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### REVISIONES

### Circadian dyssynchrony and its effect on metabolic syndrome parameters in workers: An integrative literature review

Disincronía circadiana y su efecto sobre parámetros de síndrome metabólico en trabajadores: revisión integradora de la literatura

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#### ABSTRACT:

Introduction: The loss of the circadian rhythm caused by sleep disorders is considered an important risk factor for developing metabolic diseases such as hyperglycemia and insulin resistance.

Objective: Analyze the existing information regarding studies on circadian dyssynchrony in workers and its influence on metabolic syndrome of anthropometric parameters.

Method: A search was carried out in electronic databases such as EBSCO, Thompson Reuters, PubMed, and Scopus; the selected search terms were shift work, melatonin, cortisol, metabolic syndrome, night shift, and circadian rhythm in Spanish and English published from January 2015 to December 2018. The extraction was carried out using a predesigned form.

**Results:** The search in the databases yielded 5,953 papers; after the investigation and depuration of the aforementioned papers applying the eligibility criteria, 13 papers were obtained which were organized in two dimensions for their analysis, these were called a) shift work and metabolic risk factors, and b) shift work and the circadian cycle.

Conclusions: The relationship between night work or rotating shift with various metabolic disorders is consistent.

Key words: Metabolic Syndrome, Circadian Rhythm, Shift Work Schedule, Melatonin, Cortisol.

#### RESUMEN:

Introducción: La pérdida del ritmo circadiano causado por desórdenes del sueño es considerada un factor de riesgo importante para desarrollar enfermedades metabólicas como hiperglicemia y resistencia a la insulina.

Objetivo: Analizar la literatura existente referente a estudios sobre disincronía circadiana en trabajadores y su influencia sobre parámetros antropométricos de síndrome metabólico de los mismos.

Método: Se realizó una búsqueda en las bases de datos electrónicas EBSCO, Thompson Reuters, PubMed y Scopus, los términos de búsqueda seleccionados fueron: trabajo por turnos, melatonina, cortisol, síndrome metabólico, trabajo nocturno y ritmo circadiano, en los idiomas español e inglés, publicados de enero del 2015 a diciembre de 2018. La extracción se llevó a cabo utilizando un formulario prediseñado.

**Resultados**: La búsqueda en las bases de datos arrojó 5,953 artículos, posterior a la indagación y depuración de los mismos aplicando los criterios de elegibilidad, se obtuvieron 13 artículos los cuales se organizaron en dos dimensiones para su análisis, estas se denominaron a) trabajo en turnos y factores de riesgo metabólico y b) trabajo en turnos y ciclo circadiano.

**Conclusiones:** Es consistente la relación entre el trabajo nocturno o rotatorio, con diversas alteraciones metabólicas.

**Palabras clave:** Síndrome Metabólico, Ritmo Circadiano, Trabajo por turnos, Trabajo Nocturno, Melatonina, Cortisol.

## INTRODUCTION

According to the Health Metrics and Assessment Institute, the main causes of death in Mexican people are cardiovascular illnesses, type 2 diabetes mellitus, and chronic kidney illness, therefore, these illnesses are considered as a national public health problem<sup>(1)</sup>. There are several forms of calling these illnesses, one of them is the metabolic syndrome, which according to the International Diabetes Federation is comprised by several interrelated metabolic indicators such as hyperglycemia, high blood pressure, increase in abdominal girth and triglycerides, and reduction in HDL cholesterol. The diagnosis of this syndrome is used as risk predictor for cardiometabolic diseases<sup>(2)</sup>.

In the human body there are physiological functions that repeat themselves with determined regularity and time, in relation with the day, night, and seasons cycles, which are known as biological rhytms<sup>(3)</sup>. These rhythms are controlled by internal biological clocks which are located in the central nervous system<sup>(4)</sup>, which generate a biological balance when they synchronize with external clocks known as zeitgebers, which are in charge of coordinating the activity of the nervous system with the environment<sup>(4)</sup>, all of which regulated by the light signals that travel through cells that are sensitive to the light of the retina toward the suprachiasmatic nucleus in the hypothalamus, making that people respond in this way to the day/night cycle<sup>(5)</sup>.

The circadian cycle is a biological rhythm that regulates the functions of the body through the secretion of hormones, within a system of 24 hours of duration, which influences the sleep and awake cycles, body temperature, blood pressure, release of endocrine hormones, and metabolic activity<sup>(6)</sup>. In the last decade, several studies have been carried out that relate the lost of synchrony of the circadian cycle as an important risk factor to develop metabolic illnesses such as hyperglycemia, insulin resistance, high blood pressure, and obesity, among others<sup>(7)</sup>.

Health and wellbeing are affected by several aspects, such as daily routine, life style, metabolism, and genetic factors<sup>(8)</sup>. Nowadays, work schedules, mainly night or rotating shifts, request employees to carry out activities in schedules that put out of synchrony the functions of the circadian rhythm, due to the modification of food intake schedule, sleep patterns, and social activities, all of this regulated by exogenous factors<sup>(9)</sup>. These changes in daily sleep and awake schemes generate hormonal alterations that affect the health of those who experience these alterations, increasing the risk to have breast cancer, obesity, type 2 diabetes mellitus, and metabolic syndrome. The objective of this research is to analyze the existing literature regarding scientific research with respect to

circadian dyssynchrony and its effects on parameters of the metabolic syndrome in workers.

## MATERIAL AND METHOD

This research is an integrative revision of literature, which in order to facilitate the exploration of scientific information a search strategy to put together all evidence possible to respond to a specific research question was formed<sup>(11)</sup>, that is, which is the scientific information available in relation to the circadian dyssynchrony and its effect on the metabolic syndrome parameters in workers? Eligibility criteria were the following: Papers whose population included were men or women, of legal age, workers of night, rotating, and/or day shifts, with no restrictions on study design or type of intervention used. Papers in Spanish and English published between January 01, 2015 and December 31, 2018 were included, and only papers available in full text were selected. This search took place in September 2019.

The search for papers took place in the electronic databases EBSCO, Thompson Reuters Web of science, PubMed, and Scopus. The U.S. National Library of Medicine MeSH vocabulary descriptors used were "shift work", "melatonin", "cortisol", "metabolic syndrome", "night shift", and "circadian disrupt". When necessary, the search terms were modified to be adapted to the features of the different databases. The electronic search strategy formed for the evaluation of the relationship of metabolic syndrome and circadian dyssynchrony was as follows: ("Circadian rhythm disorder" OR "Chronobiology Disorders" OR "Circadian Dysregulation") AND ("Metabolic syndrome" OR "Dysmetabolic Syndrome X") AND ("Shift work" OR "Night Shift Work" OR "Rotating Shift Work") AND ("Melatonin") AND ("Cortisol").

The selection of papers was carried out independently by two reviewers and, in case of disagreement, the support of a third reviewer was secured. The studies were selected by means of a detailed review and evaluation of the title and abstract of each paper in order to assess their relevance regarding the objective of the review; otherwise, the paper was excluded and, if the reviewer considered that more information was needed to evaluate a given paper, the complete document was consulted. The extraction was performed using an extraction form of our own design, in which the following criteria were evaluated: Objective, method/sample, results and conclusion. The search was performed considering the following variables: Work shift, fasting glucose, HDL cholesterol, triglycerides, abdominal girth, blood pressure, cortisol, and melatonin. The Cochrane Collaboration tool was used independently in the papers to assess the risk of bias (risk of selection, realization, loss and detection) and validity of the papers considering randomization, double-blind status, and description of losses during follow-up as main guidelines.

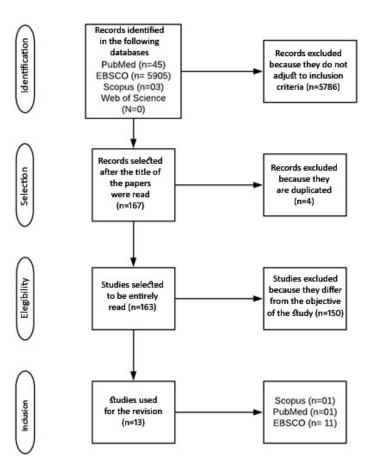
## RESULTS

Search in the databases yielded 5,953 papers. After the search and filtering of these papers, applying the eligibility criteria, 13 papers were selected as the object of the analysis. See Figure 1. The main causes of exclusion were date of publication and full text. Some papers evaluated only the circadian cycle, but not its implications in the human metabolism.

#### Enfermería Global

In terms of country of origin, 15.4% of the papers came from Brazil, 15.4% from Canada, 15.4% from China, 7.7% from the United States of America, 7.7% from Jordan, 7.7% from Germany, 7.7% from Greece, 7.7% from Poland, and 7.7% from Denmark. 53.8% of the papers were published in 2015, 30.8% in 2018, and 15.4% in 2017. All the papers were in English.

**Table 1** shows a summary of the 13 papers selected for this systematic review, which met the stipulated eligibility criteria.



### Figure 1: Diagram of Paper Selection

## Table 1: Papers that meet the eligibility criteria

Rev/Author/Year	Objective	Method/Sample	Results	Conclusions
Int J Endocrinol. Ulhôa MA (2015)	Investigate the impact of shift and night work on metabolic processes and the role of alterations in the sleep and awake cycle, food intake times and environmental changes in the occurrence of metabolic disorders.	Systematic review Search terms were: Shift work, cortisol, insulin resistance, diabetes, obesity, metabolic disorders. Search engines used: Pubmed; publications between January 2013 and March 2014 in English.	The following units were analyzed: Cortisol and work shift; obesity and work shift; metabolic syndrome, insulin resistance, diabetes. and work shift; insulin resistance; diabetes; dyslipidemias.	The physiological changes produced in workers who reverse their activity-rest cycle to comply with work schedules include disturbances of these processes.
Am J Surg Amirian I (2015)	Evaluate the effect of night shifts on the surgeons' sleep and awake cycle and circadian rhythm before and after night duty.	Prospective study. Sample: 30 surgeons.	For both, the melatonin and cortisol metabolites, a significant difference was found in the measurement period between call and pre-call values.	The circadian rhythm of the surgeons was affected by working night shifts.
PLoS One Peplonska B (2015)	Examine the association between rotating night shift work and body mass index (BMI), and abdominal adiposity, respectively, among nurses and midwives.	Cross-sectional descriptive study Sample: 724 nurses and midwives from rotating night and day shifts	Cumulative night shift work showed significant associations with BMI, as did current and cumulative night work with obesity.	The results support previously reported studies that state there is a relationship between night work and the development of obesity.
Int J Hypertens Ceïde ME (2015)	Investigate whether people who get little sleep (less than 6 hours) and who work during nights (evening) shifts were more likely to have hypertension and whether these associations varied by ethnicity.	Descriptive study Sample: 59,199.	The logistic regression analysis showed that working in shifts was significantly associated with hypertension among African American people. African American people who worked in shifts who slept less than 6 hours were significantly more likely to have hypertension, while their white counterparts did not.	The findings suggested that African American people working during night (evening) shift, especially those who did not sleep enough, were more likely to present hypertension.

## Table 1: Papers that meet the eligibility criteria (cont.)

Rev/Author/Year	Objective	Method/Sample	Results	Conclusions
Indian J Occup Environ Med Nena E (2018)	Investigate the impact of shift work on sleep and quality of life of health care workers.	Cross-sectional study Sample: 312 employees	Most shift workers were somewhat or totally dissatisfied with their sleep quality. Diabetes mellitus was the most common medical condition reported in shift workers.	Shift work impairs quality of life, while its duration and frequency, along with the age and family status of the employees may have adverse effects on sleep.
Acta Physiol (Oxf) Bescos R (2018)	Investigate the effects of 4 consecutive simulated night shifts on glucose homeostasis, mitochondrial and central function, and peripheral rhythms, compared to a simulated day shift.	Randomized controlled trial Sample: 17 healthy adults.	Increased plasma glucose levels and decreased insulin sensitivity after the night shift.	Only 4 days of simulated night shift work in healthy adults is sufficient to reduce insulin sensitivity, which would be expected to increase the risk to present type 2 diabetes mellitus.
J Occup Med Toxicol Li J (2018)	Examine the impact of shift work on the dysregulation of the hypothalamic- pituitary-adrenal axis, that is, the diurnal cortisol rhythm.	Longitudinal study Sample: 70 physicians.	In particular, cortisol levels during the follow- up were significantly higher among those engaged in shift work that those who work only day shift (p<0.01).	They support the notion that shift work changes diurnal pattern of cortisol and can predict increase of cortisol secretion.
Sleep Biol. Rhythms Akour A (2017)	Investigate the possible association between night work and insulin resistance, as well as the possible progression of serum molecular biomarkers regarding cardiovascular disease.	Cross-sectional study Sample: 128 employees.	Compared to daytime workers, night shift workers showed higher levels of insulin resistance index, higher serum thrombospondin- 1 levels, and lower oxytocin levels.	Night shift work showed that is associated to higher levels of biomarkers of cardiovascular disease progression and insulin resistance. Close monitoring of the clinical status and lifestyle of night workers is justified.

## Table 1: Papers that meet the eligibility criteria (cont.)

Rev/Author/Year	Objective	Method/Sample	Results	Conclusions
PLoS One	Evaluate the	Prospective	Night shift	Permanent and
Sun M (2018)	associations	cohort study	workers had a	irregular night shifts are
	between types of	Sample: 3,871	higher risk of	more likely to be
	night shift work	workers.	overweight and	associated with
	and different rates		obesity.	abdominal overweight
	of obesity using		Abdominal	or obesity than rotating
	baseline		obesity had a	night shifts. These
	information from a		significant but	associations should be
	prospective		weak association	verified in prospective
	cohort study of		with night work. A	cohort studies.
	night shift workers		positive gradient	
	in China.		was seen	
			between the	
			number of years	
			of night work and	
			abdominal	
			overweight or obesity.	
			Permanent night	
			work showed the	
			highest odds of	
			being overweight	
			and having	
			increased	
			abdominal	
			obesity.	
PLoS One	Investigate the	Cross-sectional	In the population-	It is suggested that the
McGlynn N (2015)	association	study	based sample,	relationship between
	between shift	Sample: 2,708	high likelihood of	shift work and obesity is
	work and obesity	women.	shift work was	complex and may be
	among Canadian		associated with	particularly susceptible
	women in a		obesity. In the	to occupational and
	diversity of		former student	educational factors
	occupations.		cohort, no	within a specific
			significant association was	population.
			detected between	
			shift work and	
			overweight or	
			obesity.	
Diabetol Metab	To identify the	Literature review	The following	Shift work and night
Syndr	most relevant	A search was	dimensions were	work appear to have a
Brum MC (2015)	aspects regarding	carried out for the	analyzed:	negative effect on the
	the therapeutic	following term:	-Cardiovascular	workers' health,
	implications	- Work shift and its	-Obesity and	possibly due to their
	following the	health effects.	overweight	impact on sleep and
	association		-Metabolic	awake cycles, eating
	between night		syndrome	and exercise habits,
	work and shift		-Diabetes mellitus	thermogenesis,
	work and		-Circadian rhythm	hormone secretion, and
		1	-Desynchroniza-	blood pressure levels.
	metabolic			
	disorders, as well		tion	
	disorders, as well as the		-Therapeutic	
	disorders, as well as the mechanisms and			
	disorders, as well as the mechanisms and pathways		-Therapeutic	
	disorders, as well as the mechanisms and pathways responsible for		-Therapeutic	
	disorders, as well as the mechanisms and pathways		-Therapeutic	

Rev/Author/Year	Objective	Mothod/Somple	Booulto	Conclusions
	Objective	Method/Sample	Results	
Health Promot	Investigate the	Cross-sectional	An association	Both the positive
Chronic Dis Prev	association	study	was seen when	association between
Can	between shift	Sample: 1,561	the worker has	rotating shift work and
Grundy A (2017)	work	men.	been working on	obesity and the positive
	(evening/night,		rotating night	association suggested
	shift and other		shifts for many	for evening/permanent
	shift schedules)		years to	night shift work in this
	with overweight		overweight and	study are consistent
	and obesity.		obesity. There is a	with previous findings.
	-		significant trend of	
			increased risk of	
			overweight and	
			obesity with the	
			increase duration	
			of rotating shift	
			work.	
Int J Occup Med	Establish a	Cohort study	Workers exposed	Changes in metabolic
Environ Health	practical method	Sample: 1,077	to rotating shifts	syndrome component
Lin YC (2015)	for assessing	employees	have a higher risk	parameters are
	general metabolic		of having	significantly different
	health conditions		metabolic	between morning and
	among different		problems, and are	rotating shift workers,
	groups of		less likely to	and are increasingly
	employees.		reduce these	associated to exposure
			levels.	to the rotating shift.

### Table 1: Papers that meet the eligibility criteria (cont.)

# DISCUSSION

In recent years, there has been an increase in research aimed at finding out the possible relationship between shift work and its implications on metabolism. Next, the different results found in this research are analyzed by grouping the papers in two dimensions: a) shift work and metabolic syndrome and b) shift work and circadian cycle.

Dimension a) Shift work and metabolic risk factors. The main result of this literature review is a consistent association between night or rotating shift work and various metabolic alterations. In two of the studies examined, a review of the literature was carried out, both of which agree that changes or alterations in the sleep and awake cycle disrupt the metabolic processes of workers<sup>(12,13)</sup>. The changes can manifest themselves as cardiovascular diseases, weight gain, metabolic syndrome, insulin resistance, and diabetes, which become an occupational risk and could lead to temporary or permanent work disability, generating loss of income and productivity for the individual, as well as high costs to the country's health budget<sup>(14)</sup>.

Most studies attempt to establish a relationship between a work shift and one or more of the components of the metabolic syndrome<sup>(15)</sup>, mainly obesity and overweight<sup>(16,19)</sup>. In all cases there is a significant difference between the day shift and the night or rotating shift in which it is observed that it is more likely to suffer from overweight or obesity if working at night, and night workers have greater difficulty in overcoming the disease. The second most observed result is an increase in fasting plasma glucose levels and insulin resistance<sup>(20-22)</sup>, which increases the risk of developing cardiovascular diseases and type 2 diabetes mellitus in workers<sup>(23)</sup>. Consequently, several studies have made

proposals to counteract the adverse effects of night work, proposing scheduled naps, extra remuneration for the risk and limitations for pregnant and breastfeeding women<sup>(24)</sup>.

Dimension b) Shift work and circadian cycle. A small percentage of the selected studies seek to find an association between work shift and changes in cortisol and melatonin parameters, as well as the sleep/wake cycle<sup>(25,26)</sup>. The result of a change in the diurnal pattern of melatonin and cortisol in participants who work night or rotating shifts is persistent, which is characterized by an increase in cortisol secretion which in turn is related to multiple metabolic alterations such as hypertension<sup>(27)</sup> and overweight<sup>(28)</sup>, this, along with stress and depression, which according to studies is shown as health risk factors in night workers<sup>(29)</sup>.

However, studies suggest that these results may be affected by various factors such as age, sex, race, unhealthy habits, genetics, and social and family life, among others<sup>(30)</sup>.

# CONCLUSIONS

This research will help to interpret that there is evidence that associates circadian cycle disturbances with metabolic risk factors in night and rotating shift workers, and that this can lead to the development of metabolic syndrome, type 2 diabetes mellitus, cardiovascular diseases, and other pathologies by these workers. Studies point to an association of circadian dyssynchrony not only to metabolic disorders, but also to psychological, social, and genetic disorders.

Although night and rotating shifts are necessary for the proper functioning of today's society, accessible and feasible alternatives must be proposed in order to limit the damage caused to the health of the workers, and, thus, contribute to the reduction of morbidity and mortality among them.

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