days of CPAP treatment generally remain non-adherent. Poor adherent patients use CPAP for shorter

durations, on average 3 hours and also skip nights of treatment and this pattern is established early, within the first week of treatment (Weaver and Sawyer, 2010). Patient characteristics, disease characteristics, technological factors, initial CPAP exposure factors, and psychosocial factors have been empirically examined as factors that may predict CPAP adherence.

8.2.4 Surgical treatment

Nasal surgery

Improvement of nasal breathing has failed to show a significant impact on adult OSA. Nevertheless, nasal surgery is very often performed in OSA patients to improve adherence to and compliance with nasal CPAP. For this reason, surgical correction of relevant impairments to nasal breathing is indicated primarily in case of subjective problems and as adjuvant treatment in problematic CPAP compliance.

Minimal invasive surgery

A surgical method is regarded as minimally invasive if the intervention can be delivered under local anesthesia and as an outpatient procedure, and if perioperative and postoperative morbidity is low and complications rare (Verse and Hörmann, 2011).

Interstitial radiofrequency therapy

Interstitial radiofrequency therapy is used for the soft palate, palatine tonsils, and the base of the tongue. Treatments can be isolated or combined. Combined radiofrequency of the soft palate and the tongue base is preferred in most patients. In the muscles of the soft palate and tongue, tissue stiffening is achieved via postoperative scarring, and in the lymphatic tissue of the tonsils, the volume effect is up to 75%. Sparing the mucosa leads to less postoperative pain and fewer complications. In OSA, primary use on the soft palate and the base of the tongue is indicated only for mild forms. In a Farad's et al. (2008) meta-analysis, the radiofrequency ablation resulted in a 31% reduction in short term (<12 month) and 45% reduction in long-term (>24 month) RDI levels. Data on the treatment of the palatine tonsils are lacking.

Soft palate implants

Palatal implants (Pillars) are cylinders of woven polyester. They are inserted into the soft palate at the junction with the hard palate and their aim is permanent stiffening of the soft palate. The overall efficacy is limited to patients with mild OSA. In a randomized, double-blind, placebo-controlled study implants were superior to placebo (Steward et al., 2008). Short-term results appear to remain stable over a one-year period.

Invasive surgery

Pharyngeal procedure

The most widely established surgical procedure is uvulopalatopharyngoplasty (UPPP). The principle is a widening of the oropharyngeal valve in the transverse as well as a sagittal direction. Uvulopalatal flap has the same indications as UPPP, except that the uvulopalatal flap is contraindicated when the palate and uvula are excessively long and bulky.

Uvulopalatopharyngoplasty

Positive predictors for therapeutic success are hyperplastic tonsils, substantial excess mucosa of the soft palate, a long uvula, longitudinal folds of the mucosa covering the back wall of the pharynx, and an observed obstruction of the soft palate on sleep endoscopy (Verse and Hörmann, 2011). The anatomy-based staging system predicted UPPP outcomes more effectively than did the severity-based staging. The anatomy-based staging system facilitates good case-selection information for counseling patients before UPPP surgery (Li et al., 2006). There is also some evidence that tonsillectomy doubles the success rate of UPPP (Maurer, 2009). In addition, Verse (2008) stressed that success rates decrease significantly above a BMI of 30.

Longterm data with a follow-up of 3–10 years showed a success rate of 49.5% (Randerath et al., 2006). UPPP is the only surgical treatment for OSA for which a reduction in the risk of incidents (Haraldsson et al., 1995) and normalization of raised specific values for serum C-reactive protein has been shown (Kinoshita et al., 2006). Side effects include difficulty swallowing/nasal regurgitation, taste disturbances, and voice changes.

UPPP with tonsillectomy seems indicated for the treatment of mild to moderate OSA if the pathoanatomical findings justify the method.

Laser-assisted uvulopalatoplasty

Laser-assisted uvulopalatoplasty involves a series of laser incisions and vaporizations designed to shorten the uvula and modify and tighten the soft palatal tissue. It is primary used in snoring. Although there was reported a remarkable significant decrease in AHI (73% reduction in AHI) in an observational study (Chisholm and Kocheda, 2007), in two other randomized control trials a very slight decrease (Fregusson et al., 2003) and even an increase in AHI (Larossa et al., 2004) were reported. Moreover, pain after LAUP is severe and long-lasting. Therefore laser-assisted uvulopalatoplasty is not recommended in OSA.

Tongue base procedures

The tongue suspension technique pulls the tongue base anteriorly using a non-resorbable thread fixed to the genioglossus tubercle. Because it is difficult to obtain the correct tension on the suture, this procedure has been abandoned by most surgeons. Hyoid suspension is a technique whereby the hyoid bone is fixed in front of the thyroid cartilage via a cervical approach. It is rarely carried out separately but chiefly used in multi-level surgery.

Multi-level surgery

In most cases of moderate to severe OSA the entire upper airway is obstructed. Nowadays, invasive surgical procedures are rarely undertaken in isolation but usually in combination. The concept of multi-level surgery addresses the palate/tonsils as well as the hypopharynx/tongue, combining procedures at both levels during one single operation.

UPPP or uvulopalatal flap including tonsillectomy are the palatal procedures employed, whereas the hypopharyngeal obstruction is variably dealt with by performing genioglossus advancement, hyoid suspension, radiofrequency of the tongue base and/or tongue base resections (Maurer, 2009). The data have shown a general effectiveness of multi-level surgery in severe OSA (Verse et al., 2009). However, it is not yet clear or foreseeable which combination of procedures will be superior.

Maxillofacial surgery

Maxillofacial surgery includes various skeletal procedures that advance the entire mandible or both the mandible and the lower maxilla. In moving the skeletal in closure, soft tissues are moved and the airway is enlarged.

Genioglossus advancement

Genioglossus advancement aims to enlarge the hypopharyngeal air space, bringing forward the base of tongue. It consists in an advancement of the genial tubercle and genioglossus muscle. It seems to be efficiently used in multiple levels surgery for treatment of hypopharyngeal airway impairment.

Maxillomandibular advancement osteotomy

Maxillomandibular advancement osteotomy simultaneously widens the nasopharynx, oropharynx, and hypopharynx by advancing the soft palate and tongue and tightening the lateral pharyngeal walls without direct manipulation of the pharyngeal tissues. It is indicated for patients with suitable anatomical conditions (retrognatia).

After tracheotomy, maxillomandibular advancement osteotomy is the most successful surgical approach for treating OSA. Compared with CPAP similar reductions of the AHI are achieved, as are a similar optimization of sleep architecture (Conradt et al., 1998). But still, maxillomandibular advancement osteotomy is a lengthy and technically challenging procedure and presents inherent risks of dental malocclusion and facial neurosensory deficits.

Tracheostomy

Bypassing the pharyngeal obstruction by tracheostomy eliminates every obstructive respiratory event during sleep. Success rates are around 96% and remain stable over a long period (Verse, 2008). Due to its invasive character it is reserved for severe and otherwise untreatable OSA and is rarely necessary.

8.2.5 Oral appliances

Oral appliances offer a non-invasive treatment option for patients with OSA. The American Academy of Sleep Medicine recommends oral appliances therapy for patients with mild to moderate OSA and for those with more severe OSA who cannot tolerate CPAP and refuse surgery (Kushida et al., 2006).

A variety of oral appliances are available that can broadly be classified as: tongue-retaining devices and mandibular advancement devices. The predominant and most common oral appliance is the mandibular advancement device, which protrudes the lower jaw and increases vertical opening during sleep to reduce airway obstruction, hypopneas, apneas, and snoring. When no dentition is present, the tongue retaining device may be used. A tongue retaining device does not use dentition to advance tissues, but, instead, suction bulbs to hold the soft tissue tongue in a more advanced position. The primary action of oral appliances is to increase and stabilize the oropharyngeal and/or hypopharyngeal airway space. They widen primarily the lateral parts of the upper airway. Oral appliances also increase respiratory related activity of upper airway muscles which can contribute to airway patency (Tsuiki et al., 2000).

A large number of proprietary mandibular advancement devices are available and differ in design, materials, and cost. They may be custom made for the patient or non-custom off-the-shelf. Both custom and off-the-shelf mandibular advancement devices may be designed to have either a fixed amount of mandibular protrusion or adjustable protrusion. It is the opinion of many that best results are achieved with adjustable device. The degree of mandibular

advancement is crucial, since a non-advanced device is ineffective on sleep apneas and may even increase the apnea frequency (Hans et al., 1997).

In mild to severe OSA patients, mandibular advancement devices treatment was effective in up to 63%. In subjects with mild to moderate OSA, mandibular advancement devices treatment efficacy was found in up to 79% (Ahrens et al., 2011). Mandibular advancement devices reduce sleep apneas and subjective daytime sleepiness and improve quality of life compared with control treatments. Mandibular advancement devices are superior to tongue-retaining devices and should be preferred in patients with OSA (Randerath et al., 2011).

Mild adverse effects, such as teeth and gums tenderness, excessive salivation, jaw discomfort and/or temporary occlusal changes are common, affecting up to 50% of patients. More severe adverse effects such as occlusal changes and myofascial pain are less common. Major adverse effects are probably determined by aggressiveness of protrusion and duration of use.

RESTLESS LEGS SYNDROME

1. History

Restless legs syndrome (RLS) was first described in the 17th century (1672/1685) by Sir Thomas Willis. The clinical picture was fully described by the Swedish neurologist Karl Axel Ekbom in 1945. Periodic leg movements in RLS were first described by Elio Lugaresi and his colleagues in 1986. Sevket Akpinar (1982) started first treatment of RLS with dopaminergic drugs. RLS was formerly termed “anxietas tibiarum” because of its relationship with anxiety and was considered psychiatric origin.

2. Definition

Restless legs syndrome is a sensorimotor disorder affecting sleep. Patients describe an urge to move their legs during rest. This may be accompanied by unpleasant sensations that are temporarily relieved by movements. The sensorimotor complains arise or worsen during the evening or night, showing a circadian pattern.

The RLS discomfort leads to a difficulty in initiating and/or maintaining sleep and/or nonrestorative sleep. Moreover, the RLS is frequently associated with periodic limb movements during sleep which causes arousals. Patients complain of insufficient sleep and/or excessive daytime sleepiness. Patients with severe RLS who experienced daily symptoms have been found to sleep only 3-5 hours per night (Allen and Earley, 2001).

3. Classification

There are two forms of RLS: primary and secondary. A primary, idiopathic form must be separated from secondary forms, as the treatment of secondary RLS often requires management of the background medical condition.

Idiopathic form accounts for 70% - 80% of all cases of RLS (Basseti et al., 2001). A large part of primary RLS comprises the hereditary form. Familiar aggregation of RLS is well documented; 40% - 90% of primary RLS cases report a positive family history (Winkelmann et al., 2000). In addition to hereditary idiopathic (primary) form, an idiopathic form exists without a positive family history too, known as a sporadic form. Familiar cases have an earlier age of onset, typically before 30 years (Winkelmann et al., 2002). Patients with a start of the disease before the age of 45 seem to be affected by a clinical form with a mild, slow progression, in contrast patients with late disease onset (after 45 years) show severe forms and rapidly progressive course (Allen and Earley, 2000).

Secondary form is caused by a specific disease. Several conditions are known to be associated with RLS. Uremia is often associated with RLS. 15% - 40% of patients undergoing hemodialysis demonstrate RLS symptomatology (Wetter et al., 1998). Uremic patients predispose to development of RLS also thanks to anemia and peripheral neuropathy. The presence of RLS in patients with end- stage renal disease increases mortality rate independently (Winkelman et al., 1996). The prevalence of RLS is reduced in kidney transplanted patients and compare to dialyzed patients and is similar to the prevalence observed in general population (Molnar et al., 2009). Other diseases and conditions associated with RLS are anemia, spinal lesions, neuropathy, fibromaylgia or pregnancy.

4. Epidemiology

The exact prevalence is not known due to important methodological differences in epidemiologic studies. Internationally recognized diagnostic criteria only became available in 1995, thus older studies are difficult to compare. The discrepancies in new studies are attributable to other methodological differences such as regional variations and different samples of probands in the studies and to used methodology.

Methodological instruments used to asses RLS in epidemiological studies are self-administered questionnaires, telephone interviews and direct observations.

The use of self administered questionnaires allows the study of large populations but leads to a risk of false diagnosis due to misunderstanding of the diagnostic criteria or presence of confounding factors. The percentages of RLS in these studies vary between 4% and 11% (Hening et al., 2004) (Nichlos et al., 2003) (Ulfberg et al., 2001). The telephone interview should be carried by an expert on sleep disorders to gain a high specificity. Studies using telephone interview obtained prevalence between 5,5% and 11,5% (Phillips et al., 2006) (Ohayon and Roth, 2002). The face to face interview has the highest specificity.

In the RLS epidemiology, symptoms and treatment trial (REST), the largest survey till date to study the prevalence of RLS, 7.2% of US and European adults reported having experienced symptoms of RLS at some point during a 1-year period, and 5% reported experiencing symptoms on a weekly basis (Phillips et al., 2000).

Prevalence of RLS varies among the countries. Low percentages are observed in Singapore – 0,1% (Tan et al., 2001), in Turkey 3,19% (Sevim et al., 2003) and among native South Americans 2% (Castillo et al., 2006). The lowest prevalence (0,013%). was observed in a Tanzanian study (Winkler et al., 2010). Higher prevalences were found in French Canadians

in Eastern Canada (Lavigne and Montplasier, 1994) and the population of Moscow (Idaho, USA) (Nichlos et al., 2003).

Most studies found that the prevalence of RLS seems to increase with age (Hening et al., 2004). However RLS symptom often starts before the age of 20, especially among familiar cases.

The prevalence of RLS in the pediatric population is lower than in adults, with approximately 2% of children between the ages of 8 and 17 years experiencing symptoms at least once a month, and 1.2% experiencing symptoms at least twice per week. Among pediatric patients, RLS is slightly more common in males than females overall (53.9% vs 46.1%), but the male preponderance is more striking when moderate-to-severe RLS (occurring at least twice a week) is measured (59.8% vs 40.2%) (Picchietti et al., 2007). Higher prevalences were found in children with ADHD and with growing pains.

Higher prevalence is found in females than in males. The REST study found that 9.0% of women and 5.4% of men had experienced RLS symptoms within the previous year. The gender difference increases when comparing the rates of symptoms experienced at least once per week. These more frequent symptoms were seen among 2.8% of men in the REST study versus 6.2% of women (Allen et al., 2005) (Berger et al., 2004).

5. Risk factors

Iron

RLS is common in subjects with iron deficiency. Some secondary causes of RLS (end-stage renal disease, iron deficiency, and pregnancy) are associated with problems maintaining adequate iron. Cerebrospinal fluid (CSF) ferritin concentrations were significantly lower in RLS subjects than in controls, whereas transferrin concentrations were significantly higher. CSF iron concentration did not significantly differ between the groups (Earley et al., 2000). In the next study Earley et al. (2005) have shown that the early-onset (less than 45 years of age) but not the late-onset (greater than or equal to 45 years of age). RLS group had significantly lower CSF ferritin levels compared with controls. There was a strong correlation between the age of symptom onset and CSF ferritin values, the earlier the age, the lower the ferritin level. A regression analysis showed that both sex and RLS subtype had significant effects on the CSF ferritin level, with women with early-onset RLS having substantial lower values than men with late-onset RLS. However, a comparison between these nighttime CSF values and previously published daytime samples suggests that diurnal changes may have

effects on the findings. Serum ferritin levels below 50 µg/L were associated with increased severity of RLS (Frauscher et al., 2009).
For the role of iron in pathophysiology of RLS see please subchapter Pathophysiology of RLS, Iron deficiency.

RLS complains are reported by 15% - 27% of pregnant women, especially in the third trimester. In most cases, women who experience RLS symptoms in **pregnancy** have not had symptoms of RLS previously. Affected women presented lower values of hemoglobin and mean corpuscular volume compared with healthy subjects. Typically, RLS symptoms resolve in most women within a few weeks to a few months after delivery. However, the transient restless legs syndrome during pregnancy is a significant risk factor for the development of a future chronic idiopathic restless legs syndrome (Manconi et al., 2004).
The presence of **neuropathy** should be especially investigated in nonhereditary, late-onset RLS, in view of a possible treatment of the underlying disease. The association of RLS with polyneuropathy is still controversial, in spite of extensive studies. Prevalence of RLS in neuropathy is extremely variable, ranging from 5.2% to 54%. High RLS prevalence of 54% was found in a selected series of patients with neuropathy with symptoms of pain or dysesthesia (Nineb et al., 2007). Various prevalences of RLS in neuropathies may be apart from methodological discrepancies in the design of the studies, the assessment of neuropathy and variations in etiology of neuropathy due to the fact that a polyneuropathy is usually an evolutive condition and the appearance or disappearance of RLS may be related to different phases of the disease (Brindani et al., 2009). It has been shown that RLS can be triggered by the small fiber sensory neuropathy (Iannaccone et al., 1995) (Polydefkis et al., 2000). Also Charcot Marie Tooth disease type II, an axonal form of polyneuropathy is frequently present with RLS in contrast to type I, a demyelization type of polyneuropathy. Therefore it could be expected that RLS prevalence in neuropathy will be higher when considering the forms with prevailing small fiber involvement, such as diabetic neuropathy (Gemignani et al., 2007).

There is also lower prevalence of positive family history of RLS among those with neuropathic RLS compare with RLS without polyneuropathy. It seem that neuropathic RLS may be a secondary form of RLS in patients with an older age of onset, secondary symptoms involving pain and absence of another affected family members.

RLS is also often found in **fibromyalgia**. Stehlik et al. (2009) found a prevalence of 64% among a group of female patients diagnosed with fibromyalgia. Viola-Saltzman et al. (2010) confirmed these findings, in their study RLS was about 10 times more prevalent in the

fibromyalgia group than among the control group. Furthermore, the odds of RLS in the fibromyalgia group were over 11.

Taylor-Gjevre et al. (2009) conducted a study to evaluate restless legs syndrome (RLS) prevalence in a **rheumatoid arthritis** (RA) and osteoarthritis (OA) population. All criteria for RLS were met by 27.7% of RA patients and by 24.4% of OA patients. A previous diagnosis of RLS was reported by 2.6% of patients. Similar results have published Ishaq et al. (2012). He found the prevalence of RLS of 20% in females with rheumatoid arthritis from Pakistan. Rheumatoid arthritis often occurs with reduced iron status that appears to predict the co-occurrence of RLS (Györfi et al., 2003). The reduced iron status may be due to the systematic inflammatory process. Moreover, rheumatologic diseases are connected with pain. Other painful conditions such as backache, headache or other pain are more common in RLS subjects than in controls (Ohayon et al., 2012).

Restless leg syndrome has been found in association with **Parkinson's disease**. Gomez-Esteban et al. (2007) found a higher prevalence rate of RLS in patients with Parkinson's disease. In a study of 114 patients, 25 out of 114 patients had RLS (21.9%). Similar prevalence found Peralta et al. (2009) 24% in a cohort of 113 patients with idiopathic Parkinson's disease and Guerreiro et al. (2010) 18,75% of RLS in 48 patients. A very low prevalence was reported in Thai Parkinson disease patients. Three out of 183 patients (1.6%) had RLS. When one patient who had a serum ferritin level of 31,9 ng/ml was excluded the prevalence fell to 0.98% (Jagota et al., 2012). Nevertheless not all authors are convinced that the prevalence of RLS in Parkinson disease patients is really high.

Leg motor restlessness (LMR) is significantly more prevalent in Parkinson disease then in controls. The occurrence of LMR may relate to the earlier onset of PD, raising the possibility of common pathophysiological mechanisms for PD and RLS, of which LMR may be an early manifestation in some patients (Rajabally and Martey, 2013).

Multiple sclerosis (MS) is associated with RLS. A large prospective, multicenter, case-control epidemiologic survey, the REMS study, reported the prevalence of RLS 19% in MS and 4.2% in control subjects, with a risk to be affected by RLS of 5.4 (95%confidence interval: 3.56-8.26) times greater for patients with MS than for control subjects. In patients with MS, the risk factors for RLS were longer MS duration; the primary progressive MS form; higher global, pyramidal, and sensory disability; and the presence of leg jerks before sleep onset (Italian REMS Study Group, Manconi et al., 2008). Vávrová found the prevalence of 32,1% in Czech subjects with multiple sclerosis and confirmed diagnosis of RLS and has

shown that this form did not share all genetic risk variants with idiopathic RLS (Vávrová et al., 2012).

The spinal cord is implicated in the pathophysiology of RLS. There are reports of RLS in patients with **spinal lesions**. Traumatic, neoplastic, demyelinating and post-infectious spinal cord lesions as well as syringomyelias precipitate RLS. Hogl et al. (2002) demonstrated the incidence of transient RLS following spinal anesthesia in subjects without any history of RLS in a prospective manner.

Ondo and Lai (2006) found a very high rate of undiagnosed RLS in patients presenting for **essential tremor**, but unlike other "secondary" forms of RLS, this finding was also associated with a high familial history of RLS, suggesting that they share some genetic similarities.

Skomro et al. (2001) found twice the prevalence of RLS in patients with **diabetes mellitus type II** in comparison with controls. Merlino et al. (2007a) in a large case-control study found a significantly higher prevalence of RLS among diabetics independent of polyneuropathy.

Dopamine antagonists (antipsychotics and antiemetics) have been shown to cause motor restlessness (akathisia) and increased periodic limb movements (PLMS) and RLS (Rye et al., 2005). Antidepressant medications, especially tricyclics, mirtazapine and SSRIs have been reported to cause or exacerbate RLS, as well as lithium and some antihistaminics (Ondo, 2005) (Sethi and Mehta, 2012). On the other hand, a review of 200 patients presenting to the sleep clinic found no incontrovertible association between RLS and antidepressant medication (Brown et al., 2005).

Other conditions anecdotally linked with RLS include congestive heart failure, hypotyreoidism and hyperthyreoidism, chronic lung disease, leukemia, Isaacs´ syndrome, stiff man syndrome, Huntington´s chorea, amyotrophic lateral sclerosis, depression, and sleep apnea (Gamaldo and Earley, 2006) (Kryger et al., 2005).

Certain lifestyle behaviors appear to be associated with increased risk for RLS, such as alcohol, tobacco, and caffeine consumption, although compelling data on these factors are lacking (Bayard et al., 2008) (Philips et al., 2000).

6. Pathophysiology

RLS is a heterogeneous disorder and its pathophysiology is likely to be multifactorial.

6.1 Genetics

There is strong evidence for a genetic contribution to RLS. A family history of RLS is present in 65% of cases (Winkelmann et al., 2002). There is also high concordance (83%). of RLS between monozygotic twins (Ondo et al., 2000a). However the RLS severity and age of onset often varied between twins. It has been suggested that early onset of RLS could be transmitted as an autosomal dominant trait with variable expressivity (Dhawan et al., 2006) (Walters et al., 1990).

Stefansson et al. (2007) reported an association between a sequence variant in chromosome 6p, an intron of BTBD9 and periodic leg movements in sleep in a distinct Icelandic and American cohorts of subjects with RLS and their families. Winklemann showed an association between RLS and the same sequence variant, as well as two additional single nucleotide polymorphisms (SNPs) in German and Canadian cohorts with RLS (Winkelmann and Muller-Myhsok, 2008).

A genomewide association study by Winkelmann et al. (2007) included 922 RLS patients and 1526 controls and tested 301,406 single nucleotide polymorphisms. Genetic risk variants for RLS have been identified in 2 genes, one of them the homeobox gene MEIS1, known to be involved in embryonic development, and variants in a second locus containing the genes encoding mitogen-activated protein kinase MAP2K5, and the transcription factor LBXCOR1. A third one, the BTBD9 gene with unknown function, encodes a BTB(POZ) domain.

6.2 Neurotransmitter dysfunction: Dopaminergic and opioid systems

A central dopamine hypothesis comes out from several lines of evidence:

1. RLS symptoms are exacerbated by dopamine antagonists and relieved by dopamine agonists (Wetter et al., 1999) (Trenkwalder et al., 2004). However, the mechanism of this improvement has never been fully elucidated. It has also been observed that co-administration of domperidone (a peripheral dopamine antagonist) does not decrease the efficacy of pergolide (a dopamine agonist) in treating RLS, which lends support to the hypothesis that central rather peripheral dopaminergic systems are responsible for RLS (Stiasny et al., 2001).

Dopaminergic receptors are distributed all over the spinal cord, in the ventral and in the dorsal horns as well as in the white matter (Venugopalan et al., 2006). Binding to ventral

horn dopaminergic receptors targets preferentially PLM, binding to dorsal horn receptors addresses paresthesias and pain receptors (Paulus and Trenkwalder, 2006) (Trenkwalder and Paulus, 2004).

2. RLS symptoms and PLMs follow a circadian pattern, occurring or worsening during the late evening or the first part of the night and improving in the morning hours (Michaud et al., 2004). Similar profile has the secretion of melatonin, which has an inhibitory effect on dopamine release and dopaminergic activity (Trenkwalder et al., 1999). Described pattern may be related to circadian fluctuations of dopaminergic activity, which increases in the morning and with a nadir in the late evening/early night (Hagan et al., 1999).

3. Imaging studies yielded conflicting results. There are three adequately controlled SPECT studies of striatal D2-receptors binding, two of which showed no statistically significant difference, while one showed a small but statistically significant difference (Chaudhuri et al., 2009). A recent study on dopamine transporter density of patients with RLS found increased in the caudate, posterior putamen, and entire striatum compared with that of normal controls. There was no difference in the D2 receptor density between patients with RLS and normal controls in the whole striatum or any of subregions in this study (Kim et al., 2012). PET studies have shown little but significant reductions of mean caudate and putamen D2-receptor binding and decreased mean putamen F-dopa uptake in RLS compared to controls (Chaudhuri et al., 2009). A recent positron emission tomography (PET) study showed a decreased number of dopamine transporters (Earley et al., 2011).

4. There is evidence that the A11 dopaminergic nucleus may play a role in development of RLS. A11 has a local anatomical connection with the suprachiasmatic nucleus of the hypothalamus, which is involved in the regulation of circadian rhythms. Its neurons descend as the sole source of spinal dopamine mainly through the dorsolateral funiculus. A11 spinal projections are most heavily concentrated in the superficial sensory-related dorsal horn and the intermediolateral nucleus, the origin of sympathetic preganglionic pathways and are believed to be involved in sensory suppression (Trenkwalder and Paulus, 2004). Injection of the dopamine antagonists 6-hydroxydopamine into the A11 systems of rats produced behavioral changes analogous to those seen in RLS (Ondo et al., 2000b).

5. The evidence supporting the involvement of opiate system is the effectiveness of opioids in RLS treatment. Administration of naloxone, an opiate receptor blocker, to opiate-treated patients reactivates RLS symptoms. In untreated patients, naloxone seemed to have no effect on RLS (Chaudhuri et al., 2009). Administration of a postsynaptic dopamine receptor

blocking agent, pimozide, blocks the therapeutic effects of opioids but not of the dopaminergic drugs. Thus, opioids probably indirectly prevent RLS symptoms by means of their impact upon the dopaminergic system (Walters, 2002).

The positive effect of the voluntary and repetitive leg movements could be due to the activation of non-pain encoding low-threshold muscle proprioceptors, acting as a gate control, able to restore the balance between excitatory and inhibitory inputs in the dorsal horn (Clemens et al., 2006).

6.3 Iron deficiency

Iron is important in brain dopamine production and synapsis density, as well as in myelin synthesis, energy production and probably in norepinephrine and serotonin neurotransmitter systems (Picchietti and Picchietti, 2010).

In an MRI study the localization of iron within the brain in RLS patients was investigated by means of T2-weighted MRI. Patients with RLS had significantly lower iron concentrations in the substantia nigra and lesser in the putamen. The deficiency of iron in the brain correlated negatively with the severity of the disease (Allen et al., 2001b).

Transcranial B-Mode sonography (TCS) of the mesencephalic brainstem has been introduced as a new method to assist the diagnostic approach to RLS. Changes in echogenicity of the substantia nigra using transcranial ultrasound have been related to changes in tissue concentrations of iron (Schmidauer et al., 2005). Typical TCS findings in RLS include hypoechogenicity of the substantia nigra and the raphe as well as hyperechogenicity of the red nucleus. The triad of substantia nigra hypoechogenicity, red nucleus hyperechogenicity, and brainstem midline raphe hypoechogenicity allows diagnosis of idiopathic RLS with 98% diagnostic certainty (Godau and Sojer 2010).

Autopsy data revealed that iron staining and H-ferritin staining was markedly decreased in the RLS substantia nigra. Although H-ferritin was minimally detected in the RLS brain, L-ferritin staining was strong. Transferrin receptor staining on neuromelanin-containing cells was decreased in the RLS brains compared to normal, whereas transferrin staining in these cells was increased (Connor et al., 2003).

The low brain iron is a well established pathology of RLS. Evidence showing a connection between RLS and low iron includes cerebrospinal fluid analysis, brain sonography, MRI

imaging and autopsy data. The brain iron deficiency particularly affects the dopamine-producing cells in substantia nigra and their terminal fields in the striatum (Salas et al., 2010). An autopsy study found increased tyrosine hydroxylase in substantia nigra and decreased D2 receptors in putamen in RLS patients (Connor et al., 2009). Cerebrospinal fluid from a part of RLS individuals contained significantly more 3-O-methyldopa than in matched controls. Increased 3-O-methyldopa significantly correlated with the cerebrospinal fluid homovanillic acid and with the RLS severity (Allen et al., 2009). This indicates that increased dopamine production is proportional to the severity of RLS symptoms.

Restless legs syndrome is a hyperdopaminergic condition with postsynaptic desensitization that overcompensates during the circadian low point of dopaminergic activity in the evening and night. Iron deficiency affects dopaminergic function by increasing tyrosine hydroxylase which then increases extracellular dopamine, resulting in a decrease in dopamine transporter on the cell surface and in extreme cases also causes a decrease in the number of D2 receptors (Salas et al., 2010).

7. Diagnosis and clinical features

RLS is a clinical diagnosis. There is no objective measurement necessary or specific to diagnose RLS.

Diagnostic criteria were developed by the International Restless Legs Syndrome Study Group (IRLSSG) in 1995 and then modified in 2003 (The International Legs Syndrome Study Group, Walters et al., 1995) (Allen et al., 2003).

The diagnosis is based on the presence of four clinical essential criteria. These criteria are based on patient's history. All the following criteria are necessary for diagnosis:

1. urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensation
2. the symptoms begin or worsen during the rest or inactivity
3. the symptoms are partially or totally relieved by movement, such as walking or stretching, at least as long the activity continues
4. the symptoms are worse in the evening or at night

In addition to the essential criteria, the IRLSSG described three supportive clinical features and three associated features useful for diagnosing RLS in uncertain cases.

Supported clinical features are:

1. Positive family history

2. Response to dopaminergic therapy
3. Periodic limb movements during wakefulness or sleep

Associated features are:

1. Natural clinical course (early onset with slow progression, late and abrupt onset and more severe disease)
2. Sleep disturbances
3. Medical examination (generally normal in primary RLS)

Patients describe uncomfortable sensations in legs using words such as tingling, crawling, creeping, jittering, burning, “internal itch”, “shocklike feeling” or painful. Up to 50% of patients with RLS describe their sensations as painful (Kryger et al., 2005). The unpleasant sensations are felt deeply in both legs. Some patients cannot describe the sensations at all (Stiasny et al., 2002). Especially affected are the regions between knees and ankles. Some people describe only an urge to move their legs without any sensory component (motor variant of RLS). In response to urge to move patients typically walk around, often rub the legs, turn in the bed, stretch and flex the legs. Relief is achieved immediately after beginning an activity, although relief is not always complete, particularly in severe disease. Symptoms resume with various latency after rest. The shorter is the latency, the more severe are symptoms. The disorder can also involve arms and another part of the body in severe cases. Legs symptoms usually precede arm involvement by several years. Involvement of arms or another body part without any involvement of legs is very rare. Symptoms peak between midnight and 3.00 a.m. Symptoms also often fluctuate throughout a patient’s life. During some periods, symptoms may be present several times a day, whereas at other time symptoms may be totally absent, disappearing without any apparent reason. Sudden remission may last several months up to several years.

The symptoms of RLS occur not only in physical rest but also in reduced central nervous system activity. Some patients are able to alleviate symptoms by engaging in activities that increase their alertness level (Merlino et al., 2007b). Sleepiness and fatigue worsen symptoms. Discomfort in a particular extremity can be relieved by moving of another part of body. Also taking a cold or less often a hot bath is helpful. Some of male patients are convinced of the positive effect of masturbation (Mathis, 2005).

7.1 Polysomnography

As reported in the IRLSSG international guidelines, poylsomnography, by detecting the presence of **periodic limb movements** (PLMs), can be useful to confirm the diagnosis in patients who satisfy only three of four essential criteria.

PLMs are present in 80% - 90% patients with RLS. They could be responsible for nonrestorative sleep. PLMs are usually present in the legs, but less common arms also may be involved. The leg movement resembles the Babinski reflex. It is characterized by extension of the great toe with fanning of the other toes. More severe movements are characterized by “triple flexion”: dorsiflexion of the ankle, partial flexion of the knee and (sometimes) the hip (Stiasny et al., 2002). Movements last between 0,5 – 5 s. Motor pattern can be variable among individuals, but is intraindividually stable (de Weerd et al., 2004). Movements are often bilateral, but may be predominant in one leg or alternate between legs.

PLMs are detected by surface electromyographic electrodes recording both tibialis anterior muscles during polysomnography. According to the scoring manual the movements are count if they persist 0,5 – 5 s, if they occur in series of 4 or more movements during sleep at intervals of 5 – 90 s. The movements have to be at least 25% as tall as the electromyography bio-calibration signal performed at the beginning of the sleep recording (The Atlas Task Force, Bonnet et al., 1993). The occurrence of PLMs is detected both in sleep (PLMS) and in wakefulness (PLMW).

Following PLM parameters/indexes are registered and calculated during a polysomnography:
PLMS index = number of limb movements in sleep per hour total sleep time
PLMS arousal index = number of PLMS associated with arousals per hour total sleep
PLMS index greater than 5 is considered as abnormal (Dickel and Mosko, 1990). However healthy individuals without any sleep complain may have the PLMS index above 10 (Carrier et al., 2005). On the other hand in 10% - 20% of RLS patients may be the PLMS index below 5 (Hornyak et al., 2005).

7.2 Suggested Immobilization Test

The Suggested Immobilization Test (SIT) is a provocative test performed as a clinical and research tool. The purpose of the test is to induce by immobility the appearance of RLS sensory and motor symptoms. During a 60 minutes period the subject is requested to remain reclined in the bed at a 45° angle with outstretched legs and open eyes. PLMW are recorded by means of surface EMG derived from bilateral anterior tibialis muscles, while sensory leg discomfort is estimated by the patient every 5 minutes using a 100mm horizontal visual

analogue scale. There is a peak of manifestations induced by immobility during the first part of the night (Michaud et al., 2005) (Hening et al., 1999). Therefore for clinical reasons, the SIT should be administrated preferably after 21.00. Unfortunately, there has been reported a huge intra-individual variability in SIT PLM index (Haba-Rubio and Sforza, 2006).

7.3 Actigraphy

Actigraphic devices (accelerometers) which detect and store occurrence of movements can be used to detect periodic limb movements. Actigraphic device is placed on the big toe, ankle or foot. Disadvantage is that actigraphy cannot differentiate between PLMS and PLMW. Therefore a sleep diary should be used in conjunction with actigraphy. In contrast, there are several advantages: actigraphy is less expensive and can be conducted in the home environment over many nights. A newer PAM-RL triaxial accelerometer includes a detector of body position and was proved for diagnostic purposes in large clinical trials (Sforza et al., 2005).

7.4 L-dopa test

L-dopa test examines the response to dopaminergic treatment, a supportive diagnostic criterion for diagnosing RLS, under standardized conditions. The test consists of the application of one single dose of 100/25 mg L-DOPA/benserazide and a subsequent observational period of 2 hours. Before, and in 15-minutes intervals after the drug intake the patients rate the severity of the "symptoms in the legs" and the "urge to move the legs" using a 100-mm visual analogue scale. 50% improvement is considered as a positive test result. The test is recommended for diagnostic decision making in all patients with an unclear RLS diagnosis according to the essential diagnostic criteria (Stiasny-Kloster et al., 2006).

Other examinations

A routine clinical examination is recommended for excluding neuropathy or vascular compromise that could mimic RLS.

7.5 Diagnostic and Severity Assessment Scales

The RLS diagnostic index has been developed on the basis of the essential and supportive and associated criteria by Benes (Benes and Kohnen, 2004). The scale examines presence or absence of diagnostic criteria and rates positive values for their presence and negative values for their absence. The total score allows making the certainty of diagnosis: definite, probable, possible, unlikely or no RLS.

The International Restless Legs Syndrome Study Group developed a 10-point scale to measure RLS severity – the International Restless Legs Scale (IRLS) (The International Restless Legs Syndrome Study Group, Walters et al., 2003). This scale is a gold standard to measure the severity or RLS. A factor analysis of the IRLS has shown that the items of IRLS can be grouped into two factors: RLS symptoms and their severity and as well consequences and impact of RLS (Allen et al., 2003b).

A single standardized question for the rapid screening of restless legs syndrome had high sensitivity and good reliability (Ferri et al., 2007). However, the final diagnosis should always be confirmed by the diagnostic features of RLS and accompanied by a careful search for comorbid conditions.

The Johns Hopkins telephone diagnostic interview (TDI) for restless legs for diagnosis of the RLS is a diagnostic interview carried out by telephone without face-to face contact. The scale was mainly developed for establishing the prevalence of the disease in large populations. It contains 17 first-order questions and 32 second- or third-order questions that are used, based upon the individual's response to the first-order questions (Hening et al., 2008).

The Cambridge-Hopkins diagnostic questionnaire for RLS (CH-RLSq) is a patient-completed diagnostic questionnaire for ascertainment of RLS in population-based studies. The questionnaire includes the basic diagnostic features of RLS and provides some basic differential diagnosis too (Allen et al., 2009).

The John Hopkins RLS Severity Scale consists of a single question which focuses on the usual time of onset of RLS symptoms (Allen and Earley, 2001).

The RLS-6 consists of six questions. Answers are given in 11 categories. It focuses mainly on severity of symptoms in different daytime and nighttime situations, satisfaction with sleep and daytime tiredness (Kohnen et al., 2003). It is used in for the assessment of efficacy of drug treatment in RLS drug studies.

There are also two scales assessing the augmentation. Augmentation severity is assessed by the Augmentation severity rating scale (ASRS) developed by the European RLS Study Group. The scale consists of three items that assess the degree of change in three specific dimensions of augmentation (earlier onset of symptoms during the day, shorter latency to occurrence of symptoms when the patient is at rest and spreading of symptoms from the legs to other parts of the body) (Garcia Borreguero et al., 2007b). The Structured Interview for

Diagnosis of Augmentation (SIDA) is derived from the published criteria for augmentation. The interviewer is guided step by step through each of the criteria and then directed to the appropriate next question as applicable, or to end the interview (Hogl et al., 2005).

8. Differential diagnosis

Akathisia is a reversible drug induce phenomenon associated with the use of antipsychotics and rarely with the use of antidepressants. Patients suffer from unpleasant sensations of inner restlessness, which leads to compulsion to move and is often accompanied by severe anxiety. The restlessness in akathisia is in contrast to RLS present all the time and there is no sensory discomfort. L-dopa does not suppress akathisia, it may even trigger akathisia. Involvement of the face, tongue and upper limbs is common in akathisia but very rare in RLS.

Myoclonus is an involuntary, brief jerking of a group of muscles. It is not accompanied by sensory symptoms. "Sleep starts" or "hypnic jerks" are a condition observed in normal subjects during the transition from wakefulness to sleep. It consists of short, massive body movements. They are associated with sudden arousal and may be accompanied by a sensation of sinking or falling. No localized discomfort exists in the legs. A special form of myoclonus, the propriospinal myoclonus is a very rare condition characterized by repetitive movements of the axial muscles of the body which spread to the limbs. Pathologic forms of myoclonus are in general suppressed during sleep. Myoclonic jerks in patients with juvenile myoclonic epilepsy occur shortly after awaking.

Nocturnal leg cramps are painful involuntary muscle contractions, usually of muscles gastrocnemius and soleus. Cramps are mostly relived by dorsiflexion of the foot. The condition is not associated with restlessness. Although leg cramps can be easily differentiated from RLS clinically, they represent a major confounding factor in epidemiologic studies because patients with nocturnal leg cramps are likely to answer positively diagnostic criteria of the International Restless Legs Syndrome Study Group Rating Scale (Kryger et al., 2005).

Positional discomfort occurs when the limbs are in one position for a longer period due to a pressure that compresses nerves or limits blood flow. The condition does not include an urge to move and is relieved only by a change of body position.

The pain or unpleasant sensations due to vascular or neurogenic claudication appear during a prolonged upright position or walking and disappear in rest.

Painful legs and moving toes is a rare disorder characterized by pain, typically of a neuropathic quality, in the feet or legs, associated with repetitive writhing (rotatory) movements of one or more toes. The syndrome may be unilateral or bilateral. Identical movements may occur without pain called "painless legs-moving toes ".The pathophysiology of painful legs and moving toes is not known but most reports an association with a peripheral lesion, usually at the level of the root or nerve (Reich, 2011). Pain is not worse at night and movement responsive.

"Vesper's curse" comprises lumbosacral and leg pain with calf cramps and fasciculations that arouse the patient from sleep. The pain and paresthesias are often accompanied by an inner urge to move the legs, similar to that seen in restless legs syndrome. The etiology of "Vesper's curse" is lumbar spinal stenosis with congestive heart failure. The symptoms may be relieved by assuming an erect or semi-reclining sleep position and are improved with adequate treatment of the congestive heart failure (LaBan et al., 1990).

Periodic limb movements (PLMS) are experienced by majority or RLS patients. But PLMS are nonspecific; occurring also in other sleep disorders such as obstructive sleep apnea or narcolepsy, or accompanying other conditions such as essential hypertension, end-stage renal disease and alcohol dependency. There is also increase in PLMS in patients treated with psychoactive substances like lithium, clomipramine, fluoxetine or venlafaxine. Periodic limb movements without RLS symptoms do not require treatment unless sleep is compromised with the consequences of insomnia or daytime sleepiness. Nevertheless, increasing attention is paid to autonomic consequences of periodic limb movements. If fatigue or insomnia are present due to increased periodic limb movements index, a diagnosis of periodic limb movements disorder can be made. Generally, all medications that are helpful for RLS seem to be effective in periodic limb movements disorder.

9. Consequences of restless legs syndrome

9.1 Sleep consequences of restless legs syndrome

The clinical observation that insomnia is a prominent consequence of untreated RLS has been confirmed by many studies. About 50% - 85% of RLS patients have insomnia. The frequency of insomnia complaint is significantly higher in RLS then in controls with odds ratios between 1,7 and 3,5 (Earley and Silber, 2010). 27,9% to 69,2% of restless legs patients reported having difficulty initiating sleep, 24% to 50,5% reported having difficulty maintaining sleep. Non-restorative sleep was more seldom, but appeared to be at least twice more frequent in RLS (Ohayon et al., 2012).

When patients were asked about the propensity to sleep during periods of wakefulness, RLS patients were two to three times more likely report excessive sleepiness. Between 32% and 42% of RLS patients complained of excessive sleepiness. However, assessment of excessive daytime sleepiness using the Epworth sleepiness scale revealed conflicting results. Three studies did not find any significant differences between RLS and non-RLS subjects, whereas three another studies found RLS patients had significantly higher scores (Ohayon et al., 2012). The relatively modest degree of sleepiness is not, however, concordant with the profound sleep loss and insomnia reported by these patients.

9.2 Mental consequences of restless legs syndrome

Several population-based studies have reported strong association between RLS and psychiatric conditions such as depression and anxiety (Picchietti and Winkelman, 2005). Lee et al. (2008) reported a strong association between RLS and DSM-IV major depressive disorder (OR 4.7) and panic disorder (OR 12.9) in the previous 12 months based on structured psychiatric interviews on 1,071 residents. In Winkelman´s et al. (2005) study, RLS patients had higher risk among other of generalized anxiety disorder (OR 3,66). Severe sleep disturbance due to the nightly occurrence of RLS symptoms may substantially contribute to the emergence of psychiatric symptoms. The treatment of depression in RLS has some unique aspects, as several antidepressants have been reported to trigger or worsen RLS. In patients with co-morbid moderate/severe depression, antidepressant therapy (bupropion) in parallel with or shortly after commencing RLS treatment is usually necessary. Data from recent trials with dopamine receptor agonists indicate that mild to moderate depressive symptoms are often relieved with improvement of RLS symptoms (Hornyak, 2010).

Cognitive functions are likely to be impaired in RLS, especially in those with frequent disease. RLS patients performed worse than controls in the area of attention and verbal fluency, and performance in these tasks was associated with RLS severity, sleep quality, depression scores, and memory (Fulda et al., 2010). The cognitive deficit seen with RLS may result from fragmented sleep and sleep loss. In contrast, RLS subjects may show a relative degree of sleep loss adaptation. A study comparing RLS patients with chronically partial sleep deprived healthy subjects found that RLS performed even better than the sleep restricted controls in two tasks particularly sensitive to sleep loss (Gamaldo et al., 2008).

9.3 Somatic consequences of restless legs syndrome

Several medical conditions can be associated with RLS. According to epidemiological studies, the general health status is poorer then in individuals without RLS (Ohayon et al., 2012).

Cardiovascular disease and heart problems were associated with RLS in many studies; people with cardiovascular diseases are twice as likely to have RLS as those without heart problems. On the other hand, risk of cardiovascular disease is increased in RLS population. In the Wisconsin Sleep Cohort study, the RLS group with daily symptoms (but not those with less frequent symptoms) had a significantly increased risk (OR 2,58) of cardiovascular disease in comparison with people without RLS (Winkelman et al., 2006). In the Sleep Heart Health Study, higher risk of cardiovascular disease (OR 2,07) was found in RLS population. Patients with symptoms occurring more than half a month and with severe symptoms had the highest risk for coronary artery disease or cerebrovascular disease (Winkelman et al., 2008a). An explanation might be the finding that periodic limb movements are associated with an increase in blood pressure and periodic limb movements that occur with microarousals had a greater increase in blood pressure than those without microarousals (Pennestri et al., 2007). Periodic limb movements trough their effect on hypertension may lead to increased risk for cardiovascular disease.

There are many other diseases associated with RLS, but they are rather a cause of secondary RLS than its consequence.

10. Treatment

10.1 Nonpharmacological treatment

Patients should maintain good sleep hygiene to prevent sleep deprivation which may increase RLS symptoms. It seems that caffeine, nicotine and alcohol, especially consumed in the evening, aggravate the symptoms. Some patients have noticed that eating refined carbohydrates seems to worsen their RLS symptoms. A diet with restriction of refined carbohydrates may be therefore useful for them. Moderate exercise has been suggested to help RLS symptoms, whereas excessive exercise worsens RLS (Kryger et al., 2005) (Hening, 2007). There are also some behavioral strategies shared with RLS patients that may alleviate symptoms. These strategies includes walking and stretching of legs, cold or less often hot bath, relaxation exercise such as yoga or meditation, massaging of legs, especially deep pressure massage, use of rocking chairs, sleeping in cold temperatures, daily schedules with shift of activities such as housekeeping, cooking as well as work activities in late evening hours.

Some types of medication are known to aggravate RLS symptoms. Dopamine blockers such as neuroleptics but also antiemetics or prokinetics provoke RLS symptoms. Sedatives and antihistaminics (diphenhydramine) as well as antidepressants, especially tricycles, SSRIs

and mirtazapine can also worsen RLS. This medication should be when possible avoiding in RLS patients.

10.2 Pharmacologic treatments

Most patients with moderate or severe RLS require medication to make symptoms tolerable. Patients with intermittent symptoms are usually managed by medication taken on-need basis. Frequent symptoms require medication on daily basis.

Dopaminergic medication

In patients with a moderate to severe symptoms, dopaminergic therapy is the therapy of the first choice (Trenkwalder and Paulus, 2005).

10.2.1 Levodopa

L-dopa given with dopa-decarboxylase inhibitor, either benserazide or carbidopa was introduced as treatment first. A usual dosage is 50 – 100mg of L-dopa given in the evening before the start of symptoms. L-dopa is given in regular release or sustained release tablets. L-dopa has a short half-life; therefore some patients need a second dosage during the night or usage of sustained release tablets. It has been proven in several studies that a standard dosage of L-dopa markedly improved RLS symptoms resulting in improved sleep quality as assessed by subjective rating, polysomnography and actigraphy with reduced sleep latency, improved sleep efficiency, a prolonged total sleep time and less nocturnal awaking. The amount of PLMs was significantly reduced (Brodeur et al., 1988) (Trenkwalder et al., 1995). A long term benefit of L-dopa was also investigated (Von Scheele and Kempi, 1990).

Side effects include gastrointestinal discomfort, nausea, vomiting, headache, orthostatic hypotension, hallucinations, insomnia and daytime sleepiness. Because patients with RLS use much lower doses than patients who have Parkinson's disease, the typical severe side effects as dyskinesias or psychosis are very rare in RLS patients. However, there are two another specific side effects: morning rebound and augmentation.

Morning rebound is characterized by presence of RLS symptoms generally late at night or in the morning as a consequence of evening or nighttime treatment. Rebound phenomenon is consequence of decrease in the L-dopa levels. Rebound phenomenon can be settled by a next L-dopa dosage or use of sustained release forms.

Augmentation is defined as paradoxical worsening of RLS during dopamine treatment. The symptoms spread on other parts of the body, occur earlier in the day compared to the

therapy start or persist 24 hours. The severity of symptoms increases and the symptoms appear with shorter latency or immediately after rest (Allen and Early, 1996).

Formal diagnostic criteria of augmentation have been published (Garcia – Borreguero et al., 2007). These criteria are:

A Basic features – all of them need to be met

- the increase in symptoms severity experienced on 5 out of 7 days during the previous week
- the increase in symptoms severity not accounted for by other factors, such as change in medical status, lifestyle, or the natural progression of the disorder
- it is assumed that there have been a prior positive response to treatment

In addition to A, either B or C (or both) need to be satisfied:

B persisting (although not immediate) paradoxical response to treatment: RLS symptoms severity increases some time after a dose increase and improves some time after a dose decrease

C earlier onset of symptoms

- an earlier onset by at least 4 hours OR
- an earlier onset (between 2 and 4 hours) occurs with one of the following compared with symptom status before treatment:
  - shorter latency to symptoms when at rest
  - extension of symptoms to other body parts
  - greater intensity of symptoms or increase in PLMS if measured by PSG or the SIT
  - shorter duration of relieve from treatment

Augmentation is seen with different frequencies in patients treated with levodopa and less frequently in patients treated with dopamine agonists. There are also articles reporting the augmentation by tramadol (Earley and Allen, 2006). More severe symptoms of RLS and higher dosages of L-dopa are associated with higher risk for development of augmentation.

The mechanism of augmentation is still unclear, although it has been proposed that augmentation may be related due to a relative overstimulation of dopamine D1 receptors, caused by a selective degradation of D2 receptors in a hyperdopaminergic state (Paulus and Trenkwalder, 2006). Iron deficiency may be a key predisposing factor of developing augmentation by causing a reduced function of the dopaminergic transporter (Trenkwalder et al., 2008a).

10.2.2 Dopamine receptor agonists

Dopamine receptor agonists should be considered as drugs of first choice in moderate to severe RLS. Dopamine receptor agonists are effective in not only relieving symptoms but also actually decrease the number of periodic leg movements at night. Cabergoline and pramipexole showed larger efficacy compared to levodopa in some outcomes (Scholz et al., 2011). Compared with levodopa, dopamine receptor agonists have longer half-lives.

Ergoline derivates such as bromocriptine, pergolid, lisurid and cabergolide are of less importance nowadays. Ergot-derivative dopamine receptor agonists' treatment is associated with clinically important heart valvular abnormalities. Retroperitoneal and pulmonal fibrosis have also been described (Mathis, 2005). Pregolid has been therefore withdrawn from the U. S. market. It is advised to monitor cardiac functions during the treatment with ergoline derivates (Simonis et al., 2007). Other side effects include nausea and orthostatic hypotension.

Bromocriptine seemed to be less effective than the other dopamine receptor agonists and is frequently associated with severe adverse effects (Stiasny et al., 2002). Cabergoline has the advantage of highly sustained action, with half-live of 65 hours and may cause less augmentation during treatment (Stiasny-Kloster at al 2004). It can be given once daily to cover both, daytime and nighttime symptoms. Lisurid may have an antagonistic action at the serotonin 5HT2B receptors, which is believed to negate the tendency to produce cardiac valvulopathies (Antonini and Poewe, 2007).

Nonergoline derivates such as ropinirol and pramipexol are the most commonly used treatment. They have generally been preferred to ergot agonists due to a lower risk of side effects. Rotigotine is used in a form of transdermal skin patch. Non-ergot dopamine receptor agonists are highly effective, demonstrated by many multicentre placebo controlled trials (Oertel et al., 2007) (Trenkwalder et al., 2004). They require slow titration to reach the effective dose. The most common side effect is nausea. Dizziness, fatigue, nasal stuffiness and insomnia are reported too. Rotigotin is associated with skin reactions to the patch. Dopamine receptor agonists are less likely to produce augmentation or rebound, and can be of benefit in patients treated with levodopa who develop these complications.

Impulse control disorders are a further potential complication of dopaminergic therapy. These disorders include gambling, compulsive shopping, hypersexuality, punding and compulsive eating. Impulse control disorders have been reported in 7% - 17% of patients with RLS using dopaminergic medication (Driver-Dunckley et al., 2007) (Cornelius et al., 2010). The

symptoms are seen also in patients with very low doses of dopaminergic receptor agonists. The symptoms commenced a mean of 9,5 months after initiation of treatment. The disorder resolved spontaneously or improved significantly within weeks after treatment discontinuation. A functional magnetic resonance study showed changes in ventral striatum response to a gambling task when RLS patients took dopaminergic medication (Abler et al., 2009). A genetic vulnerability might underlay.

10.2.3 Opioids

Opioids are mostly prescribed to patients with severe disease, especially if patients do not respond to dopaminergic treatment. Opioids are also useful during withdrawal from dopaminergic agents in patients with augmentation.

Low potency agents such as propoxyphene, codeine and tramadol may be effective in milder symptoms, while high potency agents such as oxycodon and methadone are recommended in severe affected, refractory patients (Earley and Silber, 2010). Tramadol is active on both, opioids and serotonin systems and the only one non-dopaminergic agent reported to induce augmentation (Earley and Allen, 2006).

Although opioids treatment of RLS is without much risk for addiction, patient should be monitored for possible development of dependence. Patients with long-term treatment should be monitored also for development of respiratory problems (Walters et al., 2001). Other side effects include nausea, sedation, itch, urinary retention and constipation.

10.2.4 Antiepileptics

Antiepileptics are useful second line treatment options, especially in patients with pain symptoms. Carbamazepin was the first antiepileptics to be studied. Currently, it is not often used due to its side effects. Gabapentin is well tolerated, efficacious agent for the treatment of RLS. Less serious adverse effects are fairly common and older patients may experience dizziness, somnolence, and peripheral edema. Side effects may be dose dependent. Valproic acid in a sustained release formulation has been shown to be effective in some cases, but its use is also restricted due to side effects. Topiramate has been shown to be effective in one prospective study; however the third of patients dropped out of the study because of paresthesia. There are some anecdotic reports using lamotrigine in RLS (Trenkwalder et al., 2008b).

10.2.5 Benzodiazepines and hypnotics

Benzodiazepines are used for restless legs syndrome for a long time, however there are only few small controlled trials. Benzodiazepines are effective in inducing sleep rather than directly relieving the primary symptoms of RLS (Earley and Silber, 2010). Clonazepam is probably the most often used. The main side effects associated with this drug group are respiratory depression, gait unsteadiness with falls in the elderly, cognitive impairment and risk of dependence. One study reported total remission of RLS symptoms within 5 days during the treatment with zolpidem (Bezerra and Martinez, 2002). Zolpidem may cause amnestic reactions and episodes of parasomnia. There is also risk of dependency.

10.2.6 Iron

Oral iron administration is recommended when ferritin levels are less than 45 – 50 µg/L. There are only two small trials on oral iron therapy in RLS with conflicting results (Davis et al., 2000) (O'Keeffe et al., 1994). One study have shown improvement, whereas the other no significant effect. The second study included a substantial segment of patients who were iron deficient. This study raises the possibility that oral iron may be an effective treatment for RLS patients with some degree of iron deficiency. Patients receiving regular iron therapy require monitoring of their iron levels to avoid iron overload. Gastrointestinal side effects are common. Intravenous iron therapy with iron dextran might be effective. Three studies have shown intravenous iron dextran to be efficacious for the treatment of RLS (Trenkwalder et al., 2008a). Interestingly, two studies of intravenous iron sucrose failed to demonstrate significant benefit (Earley and Silber, 2010). Patients receiving regular iron therapy require monitoring of their iron levels to avoid toxic iron load. In addition, with the dextran formulation there is the risk of an anaphylactoid reaction. The risk is higher in those with preexisting autoimmune or rheumatoid disorders.

Other

One prospective open-label case series examined the efficacy of oral amantadine with improvement in 50% patients. However, up to one-third of those receiving amantadine may have central nervous system adverse effects. One study using clonidine demonstrated selective benefit of RLS symptoms at bedtime. There is also one case series reporting improvement of RLS symptoms with the folic acid treatment and one with magnesium.

1. Glucose metabolism

Glucose is the primary source of energy for many tissues and in normal circumstances the only energy source for brain. The brain is unable to store glucose in form of glycogen and depends entirely on glucose via the circulation. Blood levels of glucose are therefore tightly regulated. Glucose homeostasis depends on the balance between glucose production by the liver and glucose utilization by insulin-dependent tissues, such as muscles and fat, and non-insulin dependent tissues, such as the brain. Glucose homeostasis is controlled primarily by insulin, an anabolic hormone produce by the pancreas in response to rising levels of blood glucose, typically after eating. Several catabolic hormones oppose the effect of insulin (glucagon, catecholamines, cortisol, growth hormone). After carbohydrate ingestion, insulin rapidly promotes glucose uptake by issues dependent on insulin to absorb glucose from the circulation and suppresses the release of glucose by liver by stopping the conversion of glycogen to glucose (Morselli et al., 2012).

Glucose homeostasis is therefore dependent on the ability of pancreatic beta cells to release insulin actually and in sustained fashion and on the ability of insulin to inhibit hepatic glucose production and to promote glucose disposal by peripheral tissues (insulin sensitivity). Reduced insulin sensitivity, called insulin resistance, occurs when higher levels of insulin are needed to reduce blood glucose levels after administration of the same amount of glucose (Morselli et al., 2012). Glucose tolerance refers to the ability to metabolize exogenous glucose and return to baseline normoglycemia.

In clinical setting, glucose tolerance is assessed by an oral glucose tolerance test (OGTT). OGTT consists of ingesting a glucose solution and measuring glucose levels at specific intervals during next 2 hours.

2. Glucose metabolism and sleep

2.1 Glucose metabolism and physiologic sleep

Glucose and insulin levels are influenced by endogenous circadian component and by sleep. Human sleep consolidated in a single 7 to 9 hour period implies that an extended period of fast must be maintained overnight. In normal subjects blood glucose levels remain stable or fall only minimally despite the extended fast overnight. Whereas in subjects awake fasting without any physical activity, glucose levels fall by an average 10-20 mg/dl over 12-hour period. Thus a number of mechanisms operative during nocturnal sleep must intervene to maintain stable glucose levels during the overnight fasting (Van Cauter et al., 1997).

In healthy subjects, glucose tolerance varies according the time of the day. Reponses to exogenous glucose are markedly higher in the afternoon and in the evening than in the morning. The term “afternoon diabetes” was coined to describe this phenomenon. There is good evidence to indicate that reduced glucose utilization, decreased insulin sensitivity, and inappropriately low insulin secretion are involved in causing decreased glucose tolerance in the later part of the day. There are no data to support a role for variations in glucose production (Van Cauter et al., 1997). Decreased glucose tolerance is also associated with both, nocturnal and daytime sleep. Glucose tolerance minimum is in the middle of the night. Overall glucose utilization is greatest during wake and lowest during non-REM sleep stages 2 and 3 + 4. Intermediate levels are then measured during REM sleep (Scheen et al., 1996).

In the first half of the night, glucose metabolism is slower, due to the predominance of slow wave sleep that is associated with 30- 40 % reduction in cerebral glucose uptake relative to waking or REM sleep (Nofzinger et al., 2002) (Boyle et al., 1994). This leads to increase in plasma glucose, followed by a more then 50% increase in insulin secretion. It is estimated that about two-thirds of fall in glucose utilization during the first half of the night is due to decrease in brain glucose metabolism related to SWS. The rest of fall in glucose uptake reflects most probably decreased peripheral utilization. To this decrease in peripheral utilization of glucose contributes diminished muscle tone during sleep and a pulse of insulin-antagonist, sleep-onset growth hormone (Møller et al., 1990).

During the second part of the night, glucose tolerance begins to improve and glucose levels progressively decrease toward morning. This increased insulin sensitivity reflects an increase in glucose uptake. This is partially due to increase in REM sleep (Scheen et al., 1996). The hypoglycemic activity of previously secreted insulin during the early sleep contributes to the decline. Moreover, this may also be a delayed effect of low cortisol levels during the first part of the night (Plat et al., 1996).

Studies of nighttime glucose tolerance during sleep used intravenous glucose infusion at a constant rate or continuous enteral nutrition and have sampled glucose and insulin without awakening the subjects.

2.2 Glucose metabolism and impaired sleep

2.2.1 Partial sleep deprivation

Partial sleep deprivation studies simulate the voluntary sleep curtailment which has become increasingly common. The first study using the paradigm of partial sleep deprivation wa the famous trail by Spiegel et al. (1999). In this experiment, healthy young men were subjected

to 6 nights of 4 hours in bed followed by 7 nights of 12 hours in bed. Examination of glucose metabolism included intravenous glucose tolerance test in the end of each bedtime condition followed by a 24-hour period of blood sampling with standardized meals. Glucose tolerance was lower in the sleep debt condition than in rested (after recovery) condition. Glucose tolerance after the partial sleep deprivation was decreased by more than 40% and reached values typical for older adults with impaired glucose tolerance. Glucose effectiveness (a measure of non-insulin dependent glucose disposal) and the acute insulin response to glucose were 30% lower.

The disposition index (DI), the product of glucose effectiveness and acute insulin response to glucose, provides an estimate of beta cell function relative to prevailing level of insulin resistance. It is a validated marker of diabetic risk (Lyssenko et al., 2005). In healthy subjects, insulin resistance is accompanied by compensatory hyperinsulinemia, which in turn maintains a constant DI. Thus low DI values represent a higher risk of type II diabetes; DI values under 1000 indicate a high risk of diabetes (Xiang et al., 2006). In the abovementioned study, in sleep debt condition, the DI was 40% lower than after sleep recovery. Moreover, 3 of the 11 probands had DI values under 1000.

These findings were confirmed by another study using hyperinsulinemic-euglycemic clamp, a gold standard method for insulin sensitivity determination (Buxton et al., 2010). Glucose metabolism was assessed after 7-8 nights of 10 hours bedtime and after 6-7 nights of 4 hours bedtime. Intravenous glucose tolerance test-derived insulin sensitivity was reduced, without significant alterations in the insulin secretory response. Similarly, insulin sensitivity assessed by clamp was reduced after sleep restriction. Glucose tolerance and the disposition index were reduced by sleep restriction too.

Effect of partial sleep deprivation on glucose metabolism was evaluated by eleven other studies, involving young and middle-aged women and men. Most of them reported impaired insulin sensitivity and a part of them observed beta cell dysfunction. There are also three negative studies, but these have used a more moderate sleep restriction paradigm (5,75 and 6,5 hours in average) or methods of insulin sensitivity quantification with lower sensitivity (Morselli et al., 2012).

The mechanism underlying alterations in glucose metabolism following partial sleep deprivation are likely to be multifactorial. Brain is a major site of non-insulin-dependent glucose uptake; therefore the decrease in glucose effectiveness might reflect decreased

brain utilization. This is consistent with PET studies that have shown reduced brain glucose utilization in sleep deprived probands (Thomas et al., 2000).

Pancreatic beta cell function is influenced by autonomic nervous activity, with sympathetic activation inhibiting and parasympathetic activation stimulating insulin release. The lack of compensatory hyperinsulinemia in response to reduced insulin sensitivity associated with sleep loss may therefore be related to an alteration of the autonomic regulation of the beta cells. During sleep restriction, cardiac sympathovagal balance, derived from estimations of heart rate variability, is elevated. This likely reflects an increased sympathetic tone (Siegel et al., 2004).

Disturbances in the secretory profiles of the counter-regulatory hormones, GH and cortisol, may also contribute to the alterations in glucose regulation observed during sleep loss. Sleep restriction is associated with extended duration of elevated nighttime GH concentrations (Spiegel et al., 2000) and with increase in evening cortisol levels (Spiegel et al., 1999). An extended exposure of peripheral tissues to higher GH levels may induce a rapid decrease in muscular glucose uptake. Elevated evening cortisol levels may result in reduced insulin sensitivity on the following morning (Van Cauter et al., 1997).

Besides that, acute sleep loss is associated with increase of proinflammatory cytokines, a low grade inflammation, which are known to predispose to insulin resistance and diabetes (Vgontzas et al., 2004).

2.2.2 Total sleep deprivation

Using total sleep deprivation paradigm (24 – 126 hours of forced wakefulness); six from seven studies reported deleterious impact of sleep deprivation on at least one parameter of glucose metabolism (Morselli et al., 2012). However, increased fasting glucose was reported after 120h of total sleep deprivation, but not after a single night, suggesting that fasting glucose may be sensitive only to severe total sleep deprivation. Interestingly, one study found increased postprandial insulin after recovery sleep, suggestive of decreased insulin sensitivity. Authors hypothesized that this result may be due to a delayed effect of sleep deprivation not counterbalanced by a single night of recovery sleep (Wehrens et al., 2010).

2.2.3 Sleep quality

Two studies have demonstrated that poor sleep quality without change in sleep duration impairs glucose regulation in healthy subjects. Tasali et al. (2008a) selectively suppressed SWS; SWS was reduced by nearly 90%. SWS decrease resulted in marked decreases in

insulin sensitivity without adequate compensatory increase in insulin release, leading to reduced glucose tolerance and increased diabetes risk. The magnitude of the decrease in insulin sensitivity was strongly correlated with the magnitude of the reduction in SWS. Data suggest that reduced sleep quality with low levels of SWS, as occurs in aging and in many obese individuals, may contribute to increase the risk of type 2 diabetes. Stamatakis and Punjabi (2010) fragmented sleep across all sleep stages for two nights using auditory and mechanical stimuli. Insulin sensitivity and glucose effectiveness decreased. The disposition index remained unchanged due to an increase in insulin release which was able to compensate the decrease in insulin sensitivity. Increases in sympathetic nervous system and adrenocortical activity could mediate the adverse metabolic effects of poor sleep quality.

2.2.4 Short and long sleep duration

The impact of short sleep duration on the risk of diabetes has been shown in several epidemiologic studies, with a significant increase in incidence of diabetes in individuals who have difficulty in maintaining sleep or who suffer from chronic short sleep duration (Van Cauter et al., 2008). Short sleep duration (mostly ≤ 5 or ≤ 6 hours) was found to predict a higher incidence of diabetes in seven of nine studies. Poor sleep quality was associated with an increased risk of diabetes in five of six studies. One study found stronger associations in older people (Knutson, 2010a). Most of these studies relied on self-reported sleep duration and quality, but one study used wrist actigraphy and found greater sleep fragmentation in those with type 2 diabetes compared to healthy controls but no difference in total sleep time (Trento et al., 2008).

Results from the largest study, the Nurses Health Study, found an increased risk of incident symptomatic diabetes over 10 years among those reporting sleep duration of 5 hours or less relative to 7-8h, even after controlling for many covariates (Ayas et al., 2003). Some studies also reported an association between self-reported long sleep duration (≥8 or ≥9 hours per night) and increased risk of diabetes (Knutson and Van Cauter, 2008).

Several prospective studies have examined the association between sleep duration or impaired sleep and incident diabetes. Most of these studies reported increased odds of diabetes associated with short sleep duration (≤5h and/or ≤6h) and many observed a U-shaped association. A meta-analysis of 10 prospective studies examined the association between the incidence of diabetes and either short sleep duration, long sleep duration or sleep disturbances. They found a stronger association between short sleep duration and incidence of diabetes among men. There was also a significant U-shaped association

between sleep duration and incident diabetes. Finally, both difficulty initiating sleep and difficulty maintaining sleep significantly predicted incident diabetes (Cappuccio et al., 2010a).

3. Glucose metabolism and sleep disorders

3.1 Obstructive sleep apnea

It is well-documented that obstructive sleep apnea is, independently of BMI and other confounders, associated with glucose intolerance, insulin resistance, and diabetes (Tasali et al., 2008a).

In patients with type 2 diabetes, the prevalence of obstructive sleep apnea, assessed with full night polysomnography, ranged from 58% - 86% (Morselli et al., 2012). In turn, seven of eight studies assessing the prevalence and incidence of type 2 diabetes in OSA have demonstrated a significantly higher prevalence of diabetes in patients with OSA as compared to those without OSA (Pamidi et al., 2010). Some studies have also found a significant dose-response relationship between the severity of OSA and the prevalence of diabetes (Tamura et al., 2008) (Reichmunth et al., 2005).

Aronsohn and colleagues (2010) run a study to determine the impact of OSA on hemoglobin A1c (HbA1c), the major clinical indicator of glycemic control, in patients with type 2 diabetes. They reported that increasing severity of OSA was associated with poorer glucose control, after controlling for confounders. Compared to patients without OSA, the adjusted mean HbA1c was increased by 1.49% in patients with mild OSA, 1.93% in patients with moderate OSA, and 3.69% in patients with severe OSA. These effect sizes are comparable, if not exceeding to those of widely used hypoglycemic medications, and thus support the hypothesis that reducing the severity of OSA may be an important therapeutic approach to optimize glucose control.

The respiratory disturbance index and sleep-related hypoxemia were associated with glucose intolerance and insulin resistance in Sleep Heart Health Study after controlling for confounders (Punjabi et al., 2004). A large study of 118 apneics without diabetes found that independently of adiposity, sleep disordered breathing is associated with impairments in insulin sensitivity, glucose effectiveness, and pancreatic β-cell function. These defects may increase the risk of glucose intolerance and type 2 diabetes mellitus in sleep apnea (Punjabi and Beamer, 2008). A prospective study from Germany of over 8000 non-diabetic men and women followed probands for an average 7,5 years. Authors demonstrated a significantly increased risk of incident type 2 diabetes for those who have reported difficulty in maintaining sleep at baseline (Meisinger et al., 2005).

One study has assessed the impact of exposure to intermittent hypoxia on glucose metabolism in men during wakefulness. Participants were subjected to intermittent hypoxia for 5h period, followed by an intravenous glucose tolerance test. Insulin sensitivity decreased by 15-20%; without compensation by increased beta cell release (Loius and Punjabi, 2009). There is evidence that intermittent hypoxia associated with sleep apnea increases the production of reactive oxygen species influencing the function of beta cells (Xu et al., 2009). Increased oxidative stress has been shown to be an important pathogenic mechanism of insulin resistance (Furukawa et al., 2004).

Elevated sympathetic activity and HPA axis and also release of proinflammatory cytokines are likely to be involved in the association of insulin resistance and obstructive sleep apnea. Sympathetic activation raises circulating levels of free fatty acids via stimulation of lipolysis and promotes insulin resistance (Kjeldsen et al., 1992).

The first-line therapy for obstructive sleep apnea is continuous airway pressure (CPAP). 17 out of 35 studies reported an improvement in at least one parameter of glucose homeostasis following CPAP treatment in sleep apnea patients. The parameter most consistently found to be positive impacted by CPAP treatment is glucose sensitivity. However, there were only five controlled studies among those 35. Three of them yielded positive results; whereas other two could not demonstrate benefit of CPAP on glucose metabolism (Morselli et al., 2012).

3.2 Restless legs syndrome

A study has reported the relationship between RLS and diabetes in 124 patients with type 2 diabetes. An increased prevalence of RLS in type 2 diabetic patients was found. RLS in diabetic patients showed a lower frequency of positive family history and late age of onset. In diabetic patients, polyneuropathy represented the main risk factor for RLS (Merlino et al., 2007b). Similar results found Lopes et al. (2005). RLS was found in 27% of patients with diabetes. Poor sleep quality was present in 45% of cases and excessive daytime sleepiness was found in 26% of diabetic patients.

However, another study on the same topic did not find a higher prevalence of RLS in diabetics (Skomro et al., 2001). They found that adult diabetes type 2 had higher rates of insomnia, excessive somnolence and hypnotic use than controls.

Bosco et al. (2009) performed OGTT in 32 consecutive patients with idiopathic RLS associated with normal fasting glycemia and 128 control subjects. After 2h-OGTT, the prevalence of glucose metabolism abnormalities was significantly higher in patients with RLS

than in controls. Impaired glucose tolerance was found in 41% patients and in 18% controls, while a new-diagnosed DM was found in 19% patients and in 6% controls.

3.3 Insomnia

There is one population based study of 1,741 men and women studied in the sleep laboratory by Vgontzas et al. (2009). Diabetes was defined as being medically treated for diabetes or having fasting blood glucose >126 mg/dl from blood drawn the morning after the sleep laboratory testing. The study demonstrated that chronic insomnia associated with objectively measured short sleep duration is a clinically significant risk factor for type 2 diabetes. More severe insomnia (i.e., complaint of insomnia for at least 1 year in this study) was significantly associated with higher odds of diabetes in the basic adjusted model. Most important, severe insomnia in combination with an objective sleep duration of <5 h was associated with a 300% higher odds for diabetes than the subjects who did not have a sleep complaint and slept for ≥6 h.

These findings are in line with data from experimental sleep restriction studies leading to impaired glucose tolerance (Spiegel et al., 1999). Same results revealed epidemiologic studies.

Studies on diabetes in primary insomnia are not available.

1. Hypothalamo-pituitary-adrenal axis

The hypothalamo-pituitary-adrenal (HPA) axis is the major neuroendocrine mediator of the stress response. The HPA axis represents a negative feedback loop regulating the release of cortisol. It is internally controlled mainly by circadian signals derived from connections between the hypothalamic nucleus paraventricularis (PVN) and the nucleus suprachiasmaticus (SCN). A stressful stimulus induces the release of corticotropin releasing hormone (CRH) from the medial parvocellular subdivision of the paraventricular nucleus of the hypothalamus. CRH is released into hypophysial portal vessels that access the anterior pituitary gland. CRH stimulates release of adrenocorticotropin hormone (ACTH) from the anterior pituitary into systemic circulation and subsequently initiates the liberation of glucocorticoids from the adrenal cortex from zona fasciculata. In turn cortisol feeds back onto the PVN and the pituitary to control CRH and ACTH synthesis and release. Whether feedback onto PVN and pituitary is inhibitory or excitatory depends on the type of receptor activated (high affinity mineralocorticoid receptors, MR´s, type I and low affinity glucocorticoid receptors, GR´s, type II) and on its location within the brain (Buckley and Schatzberg 2005).

The HPA axis has important excitatory reciprocal interactions with the brainstem sympathetic locus coeruleus - norepiephrine system. CRH activates locus coeruleus and norepinephrine activates both, hypothalamic CRH and the amygdala. Norepinephrine is known as wake-promoting substance (Tsigos and Chrousos 2002).

The **circadian rhythm** of cortisol secretion is characterized by a nadir at about midnight and an acrophase at about 9h. Cortisol levels begin to rise about 2-3 hours after sleep onset and continue to rise into the early waking hours. The acrophase occurs at about 9h. Afterwards, during the day, there is a gradual decrease in cortisol levels. As sleep ensues, there is a continual decrease to nadir. Within this cycle are about 15 – 18 pulses of corticotropin of various amplitudes (Buckley and Schatzberg 2005). Lesion of the SCN in rats results in the loss of corticosteroid periodicity (Moore and Eichler 1972).

The distinct circadian pattern of cortisol secretion may be driven not only by circadian oscillators, but also by metabolic factors. Nocturnal glucose administration in young healthy men significantly reduced the early morning rise in ACTH and cortisol concentrations, regardless of whether the subjects were asleep or awake, supporting the view that increasing energy demand of the brain toward the end of the night essentially contributes to the early morning peak in the HPA axis activity (Benedict et al., 2009).

In non-stressful situations CRH is secreted in a pulsatile fashion with a frequency of about two to three secretory episodes per hour (Engler et al., 1989). Under resting conditions, the amplitude of CRH pulses increases in the early morning hours. During acute stress, the amplitude of the CRH pulsations in the hypophyseal portal system is markedly increased.

Arginine vasopressin (AVP) is highly expressed in the magnocellular neurons of the PVN and in supraoptic and suprachiasmatic nuclei of the hypothalamus and is released directly into the systemic circulation. In addition, parvocellular cells of the PVN synthesize and release also arginine vasopressin into the portal circulation. There is a positive reciprocal interaction between CRH and AVP at the level of the hypothalamus, with each neuropeptide stimulating the secretion of the other. Arginine vasopressin acts synergistically with CRH as a potent stimulator of the ACTH secretion (Tsigos and Chrousos 2002). However AVP has little ACTH secretagogue activity alone (Lamberts et al., 1984). Other neuropeptides of importance that also activates CRH receptor are urocortines, members of the CRH peptide family. Urocortin I is predominantly expressed in the Edinger-Westphal nucleus, urocortin II secretion is restricted to the PVN and locus coeruleus. Urocortin III has a wider distribution in the brain, including perifornical area of the hypothalamus and amygdala (Vaughan et al., 1995).

It has been identified two **subtypes of CRH receptor**: CRH1 located in anterior pituitary and widely in the brain. CRH2 predominate in the periphery, but are also found in some brain regions (Tsigos and Chrousos 2002). The differential expression of CRH receptors (CRHRs) throughout the brain reflect the different actions that CRH exerts at the CNS level. CRH is a high-affinity ligand for CRHR1 and binds poorly to CRHR2, of which other CRH-related peptides such as urocortin II and III have higher affinity. Urocortin I binds with similar affinities to both CRHRs (Holsboer and Ising 2008). Clinical studies in humans support that stress-induced CRH actions are mediated through binding to CRHR1 (Holsboer 1999).

Cerebrospinal fluid CRH and cortisol rhythms are dissociated in the time (Kling et al., 1991). The mechanism for this is unclear, there are several theories: CRH measures in CSF may lag after production in the brain. Another explanation may be that CRH measures in CSF may represent extrahypothalamic sources (Watts et al., 2004). Finally, direct connections form the SCN to the adrenal cortex, which bypass the PVN, have been reported and may help explain the temporal dissociation between CRH and cortisol rhythms (Thorn et al., 2004).

Cortisol binds to high affinity mineralocorticoids receptors (MRs, type I) in the hippocampus that modulate the underlying circadian rhythm as well as to low affinity GRs (type II) in the hypothalamus, pituitary, cortex and elsewhere. Cortisol binds preferentially to high affinity receptors before filling low affinity receptors (Reul and Kloet 1985). The effect of MR predominates in the early nocturnal period and is most prominent at the time of nocturnal nadir (Spencer et al., 1998). The effect of GRs dominates in the morning, when cortisol levels are highest.

On ligand binding, the glucocorticoid receptors translocate into the nucleus, where they interacts as homodimers with specific glucocorticoid responsive elements within the DNA to activate appropriate hormone-responsive genes (Pratt 1990). The activated receptors also inhibit, through protein – protein interactions, other transcription factors, such as c-jun/c-fos and NF-kB, which are positive regulators of the transcription of several genes involved in the activation and growth of immune and other cells (Scheinman et al., 1995). Glucocorticoids change the stability of the messenger RNAs and hence the translation of several glucocorticoid-responsive proteins, as well as electrical potential of neuronal cells.

In a wider sense, the HPA axis belongs to a more complex and integrated system built by many different tissues and organs of the body as well as a great number of nuclei in the nervous system. Whereas the HPA axis exhibits a clear axial conformation, many of the molecules that constitute this axis, for instance CRH, AVP, ACTH, glucocorticoids, and all their receptors, are widely expressed throughout the brain and in a myriad of cells, tissues, and organs of the periphery. All of these molecules maintain a close anatomical and functional cross-communication that establishes an intricate network where every molecular member has additive, synergistic, and complementary, as well as overlapping and compensatory functions over other members of the network (de Kloet et al., 2005).

2. HPA axis and sleep

2.1 Effects of HPA hormones administration on sleep

There is a long-standing evidence of reciprocal interactions between the HPA system and sleep regulation.

2.1.1 Corticotropin releasing hormone

CRH can be produced in response to stress, as well as in response to SCN-mediated input. CRH has thus an arousing and waking effect even in absence of stress (Chang and Opp 2001). Exogenous CRH has been shown to increase EEG frequency, light sleep and awakenings and to decrease the amount of slow wave sleep (Holsboer et al., 1988) (Ehlers

et al., 1986). Animal data supported the hypothesis that CRH promotes REM sleep (Marrosu et al., 1990) (Gonzales and Valatx 1998), on the contrary in the human studies CRH was found to suppress REM sleep (Holsboer et al., 1988). Surprisingly, a study examining the effect of continuous nocturnal infusion of CRH on sleep did not find any influence on sleep (Born et al., 1989). Therefore time of administration, doses and way of the administration (single dose, pulsatile, continuous) may play an important role. The responsiveness of sleep EEG to CRH appears to increase during ageing, since sleep disruption with CRH is more pronounced in middle aged subjects, whereas in young men sleep EEG remained unchanged after a single dose of ovine CRH (Vgontzas et al., 2001a). Treatment of patients with depression with CRH 1 receptor antagonist NBI30775 induced a normalization of sleep EEG changes. SWS increased, REM density and the number of the awakenings decreased (Steiger et al., 2002).

2.1.2 Adrenocorticotropin hormone

Nocturnal infusions of ACTH suppressed REM sleep in normal controls (Born et al., 1981) (Gillin et al., 1974). Synthetic ACTH analogue ebiratide, which does not influence peripheral hormone secretion, induces sleep EEG changes that correspond to a general CNS activation. REM sleep, GH and cortisol levels remain unchanged (Steiger et al., 1991).

2.1.3 Corticoids

Studies focusing on the direct effects of glucocorticoids have shown dose dependent actions. Dosage of glucocorticoid influences the type of receptor activated. High affinity mineralocorticoid receptors are predominantly occupied at lower dosages of the steroid, greater occupancy of the low affinity glucocorticoid receptors is seen at higher dosages (Reul and de Kloet 1985).

Low doses of hydrocortisone decreased wakefulness and increased SWS amount in rat, whereas high doses of hydrocortisone increased wakefulness and decreased SWS amount in rat (Vazquez Palacios et al., 2001) (Bradbury et al., 1998). Same effect was observed in humans. After cortisol administration increased SWS, decreased REM and increased GH in healthy men, as well as in the elderly (Bohlhalter et al., 1997) (Friess et al., 1994). A study in depressed patients found increased duration and intensity of SWS after hourly injected cortisol, particularly in male patients, and stimulated GH release, while REM sleep parameters were not affected by the infusion (Schmidt et al., 2008). In contrast, low doses of the synthetic glucocorticoid dexamethasone reduced both SWS and REM sleep (Born et al., 1991). Dexamethasone binds in fact selectively to GR's at the level of the pituitary and produce direct negative feedback on subsequent ACTH (Born et al., 1991).

Subchronic treatment with GR agonist methylprednisolone of females with multiple sclerosis induced shortened REM latency, increased REM density, a decrease in the SWS and delta sleep ratio and a decrease in sigma EEG activity. These changes resemble the sleep aberrances in depression (Antonijevic and Steiger 2003).

Mifepristone is a mixed GR and progesterone receptor antagonist. It increased ACTH and cortisol levels and disrupted sleep quality with increased sleep latency, wake after sleep onset and decreased SWS and REM sleep (Wiedemann et al., 1994).

The effect of endogenous and exogenous cortisol on sleep depends on optimal cortisol levels to effect maximal nocturnal CRH suppression. Both, type of receptor activated and the location of receptor activated influence CRH and ultimately the sleep. MRs mediate PVN inhibition, particularly via the hippocampus, but also via the amygdala and enhance the CRH suppression (Friess et al., 2004) (Friess et al., 1994) (Born et al., 1989). Higher levels of corticoid would additionally occupy GRs, which could exert either inhibitory (via the PVN) or excitatory (via the amygdala) feedback on CRH, depending on the location of the receptor activated (Buckley and Schatzberg 2005).

Decease of SWS at high doses, where GRs are fully occupied, may reflect an overriding effect of excess GR activation at the level of the amygdala. GR activation in the amygdala, opposite to its inhibitory action at the PVN and anterior pituitary, occurs at very high doses of cortisol and at times of stress and may exert a positive feedback effect on the PVN CRH (Reul and Holsboer 2002). It might also reflect a direct inhibitory effect of excess GR on colocalized MR, thereby a limiting MR-mediated inhibition on the PVN CRH (Buckley and Schatzberg 2005).

2.2 Effects of sleep on HPA hormones

In turn, sleep and experimental sleep deprivation have modulatory effects on the HPA system.

2.2.1 Sleep onset

The pattern of cortisol secretion is widely dependent on a circadian rhythm, whereas the manipulation of the sleep – wake schedule prompts subtle changes in HPA secretion (Weitzman 1976). Sleep onset exerts a modest inhibitory effect on cortisol profile. Under free running condition, sleep was generally initiated at a later phase of the endogenous circadian cortisol rhythm (phase advance). Cortisol was secreted in large amounts prior to sleep onset. Immediately after sleep onset, cortisol dropped sharply for next 2-3 hours (Van Cauter and

Refetoff 1985). A study comparing nighttime sleep and daytime sleep during the peak of corticotropin activity found a transient decrease in cortisol levels at the time of sleep onset (Weibel et al., 1995).

2.2.2 Nocturnal awakenings

Nocturnal awakenings are consistently associated with pulsatile releases of cortisol, followed by temporary inhibition of cortisol secretion. It was hypothesized that sleep attenuates negative feedback inhibition within the HPA system, whereas wakefulness or stage 1 sleep reflects increased feedback sensitivity of this system. However, sustained sleep disruption does not enhance cortisol secretion (Späth-Schwalbe et al., 1991). Final morning awakening elicits a rapid and marked rise in cortisol levels, augmenting the circadian acrophase of cortisol concentrations, but in contrast to nocturnal awakenings persists for one hour. This period is termed awakening response. It is detectable independently of the mode of awakening (naturally or induced) (Pruessner et al., 1997). Anticipation of awakening at a certain time can augment the early morning rise of cortisol that occurs before awakening (Born at al 1999).

2.2.3 Slow wave sleep

A temporal association between low cortisol levels and high SWS has been demonstrated. The inhibitory effect that sleep onset seems to exert on the HPA axis have been attributed to SWS. Cortisol levels have been shown to decrease in the first 20 minutes after the onset of SWS (Follenius et al., 1992). Responses of ACTH and cortisol to CRH stimulation in healthy men were blunted during SWS in the early part of sleep (Späth – Schwalbe et al., 1993). Some authors have hypothesized that the growth hormone releasing hormone (GHRH) secreted during SWS exerts an inhibitory effect on corticotropic activity (Steiger et al., 1992). Other authors have questioned the direction of the inverse link found between cortisol and SWS. They suggested that a decreased HPA activity may promote sleep deepening and that increasing cortisol levels may prevent the occurrence of SWS (Weibel et al., 1995). Gonfrier et al. (1997) examined the connection between cortisol secretion and slow wave activity (SWA), the spectral power in lower frequency range (0,5 – 4,5 Hz) considered as a stable trait dependent marker of the intensity of SWS. For the period of pulsatile cortisol secretion, an inverse relationship was found with the delta band. Variations in cortisol secretory rates coincided with or anticipated opposite variations in delta wave activity by 10 or 20 minutes.

2.2.4 Rapid eye movements sleep

An association between REM and periods of decreasing cortisol levels has been reported. Rapid eye movement sleep was found to be primarily present when cortisol concentrations

were decreasing, indicating a diminished or absent secretory activity of the adrenals at that time. However, REM sleep may persist after cortisol increases again (Frollenius et al., 1992) (Born et al., 1986). In a study investigating changes in sleep duration and quality from young adulthood to old age, it was observed that a decrease in amount of REM sleep occurred in synchrony with an elevation of evening cortisol levels. A trend for an association between lower amounts of REM sleep and higher evening cortisol concentrations, independently of age, was detected too (Van Cauter et al., 2000).

2.2.5 Sleep deprivation

Leproult et al. (1997) and others (Von Treuer et al., 1996) documented enhanced HPA system activity during the night of total sleep deprivation and also during the following day, especially in the afternoon and evening, in the case of prolonged wakefulness (Chapotot et al., 2001). Hence, sleep loss seems to alter negative glucocorticoid feedback regulation. Nevertheless, there are some studies which have reported either no change (Dinges et al., 1994) or even a slight decrease in cortisol levels (Kant et al., 1984) after a total sleep deprivation. A biphasic HPA response to sleep deprivation has been therefore suggested. Activation of the HPA axis as a part of the stress response may be one of the arousal mechanism of early adaptation to sleep loss. In prolonged wakefulness, the increased sleep pressure may cause a blunting of the HPA axis activity (Chapotot et al., 2001). Cortisol levels during the recovery night after a night of total sleep deprivation were also measured. In some studies cortisol levels were almost unaffected by recovery sleep (Brun et al., 1998). Vgontzas et al. (1999) found even a decrease in the secretion of cortisol during a recovery night after experimentally induced sleep disruption. Potential explanation for these inconsistent results could be the timing of the recovery sleep.

Spiegel et al. (1999) assessed the HPA axis activity and other endocrine and metabolic parameters during a subchronic sleep deprivation (4 hours of sleep in 6 consecutive nights) in healthy young men. Cortisol levels were elevated in the afternoon and in the early evening with a shorter quiescent period. The rate of decrease of free cortisol concentrations in saliva between 16.00 a 21.00 hours was six times slower in sleep-debt condition as in fully rested condition. Sleep restriction (5 h/night) for 1 week significantly elevated salivary cortisol levels (assessed between 15.00 and 21.00 h) compared with the baseline sleep-replete condition (Buxton et al., 2010). After partial sleep deprivation of 4 hours of sleep, plasma cortisol levels over the 18.00-23.00-hour period were higher and the onset of the quiescent period of cortisol secretion was delayed by at least 1 hour (Leproult et al., 1997). Moreover, chronic short sleepers were found to have higher nocturnal cortisol levels compared with chronic long sleepers (Spath Schwalbe et al., 1992).

On the other hand, there are also studies that failed to show changes in cortisol levels in partial sleep deprivation paradigm. A single night of 4 h of sleep did not alter cortisol and glucagon levels (Donga et al., 2010). Another study investigating moderate sleep restriction to 4 h for 2 consecutive days in comparison to regular sleep of 8 h per day revealed unchanged concentrations of HPA axis hormones and IL-6 (Schmid et al., 2011). In Vgontzas et al. (2004) study of modest sleep restriction from 8 h to 6 h per night for one week, sleep restriction did not significantly affect 24-h cortisol secretion in either men or women.

Methodological differences between these studies, such as delayed bedtime vs. advanced wake time, constant recumbent condition during sleep loss vs. ambulatory with physical activity, calories given intravenously in the form of glucose vs. regular meals, may explain the variance in terms of cortisol response. Also, it has been shown that upright position (Hennig et al., 2000) or the transition from dim light to bright light (Leproult et al., 2001) in the morning induces an elevation of the cortisol level (Vgontzas et al., 2004). The frequency of blood sampling may also play a role.

3. Hypothalamo-pituitary-adrenal axis and sleep disorders

Dysfunction of the HPA axis may play a causative role in some clinical sleep disorders. In other sleep disorders, HPA axis dysfunction may be secondary to the sleep disorder and may lead to secondary complications (Buckley and Schatzberg 2005).

3.1 Insomnia

There is a clear link between insomnia and perceived stress and between perceived stress and the HPA axis. Vgontzas et al. (1998) found that 24-hour urinary free cortisol excretion was positively correlated with percent stage 1 sleep and wake time after sleep onset. They concluded that, in chronic insomnia, the activity of the stress system relates positively to the degree of objective sleep disturbance. In another study (Vgontzas et al., 2001b) 24-hour plasma cortisol and ACTH profiles were collected in young insomniacs and healthy controls. Mean cortisol and ACTH levels were higher in insomniacs compare to controls. The greatest elevations were observed in the evening and first half of the night. Insomniacs with a high degree of objective sleep disturbance (% sleep time < 70%), compared with those with a low degree of sleep disturbance, secreted a higher amount of cortisol. There were no differences in the temporal pattern of ACTH or cortisol secretion between insomniacs and controls. Similarly, Rodenbeck et al. (2002) also reported increased evening and nocturnal plasma cortisol concentrations in patients with severe primary insomnia. The survey revealed a strong positive correlation between evening cortisol secretion and the number of nocturnal

awakenings in both insomniac patients and controls. Since nocturnal exposure to increased HPA activity promotes sleep fragmentation even in healthy controls, increased evening cortisol levels may be a crucial factor in inducing and maintaining sleep disturbances. A model of HPA dysregulation in insomnia was therefore proposed (Rodenbeck and Hajak, 2001). This model is based on the hyperarousal theory of insomnia and the strong correlation between evening cortisol secretion and sleep fragmentation as a pathophysiological mechanism of a vicious cycle of insomnia. In patients with long-lasting insomnia complaints were found decreased nocturnal plasma melatonin levels thereby indicating a labialization of circadian rhythm functions (Riemann et al., 2002). Taken together, the neuroendocrine dysregulation may be a contributing factor in maintaining disturbed sleep.

On the other hand, Riemann´s study (2002) did not confirm previous findings. Cortisol secretion did not differ between healthy controls and insomnia patients. Nevertheless, patients with primary insomnia were almost indistinguishable from healthy controls on the basis of their polysomnographic recordings.

Interestingly, Backhaus et al. (2004) found significantly decreased cortisol after awakening in primary insomnia. Salivary cortisol at the time of awakening correlated negatively with the subjective estimation of sleep quality. Furthermore, awakening cortisol was negatively correlated with the Pittsburgh Sleep Quality Index and with a questionnaire on sleep-related cognitions with the subscales rumination in bed and focusing on sleep-related thoughts. Authors interpreted their results as evidence for increased nocturnal cortisol secretion.

It is still matter of a debate if the activation of the HPA axis observed in some studies in insomnia is secondary to sleep loss or is a marker of increased central CRH activity. In the latter case, the elevation of the CRH tone (hyperarousal state), may be primarily responsible for the sleep disturbance and the HPA axis dysfunction a causative factor in the pathogenesis of insomnia (Vgontzas et al., 2001a). It has been shown that CRH activates locus coeruleus and norepinephrine increases EEG frequency (Buckley and Schatzberg, 2005).

3.2 Obstructive sleep apnea

Obstructive sleep apnea when untreated is connected with major sleep disturbances, such as reduced total sleep time and sleep efficiency, fragmented sleep, increased wake after sleep onset and sleep stages 1 and 2 and markedly reduced SWS and REM sleep.

Nocturnal awakenings are associated with pulsatile cortisol release (Späth Schwalbe et al., 1991) and autonomic activation. Autonomic activation is associated with increased catecholamine release as well as CHR and cortisol release (Buckley and Schatzberg, 2005). An additional activating factor could be hypoxia, able to stimulate ACTH and cortisol secretion (Basu et al., 2002). Awakenings, autonomic activation and hypoxia may lead to a hyperactivation of the HPA axis.

Activation of the HPA axis may be a risk factor of the development of metabolic syndrome in untreated OSA. There is growing evidence that OSA may represent an independent risk factor in the pathogenesis of metabolic syndrome. It is likely that an increase in sympathetic activity and hyperactivation of the HPA axis play a role in development of metabolic abnormalities associated with OSA (Coughlin et al., 2004).

Results obtained from studies in sleep disordered breathing are quite inconsistent. Some studies reported enhanced cortisol secretion (Lanfranco et al., 2003) (Bratel et al., 1999). In one study, ACTH responsiveness to CRH stimulation was even higher in obese subjects without OSA compared with obese OSA patients and lean controls (Vgontzas et al., 2007). Carneiro et al. (2008) performed overnight cortisol suppression test with obese men with OSA and obese controls. A blunted response of cortisol suppression in obese apnoics compared with obese controls was demonstrated. In other studies alterations in HPA system activity (Dadoun et al., 2007) (Entzian et al., 1996) were not found. Noteworthy, several of these studies were limited in that cortisol was measured at a single time point.

Effect of CPAP therapy on cortisol levels has been investigated too. The results are again conflicting. Some authors reported no decrease in cortisol levels (Grundstein et al., 1989), while others referred reduced cortisol levels after CPAP treatment (Schmoller et al., 2009) (Henley et al., 2009).

3.3 Restless legs syndrome

RLS symptoms appearance is in remarkable inverse temporal relationship with cortisol secretion. The strong increase in plasma cortisol around 4-5 a.m. coincides with the amelioration of RLS symptoms. Wetter and colleagues have speculated that alteration of extrastriatal dopaminergic system may involve the HPA system (Wetter et al., 2001).

Finally, four studies assessed HPA axis activity in patients with a restless legs syndrome (RLS). Wetter et al. (2001) as well as Garcia-Borreguero et al. (2004) reported normal cortisol profiles. Wetter measured cortisol plasma levels every 20 minutes for 24 hours in 10

male never medicated RLS patients with mild to moderate symptoms, whereas Garcia-Borreguero measured plasma cortisol levels at a single time point. No differences in feedback inhibition have been reported by Hornyak et al. (2008) after a low dose of hydrocortisone in the evening. But 5 of 10 patients reported an improvement of their symptoms. However, the most recent study focusing on HPA system activity in RLS patients reported enhanced nocturnal cortisol secretion levels (Schilling et al., 2010).

4. Dexamethasone suppression/corticotropin-releasing-hormone stimulation test

One specific approach to dynamically test HPA system activity is the dexamethasone suppression/corticotropin-releasing-hormone stimulation test (DEX-CRH-test), described in detail by Heuser et al. (1994). The DEX-CRH-test has been developed to study neuroendocrine abnormalities in psychiatric disorders. This test has been shown to be sensitive in documenting HPA system overactivity in affective disorders (Heuser et al., 1994) and diminished activity in post traumatic stress disorder (Yehuda 2009). The DEX-CRH test proved to be much more sensitive in detecting HPA system alterations than the dexamethasone suppression test (Ising et al., 2006). So far, the DEX-CRH-test has not been performed in sleep disorders. Due to its high sensitivity we used this test to assess HPA system functioning in the framework of a larger endocrine and metabolic study in sleep disorders.

In this test, patients are pretreated with a single dose of dexamethasone at 11 p.m. and receive CRH intravenously at 3 p.m. the following day. In normal healthy individuals pretreatment with 1,5 mg of dexamethasone prevents of a substantial release of ACTH and cortisol after additional administration of 100µg of human CRH. If the same protocol is applied to depressed patients, an increased secretion of ACTH and cortisol are observed, exceeding by far of healthy controls (Holsboer et al., 1987).

In the DEX-CRH test, dexamethasone, which does not bind to corticosteroid-binding globulins, exerts HPA suppression primarily at the level of the pituitary corticotrophs, but does not suppress hypothalamic CRH or vasopressin as effectively as endogenous corticosteroids. The subsequent decrease in cortisol and the failure of dexamethasone to compensate for decreased cortisol levels in the nervous tissue simulates the effects of a partial or transient adrenalectomy. In response, central neuropeptides that activate ACTH secretion, mainly CRH and vasopressin, are secreted. Since hypothalamic vasopressin is higher in depressed patients compared with controls, in depressed dexamethasone-pretreated patients, secretion of ACTH in response to exogenous CRH would be greater than

in controls because of the synergistic interaction of the administered CRH bolus with a large amount of vasopressin present at the corticotrophs (Sher 2006).

EXPERIMENTAL PART 1: GLUCOSE METABOLISM IN SLEEP DISORDERS

1. Methods and procedure

The study protocol was approved by the ethics committee of the Bavarian Medical Council, Munich, Germany. All subjects provided written informed consent prior to entering the study. Of 97 subjects investigated, 25 suffered from OSA, 21 from primary insomnia, 18 from RLS and 33 were healthy controls. Subjects were recruited through advertisements in local newspapers. All subjects had normal findings on medical and neurological examination. They did not show any somatic disorder and did not have any severe somatic disorder in the past. All subjects showed normal results in numerous blood tests, including a complete blood count, prothrombin time, activated partial thromboplastin time, fibrinogen, bilirubin, aspartate aminotransferase (AST/ GOT) and alanine aminotransferase (ALT/GPT), gama-glutamyltransferase (GMT/GGT), lactatdehydrogenase, cholinesterase, amylase, lipase, triglycerides, cholesterol, HDL-cholesterol, LDL-cholesterol, total protein, albumin, transferrin, ferritin, iron, C- reactive protein (CRP), thyroid stimulating hormone (TSH), free thyroxine, free triiodthyronine, cortisol levels, creatinine, urea, uric acid, potassium, sodium, calcium, chloride, magnesium, phosphate, and protein electrophoresis. The urine analysis and urine toxicology screen were obtained. Participants did not suffer from any psychiatric disorder and did not have any psychiatric disease in the past. All subjects had a regular sleep-wake cycle. Subjects showing a shift of more than 2 hours during 8 days of wrist actigraphy were excluded. Pregnant women, shift workers and persons who had travelled across multiple time zones within 3 months prior to the study were excluded. Similarly, subjects showing other sleep disorders were excluded. All subjects showed normal EEG and ECG findings during waking.

RLS patients met the diagnostic criteria defined by the International Restless Legs Syndrome Study Group (Allen et al., 2003) and did not suffer from any somatic condition known to cause secondary RLS, such as polyneuropathy. The severity of RLS was assessed using the International Restless Legs Syndrome Study Group Rating Scale (IRLS; Walters et al., 2003). In patients suffering from primary insomnia as well as in patients suffering from OSA, diagnosis was based on the International Classification of Sleep Disorders, 2nd edition (American Academy of Sleep Medicine 2005). OSA patients with an apnea-hypopnea-index (AHI) above 15 (moderate sleep apnea) were included. Controls did not suffer from any sleep disturbances, and sleep related breathing disorder was excluded (AHI > 5) by an ambulatory sleep apnea screening (Weinmann Somnocheck, Hamburg, Germany).

Before entering the study, subjects underwent a detailed screening including a physical examination, anthropometric measurements, a survey of sleep history and a detailed medical and psychiatric interview by an experienced psychiatrist including the Beck Depression Inventory (BDI; Beck et al., 1961), Hamilton Depression Scale (HAMD; Hamilton 1960) and Hamilton Anxiety Scale (HAMA; Hamilton 1959). Probands fulfilling DSM criteria of any mental disorder were excluded from the study. In addition, sleep quality was evaluated by means of the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) and daytime sleepiness using the Epworth Sleepiness Scale (ESS; Johns 1991). To verify regular sleep-wake patterns, participants were asked to wear a wrist activity monitor (Cambridge Neurotechnology, Cambridge, UK; Actiwatch Activity Analysis, Version 5.06) in connection with a sleep diary for 8 days prior to the study. In all patients standard nocturnal polysomnography (PSG) was conducted for two nights. Polysomnographic recordings were performed from 23:00 to 06:00 h including monitoring of the electroencephalography (EEG) in two derivations (C4-A1 and C3-A2), electrooculogram, submental electromyogram (EMG), the right and left anterior tibialis surface EMG, electrocardiogram (ECG), thoracic and abdominal belts, nasal airflow, finger oximetry, microphone and video monitoring. Sleep stages were scored according to Rechtschaffen & Kales (1968). Sleep stages 3 and 4 were summed up to slow-wave sleep. Arousals (American Sleep Disorder Association 1992), PLMS (American Sleep Disorder Association, 1993), and apneas/hypopneas were scored and the number of both PLMS and apneas/hypopneas per hour of total sleep time (PLMS-index and AHI, respectively) was calculated. Additionally, we calculated the number of both PLMS and apneas/hypopneas associated with arousals (PLMS-arousal-index and apnea-arousal-index, respectively). Sleep stages and associated parameters were scored by two experienced scorers in each individual.

After the first night in the sleep laboratory subjects underwent a 4-hour oral glucose tolerance test (OGTT). All OGTTs were performed at 08:00 a.m. after an overnight fast. Fasting samples to assess glucose, insulin, and HbA1c were taken at baseline. After an oral standard load of 75 g glucose, blood samples were taken at 30, 60, 120, 180 and 240 minutes. Glucose was immediately measured using the glucose oxidase method (Synchrone DXC 800 1+2, Beckmann Coulter, USA) with an inter-assay coefficient of variation (CV) of 1.0–2.2% (DXC1) and 1.4–2.2% (DXC2). Insulin samples were measured by using an ELISA (BioSource, Germany) with an inter-assay CV of 4.2%. HbA1c measurement was based on the assessment of total Hb using the colorimetric method, the A1c concentration was determined by means of the turbidimetric immuno-inhibition method (Synchrone DXC 800 1, Beckmann Coulter, USA) with a inter-assay CV of 2.9–3.2%. Standardized to the NGSP reference range was set at 4.3–5.8%.

According to the diagnostic criteria of the American Diabetes Association (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 2003) we defined:

- normal glucose tolerance (NGT). as 2-hour plasma glucose (2h-PG) concentrations < 140 mg/dl (plasma glucose concentration 2 h after an oral glucose challenge)
- impaired glucose tolerance as 2h-PG values ≥140 mg/dl
- diabetes as 2h-PG ≥ 200 mg/dl

The total areas under the curve for glucose (AUCg) and insulin (AUCi) were calculated using the linear trapezoidal rule (Wolever and Jenkins, 1986). The combination of elevated HbA1c values (> 5.5%) and impaired fasting glucose values (FPG > 100 mg/dl) was assessed as an additional risk factor for the development of type 2 diabetes, since several studies have shown that the combination of these parameters is a stronger predictor for the risk of developing type 2 diabetes than increased fasting glucose alone (Ko et al., 2000) (Inoue et al., 2008).

Insulin resistance was assessed using the homeostasis model assessment (HOMA-IR). Homeostasis model assessment (HOMA), originally described by Matthews et al. (1985), is a method for assessing beta-cell function and insulin resistance (IR) from basal (fasting) glucose and insulin or C-peptide concentrations. The model is nonlinear, but can be simply approximated. The model highly correlates with estimates assessed by euglycemic-hyperinsulinemic clamp. Two types of HOMA scores are currently used in clinical practice for determining fasting glucose and insulin levels:

Insulin resistance:
International formula:
HOMA-IR = [Fasting plasma glucose in mmol/l] * [Fasting insulin in mU/L] / 22.5

Beta-cell function:
International formula:
HOMA-Beta = 20 * [Fasting insulin in mU/L] / ([Fasting plasma glucose in mmol/l] - 3.5) %

To encompass both hepatic and peripheral insulin (primarily muscle) sensitivity we calculated a composite measure of whole body insulin sensitivity, ISI-composite or Matsuda index recommended by Matsuda and DeFronzo (1999). Index of whole-body insulin sensitivity represents the combined effect of insulin to stimulate peripheral glucose uptake and to suppress endogenous glucose production. Index correlates with the direct measure of insulin sensitivity derived from the euglycemic insulin clamp.

ISI-composite was calculated using the following formula:

$$ISI_{(Matsuda)} = \frac{10000}{\sqrt{G_0 \times I_0 \times G_{mean} \times I_{mean}}}$$

G_0 fasting plasma glucose

I_0 fasting plasma insulin

G_{mean} mean OGTT glucose concentration

I_{mean} mean OGGT insulin concentration

2. Statistical Analysis

Statistical analysis was performed using SPSS for Windows 16.0 (SPSS Inc., Chicago, Illinois). Using Gabriel- or Games Howell corrected analysis of variance (ANOVA) tests we compared the mean values of the basic characteristics age, BMI, PSQI and ESS among the four groups. Because of their skewed distribution, HbA1c, FPG, 2h-PG, fasting plasma insulin (FPI), the area under the curve for glucose (AUCg) and the area under the curve for insulin (AUCi) were z-transformed. On metabolic parameters analysis of covariance (ANCOVA) was conducted with the BMI as covariate. A chi-square test was performed to compare the incidence of IGT and/or combined elevated HbA1c and FPG values between groups. After constructing 2x2 contingency tables odds ratios (OR) were calculated. First-order partial correlation and bivariate correlation, respectively, were done to determine the association between continuous variables. $P<0.05$ was considered as statistically significant.

3. Results

The baseline characteristics for all subjects are shown in Table 1. Groups did not differ with respect to age. As expected, OSA patients had a strongly increased BMI, whereas the BMI of RLS and insomnia patients did not differ from controls. RLS patients suffered from a severe restless legs syndrome (IRLS, 22,9 ± 5,4). OSA patients were all males, yielding a statistically significant gender difference between groups. RLS and primary insomnia patients, however, did not show gender distributions different from controls. Daytime sleepiness (ESS) was highest in OSA patients and did not differ in the other patient groups from controls. In contrast, night sleep was subjectively impaired in all three patient groups compared to controls as assessed by the PSQI, and insomniacs rated their sleep significantly worse than did OSA and RLS patients.

Table 1. Baseline characteristics of study participants

	OSA	RLS	INS	CON	P-value
Females/Males	0/25 ‡ ∇	11/7	12/9	17/16	< 0.001
Age (years)	52.3 (10.8)	52.2 (13.0)	49.1 (9.7)	46.8 (7.7)	> 0.05
BMI (kg/m^2)	32.9 (5.4) ‡	25.4 (3.7)	25.0 (4.8)	24.7 (3.5)	< 0.001
PSQI	6.7 (2.8) ‡ ∇	9.3 (4.5) ‡ $^+$	13.1 (3.7) ‡	3.0 (2.0)	< 0.001
ESS	11.2 (5.6) ‡	7.9 (4.3)	6.4 (4.0)	6.8 (2.8)	< 0.001
BDI	5.4 (3.9) †	7.8 (6.0) †	8.7 (5.6) ‡	2.3 (2.5)	< 0.001
HAMD	2.2 (2.7) * ∇	4.4 (4.0) †	7.3 (2.8) ‡	0.6 (1.2)	< 0.001
HAMA	3.6 (3.3) * ∇	6.3 (5.9) *	10.24 (5.2) ‡	1.5 (1.8)	< 0.001

Data are mean (SD). Statistical comparison was done using Gabriel- or Games-Howell-corrected oneway ANOVA.

OSA, Obstructive sleep apnea; RLS, Restless legs syndrome; INS, Insomnia; CON, Controls; BMI, Body mass index; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; BDI, Becks depression inventory; HAMD, Hamilton depression scale; HAMA, Hamilton anxiety scale.

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$, vs controls

$^+$ $p < 0.05$, $p < 0.01$, ∇ $p < 0.001$, between groups

OSA: $\chi^2(1) = 18.21$, $p < 0.001$; RLS: $\chi^2(1) = 0.433$, $p > 0.05$; INS: $\chi^2(1) = 0.163$, $p > 0.05$, vs controls

OGTT data indicated that no control and no primary insomnia patient, but four OSA patients and one RLS patient suffered from diabetes. As shown in Table 2, 12% of the controls showed 2h-PG values indicating an impaired glucose tolerance. This rate was significantly increased in OSA (40%, OR 4.9) and RLS (39%, OR 4.7) patients, but not in primary insomnia (18%, OR 1.6) patients. The rate of impaired glucose tolerance within groups was not gender dependent.

Table 2. Frequency of patients with normal glucose tolerance (2h-PG ≤ 140mg/dl) or impaired glucose tolerance (2h-PG ≥ 140mg/dl)

	Total	Normal glucose tolerance	Impaired glucose tolerance	Odd ratios
	N	N (%)	N (%)	
OSA	25	15 (60)	10 (40)	4.9
RLS	18	11 (61)	7 (39)	4.7
INS	17	14 (82)	3 (18)	1.6
CON	32	28 (88)	4 (12)	

OSA, Obstructive sleep apnea; RLS, Restless legs syndrome; INS, Insomnia; CON, Controls.

$\chi^2(3) = 7.95$, $p < 0.05$.

As shown in Table 3, mean HbA1c values were in the normal range (below 5.8%), but differed significantly between groups after adjustment for the BMI. A Sidak-corrected post-hoc test based on estimated marginal means revealed that OSA as well as RLS patients had significantly higher HbA1c values than healthy controls. In both OSA and RLS patients the rate of patients displaying elevated HbA1c and FPG was significantly increased.

Table 3: Frequency of patients with normal and elevated HbA1c (≥ 5.5%) and FPG (≥ 100 mg/dl)

	Total	Normal HbA1c&FPG	Elevated HbA1c&FPG	Odd ratio
	N	N (%)	N (%)	
OSA	25	11 (44)	14(56)	20.0
RLS	17	11 (65)	6 (35)	8.5
INS	19	18 (95)	1 (5)	0.8
CON	33	31 (94)	2 (6)	

OSA, Obstructive sleep apnea; RLS, Restless legs syndrome; INS, insomnia; CON, controls; FPG, Fasting plasma glucose.
χ^2 (3) = 25.31, p < 0.001.

Accordingly, 56% of the OSA (OR 20.0) and 35% of the RLS (OR 8.5) patients belonged to the high risk group for developing type 2 diabetes. In contrast, only 5% of the insomniacs (OR 0.82) and 6% of the controls showed elevated HbA1c plus FPG levels (see Table 4).

Table 4: Metabolic parameters

	OSA	RLS	INS	CON	BMI adjusted *P* value
HbA1c (%)	5.6 (0.4) †	5.5 (0.3) †	5.3 (0.3)	5.2 (0.3)	< 0.01
FPG (mg/dl)	110.9 (15.6)	100.4 (10.1)	98.8 (8.9)	96.0 (8.0)	> 0.05
FPI (µl/ml)	16.2 (10.5)	8.7 (3.2)	10.3 (5.4)	8.9 (3.3)	> 0.05
2h-PG (mg/dl)	139.0 (55.7)	121.1 (40.8)	120.2 (17.8)	109.5 (23.5)	> 0.05
2h-PI (µl/ml)	82.5 (67.3)	60.0 (67.8)	50.6 (21.3)	36.8 (29.2)	> 0.05
AUCg(mg/dl)	31882 (7592)	28063 (5748)	28369 (3500)	25859 (4014)	> 0.05
AUCi (µl/ml)	15024 (9396)	9873 (6921)	8437 (3588)	8307 (5258)	> 0.05
HOMA1-IR	4.7 (3.8)	2.2 (1.0)	2.5 (1.3)	2.1 (0.9)	> 0.05
ISIcomposite	3.1 (1.6)	6.3 (5.4)	5.1 (1.5)	5.5 (1.9)	> 0.05

Data are mean (SD). Statistical comparison was done using ANCOVA.
OSA, Obstructive sleep apnea syndrome; RLS, Restless legs syndrome; INS, Insomnia; CON, Controls; FPG, Fasting plasma glucose; FPI, Fasting plasma insulin; 2h-PG, 2h-Postload glucose; 2h-PI, 2h-Postload insulin; AUCg, Area under the curve for glucose; HOMA1-IR, Homeostasis model assessment-1 of insulin resistance; ISIcomposite, Insulin sensitivity index composite.
* p < 0.05, † p < 0.01, ‡ p < 0.001.

Table 5. Sleep parameters

	OSA	RLS	INS	P-value
TIB (min)	437.5 (33.1)	449.2 (32.8)	435.7 (25.8)	> 0.05
TST (min)	339.0 (58.7)	345.9 (69.5)	337.3 (55.6)	> 0.05
SEI (%)	77.5 (11.8)	77.1 (14.6)	77.2 (10.8)	> 0.05
WASO (min)	75.7 (42.8)	75.3 50.1)	61.0 (35.6)	> 0.05
REM (min)	41.4 (18.5) ‡	73.0 (24.1)	70.8 (27.2)	< 0.001
S1 (min)	92.2 (40.2) ‡	41.8 (20.0)	31.3 (14.5)	< 0.001
S2 (min)	198.0 (47.9)	204.2 (47.9)	214.9 (39.5)	> 0.05
SWS (min)	7.4 (9.5) †	26.9 (29.1)	20.4 (17.5)	< 0.01
SO (min)	21.2 (20.9)	22.3 (33.2)	22.4 (19.6)	> 0.05
SLREM (min)	137.7 (68.4) *	97.5 (72.8)	86.4 (46.9)	< 0.05
SLSWS (min)	122.8 (104.9) *	67.9 (92.6)	37.3 (26.0)	< 0.05
AHI	55.7 (27.1) ‡	3.3 (3.7)	1.6 (1.6)	< 0.001
ODI	43.6 (29.7) ‡	1.9 (3.0)	1.4 (1.6)	< 0.001
PLMS-Index	19.2 (20.4)	32.5 (33.1)	5.2 (7.2) †	< 0.01
Arousal-Index	60.2 (23.4) ‡	29.6 (16.0)	24.5 (15.0)	< 0.001
PLMS-arousal-index	12.8 (14.0)	14.8 (15.3)	2.8 (4.7) †	< 0.01
Apnea-arousal-index	33.8 (25.6) ‡	0.8 (1.8)	0.3 (0.5)	< 0.001

Data are mean (SD). Mean comparison was done using Gabriel- or Games-Howell-corrected oneway ANOVA.
OSA, Obstructive sleep apnea; RLS, Restless legs syndrome; INS, Insomnia; CON, Controls; TIB, Time in bed; TST, Total sleep time; SEI, Sleep efficiency; WASO, Wake time after sleep onset; REM, Rapid eye movement sleep; S1, Stage 1 sleep; S2, Stage 2 sleep; SWS, Slow wave sleep; SO, Sleep onset latency; SLREM, REM sleep latency; SLSWS, SWS sleep latency; AHI, Apnea-hypopnea-index; ODI, Oxygen-desaturation-index; PLMS-Index, Periodic leg movements per hour of sleep; PLMS-arousal-index, PLMS associated with arousals per hour of sleep; Apnea-arousal-index, Apneas and/or hypopneas associated with arousals per hour. * $p < 0{\cdot}05$, † $p < 0{\cdot}01$, ‡ $p < 0{\cdot}001$.

Patient groups did not differ significantly in TST, sleep efficiency and WASO. OSA patients showed less SWS and REM sleep, but more stage 1 sleep than both other patients groups. Due to the selection criteria of the present study, only OSA patients showed pathological AHI and oxygen desaturation index. Mean PLMS arousal indices were in the pathological range in OSA and RLS patients, but not in insomnia patients (Table 5). Tasali et al. (2008b) have shown that SWS suppression induced by acoustic stimulation triggering repetitive microarousals leads to a decrease in insulin sensitivity. Because OSA and RLS are characterized by repeated arousals due to apneas and PLMS, we assessed whether they were related to those metabolic parameters differing between patient groups. 2h-PG values correlated positively with the apnea arousal-index ($r=0.56$, $p<0.05$) and the ODI ($r=0.59$, $p<0.05$) in OSA, and with the PLMS-arousal-index ($r=0.56$, $p<0.05$) in RLS. HbA1c correlated

positively with the apnea-arousal-index ($r=0.50$, $p<0.05$) in OSA, which was neither the case for the ODI ($r=0.46$, p.0.05), nor for the PLMS-arousal-index ($r=0.21$, $p<0.05$) in RLS. (See graphs 1-4 in Appendix)

EXPERIMENTAL PART 2: HYPOTHALAMO-PITUITARY-ADRENAL AXIS IN SLEEP DISORDERS

1. Method and procedure:

Ten days before the PSG nights took place subjects underwent the dexamethasone suppression/corticotropin-releasing-hormone stimulation test (DEX-CRH-test). This test is a dynamic test which combines suppression and stimulation of the HPA system. A week prior the test the subjects had a regular sleep wake cycle without any sleep deprivation, there were no other medical procedures, no diet, no medication or no excessive physical activity. At 23:00 subjects received a single dose of 1.5 mg dexamethasone (Fortecortin, Merck Pharma GmbH, Darmstadt, Germany). On the following day, an indwelling catheter was inserted into antecubital vein. The subjects rested in a supine position. The baseline sample, which represents the suppressive effects of dexamethasone, was drawn at 15:00. At 15:02, 100 µg human CRH (Ferring Inc., Kiel, Germany) reconstituted in 1 ml 0.02% HCl in 0.9% saline solution was infused within 30s. After hCRH infusion four blood samples were taken at 15:30; 15:45; 16:00 and at 16:15. Blood samples were stabilized with Na-EDTA (1mg/ml) and aprotinin (300kIU/ml) and centrifuged at 4C (7 min at 2600g). Plasma was aliquoted and immediately frozen to -20C. Cortisol plasma concentrations were analyzed using a radioimmunoassay kit with a coated tube technique. For ACTH measurements a dual antibody immunoradiometric assay without extraction was used.

The mean plasma hormone concentration, after dexamethasone application, but prior the CRH injection is reported as basal concentration. This concentration reflects the suppressive effect of dexamethasone. Subjects showing basal cortisol concentration ≥ 40ng/ml (e.g. 110 mmol/l) were identified as non-suppressors. The maximal hormone response after CRH administration is reported as peak value and corrected for baseline it is reported as delta. Following hCRH infusion, cortisol and ACTH responses were calculated as the area under the time course curve (AUC) using trapezoidal rule (Wolever and Jenkins, 1986). They are reported as AUC_{total} (not baseline-corrected) and AUC_{net} (baseline-corrected). Finally, adrenocortical responsivity to ACTH is assessed by calculating two pituitary-adrenal ratios (PAR; AUC_{total} ACTH / AUC_{total} cortisol values and AUC_{net} ACTH / AUC_{net} cortisol values).

2. Statistical analysis

Statistical analysis was performed using SPSS for Windows 16.0 (SPSS Inc., Chicago, Illinois). Mean comparisons of the basic characteristics such as age, BMI, PSQI, ESS, BDI, HAMD and HAMA as well as of the calculated parameters obtained by the DEX-CRH-test were done by using Gabriel- or Games-Howell-corrected analysis of variance (ANOVA) tests.

Because of their skewed distribution HAMD and HAMA were z-transformed. Chi-square tests were performed to compare the number of non-suppressors between groups. Bivariate correlations were done to determine association between selected continuous variables. $P < 0.05$ is considered as statistically significant.

3. Results

The baseline characteristics for all subjects are shown in Table 1 (shown in Glucose metabolism part). Groups did not differ with respect to age. The OSA group exclusively comprised males; however, the other groups did not differ in means of gender distribution. OSA patients had a strongly increased BMI, whereas in RLS, insomniacs and controls the BMI was comparable. Sleep disorder groups, in particular insomniacs, showed higher scores in the self-rated questionnaire BDI as well as the observer-rated questionnaires HAMD and HAMA than controls. RLS patients, on average, suffered from a severe restless legs syndrome (IRLS, 22.9 ± 5.4). All patient groups described their sleep of poor quality (PSQI) and insomniacs rated their night time sleep worse than did OSA or RLS patients. However, only OSA patients complained about increased daytime sleepiness (ESS).

Patient groups did not differ in respect to sleep efficiency and polysomnographic measured total amount of sleep or awakenings during sleep. OSA patients spent less time in SWS and REM sleep but more in stage 1 sleep compared to RLS and insomnia patients. Due to the selection criteria of the present study OSA patients showed an AHI of 55.7 (± 27.1) and an oxygen desaturation index of 43.6 (± 29.7). PLMS-arousal index was in a pathological range for RLS and OSA patients (Table 5 shown in Glucose Metabolism part).

DEX-CRH data did not indicate differences in the number of non-suppressors between patient groups and controls. 4% of OSA, 12% of RLS and 14% of insomnia patients showed elevated basal cortisol levels. In controls 9% were found to be non-suppressors (Table 3).

Table 3. Frequency of dexamethasone suppressors and non-suppressors

	Total	Suppressors	Non-suppressors
	N	**N (%)**	**N (%)**
OSA	25	24 (96)	1 (4)
RLS	18	16 (88)	2 (12)
INS	21	18 (86)	3 (14)
CON	33	30 (91)	3 (9)

Suppressors: Basal cortisol values < 40 ng/ml; Non-suppressors: Basal cortisol levels ≥ 40 ng/ml.

OSA, Obstructive sleep apnea; RLS, Restless legs syndrome; INS, Insomnia; CON, Controls.

$\chi^2(3) = 7.95$, $p > 0.05$.

In RLS patients, the levels of ACTH after HPA axis suppression by dexamethasone was significantly lower compared to healthy controls. Basal cortisol levels were comparable between groups. The amount of cortisol and ACTH released after hCRH infusion did not differ between groups. Thus, groups show similar values of peak- , DELTA- , AUC_{total} and AUC_{net} levels in cortisol- and ACTH release (Table 4 and Table 5). Furthermore no group differences in adrenocortical responsiveness to ACTH (PAR_{total}; PAR_{net}) were found (Table 4).

Table 4. Cortisol values in ng/ml obtained by the DEX-CRH test

	OSA	RLS	INS	CON	P-value
Basal	17.5 (9.0)	19.1 (11.6)	20.6 (12.8)	21.7 (16.1)	> 0.05
Peak	50.0 (46.7)	51.0 (42.3)	64.2 (56.1)	70.5 (66.8)	> 0.05
Delta	32.4 (44.8)	31.8 (38.6)	43.6 (52.1)	48.6 (58.4)	> 0.05
AUCtotal	2651.8 (2385.3)	2554.2 (2107.2)	3085.8 (2606.6)	3422.1 (3440.8)	> 0.05
AUCnet	1339.6 (2243.9)	1121.3 (1731.6)	1543.6 (2196.2)	1775.8 (2734.8)	> 0.05
PARtotal	0.325 (0.2)	0.227 (0.1)	0.320 (0.2)	0.315 (0.2)	> 0.05
PARnet	0.094 (1.0)	- 0.367 (2.2)	- 0.044 (0.9)	1.512 (5.1)	> 0.05

Data are mean (SD). Statistical comparison was done using Gabriel- or Games-Howell-corrected oneway ANOVA.

OSA, Obstructive sleep apnea; RLS, Restless legs syndrome; INS, Insomnia; CON, Controls; Basal, basal cortisol concentration after DEX; Peak, Highest cortisol value after CRH; Delta, Baseline corrected peak value; AUCtotal, Area under curve; AUCnet, Baseline corrected area under curve; PARtotal, Pituitary-adrenal ratio; PARnet, Baseline corrected pituitary-adrenal ratio.

Table 5. ACTH values in pg/ml obtained by the DEX-CRH test

	OSA	RLS	INS	CON	P-value
Basal	2.1 (2.7)	1.1 (0.2) *	2.7 (3.5)	4.2 (6.6)	< 0.05
Peak	16.5 (14.8)	10.1(9.7)	15.0 (11.5)	15.1 (11.2)	> 0.05
Delta	14.3 (13.4)	9.1 (9.5)	12.2 (10.0)	10.7 (11.1)	> 0.05
AUCtotal	829.2 (767.2)	531.9 (543.0)	790.0 (665.6)	790.1 (605.4)	> 0.05
AUCnet	670.3 (651.7)	452.0 (528.8)	590.0 (539.7)	465.0 (580.8)	> 0.05

Data are mean (SD). Statistical comparison was done using Gabriel- or Games-Howell-corrected oneway ANOVA.

OSA, Obstructive sleep apnea; RLS, Restless legs syndrome; INS, Insomnia; CON, Controls; Basal, Basal ACTH concentration after DEX; Peak, Highest ACTH value after CRH; Delta, Baseline corrected peak value; AUCtotal, Area under curve; AUCnet, Baseline corrected area under curve.

* $p < 0.05$, vs controls

DISCUSSION

Our glucose metabolism study for the first time compared glucose metabolism in various sleep disorders. The major finding is an increased rate of impaired glucose tolerance in patients with OSA and RLS, but not in patients with primary insomnia, as compared to normal controls.

Both RLS and OSA patients were almost five times more likely to suffer from impaired glucose tolerance than healthy controls. In addition, mean HbA1c values were increased in both diagnostic groups compared to controls, and the rate of values above the reference level in both HbA1c and fasting plasma glucose levels indicated an increased diabetes risk in patients with OSA (20-fold) and RLS (9-fold), respectively.

The control group was not matched to the OSA group with respect to gender. Indeed OSA patients were exclusively males. Most population based studies have found a 3-fold higher prevalence of sleep apnea in males then in females (Punjabi, 2008). The ratio of men to women diagnosed in sleep center is even more skewed toward men, with reported ratios 8 : 1 and higher (Ye et al., 2009). Also sex differences in clinical manifestation are described; women in general suffer from less severe disease and report more frequent non-specific symptoms. Since obstructive sleep apnea patients recruited in the study had a full clinical picture of severe obstructive sleep apnea syndrome, we were unable to find women with the same clinical picture. Hence, the present results should, as far as OSA is concerned, be replicated in a gender-mixed patient group compared to gender-matched controls.

Impaired glucose tolerance and increased rates of diabetes have been frequently shown in patients with OSA (Tasali et al., 2008a) and might be related, to a great extent, to obesity, which was also documented in the present study by an increased BMI in this patient group. However, some studies suggest that OSA is related to type 2 diabetes independently of obesity. (Reichmunth et al., 2005) In a large cross-sectional analysis of a subset of data from the Sleep Heart Health Study, involving over 2500 non-diabetic individuals, the presence of OSA was associated with significantly higher odds of impaired fasting glucose and impaired glucose tolerance after controlling for age, sex, race, BMI, and waist circumference. Importantly, the magnitude of these associations was similar in non-overweight and overweight individuals (Seicnan et al., 2008). In a recent study by Pamidi et al. (2012) was assessed whether the presence of OSA affects glucose metabolism in young, lean individuals who are otherwise healthy and free of cardiometabolic disease. Men with OSA had lower insulin sensitivity (estimated by the Matsuda index) and higher total insulin

secretion than the controls. These findings provide evidence to support the hypothesis that OSA may be associated with early changes in the natural history of type 2 diabetes even in the absence of obesity.

The idea has been put forward that nocturnal breathing disorders comprise glucose metabolism either due to repeated oxygen desaturation or due to disturbed sleep per se. The present study suggests that indeed disturbed sleep itself deteriorates glucose metabolism, as non-obese RLS patients devoid of any nocturnal breathing problem showed impaired glucose tolerance to the same extent as OSA patients. The positive correlation between quantitative measures of sleep interruptions (apnea-arousal-index in OSA and PLMS-arousal-index in RLS) and 2h-plasma glucose levels in the OGTT indicate repeated arousals as a possible common mechanism of impaired glucose tolerance in both sleep disorders.

This idea is in line with the report of Tasali et al. (2008b), who induced impaired glucose tolerance in healthy volunteers by disturbing sleep by means of acoustical stimulation for three consecutive nights. This procedure did not alter the total amount of sleep, suggesting a specific effect of repeated arousals. Our results support this idea, because patients with primary insomnia and normal glucose tolerance had similar total sleep times compared to OSA and RLS patients, but lacked the repeated arousals induced by apneas or PLMS. Repeated arousals could affect glucose metabolism by altering sleep structure, in particular by preventing SWS. This is suggested by a correlation between SWS and insulin sensitivity in the study of Tasali et al. (2008b), where SWS was reduced by nearly 90%. Stamatakis and Punjabi (2010) fragmented sleep across all sleep stages for two nights using auditory and mechanical stimuli. Sleep fragmentation resulted in an increase in stage 1 sleep and a decrease in slow wave and in rapid eye movement sleep by preserved sleep duration. Following two nights of sleep fragmentation, insulin sensitivity and glucose effectiveness were significantly decreased. Interestingly, a recent study of Gonnissen et al. (2013) examined the effect of sleep fragmentation in healthy young men. Sleep fragmentation resulted in slightly reduced REM sleep and preserved SWS without changes in total sleep time. A single night of mildly fragmented sleep induced a shift in insulin concentrations, from being lower in the morning and higher in the afternoon.

Because we restricted polysomnographic recordings to the patient groups, the present study does not help to directly answer the question whether sleep duration or other quantitative aspects of night sleep, independently of arousing stimuli during sleep, affect glucose metabolism. Indirectly, similar sleep durations of 5.5 hours in all our patient groups, including primary insomnia patients who showed no impairment in glucose tolerance, suggests that

only more prominent sleep reduction might have a direct negative effect on carbohydrate metabolism. One example would be sleep curtailment to four hours of sleep for some days (Spiegel et al., 1999), which impaired glucose metabolism even in healthy people.

RLS is frequently found in patients with diabetes, which so far has mainly been explained by the fact that diabetes-induced polyneuropathy predisposes to RLS (Merlino et al., 2007a). In line with this argument, Bosco et al. (2009) found an increased incidence of small fiber neuropathy (SFN) in RLS patients with impaired glucose tolerance. Because we did not perform skin biopsies, we cannot judge the role of SNF in our sample. However, Merlino et colleagues (2007a) on the basis of multivariate analysis suggested that neuropathy only partially explains the increased prevalence of RLS in diabetics. Lim et al. (2012) postulated that abnormal sensory perception in patients with idiopathic RLS may result from impairment of central somatosensory processing rather than small fiber neuropathy. The present study for the first time suggests that not only diabetes might predispose to RLS through SNF or other mechanisms, but that in turn, RLS might be a causative factor in the development of diabetes by compromising sleep continuity due to repeated arousals.

The HPA axis study is the first one to compare the dynamic regulation of the HPA system in various sleep disorders. Compared to healthy controls, neither patients with obstructive sleep apnea, nor patients with restless legs syndrome or primary insomnia showed abnormalities in the ACTH or cortisol responses to CRH after HPA system suppression by dexamethasone. Also prior to the CRH challenge, there was no difference between groups, apart from ACTH levels which were slightly lower in RLS compared to the other samples.

These results suggest that in patients with common sleep disorders, who are carefully selected not to suffer from an affective or other psychiatric disorder, HPA system function is essentially normal.

The present findings in RLS patients are quite in line with the literature. Neither Wetter et al. (2002), Garcia-Borreguero et al. (2004), nor Hornyak et al. (2008) found abnormalities in HPA system regulation in these patients. Wetter measured cortisol plasma levels every 20 minutes for 24 hours in 10 male never medicated RLS patients with mild to moderate symptoms, Garcia-Borreguero measured plasma cortisol levels at 11 am and 11 pm in 12 patients with idiopathic RLS and matched healthy controls. No difference in feedback inhibition has been reported by Hornyak after a low dose of hydrocortisone in the evening in ten untreated patients with idiopathic RLS. Schilling et al. (2010) reported increased cortisol levels in nighttime urine. However, these results do not indicate whether this increase

observed is due to a decrease in feedback inhibition of the HPA system. Interestingly, the PLMS index and PLMS-arousal index were slightly higher in our patient's sample; sleep efficiency, a sleep parameter indicating disturbed sleep, was lower in Schilling's sample. Therefore disturbed sleep from other reasons might influence cortisol levels.

The isolated slight decrease in ACTH levels after dexamethasone suppression in RLS in the present study is probably either a finding by chance likely due to the small standard deviation observed (SD 0.2) or without major biological significance, because normal baseline cortisol levels and normal hormonal responses to CRH point to an overall normal HPA system function.

Results obtained from studies in sleep disordered breathing are quite inconsistent. Some studies reported enhanced cortisol secretion (Bratel et al., 1999) (Lanfranco et al., 2003) (Vgontzas et al., 2007). In other studies alterations in HPA system activity (Entzian et al., 1996) (Dadoun et al., 2007) were not found. Noteworthy, several of these studies were limited in that cortisol was measured at a single time point, they do not measure potential clinically important HPA system changes. Furthermore, in the majority of these studies the psychological profile, including emotional distress, anxiety, and/or depression, frequent comorbidities in OSA, were not assessed formally.

There are two studies using a CRH stimulation test in sleep apneics. In one study, ACTH responsiveness to CRH stimulation was even higher in obese subjects without OSA compared with obese OSA patients and lean controls (Vgontzas et al., 2007). In previous study, Lanfranco et al. (2004) evaluated the ACTH and cortisol response to CRH in sleep apnea patients compare with healthy obese control group and healthy non obese control group. He found the ACTH response to CRH significantly higher in sleep apnea and obese compare to non obese and even higher in sleep apnea than in obese. In both studies, basal ACTH and cortisol levels were similar in all groups and also the cortisol response to CRH was not significantly different. Exaggerated ACTH response to provocative stimuli has been already shown by several studies in obesity (Pascquali et al., 1996) (Arvat et al., 2000). ACTH hyper-responsiveness to provocative stimulation not coupled to the enhancement of the cortisol response was reported by some studies too (Tassone et al., 2002). The absence of cortisol hypersecretion in association to the enhanced ACTH response to CRH could reflect reduced adrenal sensitivity to ACTH, even more pronounced in OSA then in simple obesity (Lanfranco et al., 2004). Another explanation would be that this finding could reflect a disturbance in the control of proopiomelanocortin and related peptides such as melanocortins

and agouti-related peptides, involved in regulation of feeding behavior, insulin levels and body weight (Cone, 1999).

Only one study has been published focusing on feedback sensitivity of the HPA system in OSA patients (Carneiro et al., 2008). In this study, after administration of a low dose of dexamethasone smaller cortisol suppression has been detected in OSA patients compared to healthy controls. In our study we cannot confirm this difference in negative feedback sensitivity. The difference of our findings from that report may be a result of methodological differences. Carneiro and coworkers included OSA patients suffering from morbid obesity (BMI: 46.9 ± 2.0) while we studied less obese OSA patients (BMI: 32.9 ± 5.4). Furthermore, as negative feedback sensitivity was assessed differently, the suppressive effect of dexamethasone was measured at a different time points.

Primary insomnia is thought to be a disorder of hyperarousal. It has been shown that chronic primary insomnia is associated with increased evening and nocturnal cortisol levels (Rodenbeck et al., 2002) (Vgontzas et al., 2001a) reflected by altered parameters of the cortisol rhythm. Evening cortisol levels have been shown to be associated with the number of nocturnal awakenings during the following sleep period in chronic insomnia patients as well as in healthy controls. In contrary, our findings are in line with the study of Riemann et al. (2002) who also reported the lack of increased cortisol secretion in patients with primary insomnia. Moreover, a study in insomniacs in constant routine protocol condition (in an isolated, temperature- and light-controlled, sound-attenuated sleep laboratory) did not reveal any statistically significant difference in cortisol levels (Varkevisser et al., 2005).

Indeed, insomniacs are characterized by worrying about sleep, especially during the period of sleep (Harvey, 2000). Since the test was performed during daytime, absence of worring about sleep, conditioned arousal to the bedroom and anticipation anxiety might prevent the cortisol hypersecretion.

Our results suggest that negative feedback sensitivity is not affected by repeated arousals during night neither in OSA, RLS nor in insomnia patients. This is in line with the result obtained by Späth-Schwalbe et al. (1991) who reported a rapid habituation of the HPA system to repeated arousals during night.

We could not confirm our hypothesis that disturbed sleep from different reasons leads to increased activity in the HPA system. In contrast, we could confirm the impaired glucose tolerance in obstructive sleep apnea and restless legs syndrome, two sleep disorders

characterized by frequent repeated arousals from sleep, but not in insomnia. There are several physiological mechanisms that might link the disturbed sleep with impaired glucose sensitivity.

Repeated arousals could have a direct effect on glucose metabolism by the resulting in activation of the sympathetic nervous system. The sympathetic nervous system is regulated by sleep-wake cycles and its activity gradually decreases during the deep sleep stages of non-REM sleep whereas during REM sleep and wakefulness, sympathetic nervous activity is increased (Dijk 2008). Sleep onset itself is associated with a significant decline of circulating concentrations of catecholamines epinephrine and norepinephrine, which serve as direct readouts of sympathetic activity. Nocturnal and morning awakenings, on the other hand, are associated with increases in both hormones (Irwin et al., 1999).

Sympathetic output has been shown to be negatively affected by sleep disturbances. In a study of restricted sleep to 5.5 hours, a significant increase was observed in 24-hour epinephrine, as well as a nighttime increase in norepinephrine (Nedeltcheva et al., 2009). Reductions in sleep quality without changes in duration also have demonstrable effects on sympathetic output (Stamatakis and Punjabi, 2010).

Increases in heart rate and blood pressure are typical of both obstructive apneas and periodic leg movements, and sympathetic nervous system activation has been shown in both OSA and RLS patients (Narkiewicz and Somers, 2003) (Walter and Rye, 2009). In above mentioned Stamatakis and Punjabi´s study (2010) sleep fragmentation caused alterations in sympathovagal balance, with a shift toward increased sympathetic nervous system activity during sleep and wakefulness. Moreover, Tasali et al. (2011) found that the change in insulin sensitivity after CPAP was positively correlated with the magnitude of decrease in norepinephrine levels, the primary peripheral neurotransmitter of sympathetic activity, after controlling for BMI in young obese women with polycystic ovary syndrome. Importantly, the decrease in 24-h norepinephrine levels occurred in all subjects with greater reductions being observed with increasing hours of CPAP use.

Sympathetic activation raises levels of circulating free fatty acids due to the stimulation of lipolysis promoting insulin resistance by direct sympathetic innervations of the adipose tissue (Ip et al., 2002). Catecholamines also increase intracellular cAMP thereby inhibiting leptin mRNA expression and secretion (Slieker et al., 1996). Inhibition of leptin signaling will subsequently lead to an increase in feeding behavior, which will itself stimulate leptin production and feedback in an inhibitory manner to reduce catecholamine secretion. If

sympathetic activation remains abnormally elevated, the hunger drive would remain high as well and lead to an increase in individual susceptibility to weight gain and obesity (Broussard and Brady, 2010).

Insufficient sleep leads to a general enhancement of markers for inflammatory activity. Cytokines, such as tumor necrosis factor alpha (TNF alpha) or interleukin 1 are clearly involved in sleep wake regulation. Sleep fragmentation as well as episodic hypoxia contribute to release of proinflammatory cytokines, including tumor necrosis factor alpha and interleukin-6 (IL-6) (Kruger, 2008). These cytokines are linked with diabetes. Visceral adipose cells produce significant amounts of proinflammatory cytokines. TNF alpha may lead to insulin resistance, hyperglycemia, and compensatory hyperinsulinemia (Ruan et al., 2002). Evidence supporting a key role for TNF alpha in obesity-related insulin resistance came from studies showing that deletion of TNF alpha or TNF alpha receptors resulted in significantly improved insulin sensitivity in both diet-induced obese mice and leptin-deficient ob/ob mice (Uysal et al., 1997) IL-6 may induce gluconeogenesis in liver, hyperglycemia and compensatory hyperinsulinemia (Pradhan et al., 2001). However the effect of IL-6 on hepatic glucose production is still under debate. One may speculate that persistent systemic increases of IL-6 in states of chronic inflammation such as obesity and type 2 diabetes may trigger insulin resistance, whereas transient increases may contribute to normal glucose homeostasis (Rabe et al., 2008). TNF alpha and IL-6 modulate insulin resistance through several distinct mechanisms, including c-Jun N-terminal kinase 1-mediated serine phosphorylation of insulin receptor substrate-1 (IRS-1), IκB kinase-mediated nuclear factor-κB activation, and induction of suppressor of cytokine signaling-3 (SOCS-3) (Tigl and Hotamisligil 2006).

Conclusions

To conclude, this very fist study using the DEX-CRH-test in various sleep disorders suggests that disturbed sleep per se has no major negative impact on the negative feedback inhibition of the HPA system. Furthermore, abnormalities in HPA system regulation in OSA, RLS and insomnia patients reported earlier seem to be independent of negative feedback regulation processes of the HPA system.

The present study confirmed increased rates of impaired glucose tolerance in patients with OSA and for the first time suggests that not only diabetes might predispose to RLS through SNF or other mechanisms, but that in turn, RLS might be a causative factor in the development of diabetes by compromising sleep continuity due to repeated arousals.

Reported high prevalence of diabetes in chronic sleep disorders calls for further extended investigations, because sleep disorders are highly prevalent and might represent an important preventive target to avoid metabolic disorders. Moreover, the present results further strengthen the idea that disturbed sleep in general and chronic sleep disorders in particular might significantly contribute to the steady increase in diabetes prevalence worldwide.

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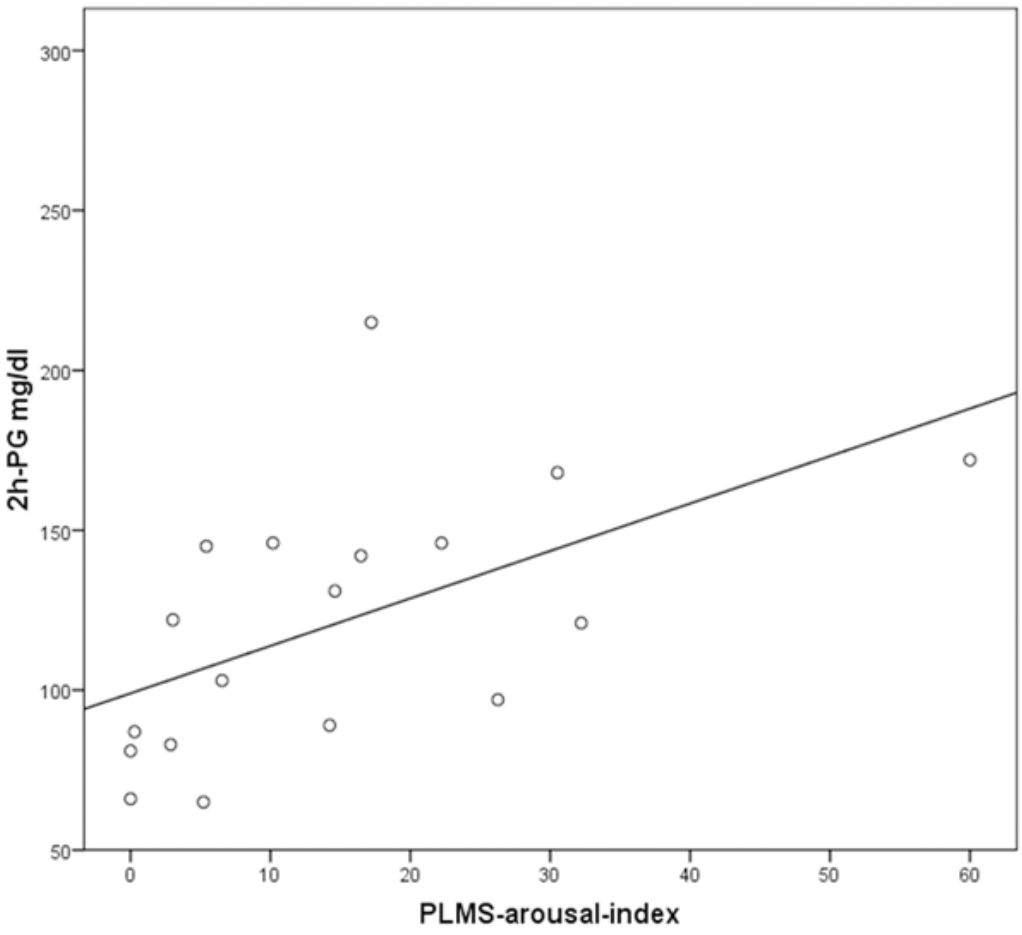
APPENDIX

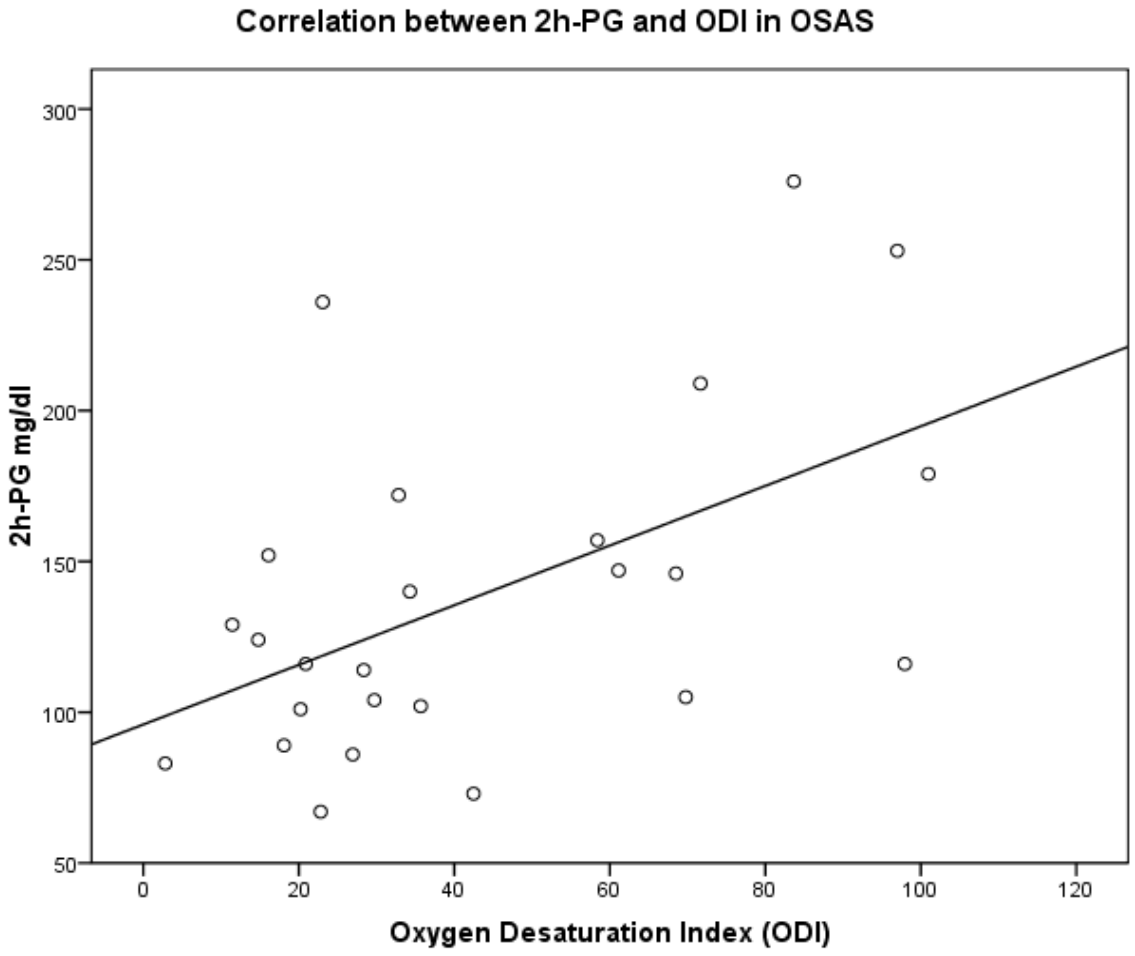
Graph 1: Experimental part 1: Glucose metabolism and sleep

Association between between 2h-PG values and the periodic leg movements -index in retless legs patients. Partial correlation coefficient (corrected for the BMI); r = 0.56, p,0.05.



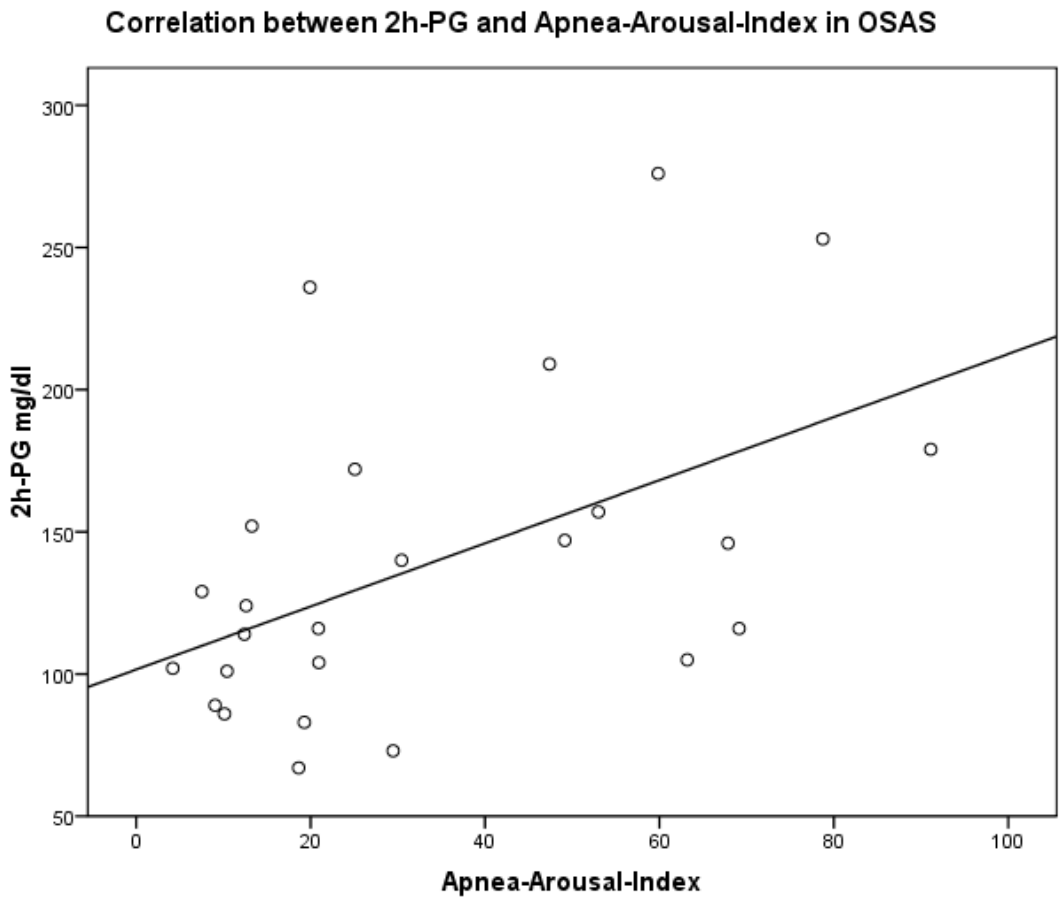
Graph 2: Experimental part 1: Glucose metabolism and sleep

Association between 2h-PG values and the oxygen-desaturation-index in obstructive sleep apnea patients. Partial correlation coefficient (corrected for the BMI); r=0.59, p,0.05.



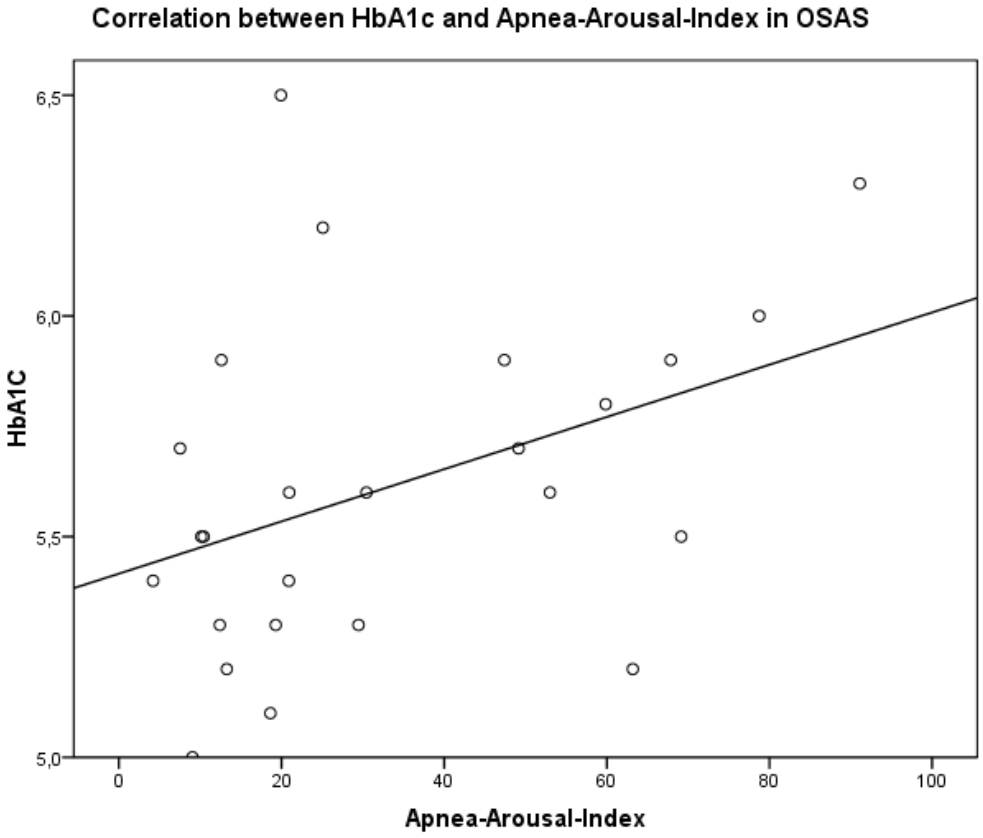
Graph 3: Experimental part 1: Glucose metabolism and sleep

Association between 2 hour-plasma glucose and the apnea-arousal-index in obstructive sleep apnea patients. Partial correlation coefficient (corrected for the BMI); r = 0.56, p,0.05.



Graph 4: Experimental part 1: Glucose metabolism and sleep

Association between HbA1c values and the apnea-arousal-index in obstructive sleep apnea patients. Partial correlation coefficient (corrected for the BMI); r = 0.50, p,0.05.



Schema 1: Mallampati score