UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
PROGRAMA DE PÓS GRADUAÇÃO EM CIÊNCIAS MÉDICAS:
ENDOCRINOLOGIA

O EFEITO DO TRABALHO NOTURNO SOBRE A SAÚDE DOS TRABALHADORES DE UM HOSPITAL UNIVERSITÁRIO

Tese de Doutorado

MARIA CARLOTA BORBA BRUM

Porto Alegre, Setembro de 2016

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
PROGRAMA DE PÓS GRADUAÇÃO EM CIÊNCIAS MÉDICAS:
ENDOCRINOLOGIA

O EFEITO DO TRABALHO NOTURNO SOBRE A SAÚDE DOS TRABALHADORES DE UM HOSPITAL UNIVERSITÁRIO

Tese de Doutorado

MARIA CARLOTA BORBA BRUM

Tese apresentada como requisito parcial
Para obtenção do título de Doutor em Ciências
Médicas: Endocrinologia, junto à Universidade
Federal do Rio Grande do Sul, Programa
de Pós Graduação em Ciências Médicas:
Endocrinologia

ORIENTADORA: Profa. Dra. Ticiana da Costa Rodrigues

Porto Alegre, Setembro de 2016

AGRADECIMENTOS

A Profª. Drª. Ticiana da Costa Rodrigues pela oportunidade de aprendizado e convivência. Obrigado pela amizade e orientação.

Ao colega Fábio Fernandes Dantas Filho pela sua amizade e presença constante em todos os momentos deste trabalho.

Às colegas Karen Dávila e Sheila Stoniosso pela amizade e colaboração.

Aos estagiários Claúdia Carolina Schnnor, Suelen Mandelli Mota e Gustavo Borchardt pelo auxílio na execução dos projetos de pesquisa.

Aos colegas Amarildo, Glória, Mary Lane, Enara, Eloísa, Elen e Mônica pelo auxílio nas coletas dos participantes da pesquisa.

À Dra. Camila Morelatto pelo apoio na análise do Questionário de Cronotipo de Munique (MCTQ).

Às colegas Martha Senger e Lethicia Rozales Ehlert pela ajuda na execução das dosagens laboratoriais de cortisol e melatonina.

Aos meus pais pelo exemplo, pelo amor e pelo carinho.

Ao meu sobrinho Carlos e minha irmã Cândida pelo carinho e apoio em todos os momentos deste trabalho.

SUMÁRIO

Artigo 1

Artigo 2

Artigo 3

LISTA DE ABREVIATURAS

ANS: Autonomic nervous system
BMI: Body mass index
CA: abdominal circumference
CAR:cortisol awakening response
CDC: Centers of Disease Control and Prevention
CK-EPI eGFR: glomerular filtration rate
CNS: Central nervous system
HR: heart rate
HDL: high density lipoprotein
IDF: International Diabetes Federation
IMC:Índice de massa corporal
PAQ: International Physical Activity Questionnaire
LDL: Low-desinty lipoprotein
MCTQ: Munich Chronotype Questionary
OD: odds ratio
OIT: Organização Internacional do Trabalho
SAH: Systemic arterial hypertension
SCN: Suprachiasmatic nucleus
WHO: World Health Organization

RESUMO

O trabalho noturno faz parte da sociedade atual de forma definitiva, incorporado em várias áreas da produção de bens e serviços. Estudos têm demonstrado as repercussões sobre a saúde dos trabalhadores, especialmente relacionados à ocorrência de patologias crônico degenerativas (síndrome metabólica, diabetes melito, obesidade e doença cardiovascular). O presente trabalho tem por objetivo avaliar o impacto do trabalho noturno sobre a saúde dos trabalhadores, de modo que possa servir como base para a elaboração de possíveis estratégias de intervenção para minimizar os problemas de saúde decorrentes desta forma de organização do trabalho.

O capítulo 1 constitui-se de um artigo de revisão sobre os efeitos do trabalho em turnos sobre a saúde dos trabalhadores, em especial distúrbios metabólicos e cardiovasculares, foi publicado na revista *Metabolic Syndrome & Diabetology* em 2015.

O segundo capítulo refere-se a um estudo transversal envolvendo 200 trabalhadores de um hospital universitário, avaliamos a associação entre turno de trabalho, obesidade e qualidade de vida. Para a execução do estudo foram aplicados questionários socio-demográfico, de qualidade de vida (BREF WHOQOL), de atividade física, o Questionário Internacional de Atividade Física (IPAQ), e o Questionário de Cronotipo de Munique (MCTQ). Distúrbios de sono foram investigados através de questões selecionadas do questionário Índice de Qualidade do Sono de Pittisburgh. Os trabalhadores do turno noturno apresentaram maior peso, maior circunferência abdominal, maior índice de massa corporal e maior frequência cardíaca que os trabalhadores diurnos. A análise múltipla demonstrou que os trabalhadores noturnos apresentaram 48% a mais de associação com obesidade abdominal, sendo que a maior duração do sono reduziu em 5% este risco. Apresentaram também uma razão de chance de 78% de associação com obesidade em comparação com os trabalhadores diurnos. A análise dos parâmetros do MCTQ demonstrou que os trabalhadores

noturnos apresentaram menor duração de sono nos dias de trabalho e também nos dias livres, associado a um maior *jetlag social* social. Os resultados confirmaram a associação do trabalho noturno com obesidade visceral e excesso de peso, seja sobrepeso ou obesidade, ao mesmo tempo em que dormir mais horas de sono ou reduzir o débito de sono atenuaram esta associação.

O terceiro capítulo refere-se a um estudo com o objetivo de avaliar o impacto da jornada de trabalho em turnos fixos durante à noite em comparação ao diurno sobre o ciclo vigília/sono e as concentrações dos hormônios cortisol e melatonina medidos na saliva durante o dia e a noite em ambos os grupos de trabalhadores, os trabalhadores noturnos foram avaliados em um dia de folga e em um dia de trabalho noturno. Para esta finalidade, foram coletadas amostras de saliva e de sangue de trabalhadores noturnos e diurnos e aplicados questionários sócio-demográfico e o Questionário de Cronotipo de Munique. Os resultados demonstraram que, enquanto os trabalhadores diurnos mantém o ritmo circadiano de secreção do cortisol, com níveis mais elevados durante a manhã e menores à noite, os trabalhadores noturnos, ainda preservam o ritmo do cortisol, tanto no plantão noturno quanto no dia de folga, porém apresentam um descenso menor dos níveis do cortisol salivar. Em relação à melatonina salivar, tanto os trabalhadores diurnos quanto os trabalhadores noturnos no dia de folga apresentaram níveis mais altos de melatonina à noite e níveis mais baixos pela manhã, os trabalhadores noturnos no dia de plantão noturno apresentaram um perfil inverso, com níveis de melatonina mais altos pela manhã e mais baixos à noite. Observou-se que os trabalhadores noturnos apresentam menos horas de sono durante os dias de trabalho em comparação aos diurnos associado a um jetlag social significativamente diferente, caracterizando uma perda crônica de sono. O trabalho noturno impacta no ritmo da melatonina e do cortisol.

ABSTRACT

Night work is part of today's society definitively, incorporated in various areas of the production of goods and services. Studies have shown the effects on the health of workers, especially related to the occurrence of chronic degenerative diseases (metabolic syndrome, diabetes, obesity, cardiovascular disease). This study aims to assess the impact of night work on the health of workers, which can serve as a basis for intervention strategies to minimize health problems arising from this form of work organization.

Chapter 1 consists of a review article on the effects of shift work on workers' health, in particular metabolic and cardiovascular disorders, was published in Metabolic Syndrome and Diabetology in 2015.

The second chapter refers to a cross-sectional study involving 200 workers of a university hospital, evaluating the association between shift work, obesity and quality of life. For the implementation of the study, a sociodemographic questionnaire, a quality of life questionnaire (WHOQOL-BREF), the International Physical Activity Questionnaire (IPAQ), and the Munich Chronotype Questionnaire (MCTQ) were applied. Sleep disorders were investigated through questions selected from the Pittsburgh Sleep Quality Index questionnaire. During the physical examination, blood pressure, heart rate, weight, height and BMI were measured, and venous blood was collected after 12-hour fasting for laboratory analysis of fasting blood glucose, glycated hemoglobin, insulin, total cholesterol and fractions, triglycerides, urea, creatinine, liver transaminases, ultrasensitive C-reactive protein, blood count, and platelets. The night shift workers have higher weight, larger waist circumference, higher BMI and higher heart rate than daytime workers. The multivariate analysis showed that night workers were 48% more likely to develop abdominal obesity, while a longer duration of sleep reduced this risk by 5%. They also showed also a risk of 78%

for obesity compared with day workers. The analysis of MCTQ parameters showed that night workers had shorter sleep duration on working days and free days, associated with a higher social jetlag social. The results confirmed the association between night work with visceral obesity and weight gain, either overweight or obesity, while sleeping for more hours or reducing the sleep debt attenuated this association.

The third chapter concerns a study intended to assess the impact of working hours on fixed shifts during the night compared to the day shift on the sleep/wake cycle and the concentrations of the hormones cortisol and melatonin during the day and night in both groups of workers. For this purpose, saliva and blood samples were collected from night and day workers and the socio demographic and Munich Chronotype Questionnaire were applied. The results showed that while day workers keep the circadian rhythm of cortisol secretion at higher levels in the morning and lower levels in the night, night workers, both in duty and after duty, have a smaller decrease in salivary cortisol levels. Regarding salivary melatonin, both daytime workers and night workers after duty had higher levels at night and lower levels in the morning, night workers on duty had an opposite profile, with higher levels of melatonin in the morning and lower levels in the night. Night workers were observed to have fewer sleeping hours during working days compared with day workers, associated with a significantly different jetlag social, characterizing a chronic sleep loss. Night work impacts the rhythm of melatonin and cortisol.

APRESENTAÇÃO

Este trabalho consiste na tese de doutorado "O Efeito do Trabalho Noturno Sobre a Saúde dos Trabalhadores de um Hospital Universitário", apresentada ao Programa de Pós-graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul em 03 de outubro de 2016. O trabalho será apresentado em 3 partes, descritas a seguir:

1. Introdução

2. Desenvolvimento

Artigo 1: Shift work and its association with metabolic disorders

Artigo 2: Night Work, short sleep and obesity

Artigo 3: Effect of night-shift work on cortisol circadian rhythm and melatonin levels

3. Considerações Finais

INTRODUÇÃO

A sociedade atual tem se caracterizado pelo oferecimento de serviços 24 horas por dia. Além dos serviços essenciais, há uma quantidade cada vez maior de produção de bens e outros serviços que funcionam ininterruptamente, visando atender às demandas relacionadas às rápidas mudanças ocorridas nos processos tecnológicos e nas sociedades de um modo em geral. Para que isto ocorra, um grande número de trabalhadores exerce as suas atividades em horários/turnos variados. Entretanto, o progresso da sociedade 24 horas tem contrapartidas negativas sobre a saúde dos trabalhadores (1).

Não há dados nacionais sobre o tema, na Europa estima-se que cerca de 20% dos trabalhadores estão expostos a trabalho noturno ou em turnos (2).

Conforme a Organização Internacional do Trabalho (OIT), trabalho em turno consiste em um método de organização em que os trabalhadores sucedem um ao outro no local de trabalho para que o estabelecimento possa operar por mais tempo. A expressão trabalho noturno designa a atividade que se realiza durante um período de pelo menos sete horas consecutivas e que envolva o intervalo compreendido entre às meia noite e as 5 horas da manhã (3).

O horário de trabalho padrão geralmente é entendido como o trabalho que ocorre à luz do dia, entre às 06:00 e 18:00 horas, com duração de 8 horas, de segunda a sexta-feira. Todo trabalho contínuo fora deste período é considerado trabalho em turno. Os turnos se caracterizam pelo número e duração de cada jornada de trabalho, pela velocidade da rotação (número de dias seguidos de cada turno) e pela direção da rotação (3).

O sistema circadiano dos mamíferos é constituído por uma rede hierarquicamente organizada de estruturas responsáveis pela geração de ritmos circadianos e da sua sincronização como ambiente (4).

Nos trabalhadores em turnos os ritmos biológicos não estão sincronizados com os ciclos externos, como o ciclo claro escuro e o horário das refeições, levando a uma dessincronização externa. A dessincronização repetida e ressincronização pode alterar a ritmicidade circadiana e causar ou acelerar o adoecimento, tais como o envelhecimento prematuro, neoplasias, doenças cardiovasculares, prejuízo cognitivo e distúrbios de humor (4).

A dessincronização circadiana, assim como a privação de sono e a supressão da melatonina noturna pela exposição à luz durante a noite têm sido apontados como os possíveis mecanismos pelos quais o trabalho em turnos traz prejuízos à saúde (5).

A melatonina é um hormônio produzido pela glândula pineal e outros tecidos corporais, secretado diretamente na corrente sanguínea, é suprimida pela luz, caracterizando-se como um hormônio de fase escura. Está associado a baixa temperatura corporal e a indução do processo de sono, além de funcionar como um sincronizador endógeno, responsável pela sincronização entre os tecidos centrais e periféricos (6,7).

O cortisol é um excelente marcador do ritmo circadiano (8) produzido pelas adrenais, obedece ao estimulo via eixo hipotálamo-hipófise-adrenal e tem funções anti-inflamatórias, metabólicas e imunossupressoras (9,10). Normalmente, o pico do cortisol se concentra nas manhãs, diminuindo ao longo do dia, sendo mínimo à noite. Neste ciclo, existe um pico de produção de cortisol denominado resposta do cortisol ao despertar (CAR – *cortisol awakening response*) (10).

Os distúrbios imediatos associados ao trabalho por turnos são sintomas como distúrbios do sono, fadiga, '*jetlag social*' e sintomas gastrointestinais, em especial a úlcera péptica. Outros distúrbios referem-se a doenças cardiovasculares, diabetes, síndrome metabólica, obesidade e até mesmo o câncer (11,12,13,14).

O trabalho em turnos alternados foi associado com aumento dos níveis de pressão arterial, mesmo ajustada para fatores de confusão como idade e índice de massa corporal (IMC) (12). A associação entre trabalho em turnos e ganho de peso também tem sido investigada por alguns autores (11,15) apesar de ainda não estar esclarecido o mecanismo fisiopatológico desta associação, alguns estudos têm demonstrado que a privação de sono tem papel importante no desenvolvimento da obesidade (16,17).

REFERÊNCIAS BIBLIOGRÁFICAS

1- Castro Moreno CR, Frida FM, Rotenberg L. A Saúde do trabalhador na sociedade 24 horas. São Paulo em Perspectiva 2003;17(1): 34-46.

2- Organização Internacional do Trabalho. Convenção sobre Trabalho Noturno – C171, 1990, Genebra.

3- Rodrigues VP. Principais impactos do trabalho em turnos: estudo de caso de uma sonda de perfuração marítima. R Un Alfenas 1998;4: 199-207.

4- Garaulet M, Ordovás JM, Madrid JA. The chronobiology, etiology and pathophysiology of obesity. Int J Obes. 2010;34:1667–83.

5- Eastman C, Smith. Shift work: health, performance and safety problems, traditional countermeasures, and innovative management strategies to reduce circadian misalignment. Nat Sci Sleep. 2012 Sep;111.

6- Cipolla-Neto J, Amaral FG, Afeche SC, Tan DX, Reiter RJ. Melatonin, energy metabolism, and obesity: a review. J Pineal Res. 2014 May;56(4):371–81.

7- Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin. Sleep Med Rev. 2005 Feb;9(1):11–24.

8- Griefahn B, Robens S. The cortisol awakening response: A pilot study on the effects of shift work, morningness and sleep duration. Psychoneuroendocrinology. 2008 Aug;33(7):981–8.

9- Niu S-F, Chung M-H, Chen C-H, Hegney D, O'Brien A, Chou K-R. The Effect of Shift Rotation on Employee Cortisol Profile, Sleep Quality, Fatigue, and Attention Level: A Systematic Review. J Nurs Res. 2011 Mar;19(1):68–81.

10- Ulhôa MA, Marqueze EC, Burgos LGA, Moreno CRC. Shift Work and Endocrine Disorders. Int J Endocrinol. 2015;2015:1–11.

11-Di Lorenzo L, De Pergola G, Zocchetti C, L'Abbate N, Basso A, Pannacciulli N, et al. Effect of shift work on body mass index: results of a study performed in 319glucose-tolerant men working in a Southern Italian industry. Int J ObesRelatMetabDisord J IntAssoc Study Obes. 2003; 27:1353–8.

12- Suwazono Y, Dochi M, Sakata K, Okubo Y, Oishi M, Tanaka K, et al. Shiftwork is a risk factor for increased blood pressure in Japanese Men: a 14-yearhistorical cohort study. Hypertension. 2008;52:581–6.

13-Guo Y, Rong Y, Huang X, Lai H, Luo X, Zhang Z, et al. Shift work and the relationship with metabolic syndrome in Chinese aged workers. In: BehrensT, editor. PLoS One, vol. 10(3). 2015. p. e0120632.

14-Knutsson A. Health disorders of shift workers. Occup Med. 2003;53:103-108.

15-Van Drongelen A, Boot CRL, Merkus SL, Smid T, van der Beek AJ. The effects of shift work on body weight change - a systematic review of longitudinal studies. Scand J Work Environ Health. 2011;37:263–75.

16-Canuto R, Pattussi MP, Macagnan JBA, Henn RL, Olinto MTA. Sleep deprivation and obesity in shift workers in southern Brazil. Public Health Nutr. 2014;17:2619–23.

17-Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB. Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. Sleep.2005;28:1289–96.

Shift work and its association with metabolic disorders

Maria Carlota Borba Brum, MD, MsC[1,2]; Fábio Fernandes Dantas Filho, MD [1,2], Claúdia Carolina Schnorr[3]; Gustavo Borchardt[3]; Ticiana C. Rodrigues,MD, PhD[2-4]

[1]Ocupational Medical Service at Hospital de Clínicas de Porto Alegre, HCPA,

[2]Post graduate program Medical Science Endocrinology, of Universidade Federal do Rio Grande do Sul.

[3]Medical School, Universidade Federal do Rio Grande do Sul

[4] Division of Endocrinology of Hospital de Clínicas de Porto Alegre,

Corresponding author
Profa Dra. Ticiana C. Rodrigues
Email: ticianacr@yahoo.com.br
Departament of Internal Medicine, Universidade Federal do Rio Grande do Sul, Division of Endocrinologyof Hospital de Clínicas de Porto Alegre,

Adress Rua Ramiro Barcelos 2350, Prédio 12, 4° andar,

Porto Alegre, RS, Brazil

Zip code 90035-003

Artigo publicado na revista Diabetology & Metabolic Syndrome
Brum et al
Diabetology & Metabolic Syndrome (2015) 7:45

Abstract

Although the health burden of shift work has not been extensively studied, evidence suggests that it may affect the metabolic balance and cause obesity and other metabolic disorders. Sleep deprivation, circadian desynchronization and behavioral changes in diet and physical activity are among the most commonly mentioned factors in studies of the association between night work and metabolic disorders. Individual adaptation to night work depends greatly on personal factors such as family and social life, but occupational interventions may also make a positive contribution to the transition to shift work, such as exposure to bright lights during the night shift, melatonin use, shift regularity and clockwise rotation, and dietary adaptations for the metabolic needs of night workers. The evaluation of the impact of night work on health and of the mechanisms underlying this relationship can serve as a basis for intervention strategies to minimize the health burden of shift work. This review aimed to identify high lights regarding therapeutic implications following the association between night and shift work and metabolic disorders, as well as the mechanisms and pathways responsible for these relationships.

Keywords: Shift work, Obesity, Metabolic syndrome, Diabetes, Hypertension, Sleep restriction, Insulin resistance

Introduction

Twenty-four hour services are a growing part of modern society. Essential services are provided without interruption, and several industries and business establishments operate on a 24 h basis so as to meet the constantly changing demands of the modern world [1]. As a result, companies require employees to work continuously, creating a need for shift- and night-work schedules.

Shift schedules allow companies to operate on a continuous basis by ensuring that positions are always filled by rotating employees. Night work is defined as a work shift lasting at least seven consecutive hours, which comprehends the interval between midnight and five o'clock in the morning [2].

Shift frequency and duration may vary between companies, and differences may also be observed in the number of consecutive work days and the direction of rotation [3]. Although no studies on the topic have been published in Brazil, European research has reported that 20 % of workers in the continent perform shift or night work [4].

The growing importance of shift and night work in meeting the demands of modern society creates an urgent need for research into the effects of such schedules on worker health.

The effects of shift work on health have only been sparsely studied, but recent findings suggest that such schedules may affect glucose tolerance and induce obesity and systemic arterial hypertension (SAH) [5–8].

This review aimed to identify highlights regarding some therapeutic implications following the association between night and shift work and metabolic disorders, as well as the mechanisms and pathways responsible for these relationships. Metabolic syndrome, diabetes, obesity and cardiovascular disease are conditions with recent association with night work.

Shift work and its effects on health

Cardiovascular

According to a recent meta-analysis, shift work is associated with an increased risk of coronary disease, acute myocardial infarctions and cerebrovascular accidents, even after adjusting for possible confounds. However, shift work was not associated with overall mortality, or cardiac or cerebrovascular death [9].

A study performed in a public university in Brazil evaluated cardiovascular risk in 211 workers of both genders aged between 30 and 64 years using Framingham scores, and found that both cardiovascular risk (28 %) and the prevalence of SAH (33.4 %) were higher in night workers than in day workers [10].

A study of worker health performed in seven French hospitals evaluated participants on two occasions and found that the systolic arterial pressure of night workers was 2.5 mmHg ($p < 0.001$) higher than that of dayworkers [11].

A British study which followed a cohort of 7839 participants from birth until age 45 found that cardiovascular risk, body mass index (BMI), abdominal circumference, total cholesterol, triglyceride levels, glycated hemoglobin and C-reactive protein levels were higher in men who performed shift work on a regular basis than in those who did not usually work in shifts. In women, shift work was positively associated with triglyceride levels, but negatively associated with diastolic arterial pressure. Adjusting for confounders (alcohol consumption, exercise, tobbaco and consumption fruits, vegetables and fried foods) had little impact on results regarding adiposity measures, but attenuated the association between shift work and the levels of cholesterol, triglyceride, glycated hemoglobin and inflammatory markers. After this adjustment, only BMI, abdominal circumference and C-reactive protein levels were still found to be higher in night workers [12]. Therefore, this large cohort shows that health habits can reduce the negative effect of shift work in cardiovascular risk.

A Japanese study compared the annual checkups of day workers with those of adults with alternating day/night shifts between 1991 to 2005. Alternating shift workers were found to have increased arterial pressure, even after adjusting for confounding factors. These findings suggested that alternating shift work may constitute an independent risk factor for increased blood pressure levels regardless of the known risk factors such as age and BMI [13].

Given the decrease in sleep duration observed over the past century, there is also a need for research into the association between sleep duration and occurrence of SAH and obesity. Currently, over 30 % of adults in the United States aged between 30 and 64 years sleep less than 6 h per night. Decreased sleep duration is often accompanied by a significant increase in the prevalence of obesity and SAH [14].

The First National Health and Nutrition Examination Survey (NHANES I) evaluated the relationship between sleep and the incidence of SAH in American adults. The incidence of SAH was associated with a sleep duration of 5 h or less (OR: 2.10; 95 % CI 1.58 - 2.79) in subjects aged 32 to 59 years. The control of confounding factors only attenuated this relationship. The risk of SAH in subjects with reduced sleep duration remained significantly elevated after adjusting for the presence of obesity and diabetes. This finding was consistent with the hypothesis that these conditions may act as partial mediators in the relationship between hypertension and sleep duration. The study concluded that sleep deprivation in healthy subjects can increase blood pressure levels and sympathetic nervous system activity [15]. Chronic short sleep duration may also contribute to the development and maintenance of SAH by inducing a prolonged increase in blood pressure levels and heart rate, increasing sympathetic activity, imposing physical and psychosocial stressors and increasing salt retention. Prolonged exposure to these factors may entrain the cardiovascular system to operate at an elevated pressure equilibrium through structural adaptations such as left ventricular hypertrophy [15].

Obesity/overweight

The association between weight-gain and night or shiftwork has also been investigated. A study performed in southern Brazil reported especially high rates of obesity in female night workers aged 40 years or older with low education levels and a family history of overweight. In this study, daily sleep duration was also divided into the three following categories: >5 h of continuous sleep, ≤5 h of continuous sleep with some additional rest, or ≤5 h of continuous sleep with no additional rest. After adjusting for confounding factors, obesity rates were found to be significantly higher in the latter two groups than in the first (composed largely of day workers), supporting the association between sleep deprivation and obesity [16].

A Japanese study which followed 21,693 men and 2109 women between 1999 and 2006 found that the relative risk of obesity was higher in men who slept for less than 5 h/24 h than in those who had at least 5 to 7 h of sleepper day. In women, these variables were not significantly associated. The study concluded that short sleep durations (<5 h) accelerated the onset of obesity in shift workers [17].

A systematic review performed by Van Drongelen [18] provided strong evidence of the association between shift work and increased body weight. Furthermore, behavioral changes potentially associated with shift work, such as reduced physical activity, may independently contribute to weight gain and the development of associated conditions such as metabolic syndrome and type 2 diabetes. However, the generalization of these findings is limited by the heterogeneity of the studies included in the meta-analysis, which varied widely in follow-up methods and periods, in the control of confounding factors, and in their definitions of shift work.

In a study performed by Di Lorenzo et al. [19], obesity was more prevalent in shift workers (20.0 %) than in dayworkers (9.7 %). Shift work was found to be associated with BMI regardless of age or duration of shift work exposure.

Despite all the evidence exposed above show great strength in the association between shift work and obesity, the mechanisms responsible for the association between these factors cannot yet be fully explained [20,21] and more studies are needed to understand the pathogenesis of this association.

Metabolic syndrome

A 5 year follow-up study of 387 female employees in Taiwan performed by Cheng Lin et al. [22] found that rotating shift work had significant deleterious effects on health, and resulted in an increased risk of metabolic syndrome. After

5 years, workers who initially had one or two risk factors for metabolic disease were 4.6 and 12.7 times, respectively, more likely to develop the condition.

Some studies have found associations between night or shift work and increased food intake, a preference for carbohydrate-rich foods, and alterations in lipid parameters, especially triglyceride levels [23].

Study conducted in China [24] with 26,382 workers (11,783 men and 14,599 women), with total of 9088 shift workers, long-term shift work was associated with metabolic syndrome without adjusting for any confounders factors. In female workers, every 10 years increase in shiftwork was associated with 10 % (95 % CI: 1 % -20 %) higher odds of metabolic syndrome. Moreover, shift work duration was significantly associated with higher blood pressure levels, higher waist circumference, and increase on glucose levels, all components of metabolic syndrome.

Study conducted by Kawabe in Japanese workers with 3094 subjects in the daytime work group, 73 in the fixed night time work group, 1017 in the shift work group and 243 in the day-to-night work group, showed that fixed night time and shift work independently contributed to the number of metabolic syndrome components, compared to daytime work [25].

Canuto et al. in a systematic review examined the association between shift work and metabolic syndrome. Eight of out 10 studies found a positive association between shift work and metabolic syndrome, after controlling for socio-demographic and behavioral factors. However, only three studies included sleep duration as a confounder, and these studies presented discordant results. Authors concluded that there was insufficient evidence regarding the association between shift work and prevalent metabolic syndrome when the confounders are taken into account [26].

Diabetes mellitus

The strongest evidence linking circadian disruption and type 2 diabetes derives from epidemiological studies which show that shift workers are at increased risk of developing this condition [27, 28].

In a sample of 2860 industry workers followed for 8 years, Morigawa et al. [7] found the incidence of diabetes to be 4.41 per 1000 people/year. The relative risk of diabetes was higher in subjects who worked consecutive night shifts than in those with administrative positions (relative risk: 2.01 after adjusting for all potential confounding factors). The study suggested that shift work is a risk factor for the development of diabetes.

A study performed by Pan et al. [27] compared the association between rotating vs. fixed shifts and type 2diabetes in 177,000 nurses aged 25–67 years. The risk of type 2 diabetes in participants exposed to rotating shiftwork for 1–2 years was 5 %. This value increased to 20 % after 3–9 years of rotating shift work, 40 % after 10–19 years, and almost 60 % after 20 years of rotating shifts.

Shift workers of a Japanese manufacturing company were evaluated for the association between shift work and diabetes mellitus according to intensity of work (seasonal or continuous), and adjusted for age, smoking status, frequency of alcohol consumption and status of cohabitation. The odds for diabetes was 0.98 (95 % confidence interval [CI]: 0.28 to 4.81) and 2.10 (95 % CI:0.77-5,71) among seasonal shift workers and continuous shift workers, respectively, compared to non-shift workers. The risk of diabetes mellitus was more pronounced in continuous shifts workers over 45 years [29]. This discrepancy may be due to circadian rhythm disturbed by a long-term continuous work, possibly causing insulin resistance and weight gain, and hence the type 2 diabetes mellitus [30].

A small study with type 2 diabetes individuals showed that glycemic control did not differ between night vs. day workers, although the night workers had a greater accumulation of visceral fat [31].

In type 1 diabetes patients, diabetes control was affect by shift work. In 296 workers, including 67 (23 %) shift workers, glycemic levels was higher in shift workers than in day worker subjects (HbA1c 9.02vs. 8.35; P <0.01) [32].

Several experimental studies in both animals and humans have sought to demonstrate the association between sleep disruption or deprivation and the risk of type 2 diabetes [33, 34].

Healthy individuals show reduced glucose tolerance and insulin sensitivity following six consecutive nights of 4 h sleep restriction [15]. In a controlled trial, which sought to determine the interference of circadian disruption on metabolism, 26 healthy adults were divided into two groups and exposed to different sleep restriction protocols. Although total sleep time per day was almost identical between groups, insulin sensitivity decreased significantly after sleep restriction, without a compensatory increase in insulin secretion. In male subjects exposed to circadian misalignment, the reduction in insulin sensitivity and increase in inflammatory activity was twice that of subjects with regular nocturnal sleep [35].

Evidence from human studies suggests that insufficient or poor quality sleep are risk factors for the development and exacerbation of insulin resistance and can increase both appetite and adiposity [36, 37]. A meta-analysis with 10 studies and 107,756 participants assessed the relationship between habitual sleep disturbances and the incidence of type 2 diabetes, and both quantity and quality of sleep predicted the risk of development of diabetes. For short duration of sleep (< or =5–6 h/night), the risk was 1.28, and for long duration of sleep (>8–9 h/night) the risk was 1.48 for incidence of type 2 diabetes and for difficulty in initiating sleep, the risk was 1.57 and for difficulty in maintaining sleep, the risk was 1.84 respectively [38].

During activity and feeding, the blood sugar content is primarily determined by nutrient intake. During rest and fasting, endogenous hepatic glucose production takes place, and glucose levels are maintained within a relatively narrow range. As such, blood glucose homeostasis is also associated with central circadian rhythmicity as well as peripheral oscillators located in regions such as the liver, pancreas, muscles and white adipose tissue [36].

Adipose tissue plays an important role in the endocrine system. In addition to functioning as a fat depot, these tissues play a role in adipokine secretion, which is involved in several physiological pathways, including sugar and energy metabolism. Leptin, adiponectin and visfatin are secreted in a circadian manner [39]. In addition to regulating satiety, leptin also increases energy expenditure and insulin sensitivity. Although it is hypothesized that alterations in the circadian rhythmicity of adipokines may induce insulin resistance, there is as yet no evidence supporting this assumption [36].

Sleep deprivation

Patel and Hu [40] also revealed an independent association between short sleep duration and weight gain. Gangwisch et al. analyzed data from the First

National Health and Nutrition Examination Survey (NHANES I) and found that subjects who slept for less than 6 h a day had higher BMI than those who slept for longer periods [15].

According to the National Health Interview Survey, which followed American adults aged 18 years or older from 1977 to 2009, subjects who slept for less than 5 h a day were 30 % more likely to be overweight and twice as likely to be obese as those who slept for 7 to 8 h a day. Similarly, subjects who slept for 5 to 6 h a day were 20 % more likely to be overweight and 57 % more likely to be obese than those who slept for longer periods of time. On the other hand, a habitual sleep duration longer than 8 h was associated with a 20 % increase in the risk of obesity, but had no impact on the likelihood of being overweight [41].

Sleep deprivation is known to decrease the concentration of leptin (an anorexigenic hormone) and increase levels of ghrelin (an orexigenic neuropeptide) [42]. According to a recent study, a short sleep duration is associated with reduced leptin levels and an increased prevalence of overweight [43]. These findings suggest that these hormonal pathways may be involved in the association between short sleep duration and obesity.

Other studies have also found that sleep deprivation may have an impact on both cognitive and physical performance, induce metabolic alterations such as the suppression of growth hormone production and of the circadian melatonin rhythm, and be associated with the development of metabolic syndrome, type 2 diabetes mellitus, hypertension and immunosuppression [44].

Circadian rhythm

The circadian rhythm has three main characteristics: it is endogenous, resistant to abrupt changes and may beslow to adapt to changing conditions. The central nervous system (CNS) is the major synchronizer of the human circadian rhythm, and coordinates circadian pacemakers in the brain and peripheral tissues through signals generated in the suprachiasmatic nucleus (SCN) of the hypothalamus which align the circadian period and phase with external stimuli [39].

The functional organization of the circadian system is comprised of three main components: inputs, which can reset the central pacemaker so that it becomes coincident with the external environment (light/dark cycles, social contacts, physical exercise, food); the central pacemaker and peripheral oscillators, present in most peripheral tissues and organs, and even under the command of SCN may occasionally desynchronize the circadian rhythm; and outputs, which are the physiological and behavioral functions, which may also provide feedback by modifying the function of the SCN, oscillators peripheral and suprachiasmatic nucleus (sleep/wakefulness, locomotor activity, endocrine rhythms, body temperature, cardiovascular rhythm, feeding time) [39, 45].

The SCN is directly connected to the retina via the retinal-hypothalamic tract. Signals sent over this pathway synchronize the circadian system to the 24 h day. The SCN then coordinates the remaining oscillators in the brain and peripheral tissues. The light–dark cycle is the most important synchronizer in the central circadian pacemaker [46], while feeding schedules are the most important Zeitgebers, or external synchronizers. As such, abrupt changes in feeding times and others several process, including peripheral temperature control and the sleep-wake cycle, can lead to the desynchronization of circadian rhythms [46, 47].

The causes and consequences of circadian desynchronization may also result from changes in physiological circadian periodicity induced by situational factors such as alterations in light–dark synchronization due to continuous or nocturnal light exposure, frequent snacking, reduced physical activity, nocturnal eating habits or physical activity, daylight savings time and changes in time zone [44]. Since night and shift work tend to affect all aforementioned factors, such schedules are likely to have a significant effect on worker health.

Desynchronization

The disruption of the internal temporal order is referred to as desynchronization. Repeated desynchronization and resynchronization may alter circadian rhythmicity and cause or accelerate disease, as shown by studies of the association between shift work and several chronic degenerative diseases.

However, despite these investigations, the mechanisms underlying the relationship between circadian desynchronization and obesity have not been fully elucidated. Factors such as frequent snacking, reduced sleep duration and increased exposure to bright light at night time may reduce the perception of internal and external rhythms. Several hypotheses have been proposed to explain the relationship between these factors.

The association among these variables may be mediated by biological processes such as autonomic dysregulation, increased hypothalamic-pituitary-adrenal axis activity or the activation of inflammatory pathways [41].

The autonomic nervous system (ANS) is responsible for controlling the internal circadian clock, especially with regard to abdominal and subcutaneous fat depots [37].

A pineal-hypothalamic-adipocyte hypothesis has also been proposed by Neel and revised by Scott and Grant [48], who suggested that, during longer summer days, pineal melatonin secretion is suppressed and food intake increases, resulting in increased fat deposition in anticipation to winter. These changes result in insulin resistance, increased leptin secretion and adiponectin suppression.

In hibernating animals, the adiponectin suppression and increased leptin secretion are coordinated to induce insulin resistance and decreased appetite in response to decreased food availability. During winter nights, melatonin secretion increases, resulting in increased adipocyte sensitivity to insulin and greater energy availability [48]. In humans, it is as if we are constantly preparing for a long and harsh winter with prolonged food deprivation which, in reality, never takes place.

Several studies have demonstrated that individuals who sleep for shorter periods of time have reduced leptin levels and increased circulating ghrelin, suggesting that sleep deprivation may affect the peripheral regulation of hunger and satiety [42, 49]. Ghrelin is a peptide produced by endocrine cells in the stomach and in the hypothalamus, which plays an important role in the energy balance by stimulating food intake and reducing fat utilization. It is also associated with gastrointestinal functioning and the kinetic properties of the stomach. Unlike most intestinal hormones, ghrelin serum levels increase during fasting and reduce after food intake [50].

An important implication of these findings is that the internal desynchronization of the circadian rhythmicity of satiety-related peptides, especially leptin, may be involved
in the imbalance between energy intake and expenditure [42, 43, 49].

Although obesity is a risk factor for the development of type 2 diabetes, recent studies have shown that insufficient sleep may also interfere with glucose metabolism and increase the risk of diabetes regardless of BMI. Sleep restriction may alter the energy balance and induce weight gain by causing both appetite dysregulation and lower calorie expenditure. Excessive weight gain can induce insulin resistance, increasing predisposition to disease and promoting adiposity [27, 34, 51].

Therapeutic implications

The adaptation to night or shift work depends of several factors, including lifestyle behaviors pertaining to one's family and social life, which usually follow a diurnal pattern. Some studies have found that exposure to bright lights during night-time and the use of melatonin may contribute to circadian synchronization, although this does not apply to all workers [52].

According to a review conducted by Roth [47], the management of shift work disorders must be adjusted to target each specific component of the disease. Circadian misalignment can be treated using melatonin or its agonist ramelteon combined with planned sleep schedules and timed light exposure. Daytime insomnia can be addressed by the use of sedative hypnotics like Zolpidem, Estazolam, Zopiclone and Triazolam, in addition to melatonin. Conversely, Modafinil, Armodafinil, caffeine and light exposure can be used to increase nighttime alertness and avoid or treat somnolence during work hours.

Circadian desynchronization and sleep disorders can also be avoided by having at least 7 h of sleep per 24 h, initiating the main sleep episode immediately after work, taking 30 min to 2 h naps prior to night shifts, napping for 20–30 min during the shift itself to help maintain wakefulness, especially in high-risk occupations, and increasing exposure to bright lights during the first half of the night shift. After the end of the night shift, workers should avoid exposure to bright lights and ensure their bedroom is quiet and dark [53].

Regular shifts and clockwise rotation may also avoid circadian desynchronization and associated health consequences. Haus [44] also recommends that, to avoid or minimize internal desynchronization, workers should be exposed to a maximum of four night shifts, followed by one night off for sleep recovery.

Cortisol levels increase upon waking and decrease over the course of the day. To maintain cortisol rhythmicity, diurnal light exposure should be kept constant, and mealtimes and exercise should follow a regular schedule [54].

Circadian variations in arterial pressure, which usually fluctuates over the course of the day and decreases at night, must also be monitored in shift workers and considered when prescribing anti-hypertensive medications.

These measures may attenuate the impact of night or shift work on health and must be addressed when organizing shift or night work schedules.

Conclusions

Shift and night work appear to have a negative effect on worker health, possibly due to its impact on sleep-wake cycles, eating and exercise habits, thermogenesis, hormone secretion, and blood pressure levels [39, 54, 55].

By identifying the association between shift characteristics and their impact on the body, we can find ways to minimize the health burden of shift work, so that societal demands can be met without compromising worker health. The comprehension of the mechanisms responsible for the effects of shift work on the body may contribute to the development of weight reduction strategies or elucidate ways to avoid weight gain altogether based on low-calorie diets, personalized health care and nutritional orientations, in addition to physical exercise programs which can be adapted to the worker's routine [45, 52, 54].

Abreviations:

ANS: Autonomic nervous system
BMI: Body mass index
CNS: Central nervous system
LDL: Low-desinty lipoprotein
SAH: Systemic arterial hypertension
SCN: Suprachiasmatic nucleus

References

1. de C Moreno CR, Fischer FM, Rotenberg L. A saúde do trabalhador na sociedade 24 horas. São Paulo Em Perspect. 2003;17:34–46.

2. Organização Internacional do Trabalho: Convenção sobre Trabalho Noturno–C171, 1990,Genebra. http://www.ilo.org/dyn/normlex/en/f

3. Rodrigues VP. Principais impactos do trabalho em turnos: estudo de caso de uma sonda de perfuração marítima. R Un Alfenas. 1998;4:199–207.

4. Burchell B. European foundation for the improvement of living and working conditions. Working conditions in the European union: working time and work intensity. Luxembourg: Office for Official Publications of the European Communities; 2009.

5. Karlsson B. Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27 485 people. Occup Environ Med. 2001;58:747–52.

6. De Bacquer D, Van Risseghem M, Clays E, Kittel F, De Backer G, Braeckman L. Rotating shift work and the metabolic syndrome: a prospective study. Int J Epidemiol. 2009;38:848–54.

7. Morikawa Y, Nakagawa H, Miura K, Soyama Y, Ishizaki M, Kido T, et al. Shiftwork and the risk of diabetes mellitus among Japanese male factory workers. Scand J Work Environ Health. 2005;31:179–83.

8. Froy O. The relationship between nutrition and circadian rhythms in mammals. Front Neuroendocrinol. 2007;28:61–71.

9. Vyas MV, Garg AX, Iansavichus AV, Costella J, Donner A, Laugsand LE, et al. Shift work and vascular events: systematic review and meta-analysis. BMJ.2012;345:e4800–0.

10. Pimenta AM, Kac G, Souza RR, Ferreira LM, Silqueira SM. Trabalho noturno e risco cardiovascular em funcionários de universidade pública. Rev Assoc Médica Bras. 2012;58:168–77.

11. De Gaudemaris R, Levant A, Ehlinger V, Hérin F, Lepage B, Soulat J-M, et al. Blood pressure and working conditions in hospital nurses and nursing assistants. The ORSOSA study. Arch Cardiovasc Dis. 2011;104:97–103.

12. Thomas C, Power C. Shift work and risk factors for cardiovascular disease: a study at age 45 years in the 1958 British birth cohort. Eur J Epidemiol.2010;25:305–14.

13. Suwazono Y, Dochi M, Sakata K, Okubo Y, Oishi M, Tanaka K, et al. Shiftwork is a risk factor for increased blood pressure in Japanese Men: a 14-year historical cohort study. Hypertension. 2008;52:581–6.

14. Gallup Organization. Sleep in America. Gallup Organization; 1995. National Center for Health Statistics. Quick Stats: percentage of adults who reported an average of < 6 hours of sleep per 24 hour period, by sex and age group– United States, 1985 and 2004. MMWR Morb Mortal Wkly Rep. 2005;54:933.

15. Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB. Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. Sleep.2005;28:1289–96.

16. Canuto R, Pattussi MP, Macagnan JBA, Henn RL, Olinto MTA. Sleep deprivation and obesity in shift workers in southern Brazil. Public Health Nutr. 2014;17:2619–23.

17. Itani O, Kaneita Y, Murata A, Yokoyama E, Ohida T. Association of onset of obesity with sleep duration and shift work among Japanese adults. Sleep Med. 2011;12:341–5.

18. Van Drongelen A, Boot CRL, Merkus SL, Smid T, van der Beek AJ. The effects of shift work on body weight change - a systematic review of longitudinal studies. Scand J Work Environ Health. 2011;37:263–75.

19. Di Lorenzo L, De Pergola G, Zocchetti C, L'Abbate N, Basso A, Pannacciulli N, et al. Effect of shift work on body mass index: results of a study performed in 319 glucose-tolerant men working in a Southern Italian industry. Int J Obes Relat Metab Disord J Int Assoc Study Obes. 2003;27:1353–8.

20. Van Amelsvoort LGPM, Schouten EG, Kok FJ. Impact of one year of shiftwork on cardiovascular disease risk factors. J Occup Environ Med Am Coll Occup Environ Med. 2004;46:699–706.

21. Hannerz H, Albertsen K, Nielsen ML, Tuchsen F, Burr H. Occupational factors and 5-year weight change among men in a danish national cohort. Health Psychol Off J Div Health Psychol Am Psychol Assoc. 2004;23:283–8.

22. Lin Y-C, Hsiao T-J, Chen P-C. Persistent rotating shift-work exposure accelerates development of metabolic syndrome among middle-aged female employees: a five-year follow-up. Chronobiol Int. 2009;26:740–55.

23. Al-Naimi S, Hampton SM, Richard P, Tzung C, Morgan LM. Post prandial metabolic profiles following meals and snacks eaten during simulated night and day shift work. Chronobiol Int. 2004;21:937–47.

24. Guo Y, Rong Y, Huang X, Lai H, Luo X, Zhang Z, et al. Shift work and the relationship with metabolic syndrome in Chinese aged workers. In: Behrens T, editor. PLoS One, vol. 10(3). 2015. p. e0120632.

25. Kawabe Y, Nakamura Y, Kikuchi S, Murakami Y, Tanaka T, Takebayashi T, et al. Relationship between shift work and clustering of the metabolic syndrome diagnostic components. J Atheroscler Thromb. 2014;21:703–11.

26. Canuto R, Garcez AS, Olinto MTA. Metabolic syndrome and shift work: a systematic review. Sleep Med Rev. 2013;17:425–31.

27. Pan A, Schernhammer ES, Sun Q, Hu FB. Rotating night shift work and risk of type 2 diabetes: Two prospective cohort studies in women. PLoS Med.2011;8, e1001141.

28. Kroenke CH, Spiegelman D, Manson J, Schernhammer ES, Colditz GA, Kawachi I. Work characteristics and incidence of type 2 diabetes in women. Am J Epidemiol. 2006;27(165):175–83.

29. Ika K, Suzuki E, Mitsuhashi T, Takao S, Doi H. Shift work and diabetes mellitus among male workers in Japan: does the intensity of shift work matter? Acta Med Okayama. 2013;67:25–33.

30. Kivimäki M, Batty GD, Hublin C. Shift work as a risk factor for future type 2 diabetes: evidence, mechanisms, implications, and future research directions. PLoS Med. 2011;8:e100–138.

31. Rodrigues TC, Canani LHS. A influência do turno de trabalho em pacientes com diabetes mellitus tipo 2. Rev Assoc Médica Bras. 2008;54:160–2.

32. Young J, Waclawski E, Young JA, Spencer J. Control of type 1 diabetes mellitus and shift work. Occup Med. 2013;63:70–2.

33. Gale JE, Cox HI, Qian J, Block GD, Colwell CS, Matveyenko AV. Disruption of circadian rhythms accelerates development of diabetes through pancreatic beta-cell loss and dysfunction. J Biol Rhythms. 2011;26:423–33.

34. Buxton OM, Cain SW, O'Connor SP, Porter JH, Duffy JF, Wang W, et al. Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. Sci Transl Med. 2012;4:129–43.

35. Van Cauter E. Sleep disturbances and insulin resistance. Diabet Med J Br Diabet Assoc. 2011;28:1455–62.

36. Kalsbeek A, la Fleur S, Fliers E. Circadian control of glucose metabolism. Mol Metab. 2014;3:372–83.

37. Perez-Tilve D, Stern JE, Tschöp M. The brain and the metabolic syndrome: not a wireless connection. Endocrinology. 2006;147:1136–9.

38. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2010;33:414–20.

39. Garaulet M, Ordovás JM, Madrid JA. The chronobiology, etiology and pathophysiology of obesity. Int J Obes. 2010;34:1667–83.

40. Patel SR, Hu FB. Short sleep duration and weight gain: a systematic review. Obesity. 2008;16:643–53.

41. Jean-Louis G, Williams NJ, Sarpong D, Pandey A, Youngstedt S, Zizi F, et al. Associations between inadequate sleep and obesity in the US adult population: analysis of the national health interview survey (1977–2009).BMC Public Health. 2014;14:290.

42. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med. 2004;1, e62.

43. Chaput J-P, Després J-P, Bouchard C, Tremblay A. Short sleep duration is associated with reduced leptin levels and increased adiposity: results from the Québec family study*. Obesity. 2007;15:253–61.

44. Haus E, Smolensky M. Biological clocks and shift work: circadian dysregulation and potential long-term effects. Cancer Causes Control.2006;17:489–500.

45. Antunes LC, Levandovski R, Dantas G, Caumo W, Hidalgo MP. Obesity and shift work: chronobiological aspects. Nutr Res Rev. 2010;23:155–68.

46. Morris CJ, Aeschbach D, Scheer FAJL. Circadian system, sleep and endocrinology. Mol Cell Endocrinol. 2012;349:91–104.

47. Qin L-Q, Li J, Wang Y, Wang J, Xu J-Y, Kaneko T. The effects of nocturnal life on endocrine circadian patterns in healthy adults. Life Sci. 2003;73:2467–75.

48. Scott EM, Grant PJ. Neel revisited: the adipocyte, seasonality and type 2 diabetes. Diabetologia. 2006;49:1462–6.

49. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med. 2004;141:846–50.

50. Correa-Silva SR, de Sá LBPC, Lengyel A-MJ. Ghrelina e secretagogos do hormônio de crescimento (GHS): modulação da secreção do hormônio decrescimento e perspectivas terapêuticas. Arq Bras Endocrinol Metabol.2008;52:726–33.

51. Nedeltcheva AV, Kessler L, Imperial J, Penev PD. Exposure to recurrent sleep restriction in the setting of high caloric intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance. J Clin Endocrinol Metab. 2009;94:3242–50.

52. Crowley SJ, Lee C, Tseng CY, Fogg LF, Eastman CI. Combinations of bright light, scheduled dark, sunglasses, and melatonin to facilitate circadian entrainment to night shift work. J Biol Rhythms. 2003;18(6):513–23.

53. Rajaratnam SMW, Howard ME, Grunstein RR. Sleep loss and circadian disruption in shift work: health burden and management. Med J Aust.2013;199:S11–5.

54. Van Someren EJW, Riemersma-Van Der Lek RF. Live to the rhythm, slave to the rhythm. Sleep Med Rev. 2007;11:465–84.

55. Knutsson A. Health disorders of shift workers. Occup Med. 2003;53:103–8.

Artigo 2

NIGHT WORK, SHORT SLEEP AND OBESITY

Maria Carlota Borba Brum, MD, MsC[1,2]; Camila Morelatto de Souza MD, PhD[3], Fábio Fernandes Dantas Filho, MD[1,2], Claúdia Carolina Schnorr[4], Otávio Azevedo Bertoletti[1]; Gustavo Borchardt[4]; Ticiana C. Rodrigues, MD, PhD[2,4,5]

[1]Division of Occupational Medicine, Hospital de Clínicas - Porto Alegre/ Brazil.

[2] Post-graduate program Medical Sciences: Endocrinology, Universidade Federal do Rio Grande do Sul.

[3]Laboratory of Chronobiology, Hospital de Clínicas - Porto Alegre/ Brazil.

[4]Department of Internal Medicine, Medical School, Universidade Federal do Rio Grande do Sul.

[5] Division of Endocrinology, Hospital de Clínicas - Porto Alegre/ Brazil.

Corresponding author
Maria Carlota Borba Brum
Email: mcarlotabrum@gmail.com
Division of Occupational Medicine, Hospital de Clínicas de Porto Alegre,

Address: Rua Ramiro Barcelos 2350

Porto Alegre, RS, Brazil

Zip code 90035-003

Abstract

Background: Obesity is associated with increased overall mortality and comorbidities. Possibly caused by lifestyle factors, such as excessive calorie intake, physical inactivity and genetic profile, other factors have been implicated in the pathogenesis of obesity, such as sleep duration and shift work.

Objectives: The aim of this study was to evaluate the association between shift work, quality of life and obesity among healthcare professionals of a brazilian university hospital.

Methods: Cross-sectional study performed April 2013-December 2014 with 200 workers of a university hospital. Sociodemographic data evaluated and BREF WHOQOL used for quality of life. The physical activity was evaluated using the International Physical Activity Questionnaire (IPAQ), Chronotypes and daily sleep preference investigated using Munich Chronotype Questionnaire (MCTQ). Sleep disorders investigated using questions from Pittsburth Sleep Quality Index. Physical examination performed and venous blood collected after 12-hour fasting for laboratory tests.

Results: In this sample, the night workers have higher income, are older and are more experienced compared to day workers. Regarding lifestyle, night workers sleeps less hours ($p = 0.003$) and are more active (35.3%; $p = 0.034$) than day workers, but the last consume more alcohol (62.3%, $p = 0.017$). The night workers have higher weight, BMI, waist circumference and heart rate when compared to day workers. Multiple analysis showed that night workers are 48% more likely to develop abdominal obesity and 78% to obesity compared with day workers, however, longer duration of sleep reduced at 5% the risk of abdominal obesity. Analysis of MCTQ parameters showed that night workers had lower sleep duration at working days and free days, associated with a higher social jetlag social.

Conclusions: The results show that night work is a risk factor for weight gain, both overweight and for obesity, and for the accumulation of visceral fat.

Key words: obesity, overweight, night work, sleep restriction.

Introduction

Shift work has been definitively incorporated to society today, and is no longer limited to essential services such as health, public safety and heavy industry, but also occurs in other goods and services production branches. Shift work can be continuous, where workers follow each other at the workplace, or in rotating shifts (1). In the USA and Europe it is estimated that about 18 to 20% of workers are involved in night work or in shifts (2).

Night work or shift work presents common characteristics which may interfere in the circadian physiological process causing desynchronization. Exposure to continuous light during the night, frequent snacks, little physical activity, nocturnal eating habits and nocturnal physical activities are among the possible triggering factors (3).

Several studies have demonstrated that shift work may induce the development of dyslipidemias, diabetes mellitus (4,5) and systemic arterial hypertension (SAH). The prevalence of obesity has grown gradually in the last few decades in the USA (6) and is associated with an increase in overall mortality and comorbidities secondary to the disease, especially SAH, insulin resistance, dyslipidemia and atherosclerosis (7). It is acknowledged that life style related factors, such as the excessive intake of calories, genetic profile and sedentarism are the main factors responsible for increased obesity. However, other factors have been implicated in its pathogenesis, such as duration of sleep and shift work. A few authors observed a positive relationship between work in night shifts or shifts with the increased body mass index (BMI), and this is significantly greater compared to the day shift workers (9,10) Knutson et cols found that the reduction of sleep duration may also increase the risk of cardiovascular diseases, insulin resistance, diabetes and also obesity (11).

Short sleep (defined as ≤6 h of sleep/day) and sleep disorders due to shift work, have been associated with negative effects on the hormone profile and a positive energy balance (12). Restricted sleep has metabolic and endocrine consequence, including reduction of glucose tolerance and insulin sensitivity, increased serum concentration of nocturnal cortisol, rise of ghrelin levels, reduction of leptin levels and increased feeling of hunger and appetite (13–15). In this sense, it is believed that the reduction in the number of hours of sleep may be related to the increased incidence of obesity and overweight, although the mechanisms of such a relationship are not yet fully known (7)

The objective of this study was to evaluate the association between work shift and obesity, as well as quality of life among the workers at a university hospital, identifying the individuals who are more vulnerable or at greater risk for this condition.

Material and Methods

The study was performed during the period from April 2013 to December 2014, participants were recruited in annual medical exams at a university hospital in the city of Porto Alegre, southern Brazil. The study included 200 employees of the departments of administration, support, direct patient care, and maintenance of hospital machinery and equipment, who worked in the day and night shifts and accepted to participate in the study. The exclusion criteria in the study were professionals on a limited time contract, off work for more than 15 days, pregnant women or employees who were in the process of retiring.

As to the work hours, the day shift is from 6 to 8 hours a day (from 7 am to 1 pm, from 8 am to 5 pm and from 1 pm to 7 pm), on work scales of 5 days/2 days, 6 days/1 day, considering days of work and days of rest, and on duty periods of 12 hours at weekends For the night shift the work hours are 6 to 12 hours (from 6 pm to 12 midnight and from 7 pm to 7 am) on work scales of 12/60 hours or 12/24 hours, or 6 nights/1 day, 5 nights/2 days, or 4 nights/3 days, considering the days on duty and the days of rest.

The information concerning age (collected as a continuous variable), race (classified as white or other), sex, marital status (classified as with or without a partner), number of children, level of schooling income (categorized as years of study), professional activity (categorized as administrative, health professionals, support and maintenance), time at activity, time in the company, work hours, time on shift, work scales, another job, shift at another job, personal history of hypertension, diabetes, angina, dyslipidemia and glucose intolerance, smoking habit (self reported as a smoker or non-smoker last month), drinking alcoholic beverages (self reported as which drink, consumption of time and number of cups per week), hours of sleep was evaluated using the self-applied questionnaire. In order to evaluate the health status, a physical examination was performed (weight, height, blood pressure, heart rate, measurements of abdominal circumference and venous blood collected after 12 hours fasting for laboratory tests of fasting glycemia, glycated hemoglobin, insulin, total cholesterol and fractions, triglycerides, urea, creatinine, alanine aminotransferase, ultrasensitive C-reactive protein, blood count and platelets). The interviewers were trained in the technique used to check the measures of weight, height, body mass index (BMI) and abdominal circumference (AC).

A Welmy anthropometric balance, model R/1W-200 with a capacity of 200 kg and precision of 0.100 grams was used to measure weight. A Tonelli stadiometer with a centimeter decimals scale was used to check heights. The blood pressure in both arms was measured with the patients seated. After 10 minutes rest it was done with a digital apparatus, Welch Ally, model Vital Signs Monitor 300 series.

The BMI was calculated with the measures of weight and height according to the following formula BMI = weight (kg)/height^2. The cutoff points adopted for BMI were those suggested by WHO9, ie. eutrophy (18,5-24,99); overweight (25-29,99) and obesity (≥ 30,00). The abdominal circumference was obtained at the midpoint between the last arch and the iliac crest and with a flexible and inelastic measuring tape without compressing the tissues. Abdominal obesity defined waist circumference was greater than or equal to men and greater than or equal to 88 for women

Physical activity

Physical activity practiced by the individuals participating in the study was evaluated using the *International Physical Activity Questionnaire* (IPAQ), short version, classifying the level of physical activity as sedentary, irregularly active, active and very active, based on the information in meters/minute/week (16).

Quality of Life

Quality of life was evaluated using the WHOQOL BREF questionnaire version 1998 (WHO). For the purpose of evaluating quality of life, it is understood as a greater variety of conditions that may affect the individual's perception, their feelings, and behavior related to their daily functioning, including but not limited to their health status and medical interventions. WHOQOL BREF evaluates 4 domains and their respective facets: physical, psychological, personal relations and the environment, how the individual evaluates their quality of life and satisfaction with their health. The answers to the question were given on a scale with a single interval of 0 (zero) to 5 (five) and the final scores of each domain were calculated by a syntax that considers the answers of each question that makes up the domain, on a scale of 4 to 20 and later standardized on a scale of 0 to 100 (17).

Chronotype and Quality of sleep

The chronotypes and daily sleep preferences were investigated during the self-evaluation Munich Chronotype Questionnaire (MCTQ), elaborated and validated by Roenneberg et al., 2003 (18). The MCTQ is a structured questionnaire on the behavior of wakefulness and sleep, and exposure to sunlight on work days and days of rest. The interviewees inform how many days during the week they were involved in a regular work routine and the times at which they go to bed, are ready to go to sleep, fall asleep, and after how many minutes they get up, and how much time they spend in the open air. The following were calculated based on this information: sleep duration, midpoint of sleep for days of work and of rest, and jetlag social, which is the difference between the individual's "biological clock", and the "social clock", that defines the social commitments of an individual throughout the day.

Three questions from the Pittsburgh Questionnaire were used to evaluate the quality of sleep, considering the capacity to fall asleep, awake in the middle of the night, and quality of sleep in the last month (19), to evaluate the quality and sleep efficiency.

The diagnosis of Metabolic Syndrome was defined according to the updated criteria of the International Diabetes Federation (IDF): association between centripetal obesity (specific abdominal circumference for each ethnic group and gender) with two or more of the following parameters: triglycerides > or equal to 150mg/dl or specific treatment for dyslipidemia; HDL cholesterol < or equal to 50 mg/dl in women and < or equal to 40 mg/dl in men, or specific treatment for dyslipidemia; elevation of systolic blood pressure > or equal to 130 mmHg or diastolic > or equal to 85 mmHg, or prior diagnosis of SAH, fasting glycemia > or equal to 100 mg/dl, or prior diagnosis of type 2 diabetes mellitus (20).

The criteria used to classify blood pressure were according to the 6th Brazilian Guidelines on Arterial Hypertension; normal diastolic blood pressure (arterial pressure < 90 percentile), pre-hypertension (arterial pressure between percentiles 90 to 95), stage 1 hypertension (95 to 99mmHg percentile plus 5 mmHg), stage 2 hypertension (arterial pressure> percentile 99 percentile plus 5mmHg)(21).

The present study was conducted with the approval of the Institution's Ethics Committee. All the participants signed the Free and Informed Consent Form.

Statistical Analysis;

Descriptive statistics was used to characterize the sample and the results were presented using central (median or mean) and variability measures (standard deviation or percentiles (25 and 75), besides absolute and relative frequencies, according to the type of variable. Normality was verified using the Shapiro-Wilk test.The sociodemographic variables on health conditions, living habits, clinical and laboratory characteristics were presented and analyzed in all individuals. Statistical differences between the shifts and according to the sex of the professionals were evaluated using Pearson's Chi-Square tests (or Exact

Fisher test, when necessary) and the Student t test (or Mann-Whitney) for the categorical and continuous variables, respectively.

The associations of factors being studied (jetlag social, hours of sleep, duration of sleep and work shift) with the outcomes of obesity, excess weight (which was defined as overweight plus obesity) and high abdominal circumference were evaluated by Poisson regression analyses with a robust estimate of variance, always adjusted by sex and age. The Wald test was used to test the significance of variables and estimates of the prevalence ratios (PR) were presented with a 95% confidence interval.

The correlations of the MCTQ variables with the clinical and laboratory variables and age were evaluated through the Spearman correlation coefficient. Differences in the MCTQ score regarding shift were evaluated using the Student t test (or Mann-Whitney) and the same analysis was performed stratifying according to sex. As to BMI, ANOVA or Kruskal-Wallis) was applied and also stratified according to sex.

The quality of life scores were compared between the work shifts and between the number of hours of sleep, which was divided into two categories – more than 6 hours and less or equal to 6 hours - using the Student t test for 119 individuals. These comparisons were also performed with the stratified sample according to sex. All analyses were performed using the *Statistical Package for Social Sciences* (SPSS) software, version 21 and the statistical significance adopted was 5%.

Results:

Two hundred workers were included in the study, 69.5% (139) women and 30.5%(61) men. Considering the health conditions and living habits of the workers included in the sample, it was observed that the day shift workers had a higher prevalence of alcohol consumption (62.3%; p = 0.017), without a difference in the consumption profile (duration, quantity and type of beverage) between shifts (Table 1).

As to the classification of physical activity, only 6.7% of the male workers in the day shift were classified as very active, while in the night shift this prevalence was 35.3% (p = 0.034). Among the women, no significant associations were observed (p=0.9'75) (Table 1).

Three questions from the Pittsburgh Questionnaire were used to evaluate the quality of sleep, considering the capacity to fall asleep, awake in the middle of the night and the quality of sleep in the last month. No significant changes were found between the shifts, even after stratification by sex.

As to WHOQOL bref, 60% (119) of the questionnaires were answered and 78 (65.5%) of the professionals evaluated their quality of life as good.

In the evaluation of domains, the physical domain presented the highest mean of scores (68.6 ±15.9) followed by the social relations (66.6±18.7), psychological (66.5± 14.1) and environmental domains (59.9 ±14.5). Considering the work shifts, the day shift did better in all domains, except the environment, but the differences observed were not significant.

Stratifying by sex, it was observed that in men, the scores of the physical domain of night shift workers were lower than those of the day shift (65.7±18.1 vs 76.7±12.9, respectively; p-value= 0.047), as well as the scores of psychological well-being (65.5±13.8 vs 76.0±10.6, respectively, p-value 0.017). The domains of social relations and the environment did not show significant differences, and in women no significant differences were found either in the four domains of quality of life regarding work shift.

The scores of the physical domain were lower in the sample that reported <= 6 hours of sleep compared to those who sleep >6 hours (65.0±14.7 vs. 72.42±16.9, respectively; p =0.013). Similar behavior was observed for the psychological domain (63.6±14.0 vs 70.1±13.3, respectively; p =0.013).

In night shift workers on their days off, a negative correlation was found between systolic blood pressure (r_S=-0.275; p=0.040), diastolic pressure (r_S=-0.309; p=0.019) and heart rate (r_S=-0,289; p=0.031) with duration of sleep. A negative correlation was also observed between weight and jetlag social (r_S=-

0.301; p=0.023) and between age and duration of sleep on work days (r_S=-0.263; p=0.048).

Analysis of the MCTQ parameters showed that the night shift workers had a midpoint of sleep on work days [5:30 (4:09-10:30) vs. 3:41 (2:48-4:31) p <0.001], greater social jetlag social [-0:27 (-6:26-0:06) vs. 1:03 (0:06-1:56) p <0.001], and shorter duration of sleep on the work days (6:00±2.27 vs. 7:03±1.39 p 0,007) compared to the day shift. (Table 3).

In the analysis without adjustment, the night shift workers presented a 52% higher risk of abdominal obesity than the day shift ones (PR=1.52 (CI95%: 1.27-1.83); p<0.001). For each increased jetlag social unit, 3% less risk of abdominal obesity were observed (RP=0.97 (CI95%: 0.94 – 0.99); p=0.007), and every additional hour of sleep duration reduces the chance of abdominal obesity by 5%(PR=0.96 (CI95%: 0.91 – 1.00); p=0.049). In the multiple analysis, controlled for age and sex, the shift was the only variable that remained significantly associated, where the risk of abdominal obesity increases 48% [PR=1.48 (CI95%: 1.25 – 1.76); p < 0.001] for the employees who work at night compared to the day shift workers (Table 4).

The night shift workers presented a 38% higher risk of developing excess weight (overweight + obesity) than the day shift [PR=1.38 (CI95%: 1.13-1.68); p=0.002] and for every increased unit of jetlag social and hour of sleep there was 3% [Pr=0.97 (CI 95%, 0.94 – 0.99); p=0.003] and 7% [PR=0.93 (CI95%: 0.88 – 0.98); p=0.010] reduction of risk of presenting excess weight, respectively. In the multiple analysis, controled for age and sex, there was a tendency to reduce the risk of excess weight by around 2% (PR=0.98 (CI95%: 0.95 – 1.00); p = 0.052) for every increased unit of jetlag social, but it was not significant (Table 4).

The chance of obesity increases by 78% in night shift workers compared to the day shift [PR=1.78 (CI95%: 1.13-2.81); p=0.013] and for every increased unit of jetlag social there was 7% (RP=0,93 (IC95%: 0,88 - 0,98); p=0,007) reduction of this risk. In the multiple analysis, controlled for age and sex, it was observed that at every increase in jetlag social, 7% reduction of the risk of developing obesity was maintained (PR=0.93 (CI95%: 0.88 – 0.99); p = 0.018) (Table 4).

Among the night shift workers, a higher prevalence of people who sleep a smaller amount of hours was observed, equal to or less than six hours /day, compared to day shift workers (p = 0.003). In the stratified analysis for sex it was observed that this behavior is present only in night shift women workers compared to the day shift ones, 66% vs. 33% (p = 0.006) respectively.

Discussion:

This study evaluated the association between work shifts and the presence of excess body weight. The results showed that night shift work was a determining risk factor for weight increase, whether it be obesity or overweight, and also for the accumulation of visceral fat.

Regarding the profile of night shift workers in our sample, we observed that they were older, had a higher income, drank less alcohol and had the same frequency of distribution by sex compared to the day shift workers. The night shift workers have less hours of sleep, both on their work days and on their free days compared to people who work in the daytime. However, even having slept a greater number of hours on their days off compared to the days worked, those who work at night do not manage to recover the sleep deficit produced by the days of work (jetlag social).Social jetlag social is calculated based on the difference between the of sleep on the work days and the free days, enabling a quantification of the difference between the biological and social clocks, resulting in chronic loss of sleep (18).This sleep debt may be due to many reasons, mainly the presence of light during the time for sleep, the increased temperature and an altered cortisol secretion. All of them affect duration and quality of sleep. (22)

The association between night work or shift work and increased body weight is present in some studies (23,24), however, the pathophysiological mechanisms of this association are not yet clear. A systematic review performed by Van Drongelen (24) showed evidence of the association between shift work and increased body weight, and the generalization of these findings is limited by the heterogeneity of the studies included in the meta-analysis. For Di Lorenzo et al (9), obesity was more prevalent in rotating shift work (20.0%), than among daytime workers (9.7%), independent of age or time of exposure to the risk.

In a review performed by Peplonska et al (26), a significant linear observation was made between night work (number of years and hours of work) and BMI and abdominal circumference. A Brazilian study performed at 18 public hospitals with 2,371 nursing staff (27) identified an association between years of exposure to night work and BMI for both sexes after adjusting for all covariables. The effect of night work was greater among the men than among the women. For women who worked at night, for 20 years, the estimated mean of the BMI was 25.6 kg / m2 (25.0-26.2). As to the men, after 20 years of exposure to night work, the mean BMI estimated was 26.9 kg / m2 (25.6-28.1).

Ramin et al examined the association between night work and age and malignant neoplasm and risk factors for cardiovascular diseases in the Nurses' Health Study (NHS II), including 54,724 participants, 72% of them night shift workers. The results showed that the night workers had a greater chance of obesity (OR = 1.37, 95% CI 1.31-1.43); compared to the daytime workers. They observed that younger workers suffer less impact from night work on their risk of becoming obese, while the older ones are more exposed to this outcome (28).

Systolic AP, diastolic AP and heart rate were negatively influenced by the shorter duration of sleep, the same happening with body weight and jetlag social in people who work at night. On the other hand, in the daytime workers, jetlag social had a negative influence on the AC. Some studies have associated the development and maintenance of systemic arterial hypertension with the diminished duration of sleep (29,30). Sleep deprivation in healthy individuals may increase the levels of blood pressure and the activity of the sympathetic nervous system (29).

Our results confirmed the association between night work and visceral obesity and increased weight, whether it be overweight or obesity, at the same time as we show that sleeping more hours or reducing the sleep debt attenuated this association.

Leproult et al, in their broad review on the topic, concluded that the risk of obesity in general increases for individuals who sleep less than 6 hours, with a significant association between short duration of sleep and weight gain, incidence of overweight and obesity throughout the follow up period (13). More recently, an American study with 883 individuals (31) demonstrated that the worst quality and shortest duration of sleep were significantly associated with the incidence of obesity (OR: 1.10; CI 95%: 1.03-1.18). This was partly explained by a breakdown in the circadian rhythm causing an increase of inflammatory markers and an imbalance of the body metabolism.

The preference of sleeping and waking (individual chronotype of each subject) is regulated by the biological clock, among other factors such as age, sex and environmental variables (32). We do not observe significant differences in the midpoint of sleep on free days among workers in both shifts. The means of the midpoint of sleep on the free days, in both work shifts, stayed in the range that suggests an intermediate chronotype pointed out as a more flexible profile that adjusts better to the timetables imposed by daily routines (day of work and/or study)(33).

The mechanisms that determine weight increase in situations of shift work have not been completely defined. The desynchronization of rhythmic physiological functions, that also impairs the duration and quality of sleep , interferes in the control of food intake, manifested metabolically by the increased levels of ghrelin and reduced levels of leptin, and may contribute to possible pathological mechanisms (3,34).

Among the possible limitations of our study there is emphasis on a cross-sectional design which does not allow establishing the causal relationship between shift work and obesity, and the absence of an evaluation of the food profile of the cohort studied, which might help differentiate shifts regarding eating behavior. The healthy worker effect is another aspect to be considered in relation to selection of the sample. However, such factors do not compromise the results, given the scarcity of information and the very relevance of the topic discussed.

The information obtained in our study is consistent with the data from recent research studies, insofar that it finds a positive association between night work, sleep reduction and obesity. The mechanisms of these changes are related to the circadian desynchronization, sleep deprivation and, possibly, to the neuro-hormonal regulation of appetite.

In order to support the evidence, further studies with long follow ups are necessary, so that it will be possible to elucidate the contribution of time of work in the shift and timetables of work to weight gain and work schedules on weight gain and even on cardiovascular outcomes.

Besides the better organization of the work structures, structuring personal life by organizing the sleep patterns appears to be extremely important for people who work at night.

References

1. Akerstedt T, Wright KP. Sleep Loss and Fatigue in Shift Work and Shift Work Disorder. Sleep Med Clin. 2009; **4(2)**: 257–71.

2. McMenamin TM. Time to work: recent trends in shift work and flexible schedules, A. Mon Lab Rev. 2007; **130**:3-15.

3. Garaulet M, Ordovás JM, Madrid JA. The chronobiology, etiology and pathophysiology of obesity. Int J Obes. 2010; **34(12)**: 1667–83.

4. Morikawa Y, Nakagawa H, Miura K, Soyama Y, Ishizaki M, Kido T, et al. Shift work and the risk of diabetes mellitus among Japanese male factory workers. Scand J Work Environ Health. 2005; **31(3)**: 179–83.

5. Copertaro A, Barbaresi M, Bracci M. [Shift work and cardiometabolic risk]. Recenti Prog Med. 2009; **100(11)**: 502–7.

6. Hill JO, Wyatt HR, Reed GW, Peters JC. Obesity and the environment: where do we go from here? Science. 2003; **299(5608)**: 853–5.

7. Ekmekcioglu C, Touitou Y. Chronobiological aspects of food intake and metabolism and their relevance on energy balance and weight regulation: Chrononobiology and energy balance. Obes Rev. 2011; **12(1)**: 14–25.

8. Atkinson G, Fullick S, Grindey C, Maclaren D. Exercise, energy balance and the shift worker. Sports Med. 2008; **38(8)**: 671–85.

9. Di Lorenzo L, De Pergola G, Zocchetti C, L'Abbate N, Basso A, Pannacciulli N, et al. Effect of shift work on body mass index: results of a study

performed in 319 glucose-tolerant men working in a Southern Italian industry. Int J Obes Relat Metab Disord J Int Assoc Study Obes. 2003; **27(11)**: 1353–8.

10. Biggi N, Consonni D, Galluzzo V, Sogliani M, Costa G. Metabolic syndrome in permanent night workers. Chronobiol Int. 2008; **25(2)**: 443–54.

11. Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. Sleep Med Rev. 2007; **11(3)**: 163–78.

12. Schiavo-Cardozo D, Lima MMO, Pareja JC, Geloneze B. Appetite-regulating hormones from the upper gut: disrupted control of xenin and ghrelin in night workers. Clin Endocrinol (Oxf). 2013; **79(6)**: 807–11.

13. Leproult R, Van Cauter E. Role of Sleep and Sleep Loss in Hormonal Release and Metabolism. In: Loche S, Cappa M, Ghizzoni L, Maghnie M, Savage MO, editors. Endocrine Development [Internet]. Basel: KARGER; 2009 [cited 2015 Oct 21]. p. 11–21. Available from: http://www.karger.com/doi/10.1159/000262524

14. Taheri S, Lin L, Austin D, Young T, Mignot E. Short Sleep Duration Is Associated with Reduced Leptin, Elevated Ghrelin, and Increased Body Mass Index. PLoS Med. 2004; **1(3)**: e62.

15. Nedeltcheva AV, Kessler L, Imperial J, Penev PD. Exposure to Recurrent Sleep Restriction in the Setting of High Caloric Intake and Physical Inactivity Results in Increased Insulin Resistance and Reduced Glucose Tolerance. J Clin Endocrinol Metab. 2009; **94(9)**: 3242–50.

16. Braggion G MS. Questionário internacional de atividade física(IPAQ): estudo de validade e reprodutibilidade no Brasil. 2001; **6(2)**: 05–18.

17. The Whoqol Group. The World Health Organization quality of life assessment (WHOQOL): Development and general psychometric properties. Soc Sci Med. 1998; **46(12)**: 1569–85.

18. Roenneberg T, Wirz-Justice A, Merrow M. Life between clocks: daily temporal patterns of human chronotypes. J Biol Rhythms. 2003; **18(1)**: 80–90.

19. Bertolazi, Alessandra N. Tradução, adaptação cultural e validação de dois instrumentos de avaliação do sono : escala de sonolência de Epworth e índice de qualidade de sono de Pittsburgh [Internet]. 2008 [cited 2015 Dec 11]. Available from: http://www.lume.ufrgs.br/handle/10183/14041

20. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the Metabolic Syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; **120(16)**: 1640–5.

21. Departamento de Hipertensão Arterial da Sociedade Brasileira de Cardiologia. VI Diretrizes Brasileiras de HIpertensão. Braz J Hypertens. 2010; **17(1)**: 01–69.

22. Niu S-F, Chung M-H, Chen C-H, Hegney D, O'Brien A, Chou K-R. The Effect of Shift Rotation on Employee Cortisol Profile, Sleep Quality, Fatigue, and Attention Level: A Systematic Review. J Nurs Res. 2011; **19(1)**: 68–81.

23. Morikawa Y, Nakagawa H, Miura K, Soyama Y, Ishizaki M, Kido T, et al. Effect of shift work on body mass index and metabolic parameters. Scand J Work Environ Health. 2007; **33(1)**: 45–50.

24. Buchvold HV, Pallesen S, Øyane NMF, Bjorvatn B. Associations between night work and BMI, alcohol, smoking, caffeine and exercise - a cross-sectional study. BMC Public Health [Internet]. 2015 Dec [cited 2016 Apr 29];**15(1)**. Available from: http://www.biomedcentral.com/1471-2458/15/1112

25. Van Drongelen A, Boot CRL, Merkus SL, Smid T, van der Beek AJ. The effects of shift work on body weight change - a systematic review of longitudinal studies. Scand J Work Environ Health. 2011; **37(4)**: 263–75.

26. Peplonska B, Bukowska A, Sobala W. Association of Rotating Night Shift Work with BMI and Abdominal Obesity among Nurses and Midwives. Sirtori CR, editor. PLOS ONE. 2015; **10(7)**: e0133761.

27. Griep RH, Bastos LS, Fonseca MJ, Silva-Costa A, Portela LF, Toivanen S, et al. Years worked at night and body mass index among registered nurses from eighteen public hospitals in Rio de Janeiro, Brazil. BMC Health Serv Res. 2014; **14(1)**: 603-10.

28. Ramin C, Devore EE, Wang W, Pierre-Paul J, Wegrzyn LR, Schernhammer ES. Night shift work at specific age ranges and chronic disease risk factors. Occup Environ Med. 2015; **72(2)**: 100–7.

29. Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB. Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. Sleep. 2005; **28(10)**: 1289–96.

30. Suwazono Y, Dochi M, Sakata K, Okubo Y, Oishi M, Tanaka K, et al. Shift Work Is a Risk Factor for Increased Blood Pressure in Japanese Men: A 14-Year Historical Cohort Study. Hypertension. 2008; **52(3)**: 581–6.

31. Ko SB. Night Shift Work, Sleep Quality, and Obesity. J Lifestyle Med. 2013;3(2):110.

32. Roenneberg T, Allebrandt KV, Merrow M, Vetter C. Social jetlag social and obesity. Curr Biol CB. 2012; **22(10)**: 939–43.

33. Alam MF, Tomasi E, Lima MS de, Areas R, Menna-Barreto L. Caracterização e distribuição de cronotipos no sul do Brasil: diferenças de gênero e estação de nascimento. 2008 [cited 2016 Apr 22];Available from: http://dms.ufpel.edu.br/ares/handle/123456789/298

34. Crispim CA, Zalcman I, Dáttilo M, Padilha HG, Tufik S, Mello MT de. Relation between sleep and obesity: a literature review. Arq Bras Endocrinol Metabol. 2007; **51(7)**: 1041–9.

Table 1. Demographic and occupational characteristics of workers according to work shift in southern Brazil.

Variables	Total	Day (n=94)	Night (n=106)	p
Age	43.2±9.3	40.4±9.2	45.6±8.6	**<0.001***
Sex (n=200)				0.958##
Female	139 (69.5)	66 (70.2)	73 (68.9)	
Male	61 (30.5)	28 (29.8)	33 (31.1)	
Race (n=200)				
White	155 (77.5)	74 (78.7)	81 (76.4)	0.825##
Non white	45 (22.5)	20 (21.3)	25 (23.6)	
Life partner (n=200)				0.106##
Yes	89 (45.5)	48 (51.1)	41 (38.6)	
No	111 (55.5)	46 (48.9)	65 (61.4)	
Children (n=124)				0.318##
Yes	92 (73.6)	39 (68.4)	53 (77.9)	
No	33 (26.4)	18 (31.6)	15 (22.1)	
Level of Schooling (n=200)				0.668#
Up to the age of 8 years	11 (5.5)	5 (5.3)	6 (5.6)	
From 8 to 11 years	123 (61.5)	55 (58.5)	68 (64.2)	
Above 11 years	66 (33.0)	34 (36.2)	32 (30.2)	
Smoking (n=117)				1.000¥
Smoker	11 (9.4)	5 (10.0)	6 (9.0)	
Non smoker	106 (90.6)	45 (90.0)	61 (91.0)	
Alcohol consumption (n=118)				0.017##
Yes	58 (49.2)	33 (62.3)	25 (38.5)	
No	60 (50.8)	20 (37.7)	40 (61.5)	
Treatment for SAH		7 (12.5)	14 (20.6)	0.340##
Treatment for diabetes		2 (3.6)	6 (8.8)	0.292¥
Treatment for dyslipidemia		5 (8.9)	4 (5.9)	0.730¥
IPAQ (n=112)				0.638#
Sedentary	14 (12.5)	5 (10.2)	9 (14.3)	
Irregularly active	14 (12.5)	7 (14.3)	7 (11.1)	
Active	61 (54.5)	29 (59.2)	32 (50.8)	

Very active	23 (20.5)	8 (16.3)	15 (23.8)	
Function (n=200)				**<0.001**#
Administrative	32 (16.1)	**22 (23.7)**	10 (9.4)	
Health professionals	125 (62.8)	44 (46.2)	**82 (77.4)**	
Support	32 (16.1)	**23 (24.7)**	9 (8.5)	
Maintenance	10 (5.0)	5 (5.4)	5 (4.7)	
Works elsewhere (n=124)				0.340#
Yes	15 (12.1)	9 (16.1)	6 (8.8)	
No	109 (87.9)	47 (83.9)	62 (91.2)	
Income (n=115)				0.001#
Up to 4 MW	31 (27.0)	**23 (44.2)**	8 (12.7)	
From 4.1 to 5 MW	46 (40.0)	14 (26.9)	**32 (50.8**)	
Above 5 MW	38 (33.0)	15 (28.8)	23 (36.5)	
Time at hospital (years)	11.1 (4.8-17.5)	6.2 (2.5-12.5)	15.6 (9.3-20.0)	**<0.001****
Time on shift (years)	5.3 (1.4-13.8)	3.8 (1.3-11.9)	7.2 (1.6-15.7)	0.076**

* Student t test; ** Mann-Whitney test; # Pearson's Chi-Square test; ## Pearson's Chi-Square test with continuity correction; ¥Exact Fisher test; Quantifiable variables with symmetrical distribution described by mean ± deviation. Quantitative variables with asymmetrical distribution described by the median (P25-P75). Categorical variables described by frequencies (percentages). (MW Minimum Wage)

Table 2. Clinical and laboratory characteristics of workers between day and night shifts in southern Brazil.

Variables	General			Women			Men		
	Day	Night	p	Day	Night	p	Day	Night	p
Weight (kg)	72.4±15.5	77.9±15.4	__0.011__**	69±13.1	72.6±12.8	0.128**	80.5±18.0	89.8±14.2	__0.030__*
BMI	26.4±4.6	28.7±4.8	__<0.001__**	26.3±4.6	28.4±4.9	__0.014__**	26.7±4.7	29.5±4.3	__0.018__*
AC	89.4±12.3	96.4±12.1	__<0.001__**	88.7±12.0	92.9±12.7	__0.009__**	92.9±12.7	100.7±11.7	__0.017__*
Presence MS	19 (29.2)	32 (43.2)	0.125$^{\#\#}$	13 (28.9)	21 (40.4)	0.332$^{\#\#}$	6 (30.0)	11 (40.0)	0.315$^{\#\#}$
SAP-right	116.0 (109.3-127.8)	120.0 (110.0-131.0)	0.240**	116.0 (109.0-127.5)	120.0 (110.0-129.0)	0.591**	121.0 (111.0-128.0)	120.0 (112.5-138.0)	0.180**
SAP-left	117.0 (108.0-125.0)	119.0 (110.0-130.0)	0.196**	115.0 (108.0-123.0)	118.0 (109.0-127.0)	0.424**	119.0 (111.0-131.0)	125.0 (112.5-139.0)	0.223**
DAP right	75.5 (68.0-84.8)	78.0 (70.5-86.0)	0.269**	76.0 (68.0-85.5)	77.0 (70.0-84.0)	0.790**	75.7±9.8	81.0±11.2	0.060*
DAP left	76.4±11.1	77.5±10.5	0.458*	77.0 (68.0-84.8)	77.0 (69.5-83.0)	0.890**	75.6±8.9	79.1±12.0	0.205*
HR	73.0±12.3	77.9±11.9	__0.006__*	74.5 (66.0-82.8)	76.0 (68.0-83.0)	0.307**	68.7±13.3	80.4±13.6	__0.001__*
TC	192.7±32.5	200.0±36.0	0.225*	195.7±33.4	200.5±32.4	0.474*	185.2±29.8	198.5±44.9	0.294*
HDL	49 (44-61.5)	47 (40-55.3)	0.070**	55.3±10.5	50.5±12.2	__0.041__*	44.0 (36.8-48.5)	43.0 (39.8-47.5)	0.980**
LDL	121.0±28.9	129.7±35.0	0.155*	123.4±30.7	127.6±27.1	0.522*	116.9±25.5	134.9±50.2	0.183*
Triglycerídes	97 (58.3-133.5)	100.0 (74.5-147.0)	0.257**	97.0 (58.0-125.0)	91.5 (68.5-135.4)	0.534**	100.0 (62.0-163.0)	120.0 (82.0-172.0)	0.294**
Glycemia	89.0 (81.0-95.8)	90.5 (85.0-99.8)	0.124**	89.0 (81.0-90.0)	89.0 (84.0-96.0)	0.215**	94.5 (80.8-99.0)	96.0 (88.0-108.0)	0.267**
Glycated Hb	5.4 (5.1-5.7)	5.5 (5.1-6.0)	0.271**	5.4±0.5	5.5±0.6	0.574	5.4 (5.2-5.5)	5.5 (5.1-6.6)	0.251**
Insulin	11.0 (8.5-15.8)	10.5 (7.6-13.9)	0.693**	11.1 (8.6-15.9)	12.2 (7.7-16.1)	0.789**	10.6 (7.5-15.2)	9.7 (7.5-10.7)	0.287**
Creatinine	0.7 (0.6-0.8)	0.7 (0.6-0.8)	0.487**	0.6 (0.5-0.7)	0.7 (0.6-0.7)	0.139**	0.9 (0.8-1.0)	0.9 (0.7-1.0)	0.657**
CKD-EPI TFG	111.0 (101.0-122.0)	104.5 (93.0-113.0)	__0.017__**	112.1±14.4	103.7±14.5	__0.006__*	102.8±13.7	99.6±19.5	0.583*
Urea	31.0 (26.0-37.0)	31.0 (27.0-38.0)	0.745**	29.0 (24.8-35.0)	30.0 (27.0-34.0)	0.429**	35.0 (29.5-41.0)	35.0 (30.0-41.0)	0.925**
TGO	21.0 (18.0-26.0)	21.5 (19.3-25.8)	0.412**	19.0 (17.8-25.0)	20.0 (19.0-24.0)	0.325**	24.5 (20.8-30.5)	30.5 (20.8-35.8)	0.372**
TGP	21.0 (14.3-28.8)	20.0 (16.0-25.0)	0.898**	18.0 (13.0-25.0)	18.0 (16.0-21.0)	0.554**	30.5 (20.8-35.0)	28.5 (20.0-55.5)	1.000**

US -PCR	2.2 (0.7-5.6)	2.5 (0.7-5.4)	0.992**	2.7 (1.1-7.2)	2.3 (0.7-6.8)	0.442**	0.9 (0.5-3.1)	2.5 (0.8-4.1)	0.179**

* Student’s t test; ** Mann-Whitney test; # Pearson’ s Chi-Square test; ## Pearson’s Chi-Square test with continuity correction; AC: Abdominal circumference in cm; BMI: b DAP: Diastolic arterial pressure (mmHg); HR: Heart rate; Hb: Glycated hemoglobin; HDL: high density lipoprotein; LDL: low density lipoprotein; MS: Metabolic syndrome; SAP: Systolic arterial pressure (mmHg); TGP: alanine aminotransferase; TGO: aspartate aminotransferase; TC: Total Cholesterol; US-PCR: ultrasensitive C-reactive protein;., Quantitative variables with symmetrical distribution described by mean ±deviation. Quantitative variables with asymmetrical distribution described by the median (P25-P75). Categorical variables described by frequencies and percentages

Table 3. Description of sleep variables according to sex and work shift, of workers in southern Brazil (n: 130)

MCTQ	General			Women			Men		
	Day	Night	p-value	Day	Night	p-value	Day	Night	p-value
Sleep midpoint working days	3:41 (2:48-4:31)	5:30 (4:09-10:30)	**<0.001****	3:45 (2:47-4:27)	4:45 (4:09-10:17)	**<0.001****	3:38 (2:47-4:38)	9:25 (5:07-12:38)	**<0.001****
Sleep duration working days	7:03 ± 1:39	6:00 ± 2:27	**0.007***	7:11±1:48	6.09±2:39	**0.040***	6:57±1:20	5:50±2:20	0.080*
Sunlight working days (hours)	1:00 (0:18-2:00)	1:00 (0:25-3:00)	0.433**	1:00 (0:30-2:00)	2:00 (0:40-3:00)	0.081**	2:00 (1:00-3:30)	1:00 (0:45-3:08)	0.262**
Midpoint days off	4:47 (4:03-5:42)	4:30 (3:48-5:53)	0.772**	4:50 (3:40-6:00)	4:30 (4:00-5:40)	0.650**	4:40 (4:08-5:30)	4:57 (3:06-6:21)	0.783**
Sleep duration days off	8:10 ± 1:59	7:40 ± 2:12	**0.046****	8:18 ± 2:21	7.54 ± 2:14	0.111**	8:01 ± 1:45	7:09 ± 2:18	0.191**
Sunlight days off (hours)	3:00 (2:00-5:00)	3:00 (1:09-4:09)	0.168**	2:45 (2:00-4:53)	2;30 (1:00-5:00)	0.741**	4:00 (3:00-6:30)	3:00 (1:11-4:00)	**0.048****
Jetlag social	1:03 (0:06-1:56)	-0:27 (-6:26-0:06)	**<0.001****	1:00 (0:00-2:17)	0:00 (-5:47-0:12)	**<0.001****	1:15 (0:30-1:45)	-1:30 (-7:50-0:05)	**<0.001****
Does not use alarm clock on days off	59 (85.5)	35 (62.5)	**0.006**##	40 (85.1)	26 (65.0)	0.053##	19 (86.4)	9 (56.3)	0.088##
Awakes with the alarm clock	26 (52.0)	7 (24.1)	**0.029**##	18 (54.5)	4 (20.0)	**0.029**##	8 (47.1)	3 (33.3)	0.797##

* Student t test; ** Mann-Whitney test; ## Pearson's Chi-Square test with continuity.

Table 4. Individual models of raw regressions and adjusted for outcomes of abdominal circumference, overweight and obesity of workers in southern Brazil, (n: 200)

			n (%)	RP$_{gross}$raw(CI95%)	p-value	RP$_{adjusted}$(CIC95%)$^{\#}$	p-value
Abdominal circumference	Jetlag social		-	0.97 (0.94-0.99)	**0.007**	0.98 (0.95-1.01)	0.127
	Hours of sleep		-	0.98 (0.94-1.02)	0.293	1.00 (0.94-1.07)	0.930
	Sleep duration DW			0.96 (0.91-1.00)	**0.049**	0.99 (0.94-1.05)	0.865
	Shift						
		Day	54 (58.7)	1		1	
		Night	95 (89.6)	1.52 (1.27-1.83)	**<0.001**	1.48 (1.25-1.76)	**<0.001**
Overweight	Jetlag social		-	0.97 (0.94-0.99)	**0.003**	0.98 (0.95-1.00)	**0.052**
	Hours of sleep		-	0.93 (0.88-0.98)	**0.010**	1.00 (0.91-1.10)	0.998
	Sleep duration DW			0.96 (0.91-1.01)	0.107	0.99 (0.93-1.06)	0.743
	Shift						
		Day	53 (57.6)	1		1	
		Night	84 (79.2)	1.38 (1.13-1.68)	**0.002**	1.14 (0.87-1.28)	0.352
Obesity	Jetlag social		-	0.93 (0.88-0.98)	**0.007**	0.93 (0.88-0.99)	**0.018**
	Hours of sleep		-	0.93 (0.82-1.05)	0.245	0.95 (0.78-1.18)	0.642
	Sleep duration DW			0.95 (0.84-1.08)	0.418	1.06 (0.86-1.30)	0.592
	Shift						
		Day	20 (21.7)	1		1	
		Night	41 (38.7)	1.78 (1.13-2.81)	**0.013**	1.00 (0.39-2.57)	0.997

Caption: $^{\#}$ Adjustment for sex and age. Excess weight: obesity + overweight.

Effect of night-shift work on cortisol circadian rhythm and melatonin levels

Maria Carlota Borba Brum, MD, MSc[1,2]; Marta Senger[3], Claúdia Carolina Schnorr[4], Suelen Mandelli Mota[4], Lethicia Rozales Ehlert[3], Ticiana C. Rodrigues, MD, PhD[2,3,5]

[1] Division of Occupational Medicine, Hospital de Clínicas de Porto Alegre, Brazil.

[2] Graduate program in Medical Sciences: Endocrinology, Universidade Federal do Rio Grande do Sul, Brazil.

[3] Division of Clinical Pathology, Hospital de Clínicas de Porto Alegre, Brazil.

[4] Department of Internal Medicine, Universidade Federal do Rio Grande do Sul School of Medicine, Brazil.

[5] Division of Endocrinology, Hospital de Clínicas de Porto Alegre, Brazil.

Corresponding author:

Maria Carlota Borba Brum
Email: mcarlotabrum@gmail.com
Division of Occupational Medicine, Hospital de Clínicas
Rua Ramiro Barcelos, 2350
Porto Alegre, RS 90035-003
Brazil

Abstract:

Night work has been associated with several negative effects on worker health, possibly due to circadian desynchronization, sleep deprivation, and suppression of night-time melatonin secretion as a result of light exposure during the work shift. The objective of this study was to evaluate the impact of fixed night-shift versus day-shift work on the sleep–wake cycle and on nighttime and daytime cortisol and melatonin levels. The sample comprised night-shift and day-shift workers who provided saliva and blood specimens and completed the Munich Chronotype Questionnaire. In this sample, melatonin levels in day-shift workers and in post-shift night-shift workers were high at night and low in the morning. In night-shift workers on the day of their shift, the inverse was observed, with melatonin values lower at night and higher in the morning. Salivary cortisol exhibited a normal circadian rhythm in day-shift workers, but was attenuated in night-shift workers during their working day. On their day off, night-shift workers did not differ significantly from day-shift workers. Shift work affects the circadian rhythm of melatonin and cortisol. Intervals between shifts may be beneficial to allow recovery of the hypothalamic-pituitary-adrenal axis.

Keywords: cortisol, melatonin, night work, circadian rhythm

Introduction

Shift work is associated with several negative effects, including sleep disorders, fatigue, reduced alertness, cognitive deficits, and increased accident rates (1). Furthermore, it is implicated in higher rates of metabolic disorders and cardiovascular disease (2–5).

The circadian cycle is regulated by a structure of central and peripheral oscillators. These are coordinated by the central nervous system (CNS) through neuronal and humoral signals generated in the suprachiasmatic nucleus (SCN) of the hypothalamus. Biological rhythm regulation is mediated both by photic stimuli, generated by the retinohypothalamic tract, and by nonphotic stimuli, such as social and behavioral factors (6).

Changes in light–dark synchronization as a result of continuous light exposure may contribute to a loss of biological clock entrainment. Evidence has suggested that circadian desynchronization, sleep deprivation, and suppression of nighttime melatonin release by light exposure constitute one of the pathological mechanisms whereby night-shift work exerts harmful effects on worker health (7).

The hormones melatonin and cortisol are intrinsically related to the circadian cycle. Melatonin is produced by the pineal gland and released directly into the bloodstream, in a process controlled by the SCN of the hypothalamus. Concentrations peak between 9:00 p.m. and 7:00 a.m., with great individual variation (8). Melatonin production is entrained by the light–dark cycle; exposure to light blocks its secretion. There is no melatonin storage in the body, and its plasma levels thus reflect pineal activity (9,10). The main role of melatonin is to act as an endogenous synchronizer of central and peripheral tissues (9). In addition to its key role of promoting sleep, melatonin has antioxidant, oncostatic, antiapoptotic, and immunomodulatory effects (10). The pattern of melatonin secretion in plasma, saliva, or urine is the best peripheral marker of entrainment of the central oscillator in humans (8).

Cortisol is an excellent marker of circadian rhythm (11). It is controlled by the hypothalamic-pituitary-adrenal (HPA) axis and has anti-inflammatory, metabolic, and immunosuppressive effects (1,12). Cortisol levels usually peak in the morning and decline over the course of the day; concentrations are minimal at night. This cycle features what is known as the cortisol awakening response (CAR), a peak in cortisol production that takes place 20 to 30 minutes after awakening (12).. Factors that influence cortisol secretion include diurnal rhythm, consciousness, and the sleep–wake cycle, alongside neural pressure signals (1).

The objective of this study was to evaluate the impact of fixed night-shift versus day-shift work on the sleep–wake cycle and on nighttime and daytime cortisol and melatonin levels.

Materials and methods

This study was conducted from April 2015 to March 2016 . Participants were recruited from the fixed day and night shifts of a university hospital in the city of Porto Alegre, Southern Brazil. The sample was composed of hospital staff members of both sexes, recruited from the following areas: administrative/management; patient care; and maintenance/engineering. All agreed to take part in the study and provided written informed consent. At the facility in which the study was conducted, the day shift started at 7:00 a.m. and ended at 7:00 p.m., whereas the night shift started at 7:00 p.m. and ended at 7:00 a.m. Day-shift workers worked Monday through Friday, whereas night-shift workers worked one 12-hour shift every 60 hours.

A self-report questionnaire was used to collect demographic and personal information: age, collected as a continuous variable; ethnicity, classified as white and other; sex; marital status, classified as with or without a partner; number of children; educational attainment, categorized as years of study; professional activity (categorized as administrative, health professionals, support and maintenance); salary income; current job; time working current job; time working at facility; working hours; time working current shift, collected as a continuous variable; shift schedule; other jobs; shift schedule at other job; personal history of high blood pressure, diabetes, angina, dyslipidemia, or glucose intolerance; smoking habit, self reported as a smoker or non-smoker; alcohol use, self reported as which drink, consumption of time and number of cups per week; and hours of sleep. Health status was assessed through a physical examination that included measurement of weight, height, blood pressure, heart rate (HR), and waist circumference (WC). Interviewers were trained in weight, height, body mass index (BMI), and WC measurement techniques.

Venous blood samples were collected after a 8-hour fast for measurement of fasting blood glucose, glycated hemoglobin, insulin levels, cholesterol profile, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, complete blood count, and platelet count.

BMI was calculated using the formula weight (kg) / height^2 = BMI. WC was measured at the midpoint between the last arch and iliac crest, using a non-stretch tape measure, without compressing the underlying tissue.

Weight was measured on a Welmy R/1W-200 digital scale (capacity 200 kg, resolution 0.100 g). Height was measured with a millimeter-scale Tonelli stadiometer. Blood pressure was measured in both arms, with participants in the seated position, after a 10-minute rest period, using a Welch Allyn 300 series digital Vital Signs Monitor.

Chronotype and Sleep Quality

Chronotype and sleep preferences were assessed by the self-report Munich Chronotype Questionnaire (MCTQ), developed and validated by Roenneberg et al, 2003 (13). The MCTQ is a structured questionnaire on sleep–wake behavior and sunlight exposure during working days and free days. In the questionnaire, respondents are asked how many days per week they have a regular work schedule, the time they go to bed, the time they are actually ready to fall asleep, how many minutes they need to fall asleep, the time they wake up, how many minutes after waking up they actually get out of bed, how many hours they spend outdoors, and whether they wake up with an alarm clock. Responses must be provided for working days and free days. These data are used to calculate sleep duration and the midpoint of sleep for working and free days, as well as jet lag. This is defined as the difference between the respondent's "biological clock" and their "social clock", i.e., their social commitments over the course of the day, and is calculated as the difference between the midpoint of sleep on working days and the midpoint of sleep on free days (14).

The exclusion criteria were: workers on fixed-term contracts; those who had been off work for more than 15 days; pregnant women; subjects aged > 60 years; diabetes; insulin, corticosteroid, or antiarrhythmic therapy; hypertension; dyslipidemia; chronic liver, kidney, or thyroid disease; severe sleep disorders; history of drug or alcohol abuse in the preceding 12 months; and active periodontal disease severe enough to preclude saliva collection.

The present study was conducted with Research Ethics Committee approval. All participants signed an informed consent form.

Cortisol and Melatonin Sampling

Cortisol was measured in saliva, due to the ease of collection of this route and because it faithfully represents biologically active hormone concentrations and correlates well with plasma cortisol levels (15). Melatonin was also measured in saliva.

In night-shift workers, saliva sampling for measurement of melatonin and cortisol levels started on the night of their shift, between 10:00 p.m. and 12:00 a.m., and continued on the morning after, between 6:00 and 8:00 a.m. Samples were again collected on the first post-shift night and on the morning of the second post-shift day. In day-shift workers, sampling was performed between 6:00 and 8:00 a.m. and again between 10:00 p.m. and 12:00 a.m., on a regular working day.

All samples were collected into Salivette® collection tubes, in accordance with manufacturer instructions (IBL Hamburg, Germany). Saliva was deposited by participants themselves into the tube to the 1-mL mark. Participants were instructed to collect saliva samples while fasting or 30 minutes after eating, drinking, chewing gum or candy, or brushing teeth; to avoid chewing gum; and to refrain from collecting blood-tinged saliva. They were also instructed to collect samples in a seated or reclined position and in dim light, preferably away from computer monitors, TVs, or other sources of direct light. After collection, Salivettes® were stored in the participants' home freezers and transported to the study facility in polystyrene foam coolers. After receipt by the investigator, samples were stored at -80°C.

Cortisol and melatonin measurements were then performed using commercially available kits (IBL Hamburg, Germany), following manufacturer instructions. The cortisol detection limit was < 0.03 to > 4.0 µg/dL, and the melatonin detection limit was < 0,50 µg/dL.

Statistical Analysis

Quantitative variables were described as mean and standard deviation or median and interquartile range. The Shapiro-Wilk test was used to assess normality of distribution. Categorical qualitative variables were expressed as absolute and relative frequencies. The chi-squared test and Fisher's exact test were used as appropriate for between-group comparisons of qualitative variables. For between-group comparisons of quantitative variables, the Student *t*-test and Mann–Whitney test were used as appropriate. For comparisons of hormone levels between day-shift and night-shift workers (including shift-day and post-shift measurements for the latter), the Mann–Whitney test was used, while the Wilcoxon test was used for comparisons between shift-day and post-shift measurements within night-shift workers and between morning and evening levels within each group. The delta is the difference between the night sample measurement and the day sample measurement for cortisol and the difference between the day sample measurement and the night sample measurement for melatonin.

All statistical analyses were performed in the Statistical Package for the Social Sciences (SPSS) Version 23 software environment (IBM Corp., Armonk, NY). The statistical significance level was set at 5% ($p<0.05$).

Results

The study sample comprised 36 workers (24 women and 12 men); 19 (52.8%) worked the day shift and 17 (47.2%) worked the night shift. There were no significant differences in age, ethnicity, marital status, children, educational level, monthly income, time working at the study facility, time working the current shift, other jobs, or smoking status between the day-shift and night-shift groups. However, day-shift workers had a significantly higher prevalence of alcohol consumption between shifts (77.8% vs.17.6%, p = 0.001). Health professionals were more prevalent among night -shift workers, while administrative support personnel were more prevalent in the day-shift group (Table 1).

Weight, BMI, WC, and laboratory test results also did not differ significantly between shift groups (Table 2).

In the day-shift group, we observed a significant decline in cortisol levels in midnight samples (median: 0.19; IQR: 0.09 to 0.29 µg/dL) as compared to morning samples (median: 0.97; IQR: 0.59 to 1.31 µg/dL, p<0.001) (Table 3).

Among night-shift workers, we observed a significant difference in cortisol levels between samples obtained during the night of their shift (median: 0.23; IQR: 0.20 to 0.32 µg/dL) and those collected on the morning after, at the end of the shift (median: 0.42; IQR: 0.30 to 0.73 µg/dL, p=0.015). On free-day samples from night-shift workers, cortisol levels were also lower in night samples than in morning samples (median: 0.24; IQR: 0.20 to 0.31 µg/dL *vs.* 0.69; IQR: 0.18 to 1.64 µg/dL respectively, p=0.013) (Table 3).

Between-group comparisons showed that morning cortisol levels were significantly higher in day-shift workers than in night-shift workers upon leaving their shifts (0.97 vs. 0.42 µg/dL; p= 0,002), but morning cortisol in day-shift workers and morning cortisol in night-shift workers on their free days did not differ (0.97 vs. 0.69 µg/dL, p<0.650) (Table 3).

Comparison of midnight cortisol levels between day-shift workers and night-shift workers on the night of their shifts showed that levels were lower in day-shift workers than in night-shift workers (0.19 vs. 0.23 µg/dL; p=0.596). A similar finding was observed for post-shift samples from night-shift workers (0.19 vs. 0.24 µg/dL; p=0.254), but the difference was not significant (Table 3).

Assessment of cortisol delta revealed that day-shift workers exhibit greater variability in cortisol levels than night-shift workers on the night of their shifts (0.64; IQR:0.32 to 1.10 *vs.* 0.20; IQR: 0.10 to 0.46 µg/dL; p=0.003). However, cortisol delta in day-shift workers did not differ significantly from that of night-shift workers in the post-shift period (0.64; IQR: 0.32-1.10*vs.* 0.58; IQR: -0.12 to -1.38 µg/dL; p=0.705) (Table 3).

Regarding melatonin levels, in the day-shift group, no significant reduction was observed in morning samples (2.40; IQR: 1.53 to 14.52 µg/dL) as compared to evening samples (3.30; IQR: 1.07 to 6.09 µg/dL, p=0.638) (Table 4).

In night-shift workers on the day of their shift, evening melatonin levels were lower than morning levels, but the difference was not significant (1.45; IQR: 1.30 to 3.39 *vs.* 2.45; IQR: 0.52 to 2.90 µg/d, p=0.953). In night-shift workers on their free days, nighttime melatonin levels were also higher than morning levels, but again the difference was not significant (2.53; IQR: 1.30 to 3.39 *vs.* 1.17; IQR: 0.93 to 3.07 µg/d, p=0.260) (Table 4).

Comparison of morning melatonin levels in day-shift versus night-shift workers revealed no significant difference between day-shift workers and night-shift workers on the night of their shift (2.40; IQR: 1.53 to 14.52 *vs.* 2.45; IQR: 0.52 to 2.90 µg/d; p=0.336), nor between day-shift workers and night-shift workers in the post-shift period (2.40; IQR: 1.53 to 14.52 *vs* 1.17; IQR: 0.93 to 3.07 µg/d; p=0.109) (Table 4).

Comparison of nighttime melatonin levels in day-shift versus night-shift workers also showed no significant difference between day-shift workers and night-shift workers on the night of their shift (3.30; IQR: 1.07 to 6.09 *vs.* 1.45; IQR: 0.68 to 2.50 µg/d; p=0.159), nor between day-shift workers and night-shift workers in the post-shift period (3.30; IQR: 1.07 to 6.09 *vs*. 2.53; IQR: 1.30 to 3.39 µg/d; p=0.516)(Table 4).

Comparison of variability in nighttime melatonin levels as compared to morning levels in day-shift versus night-shift workers revealed no significant difference between day-shift workers and night-shift workers on the night of their shift (0.13; IQR: 1.91 to 4.95 *vs* 0.29; IQR: -1.92 to 1.03 µg/dL; p=0.734), nor between day-shift workers and night-shift workers in the post-shift period (0.13; IQR: -1.91 to 4.95 *vs*. 0.84; IQR: -0.66 to 2.12 µg/dL; p=0.643)(Table 4).

Regarding MCTQ results, on working days, duration of sleep was significantly shorter in night-shift workers than in day-shift workers (03:40 [01:31] *vs.* 06:39 [00:59], p<0.001). The midpoint of sleep also differed significantly (11:09 [02:27] *vs.* 02:59 [00:49]; p<0.001). On free days, there were no significant differences in duration of sleep or midpoint of sleep between day-shift and night-shift workers. Regarding jet lag, day-shift and night-shift workers differed significantly (01:30; IQR: 00:45 to 02:00 vs. -06:34; IQR: -08:49 to -05:45, p<0.001). (Table 5).

Discussion

In day-shift workers, salivary cortisol levels obeyed their usual circadian rhythm, which corresponds to a rise in levels during the day followed by a decline at night. In night-shift workers, both during and after their shifts, the circadian rhythm of cortisol was preserved, with higher levels in the morning and a nadir at night.

As expected, the circadian rhythm was preserved among day-shift workers. Comparison of morning cortisol revealed that levels in day-shift workers were similar to those measured on the free days of night workers, but strikingly different from those measured on the morning after a night shift. A similar phenomenon was observed for evening levels, although not significantly. This demonstrates that the circadian rhythm of cortisol is attenuated on the working days of night-shift workers. Analysis of the cortisol delta, which was wider in day-shift workers and relatively blunted during the working nights of night-shift workers, provides even clearer evidence of this. However, on free days, this delta was not significantly different in night-shift workers, which suggests that two consecutive nights of rest tend to lead to recovery of normal HPA axis function, with a higher rise in morning cortisol levels.

Regarding melatonin levels, both day-shift workers and night-shift workers on their free days exhibited high levels at night and lower levels in the morning, although the difference was not significant in this sample. However, on their working nights, the same night-shift workers had lower nocturnal melatonin levels than in their morning samples. This may be related to light exposure during the work shift. Melatonin levels are not only influenced by the phases of the light–dark cycle, but also by variations in intensity and history of exposure to light (16); even the normal range of melatonin levels may vary substantially across individuals (17).

A study that followed surgeons on 4 consecutive days and measured melatonin levels in 24-hour urine and cortisol in saliva found that melatonin levels declined significantly while surgeons were on call, returning to pre-call levels in the 2 days that followed. Cortisol levels were higher on pre-call mornings and in the 2 days that followed each call period, declining normally during the night of call. This confirms that melatonin levels during a night of shift work are sensitive to light exposure, and demonstrates that the nocturnal nadir of cortisol levels is preserved (18). A similar finding was observed in our study.

In this line, Niu et al (19) found that the pattern of cortisol secretion in female night-shift workers returns to day-worker levels on the second free day, which suggests that women who work nights would benefit from being off work for more than 2 days between shifts to restore their diurnal circadian rhythms.

Kudielka et al (20), in a study of saliva samples collected on waking and 30, 45, and 60 min and 4, 8, 12, and 16 hours thereafter on working and free days, found that permanent night-shift workers (i.e., working a rotation of 6 consecutive nights for 3 weeks followed by 1 week off) exhibit a blunted cortisol profile during their work nights and days off. This demonstrates that continuous shift work interferes with the circadian rhythm of cortisol, and that the HPA axis is unable to recover due to the prolonged sequence of working nights.

Regarding melatonin, a study conducted by Ferguson et al (21) in mine operators who worked to a to a consecutive 7-day, 7-night shift pattern followed by 7 days off found that the time of onset of melatonin secretion in saliva changed significantly across the working week, during day and night shifts alike (9:04 p.m. ± 16 min vs. 9:30 p.m. ± 16 min respectively), but the small magnitude of change indicated a lack of true circadian rhythm adaptation to this shift pattern.

Adaptation of the circadian system to night-shift work depends on a wide range of factors, including exposure to light, environmental conditions, time of awakening, work start and finish times, and individual characteristics (21).

In our study, we found that night-shift workers sleep fewer hours on their working days than day-shift workers do, which constitutes a chronic sleep debt situation, as demonstrated by the negative social jet lag in the night-shift group. Cumulative sleep deprivation is often associated with working patterns that involve night or morning shifts (21).

According to Boivin (22), night-shift workers that sleep during the day suffer a circadian desynchronization similar to that of travelers who cross several time zones rapidly. However, in night-shift workers, circadian adaptation is more problematic, as the individual remains exposed to day-oriented exogenous stimuli. Cortisol levels during diurnal sleep in shift workers are higher than those measured during nocturnal sleep in day workers.

Other relevant aspects include the neurobehavioral consequences of sleep deprivation and its effects on cognitive function. A study conducted by Huffmyer (23) showed that medical residents exhibited extremely impaired control of speed and other measures of driver performance in a driving simulator, including collision with obstacles, after 6 consecutive night shifts. Reaction times to stimuli were also impaired, and the number of lapses in attention was increased. Other studies (24,25) have also demonstrated that prolonged work shifts and sleep deprivation are associated with poor performance (lapses in attention and medical error) in residents.

Possible limitations of this study include the small sample size, which may have contributed to the non-significant results of some statistical tests. However, our sample size was calculated with sufficient statistical power to discriminate primary objectives. The cross-sectional design precludes any causal inferences. Finally, the small number of saliva samples collected reflected individual discrepancies in the patient groups and may have prevented demonstration of wider variation in hormone levels. Nevertheless, these limitations do not minimize the importance of the present study in characterizing the effects of night-shift work on the circadian axis.

We conclude that night-shift work has a definite impact on the circadian rhythms of cortisol and melatonin. Night work is inexorable, insofar as it will never cease to exist. In this context, mandating adequate time off after night shifts to minimize their negative impact on workers' health and facilitate HPA axis recovery is warranted. Night shifts should not be scheduled on consecutive days.

ABBREVIATIONS:

CNS: central nervous system

SCN: suprachiasmatic nucleus

WC: waist circumference

BMI: body mass index

MCTQ: Munich Chronotype Questionnaire

Table 1 Bivariate analysis of demographic, occupational, and lifestyle variables of workers in southern Brazil, (n:36)

Variable		**Shift**		**p-value**
		Day	**Night**	
Age		44.05±10.07	46.18±7.15	0.468*
Income		7.26±4.45	6.06±1.89	0.292*
Time working at facility (months)		6.5 (2.8-26.0)	15.1 (9.5-19.0)	0.424**
Time working current shift (years)		4.1 (1.4-20.0)	8.0 (5.5-17.0)	0.219**
Sex				0.906##
	Female	12 (63.2)	12 (70.6)	
	Male	7 (36.8)	5 (29.4)	
Race				0.092¥
	White	13 (68.4)	16 (94.1)	
	Brown or black	6 (31.6)	1 (5.9)	
Marital status				0.757#
	Single	7 (36.8)	8 (47.1)	
	Married/Cohabiting	9 (47.4)	6 (35.3)	
	Divorced/Separated	3 (15.8)	3 (17.6)	
Children				0.854##
	Yes	9 (50.0)	10 (58.8)	
	No	9 (50.0)	7 (41.2)	
Educational level				0.681#
	Completed secondary education	5 (26.3)	6 (35.3)	
	Incomplete higher education	5 (26.3)	2 (11.8)	
	Higher education	3 (15.8)	4 (23.5)	
	Graduate/postgraduate education	6 (31.6)	5 (29.4)	
Smoking				0.486¥
	Yes	0 (0.0)	1 (5.9)	
	No	18 (100.0)	16 (94.1)	
Alcohol consumption				**0.001##**
	Yes	**14 (77.8**)	3 (17.6)	
	No	4 (22.2)	14 (82.4)	
Role				**0.020#**
	Support	**7 (36.8)**	1 (5.9)	
	Health provider	10 (52.6)	**16 (94.1)**	

	Maintenance	2 (10.5)	0 (0.0)	
Works other job				>0.999[¥]
	Yes	3 (16.7)	3 (17.6)	
	No	15 (83.3)	14 (82.4)	

* Student *t*-test; ** Mann–Whitney test; [#] Pearson chi-square test; [##] Pearson chi-square test with correction for continuity; [¥] Fisher's exact test. Symmetrically distributed quantitative variables are expressed as mean ± SD. Asymmetrically distributed quantitative variables are expressed as median (interquartile range). Categorical variables are expressed as frequencies and percentages.

Table 2 Analysis of clinical and laboratory variables in day-shift and night-shift workers in southern Brazil (n: 36)

Variable	**Shift**		**p-value**
	Day	**Night**	
Weight (n=36)	73.12±18.66	73.73±11.88	0.905*
BMI (n=36)	25.82±4.70	26.64±3.01	0.609*
WC (n=36)	89.13±12.07	92.24±7.67	0.355*
HR (n=35)	74.77±10.90	77.06±12.92	0.497*
RBC count (n=32)	4.62±0.38	4.53±0.39	0.536*
Hemoglobin (n=32)	13.60±1.12	13.64±1.57	0.920*
Hematocrit (n=32)	40.42±2.84	40.29±4.01	0.916*
MCV (n=32)	87.47±4.99	88.81±3.93	0.404*
WBC count (n=32)	5.92±1.61	6.51±1.89	0.343*
Bands (n=32)	3.36±1.13	3.42±1.24	0.893*
Eosinophils (n=32)	0.13 (0.06-0.31)	0.12 (0.09-0.26)	0.956**
Basophils (n=32)	0.03 (0.01-0.05)	0.03 (0.02-0.04)	0.752**
Monocytes (n=32)	0.49±0.19	0.47±0.19	0.875*
Lymphocytes (n=32)	2.24±0.72	2.40±0.76	0.531*
Platelets (n=31)	269,333±57,669	265,250±85,130	0.878*
Total cholesterol (n=33)	211.94±48.41	207.31±41.28	0.770*
HDL cholesterol (n=33)	53.24±15.53	48.31±15.92	0.376*
LDL cholesterol (n=31)	135.25±42.66	133.41±32.92	0.894*
Blood glucose (n=33)	86.18±7.43	86.50±9.11	0.911*
HbA1c (n=31)	5.27±0.37	5.20±0.56	0.686*
Insulin (n=30)	10.21±4.94	9.26±6.98	0.676*
Urea (n=31)	34.07±11.38	31.69±10.31	0.546*
Creatinine (n=32)	0.86±0.23	0.82±0.11	0.531*
eGFR (CKD-EPI) (n=31)	94.13±17.85	93.63±13.17	0.928*
SGOT (n=32)	20.00 (19.00-26.75)	20.00 (16.00-23.75)	0.468**
SGPT (n=32)	20.50 (13.50-40.0)	17.00 (14.00-22.50)	0.402**
hsCRP (n=12)	1.83 (1.36-3.07)	4.26 (0.45-10.90)	0.662**

* Student *t*-test; ** Mann–Whitney test. Symmetrically distributed quantitative variables are expressed as mean ± SD. Asymmetrically distributed quantitative variables are expressed as median (interquartile range).

Table 3 Analysis of cortisol levels (µg/dL) in day-shift and night-shift workers in southern Brazil (n: 36).

	Time of day		
	Morning	**Night**	**Delta**
Day-shift workers	0.97 (0.59 to 1.31)*&	0.19 (0.09 to 0.29)	0.64 (0.32 to 1.10)#
Night-shift workers, work day	0.42 (0.30 to 0.73)*	0.23 (0.15 to 0.32)	0.20 (0.10 to 0.46)
Night-shift workers, off day	0.69 (0.18 to 1.64)*	0.24 (0.20 to 0.31)	0.58 (-0.12 to 1.38)

Variables expressed as median (interquartile range).

*** Comparison between morning and evening cortisol, same group, p<0.01**

& Comparison of morning cortisol, day-shift vs. night-shift group, p<0.01

 # Comparison of delta, day-shift vs. night-shift group

Other comparisons non-significant (all p>0.05).

Table 4 Analysis of melatonin levels (µg/dL) in day-shift and night-shift workers in southern Brazil (n: 36).

	Time of day		**Delta**
	Morning	**Night**	
Day-shift workers	2.40 (1.53-14.52)	3.30 (1.07-6.09)	0.13 (-1.91-4.95)
Night-shift workers, work day	2.45 (0.52-2.90)	1.45 (0.68-2.50)	0.29 (-1.92-1.03)
Night-shift workers, off day	1.17 (0.93-3.07)	2.53 (1.30-3.39)	0.84 (-0.66-2.12)

Variables expressed as median (interquartile range).

Table 5 Descriptive analysis of sleep-related variables, stratified by work shift, in day-shift and night-shift workers in southern Brazil (n: 36)

MCTQ	**Current shift**		**p-value**
	Day (n=19)	**Night (n=17)**	
Sleep duration, working day	06:39 (00:59)	03:40 (01:31)	<0.001*
Midpoint of sleep, working day	02:59 (00:49)	11:09 (02:27)	<0.001*
Sleep duration, free day	08:39 (01:36)	07:34 (01:53)	0.073*
Midpoint of sleep, free day	04:04 (00:50)	04:18 (01:27)	0.566*
Jet lag	01:30 (00:45; 02:00)	-06:34 (-08:49; -05:45)	<0.001**

* Student *t*-test; ** Mann–Whitney test. Variables expressed as median (interquartile range) or mean ± SD.

References

1. Niu S-F, Chung M-H, Chen C-H, Hegney D, O’Brien A, Chou K-R. The Effect of Shift Rotation on Employee Cortisol Profile, Sleep Quality, Fatigue, and Attention Level: A Systematic Review. J Nurs Res. 2011 Mar;19(1):68–81.
2. Karlsson B. Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27 485 people. Occup Environ Med. 2001 Nov 1;58(11):747–52.
3. De Bacquer D, Van Risseghem M, Clays E, Kittel F, De Backer G, Braeckman L. Rotating shift work and the metabolic syndrome: a prospective study. Int J Epidemiol. 2009 Jun 1;38(3):848–54.
4. Morikawa Y, Nakagawa H, Miura K, Soyama Y, Ishizaki M, Kido T, et al. Effect of shift work on body mass index and metabolic parameters. Scand J Work Environ Health. 2007 Feb;33(1):45–50.
5. Vetter C, Devore EE, Wegrzyn LR, Massa J, Speizer FE, Kawachi I, et al. Association Between Rotating Night Shift Work and Risk of Coronary Heart Disease Among Women. JAMA. 2016 Apr 26;315(16):1726.
6. Garaulet M, Ordovás JM, Madrid JA. The chronobiology, etiology and pathophysiology of obesity. Int J Obes. 2010 Dec;34(12):1667–83.
7. Eastman C, Smith. Shift work: health, performance and safety problems, traditional countermeasures, and innovative management strategies to reduce circadian misalignment. Nat Sci Sleep. 2012 Sep;111.
8. Arendt J. Shift work: coping with the biological clock. Occup Med. 2010 Jan 1;60(1):10–20.

9. Cipolla-Neto J, Amaral FG, Afeche SC, Tan DX, Reiter RJ. Melatonin, energy metabolism, and obesity: a review. J Pineal Res. 2014 May;56(4):371–81.

10. Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin. Sleep Med Rev. 2005 Feb;9(1):11–24.

11. Griefahn B, Robens S. The cortisol awakening response: A pilot study on the effects of shift work, morningness and sleep duration. Psychoneuroendocrinology. 2008 Aug;33(7):981–8.

12. Ulhôa MA, Marqueze EC, Burgos LGA, Moreno CRC. Shift Work and Endocrine Disorders. Int J Endocrinol. 2015;2015:1–11.

13. Roenneberg T, Wirz-Justice A, Merrow M. Life between clocks: daily temporal patterns of human chronotypes. J Biol Rhythms. 2003 Feb;18(1):80–90.

14. Wittmann M, Dinich J, Merrow M, Roenneberg T. Social jetlag social: misalignment of biological and social time. Chronobiol Int. 2006;23(1-2):497–509.

15. Wirth M, Burch J, Violanti J, Burchfiel C, Fekedulegn D, Andrew M, et al. Shiftwork Duration and the Awakening Cortisol Response Among Police Officers. Chronobiol Int. 2011 May;28(5):446–57.

16. Hébert M, Martin SK, Lee C, Eastman CI. The effects of prior light history on the suppression of melatonin by light in humans. J Pineal Res. 2002;33(4):198–203.

17. De Almeida EA, Di Mascio P, Harumi T, Warren Spence D, Moscovitch A, Hardeland R, et al. Measurement of melatonin in body fluids: Standards, protocols and procedures. Childs Nerv Syst. 2011 Jun;27(6):879–91.

18. Amirian I, Andersen LT, Rosenberg J, Gögenur I. Working night shifts affects surgeons' biological rhythm. Am J Surg. 2015 Aug;210(2):389–95.

19. Niu S-F, Chung M-H, Chu H, Tsai J-C, Lin C-C, Liao Y-M, et al. Differences in cortisol profiles and circadian adjustment time between nurses working night shifts and regular day shifts: A prospective longitudinal study. Int J Nurs Stud. 2015 Jul;52(7):1193–201.

20. Kudielka BM, Buchtal J, Uhde A, Wüst S. Circadian cortisol profiles and psychological self-reports in shift workers with and without recent change in the shift rotation system. Biol Psychol. 2007 Jan;74(1):92–103.

21. Ferguson SA, Kennaway DJ, Baker A, Lamond N, Dawson D. Sleep and circadian rhythms in mining operators: limited evidence of adaptation to night shifts. Appl Ergon. 2012 Jul;43(4):695–701.

22. Boivin DB, Boudreau P. Impacts of shift work on sleep and circadian rhythms. Pathol Biol. 2014 Oct;62(5):292–301.

23. Huffmyer JL, Moncrief M, Tashjian JA, Kleiman AM, Scalzo DC, Cox DJ, et al. Driving performance of residents after six consecutive overnight work shifts. J Am Soc Anesthesiol. 2016;124(6):1396–403.

24. Landrigan CP, Rothschild JM, Cronin JW, Kaushal R, Burdick E, Katz JT, et al. Effect of reducing interns' work hours on serious medical errors in intensive care units. N Engl J Med. 2004;351(18):1838–48.

25. Lockley SW, Cronin JW, Evans EE, Cade BE, Lee CJ, Landrigan CP, et al. Effect of reducing interns' weekly work hours on sleep and attentional failures. N Engl J Med. 2004;351(18):1829–37.

CONSIDERAÇÕES FINAIS

Apesar de o trabalho noturno estar integrado à sociedade atual, ele pode trazer vários prejuízos à saúde, resultando em privação do sono e colaborando no desenvolvimento de distúrbios como a obesidade e sobrepeso, que constituem em fatores de risco para uma série de patologias, entre elas a hipertensão arterial, síndrome metabólica, doença cardiovascular e neoplasias.

Considerando estas repercussões, a compreensão dos mecanismos responsáveis pelos efeitos do trabalho noturno sobre o organismo pode contribuir para o desenvolvimento de estratégias de prevenção. Do ponto de vista prático, é necessária uma criteriosa avaliação médica dos trabalhadores noturnos visando prevenir ou identificar precocemente agravos relacionados ao trabalho em turnos.

Outros aspectos que devem ser abordados relacionam-se ao estímulo a uma alimentação saudável, a prática regular de exercício físico e uma higiene do sono adequada.

A organização do trabalho deve respeitar as variáveis biológicas individuais dos trabalhadores, especialmente em relação a duração e frequência dos turnos de trabalho visando atenuar o desgaste físico e as repercussões na vida pessoal e familiar.