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ALTERACIONES DEL SUEÑO Y COMORBILIDADES EN POBLACIÓN MEDITERRÁNEA: EL CASO DE LA APNEA DEL SUEÑO

SLEEP DISTURBANCES AND COMORBIDITIES IN MEDITERRANEAN POPULATION: THE SLEEP APNEA CASE

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Sigue siempre adelante, abriendo nuevas puertas y haciendo cosas nuevas. Sé curioso… porque la curiosidad nos hace seguir nuevos caminos.

Walt Disney (los Robisons)

Dedicada a todas las personas de mi vida que se han sacrificado para hacer mis sueños realidad

This thesis is dedicated to those in my life who have sacrificed to make my dreams a reality

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RESUMEN

El sueño ha sido hasta hace poco una entidad relegada a un lugar secundario en la medicina, y de igual manera por el resto de las profesiones de la salud. Sin embargo, las ciencias médicas han girado ahora su mirada hacia un aspecto que ocupa un tercio de nuestra vida como el sueño y sus patologías.

El conocimiento de los efectos y utilidad del sueño han desencadenado este cambio de situación, centrándose en la monitorización y tratamiento del sueño profesionales de todas ciencias médicas.

La fisioterapia es una de las disciplinas que aun no se ha interesado en este campo.

El sueño y su calidad, duración y arquitectura se han mostrado como datos clínicos de gran relevancia en cualquier historia clínica.

En esta memoria de tesis se ha profundizado en las alteraciones del sueño como síntoma clínico de gran importancia para la Fisioterapia, a través del Síndrome de Apnea de Sueño como una de las patologías del sueño más frecuentes.

Los resultados obtenidos en esta tesis demuestran que las alteraciones del sueño son muy prevalentes en los pacientes que acuden a consulta de Fisioterapia y que presentan una asociación significativa con el perfil clínico y sintomático de los pacientes.

Adicionalmente, los resultados obtenidos han mostrado una asociación entre diferentes factores de riesgo cardiovascular y la severidad de las alteraciones del sueño en una población con apnea de sueño.

ABSTRACT

The sleep has been until recently an entity relegated to a secondary place in medicine, and in a consecutive way elsewhere in the health professions. However, medical sciences have turned his gaze to one aspect that occupies one-third of our lives like the dream and its pathologies.

Knowledge of the effects and usefulness of sleep, have triggered this change in status, becoming the monitoring and treatment of sleep an aspect in which professionals of all health sciences are grouped.

Physiotherapy is one of the disciplines that have not been yet interested in this field. Sleep and its quality, duration and architecture have proved to have clinical relevance in any medical history, because it has recognized repercussions in the patient symptoms and evolution.

With this memory of thesis we have pursued to show the importance of the sleep disturbances as a common pathologies and main clinical symptom for the physiotherapy, focussing our studies in Sleep apnoea.

The results obtained in this thesis suggests no doubt in that sleep disturbances are a target of first level for physical therapy, that involve a little researched aspect so far in patients who attend physical therapy consultation. At the same time the results have allowed the development of a clinical profile of patients with Mediterranean population in sleep apnea.

INTRODUCCIÓN

Esta tesis no pretende explorar una lista exhaustiva de los desordenes del sueño; sin embargo, pretende esclarecer algunos de los desordenes más prevalentes y sus asociaciones con otras patologías y síntomas. En esta disertación se presenta una síntesis de la literatura sobre los factores asociados a las alteraciones del sueño y su importancia terapéutica, al mismo tiempo que analiza el perfil sintomático y patológico en un grupo poblacional con alteraciones del sueño.

El sueño que se define en el plano de la conducta por la suspensión normal de la conciencia y desde un punto de vista electrofisiológico por criterios de ondas encefálicas específicas, consume un tercio de nuestra vida[1]. Por ello, en los últimos años las patologías del sueño y sus repercusiones clínicas se han destacado como un objetivo prioritario por gran parte de la comunidad científica.

Ciclo de sueño vigilia: El sueño surge como un conjunto o constelación de cambios fisiológicos rítmicos y reversibles en el que participan distintos sistemas del organismo, regulados por el sistema nervioso central (SNC). Se caracteriza por la abolición de la conciencia vigil y la reducción de la respuesta a los estímulos ambientales, que se acompaña de cambios en múltiples funciones, y que se puede dividir en al menos dos estados: sueño lento, en el cual se reconocen 4 etapas, y sueño paradójico[2].

Durante el sueño se producen múltiples cambios en el organismo que afectan prácticamente a todos los sistemas; disminuye la frecuencia respiratoria y el ritmo cardíaco, se relaja la musculatura y la temperatura corporal disminuye. A su vez se segregan diversas hormonas que afectan a la regulación de la energía, el peso, el crecimiento y el estrés. Simultáneamente se producen procesos muy activos que implican cambios en el funcionamiento global del cerebro.

La vigilia posee diversas características que le son propias, y entre las que se encuentran el control homeostático de diversas funciones vitales (cardiovasculares, respiratorias, endocrinas, etc). La organización y la ejecución de movimientos que actuarán sobre el ambiente y la actividad psíquica que continuamente nos acompaña, son también características indicativas de que todo el cerebro, de una forma u otra, es utilizado para proporcionar la condición de vigilia. Existe además, una forma de recepción y procesamiento de la información sensorial proveniente del ambiente y del propio cuerpo diferentes de aquellas efectuadas en el estado hípnico[3].

Neurofisiología de la respiración durante el sueño

En la respiración se distinguen al menos dos procesos diferenciados: el intercambio gaseoso alvéolo-capilar, y la renovación del aire o ventilación. De estos dos procesos, el último es extraordinariamente dependiente del SNC, ya que no tienen autonomía local y depende de una bomba neuromuscular (fuelle torácico) y de la permeabilidad de la vía aérea superior que también posee un importante componente neuromuscular.

La actividad ventilatoria es controlada por dos sistemas relativamente interdependientes pero con diferentes propiedades:

1) sistema involuntario, automático, regido por las necesidades metabólicas del organismo, que se puede alterar voluntariamente pero sólo por un tiempo limitado (por ej., contener la respiración), activo en condiciones de anestesia, coma y sueño lento. Esta información se integra a nivel bulbo-protuberancial.

   Este sistema está a cargo del mantenimiento del ritmo respiratorio. El mecanismo por el cual ocurre esto todavía no está totalmente aclarado; por ejemplo, las neuronas respiratorias no poseen marcapasos como en el corazón. El control involuntario de la inspiración y la espiración no depende de centros nerviosos específicos, sino de una red difusa de neuronas interconectadas. El modelo que se acepta actualmente consiste en grupos de neuronas o redes neuronales: grupo A, grupo respiratorio dorsal; grupo B, grupo respiratorio ventral que forma parte del núcleo retroambiguo; grupo C, localizado en la zona ventral

> del núcleo retroambiguo. Un cuarto grupo de neuronas, el grupo P o centro neumotáxico, cuya interacción origina el ritmo respiratorio básico, que recibiría señales de los centros superiores, puede estimular directamente al grupo C y llevar en último término a la inhibición de la inspiración. Mientras la interacción entre los grupos A-C sería responsable del ciclo respiratorio básico, los estímulos externos originados en el centro neumotáxico y en los diversos receptores modularían la actividad de los grupos neuronales, modificando la velocidad del ciclo y la intensidad de la respuesta. De esta manera es posible variar la frecuencia respiratoria y el volumen de aire corriente.

Este sistema neuronal está influido por el sistema reticular activador que consiste en una red de neuronas que modula la actividad del sistema de control por medio de cambios en el estado de excitabilidad del sistema nervioso durante el sueño y la vigilia. El sistema reticular activador disminuye su actividad durante el sueño. Estas estructuras, que filogenéticamente son más antiguas, están reguladas, a su vez, por los centros superiores de la corteza cerebral y el tálamo, que están involucrados en el control de actividades voluntarias que conciernen al tórax y a los pulmones.

2) El otro mecanismo es voluntario, conductual, relacionado con las actividades no respiratorias de la ventilación, como por ejemplo la fonación, la deglución, la tos, etc; es activo en la vigilia y se cree que también en el sueño paradójico (como algunos autores sugieren por el hecho de la irregularidad del patrón respiratorio, que no responde a las modificaciones de los impulsos del sistema automático vagales o químicos).

En líneas generales el sistema de control de la ventilación consta de receptores localizados en diferentes áreas del organismo, que son activados por una variada serie de estímulos químicos y físicos. Estos receptores envían mensajes a un sistema de control que procesa la información y envía señales a los efectores, los cuales modifican su actividad de acuerdo con el tipo de mensaje recibido. Este sistema mantiene un nivel de ventilación estrechamente vinculado a las necesidades metabólicas.

CONSECUENCIAS DE LAS ALTERACIONES DEL SUEÑO

El sueño es parte universal de nuestra vida. Su naturaleza recuperadora permite sentirse descansado y con energías durante el día, como resultado de una noche de buen sueño. Aun así, la mayoría de las personas tienen algún tipo de problema con su sueño a lo largo de su vida debido al estrés, preocupaciones, enfermedad, o similar. Desafortunadamente, muchas personas experimentan problemas de sueño durante un periodo importante de tiempo antes de ser diagnosticadas de un trastorno del sueño.

El sueño alterado tiene efectos que han sido menospreciados sobre la salud, tal y como ha sido evidenciado por diversos informes de los sistemas e institutos de Salud de multiples paises [4].

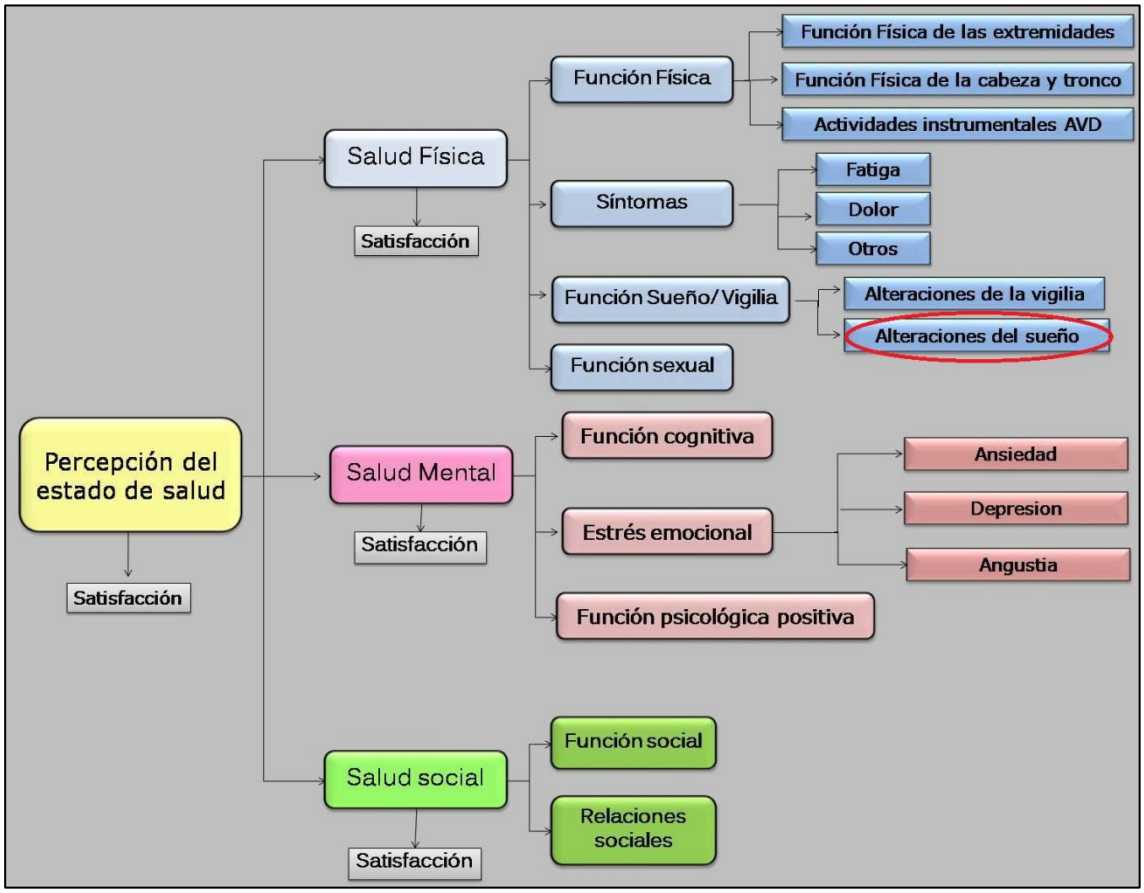

Figura 1: Interrelación entre alteraciones del sueño y salud general

Aunque el sueño alterado no recibe mucha atención respecto a otros problemas sanitarios, existe gran cantidad de literatura sobre el sueño.

Muchos investigadores han estudiado el impacto sobre la salud pública de las alteraciones del sueño. Se estima que millones de personas en los EEUU tienen desórdenes del sueño crónicos, lo que supone un coste social de 90 millones de dólares[5] .

Muchos investigadores han examinado el efecto del sueño sobre diferentes causas de mobimortalidad, patología cardiovascular y diabetes[6].

Se sabe poco sobre todos los factores que pueden estar asociados al sueño poco reparador. Sin embargo, existen gran cantidad de escalas para identificar aspectos del sueño y muchas contienen información útil y completa[7] .
El Plan Nacional de EEUU para la Investigación sobre los Desordenes del Sueño[8] ha planteado numerosas recomendaciones para investigaciones futuras que incluyen la necesidad de mejores métodos de medición, al igual que recomienda la focalización en las desigualdades debidas a género, grupo humano y perfil socioeconómico en las terapéuticas del sueño[8].

Las diferentes organizaciones para la salud insisten en estos últimos años sobre la necesidad de examinar los efectos del sueño sobre la salud, ya que se están convirtiendo en un problema de salud pública de primer nivel. Todos los profesionales de la salud deben conocerlos y comprender su repercusión, mucho mayor de lo que se había pensado hasta hace poco tiempo.

El síndrome de Apnea del Sueño (SAS)

También llamado síndrome de Apneas-Hipoapneas del Sueño es uno de los trastornos del sueño de mayor prevalencia, oscilando en la población general entre un 1 a un 2%[9], y se caracteriza por un cuadro de episodios repetidos de obstrucción de la vía aérea superior, acompañada por esfuerzo respiratorio inefectivo y apneas seguidas habitualmente por respiraciones amplias de recuperación (llamadas hiperpneas) durante el sueño, que provocan constantes desaturaciones de la oxihemoglobina y despertares transitorios.

La apnea, definida como la interrupción completa del flujo inspiratorio superior a 10 segundos, puede diferenciarse en función de su origen.

Si se mantiene el esfuerzo ventilatorio durante este tiempo, la apnea se considerará de origen obstructivo, y si no existe este esfuerzo se considerará como de origen central. Una hipoapnea es un episodio de definición más compleja consistente en la obstrucción parcial de las vías aéreas superiores y que produce una clara disminución del flujo aéreo en boca-nariz de duración igual o superior a 10 segundos. Se acompaña de un despertar transitorio y/o desaturación cíclica de la oxihemoglobina. Un índice de apnea e hipoapnea (IAH) (número de apneas + número de hipoapneas por hora de sueño) superior a 5 por hora se considera patológico.

El Síndrome de apnea de sueño suele afectar la vida diaria de los sujetos que la padecen. Son numerosas las complicaciones que la gente experimenta debido a la AS, siendo las complicaciones pulmonares y la somnolencia las más comunes. Algunos síntomas frecuentemente asociados son las apneas observadas, los procesos asfícticos, la fatiga diurna, ronquidos nocturnos importantes, despertares frecuentes que pueden estar acompañados de nicturia, dolores de cabeza frecuentes e hipertensión, que pueden ser observados por el propio sujeto o por su entorno [10].
Accidentes de tráfico y pérdida de la productividad son dos de los problemas más comunes causados por la somnolencia[11].

Algunas de las repercusiones diurnas exhibidos por pacientes con síndrome de apnea de sueño son somnolencia diurna, depresión, disminución de la libido, fatiga, dolor de cabeza y ronquidos[12] . Algunas de la complicaciones que puede causar el SAS pueden ser metabolismo alterado de la glucosa, patología cardiovascular aguda y crónica, accidente cerebro vascular y deterioro cognitivo[13].

Existen tres tipos de Apnea de Sueño, central obstructiva y mixta.
● La apnea central es aquella apnea en la que no se produce esfuerzo respiratorio debido a un fallo de la conexión entre el sistema nervioso y el sistema respiratorio, resultando una falta de señal hacia los músculos respiratorios.

●La apnea obstructiva, en la que se produce esfuerzo respiratorio. Los músculos respiratorios se contraen, pero esta contracción es ineficaz debido a la obstrucción total o parcial de la vía aérea superior.
●La apnea de tipo mixto, es una combinación de la apnea central y de la apnea obstructiva. La apnea mixta comienza habitualmente como una apnea central y continua como una apnea obstructiva tras la recuperación de la actividad muscular respiratoria[13].

Los pacientes pueden mostrar todas las formas de Apnea durante el sueño. Habitualmente los sujetos presentan una combinación de todos los tipos y son diagnosticados de aquel tipo que prevalece. La apnea obstructiva en la forma más común de apnea y la apnea central es la menos frecuente, siendo diagnosticada tan solo en el 10% de los casos[12] . Todas las formas de AS muestran alguna forma de respiración intermitente durante el sueño[13].

El conocimiento de la apnea ha progresado gracias al aumento del conocimiento sobre los mecanismos del sueño. El hecho de que la apnea del sueño se caracterice por un colapso recurrente de la vía aérea superior durante el sueño ha sido aceptado, sin embargo el mecanismo de producción exacto y su por qué es algo que numerosos investigadores están intentando comprender[14].

Más del 5% de los adultos se encuentran afectados por algún tipo de alteración respiratoria durante el sueño[10]. La incidencia de la AS ha aumentado de manera significativa durante los últimos diez años, debido a la mayor atención y reconocimiento por parte de los diferentes profesionales sanitarios. Los estudios de sueño son solicitados cada vez con más frecuencias solicitadas para el diagnóstico de la apnea, permitiendo a los profesionales sanitarios determinar el tipo y severidad de las alteraciones del sueño.

El Síndrome de Apnea Obstructiva del Sueño y alteraciones cardiovasculares

La apnea obstructiva del sueño (SAOS) es una patología de tipo crónico caracterizada por obstrucciones repetidas de la vía aérea superior durante el sueño. Recientes investigaciones demuestran una conexión entre estas oclusiones repetitivas de la vía aérea superior y anormalidades cardiovasculares. Por ejemplo,

correlaciones significativas demostradas entre SAOS e hipertensión pulmonar sistémica[15,16,17], isquemia cardiaca y disritmias[16,18] , y accidentes cerebrovasculares[16,19].

La hipertensión sistémica (HTA) está frecuentemente asociada al SAOS y puede estar directamente relacionado con los episodios parciales y repetidos de apnea que interrumpen los reflejos cardiovasculares durante el sueño[20,21,22,23]. La prevalencia de la HTA en los pacientes con SAOS puede ser de un 50%[24].

La reducción de flujo de aire durante el sueño se traduce en una reducción en los niveles de oxigeno en sangre y un incremento en la retención de dióxido de carbono; ambos causan un incremento en la actividad nerviosa simpática y conducen aumentos de la tensión arterial[25].

Los pacientes con SAOS también presentan un aumento de la actividad simpática durante el día[26,27]. Estas fluctuaciones en el sistema nervioso simpático pueden estar relacionadas con la patogénesis de la HTA.

Sin embargo, estudios que relacionan la SAOS con la HTA, han mostrado una disminución de la actividad nerviosa simpática[28] y la tensión arterial[29,30] después del tratamiento con presión espiratoria positiva (nCPAP)[19].

Adicionalmente, la SAOS se asocia a los efectos agudos y crónicos de la simpático-excitación, que dando lugar a una adaptación vascular reducida[32]. De cualquier manera, se ha aceptado que el SAOS afecta de manera adversa la homeostasis de diferentes mecanismos cardiovasculares, aunque los mecanismos reguladores vasculares no han sido investigados en la SAOS, tales como la hipoxia asociada o las sustancia vasoactivas derivadas (adenosina, prostanoides, endotelina y oxido nítrico (NO)[31]).

El Sleep Heart Health Study conducido por Mehra encontró que los pacientes con SAOS moderado se encuentran en serio riesgo de padecer patología vascular oclusiva[32].

Estos investigadores, al igual que Lavie y cols[33] encontraron que el riesgo no se incrementaba proporcionalmente en los sujetos con SAOS severo.

Estos estudios se confirman por las observaciones clínicas en las que aun en presencia de desaturaciones nocturnas severas, no todos los SAOS sufren co-morbilidades cardiovasculares[34].

Como consecuencia, se sabe con certeza que aun existen mecanismos desconocidos aún que relacionan el SAOS y algunas complicaciones cardiovasculares.

Mecanismos de asociación entre apnea del sueño y arritmia cardíaca

Los mecanismos que vinculan la AS y las arritmias cardíacas continúan siendo objeto de especulación y debate continuo.

Uno de los mecanismos potenciales de asociación es la interrelación entre el efecto proarrítmico de los episodios intermitentes de hipoxia nocturna, isquemia miocárdica y el aumento de la actividad simpática, lo que conlleva un incremento de las concentraciones plasmáticas de catecolaminas[35,36]. Sin embargo, las especulaciones sobre los diferentes mecanismos de asociación tan solo han sido confirmadas parcialmente.

Adicionalmente, como resultado de la actividad simpático secundaria a los episodios de apnea, se producen oscilaciones en la frecuencia cardiaca y en la tensión arterial, al igual que un incremento de las arritmias ventriculares y auriculares[37]. En un estudio sobre 400 pacientes, se registraron arritmias en más de la mitad de los sujetos[38]. La mayoría de estas alteraciones cardiacas fueron bradiarritmias con 43 de los 400 pacientes que registraron paradas sinusales de 2.5 a 13 segundos.

En estudios posteriores, las arritmias ventriculares fueron relativamente poco comunes[39]. Algunos investigadores discuten la alta prevalencia de las arritmias asociadas a la SAOS, justificándose en que los pacientes incluidos en los estudios hasta ahora tienen apnea severa y no son representativos de un espectro más amplio del síndrome[37].

En resumen, el SAOS predispone a los individuos a un aumento de la morbi-mortalidad cardiovascular[24]. Este mayor riesgo patológico se agrava por factores como la edad, índice de masa corporal (IMC), hipertensión arterial y polisomnografía con índices elevados[40].

Por lo tanto, no puede ser subestimada la importancia de la detección temprana y tratamiento precoz. Las intervenciones adecuadas han demostrado mejorar el rendimiento del neuropsiquiátrico, la lucidez mental y la calidad de vida, los valores

de hipertensión diurna, y la reducción de desaturaciones nocturnas y las hipopneas respiratorias[16,41].

Diversos estudios epidemiológicos se han centrado en describir patologías cardiovasculares concretas en grupos poblacionales; sin embargo, apenas existen estudios en poblaciones mediterráneas y aun menos en poblaciones españolas. Así, el presente estudio evaluó sistemáticamente la intrincada relación entre los factores de riesgo cardiovascular y las diferentes severidades de apnea de sueño en una población de Granada.

INTRODUCTION

This thesis doesn´t want to explore all the sleep disturbances, but it wants to review some of the more prevalent disorders and its associations with other pathologies and symptoms. This thesis presents a review of the literature about the associate factors to the sleep disturbances and its therapeutic importance.

Sleep is defined, in a behavioral and electrophysiological way, as the suspension of the consciousness and as specific encephalic waves. This represents the third part of our lives[1]. In the last years the sleep pathologies and its clinical repercussions have become a first objective by the scientific community.

Sleep-wake cycle: the sleep is a group of rhythmic physiological changes who are made by all the organic systems, always controlled by the central nervous system. It's characterized by the loose of the consciousness and the reduction of the environment stimuli response. Its accompanied by a change in different functions and can be divided in two stages: slow sleep (with four different stages) and paradoxal sleep[2].

During the sleep numerous changes are made, affecting practically all the systems. It reduce the respiratory frequency and cardiac rhythm, it relax the muscles and reduces body temperature. At the same time many hormones are segregated regulating the energy, growing and stress process. Changes in the global brain function occur at the same time becoming a very active process.

The consciousness time have its own characteristics that included the homeostatic control of different vital functions. The organization and execution of movements are a signal of the environment and the physic activity that usually are together. There is a way of reception and information processing of the sensorial information that becomes from the environment and from the own body, different from the sleep processes[3].

Breathing Neurophysiology during the sleep

In the respiration we can recognize two different processes: the renewal of air or ventilation and the diffusion alveoli-capillary. Between this processes, the diffusion is controlled by the central nervous system and is dependent of the thoracic pump and the upper airway permeability.

Ventilatory activity is controlled by two relatively independent systems but with different properties:

1) Involuntary system, automatic and regulated by the metabolic necessities of the body. Is active in conditions of anesthesia, slow sleep and all this information's are processed in the brain protuberance level. This system is maintaining the breathing rhythm. The relationship does not fully understand.
2) The involuntary control of the inspiration and expiration is not controlled of the specific nervous centers, is regulated by a diffuse mesh of neurons. The actually accepted model consist in neurons groups: group A who is the respiratory dorsal group, group B who is the ventral respiratory group, and group C. a fourth group, called P or neumotaxic centre, can directly origin the basic breathing rhythm. The interaction between A-C groups will be responsible of the modulation of the breathing rhythm, changing the velocity and intensity of the respiratory answer.

This neural system in influenced by the reticular system, the reticular system can modulate de activity of the control system with changes in the excitability of the nervous system during the sleep and wake cycle. The reticular system reduces its activity during the sleep.

The other mechanism is voluntary, conductual and related to other activities that are not only the respiration like phonation, deglution, cough…

In general, the control system of ventilation is made by receptors distributed in different areas of the body that are activated by series is chemical and physical stimuli. These receptors send messages to a control system that process the information and send signals to the effectors who modify their activities in line with the orders.

This system maintains the level of ventilation required to the metabolic demands.

Consequences of sleep disturbances on health

Sleep is a universal part of life. Its naturally restorative properties allow many to feel refreshed and energized during the day, as a result of a good night's sleep. However, most people experience a problem with sleep at some point, due to stress, worry, physical illness, or the like. Unfortunately, many people experience sleep problems over a longer period of time and are then diagnosed with a sleep disorder. Such people fail to benefit from the recuperative effects of sleep. Poor sleep has under-appreciated impacts on health, as evidenced by numerous reports[4]. Although poor sleep may not receive as much attention as other health problems, a wealth of literature exists on sleep.

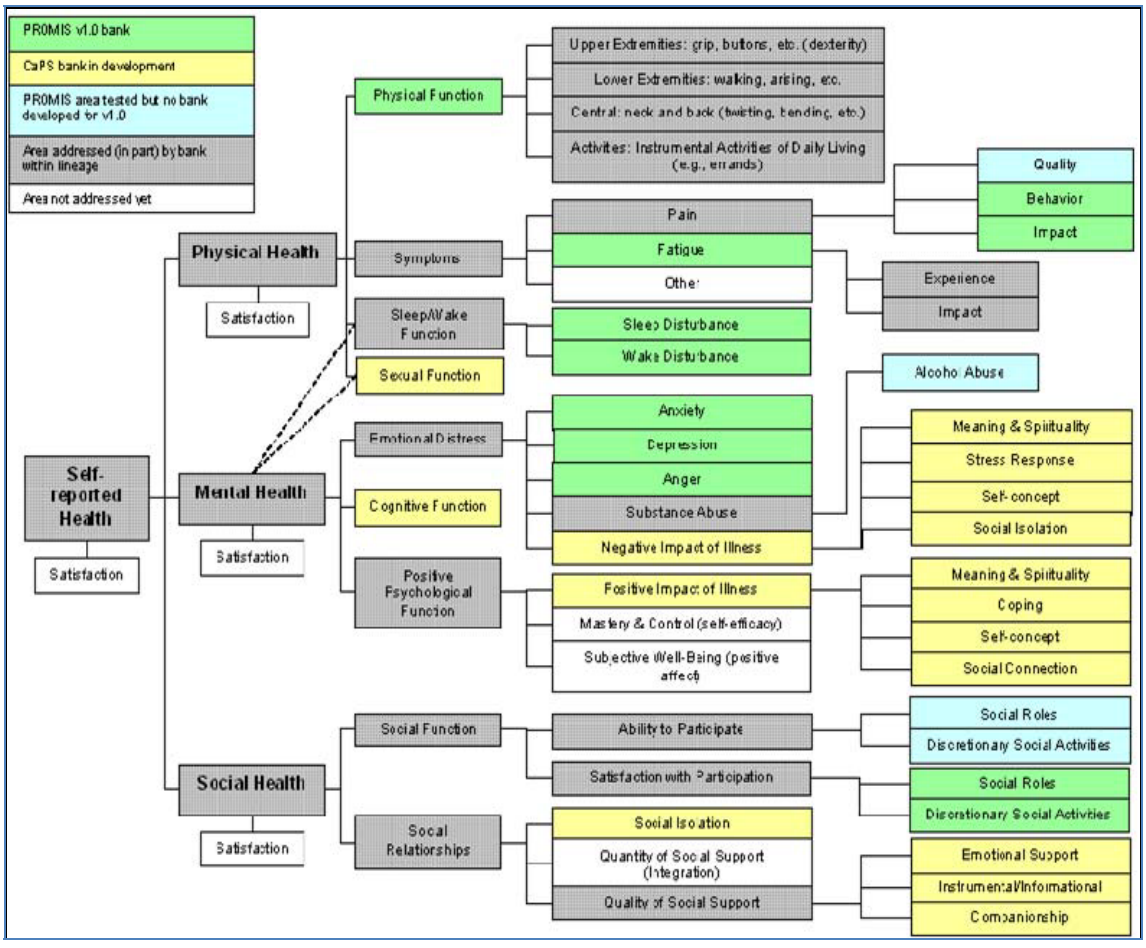

Figure 1: Interrelationship between sleep disturbances and general health

Researchers have investigated the public health impact of poor sleep. It is estimated that approximately 40 million United States citizens have chronic sleep disorders, costing society roughly $90 billion dollars[5] .

Many researchers examine sleep's contribution to all-cause mortality, cardiovascular disease, and diabetes[6].

The medical objectives range from improving the medical management of sleep problems to decreasing vehicular crashes that result from driver sleepiness. Unfortunately, poor sleep does not always receive as much consideration as other, perhaps more prominent, physical conditions. It is often difficult, if not impossible, to identify if poor sleep is a side effect of another condition or the cause of a particular health condition.

Little is understood about the many factors associated with poor sleep. While many scales exist to assess sleep, few contain complete and adequate information[7] .
The National Sleep Disorders Research Plan put forth several recommendations for future research, including a need for more methods to measure sleep, as well as focuses on gender, racial, and ethnic disparities in sleep disorder outcomes[8].
While there are many complications that people experience due to SAS, pulmonary complications and sleepiness are the most common complications. Some common symptoms that may be indicative of sleep apnea are apnea; snorting, or choking that their significant other may observe during the day; loud snoring every night; frequently waking during the night which can be accompanied by the need to urinate; recurrent headaches in the morning; and hypertension[8].

The different health organizations are promoting in this last year's about the clinical importance to examine the sleep effects on health. The sleep disturbances are becoming a public health burden and all the health professionals has to know them and understand its repercussions.

Sleep Apnea Syndrome

The sleep apnea syndrome, also called apneas-hipopneas syndrome is one of the major sleep disturbances in prevalence rates, rating from 1 to 2%[9] .Is characterized by repetitive obstruction of the upper airway, accompanying by respiratory ineffective effort and consecutive apneas followed by deep breathing cycles (called hiperpneas) during the sleep, with constantly desaturation of oxyhemoglobine and transient awakes.

The apnea, defined as the complete interruption of inspiratory flow more than 10 seconds, can be differentiated by its origin. If the breathing work is maintained during this time, the apnea can be considered obstructive, if it doesn´t exists can be considered as central.

A hypopnea is an episode more complex, because consist in a partial obstruction of the upper airways and a clear reduction of air flow in mouth-nose of a 10 seconds or more duration. Is accompanied by a transient awake and/or cyclic desaturation of the oxihemoglobin. And index of apnea and hipopnea more than 5 per hour is considered pathological.

Sleep apnea syndrome can affect patients' daily lives. There are many complications and symptoms that are associated with sleep apnea. Motor vehicle accidents and loss of productivity at work are two problems caused by sleepiness[10]. Some of the symptoms exhibited by patients with sleep apnea syndrome are daytime sleepiness, depression, decreased libido, fatigue, headaches, and snoring[11] . Some of the complications that sleep apnea syndrome may cause are, glucose metabolism disorders, acute and chronic cardiovascular disease, stroke, and cognitive decline[12].

There are three different forms of sleep apnea syndrome (SAS), central, obstructive, and mixed.

- Central SAS refers to sleep apnea in which there are no respiratory attempts because there is a break in the connection between the nervous system and the respiratory system resulting in no signals to the respiratory muscles.
- Obstructive SAS there are breathing movements, the respiratory muscles work, but there is no airflow due to partial or incomplete obstruction of upper airways.

●Mixed SAS is a combination of central and obstructive SAS. Mixed SAS may start as central SAS and then continue as obstructive SAS after recovery of respiratory musculature activity[15] .
Patients may exhibit all forms of SAS during a night of sleep. Usually patients exhibit a combination of the types so they are diagnosed as the type of SAS that occurs the most. Obstructive sleep apnea (OSA) is the most common type of sleep apnea, and central sleep apnea is the least common type of sleep apnea, being diagnosed in only 10% of cases[16] . All of the forms of SAS exhibit some form of intermittent breathing interruption during sleep[17].

Knowledge about sleep apneas has progressed along with an increased knowledge about mechanisms of sleep. The fact that sleep apnea is characterized by recurrent collapse of the upper airway during sleep has been common knowledge for many years.
Exactly how this occurs and why it only occurs in certain individuals is something that researchers are still trying to fully understand[18].
Up to 5% of adults are affected by some type of breathing problems during sleep[19].
Incidences of OSA have increased greatly over the past ten years because medical professionals are more aware of the signs and symptoms of this condition and are recognizing it more. Sleep studies are now done to diagnose a person with sleep apnea. This allows medical professionals to determine the type and severity of the patients' condition.

Sleep Apnea and cardiovascular alterations

Recent studies demonstrate a link between the repetitive occlusions in the upper airway and cardiovascular abnormalities. For example, significant correlations have been demonstrated between OSA and systemic and pulmonary hypertension[20,21,22], cardiac ischemia and dysrhythmias[23,24], and cerebrovascular accidents[25,26].
Systemic hypertension (HTN) is frequently associated with OSA and can be directly ascribed to the repeated and partial apneic events that disrupt autonomic cardiovascular reflexes during sleep[27,28,29,30]. The prevalence of HTN in OSA patients may be as high as 50%[31]. Diminished airflow during sleep results in decreased blood oxygen levels and increased carbon dioxide retention, both of which cause increased sympathetic nerve activity resulting in elevations in blood pressure[32].
Patients with OSA also exhibit increased sympathetic activity during the day[33,34]. These fluctuations in sympathetic nervous system activity may be involved in the pathogenesis of HTN.
Furthermore, studies supporting this link between OSA and HTN have reported a decrease in resting sympathetic nervous system activity[35] and blood pressure[36,37] following nasal continuous positive airway pressure (nCPAP) treatment[38].
In addition, OSA is associated with both acute and chronic effects of sympatho-excitation, resulting in decreased vascular compliance[38] [Chittenden et al, 2002]. It has long been postulated that the increased vascular tone in OSA leads to abnormal diurnal blood pressure control and increases in the incidence of myocardial infarction and stroke. Therefore, it is likely that OSA adversely affects several different cardiovascular homeostatic mechanisms. Although these vascular regulatory mechanisms have not been thoroughly investigated in OSA patients, disease-related hypoxia might abate vascular function by depravation of tissue-derived or blood vessel-derived vasoactive substances such as adenosine, prostanoids, endothelin, and nitric oxide (NO)[39].

Attributed to these recent findings, researchers are now suggesting the processes of neovascularization and the resultant decrease in vascular compliance may explain the decline in morbidity and mortality associated with long-standing sleep apnea pathology. The Sleep Heart Health Study recently indicated that patients with mild OSA are at enhanced risk for occlusive vascular disease[36].

However, these investigators also found that the risk did not rise further in patients with more severe OSA. This appears to support the findings of Lavie et al[42]. These researchers witnessed decreases in cardiovascular morbidity and mortality in ~1500 men Israeli men after the eighth decade of life.

These studies are supported by the clinical observations that, even in the presence of severe nocturnal oxygen desaturations, not all OSA patients suffer from cardiovascular co-morbidity[43].

Consequently, it may be considered that certain as yet unrevealed mechanism(s) shield some OSA patients from developing cardiovascular complications.

Mechanism relating SA and cardiac rhythm disturbances

The mechanism between AS and cardiac arrhythmias are a first research objective in the last years.

One of the first links is the relationship between the proarrythmic effect of the hypoxic episodes, the myocardial ischemia and the increase of sympathic activity. These implies an increase of plasmatic concentration of cathecolamines[44,45].

Additionally, As a result of increased sympathetic activity secondary to apneic episodes, oscillations in both heart rate and blood pressure occur as well as an increase in the frequency of atrial and ventricular arrhythmias[46]. In one large study of 400 patients, cardiac arrhythmias were noted in almost half the subjects[46]. The majority of these cardiac disturbances noted were bradyarrhythmias with 43 of the 400 patients experiencing sinus arrest of 2.5 to 13 seconds. In subsequent studies, ventricular arrhythmias were relatively uncommon[47]. Some investigators dispute the high prevalence of arrhythmias associated with OSA, claiming that the patients in the aforementioned studies had severe sleep apnea and were not representative of a greater spectrum of disease severity[49].

In summary, OSA predisposes individuals to increased cardiovascular morbidity and mortality [50]. This increased pathological risk is exacerbated by factors of age, body mass index (BMI), elevated blood pressure, and aberrant polysomnography indices[51]. Thus, the importance of early detection and treatment cannot be understated. Adequate intervention has been shown to improve daytime alertness and quality of life, daytime hypertension, neuropsychiatric performance, and reduce nocturnal oxyhemoglobin desaturation and respiratory arousals[52,53].

Different epidemiological studies have been focused in the description of cardiovascular pathologies and risk factors in different populations groups, but there is no frequent in mediterranean subjects and less frequent in Spanish populations.

The present study has the purpose to evaluate systematically the relationship between cardiovascular risk factors and the different severities of sleep apnea in a Granada population (Spain).

OBJETIVOS

General

El objetivo general de esta tesis doctoral internacional es demostrar las repercusiones sobre la salud de las alteraciones del sueño, profundizando en el Síndrome de la Apnea del Sueño como patología central, en una población de Granada.

Específicos

1. Determinar la importancia y repercusión que pueden tener las alteraciones del sueño para la fisioterapia

2. Evidenciar y examinar las relaciones entre alteraciones del Sueño y dolor

3. Presentar la asociación entre alteraciones del sueño y perfil clínico en población granadina

4. Profundizar en la interrelación entre factores de riesgo cardiovascular y apnea de sueño

5. Estudiar los mecanismos de asociación entre apnea del sueño y Arritmia cardiaca

AIMS

General

The main purpose in this Phd international dissertation was to explore the sleep disturbances effects on health, with a focus on Sleep Apnea as a prevalent pathology in a Granada Population.

Specifics

1. To determine the importance and repercussions of sleep disturbances in physiotherapy practice.

2. To evidence the relationship between sleep and pain

3. To present the association between sleep disturbances and clinical profile in a population from Granada

4. To search in the relationship between cardiovascular risk factors and sleep apnea syndrome

5. To study the association mechanism between sleep apnea and cardiac arrythmias

MATERIAL Y MÉTODOS

Objetivo I

Determinar la importancia y repercusión que pueden tener las alteraciones del sueño para la fisioterapia

Articulo I:

Valenza MC, Rodenstein DO, Fernandez-de-las-Peñas C. Consideration of sleep dysfunction in rehabilitation. Journal of Bodywork and Movement Therapies, Volume 15, Issue 3, July 2011, 262-267.

Metodología:

Revisión bibliográfica exhaustiva de las diferentes bases de datos, Pubmed, Scopus, Ovid, Science Direct y Web of Science.

Palabras clave: *Sleep disturbances, sleep alterations, sleep disorders, health consequences, clinical profile, pain, fatigue*.

MATERIAL Y MÉTODOS

Objetivo II

Evidenciar y examinar las relaciones entre alteraciones del Sueño y dolor

Articulo II:

Valenza MC, Valenza G, Gonzalez-Jimenez E, Isabel-de-la-Llave-Rincon A, Arroyo-Morales M, Fernandez-de-las-Peñas C. Alteration in Sleep Quality in patients with mechanical insidious neck pain and whiplash-associated neck pain. American Journal of Physical Medicine & Rehabilitation. 2012 91,1:584-591

Metodologia:

Diseño: Estudio descriptivo con casos y controles.

Muestra: 19 sujetos con dolor mecánico cervical, 22 sujetos diagnosticadas de latigazo cervical y 18 controles sanos.

Variables estudiadas: dolor, discapacidad y calidad y perfil de sueño.

MATERIAL Y MÉTODOS

Objetivo III

Presentar la asociación entre alteraciones del sueño y perfil clínico en población granadina

Articulo III:

Valenza MC, Valenza G, Muñoz-Casaubon T, Botella-Lopez M, Puentedura EJ, Arroyo-Morales M, Fernandez-de-las-Peñas C. Epidemiology of sleep-related complaints associated with obstructive sleep apnea, insomnia and non-restorative sleep in an at-risk population in Granada, Spain. Sleep and Biological Rhythms 2012; 10 (3)222–230.

Metodologia:

Diseño: Estudio descriptivo.

Muestra: 1009 sujetos con derivados al laboratorio del sueño por sospecha de Apnea de Sueño.

Variables estudiadas: prevalencia de Apnea de sueño, Insomnio y sueño no reparador junto con el perfil clínico y sintomático y los resultados polisomnograficos

MATERIAL Y MÉTODOS

Objetivo IV

Profundizar en la interrelación entre factores de riesgo cardiovascular y apnea de sueño

Articulo IV:

Valenza MC, Martín Martín L, González Jiménez E, Aguilar Cordero MJ, Botella López M, Muñoz Casaubon T, Valenza Demet G. Factores de riesgo para el síndrome metabólico en una población con apnea del sueño; evaluación en un grupo de pacientes de Granada y provincia; estudio GRANADA. Nutrición Hospitalaria 2012;27(4):1255-160.

Metodologia:

Diseño: Estudio descriptivo.

Muestra: 1019 sujetos con derivados al laboratorio del sueño por sospecha de Apnea de Sueño.

Variables estudiadas: prevalencia de factores de riesgo cardiovascular, perfil sintomático y resultados polisomnograficos

MATERIAL Y MÉTODOS

Objetivo V

Estudiar los mecanismos de asociación entre apnea del sueño y Arritmia cardiaca

Articulo V:

Valenza MC, Valenza G, Muñoz-Casaubon T, Botella-Lopez M, Puentedura EJ, Arroyo-Morales M, Fernandez-de-las-Peñas C. Apnea del Sueño y Arritmias Ventriculares. Revista Iberoamericana de Arritmologia 2012 ;12 (2)208-318

Metodologia:

Revisión bibliográfica exhaustiva de las diferentes bases de datos, Pubmed, Scopus, Ovid, Science Direct y Web of Science.

Palabras clave: *Sleep disturbances, sleep alterations, sleep disorders, cardiac arrhythmias, ventricular arrhythmias and atrial arrhythmias.*

RESULTADOS

RESULTADOS

Los resultados de esta tesis se agrupan en torno a cinco artículos que han sido publicados o aceptados para su publicación en revista de difusión internacional.

Tres de las revistas en las que se han expuesto resultados relacionados con esta tesis se encuentran incluidas en el Journal Citation Reports en diferentes categorías como: rehabilitación, neurociencias y nutrición.

El índice de impacto de cada revista en las que se ha difundido artículos relacionados con esta tesis y la posición en las categorías correspondientes se exponen a continuación

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Abstracting and Indexing

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- CINAHL
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- Neuroscience Abstracts
- Scopus

RESULTADOS y DISCUSION (Results and Discussion)

Los resultados de esta tesis se agrupan en torno a cinco artículos que han sido publicados o aceptados para su publicación en revista de difusión internacional.

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Abstracting and Indexing

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Articulo I:

Valenza MC, Rodenstein DO, Fernandez-de-las-Peñas C. Consideration of sleep dysfunction in rehabilitation. Journal of Bodywork and Movement Therapies, Volume 15, Issue 3, July 2011, 262-267.

Abstract

The physiology of sleep is not completely understood but it is widely accepted that sleep is important to the human body in the recovery of metabolic and neurological processes. This paper summarizes the effects of sleep dysfunction on different systems and considers implications in the context of rehabilitation. When sleep is experimentally completely or partially curtailed important brain functions are impacted leading to psychological and neurological disturbances. Increased cortisol levels, reduction of glucose tolerance, and increased sympathetic nervous system activity have also been identified in healthy subjects under such conditions. Several studies show that 50–80% of patients with chronic pain suffer from sleep dysfunction. It has been suggested that on the one hand pain can cause sleep dysfunction and on the other hand that sleep dysfunction can aggravate pain. The physiologic mechanism behind this interaction is not completely clear; although most authors describe the relationship between pain and sleep dysfunction as aberrant processing of tactile-cutaneous sensory inputs at the meso-encephalic level and in the trigeminal nucleus both when asleep and awake. Decreased duration of sleep also increases heart rate, blood pressure and sympathetic activity magnifying the individual's response to stressful stimuli. Possible causal mechanisms for the established connection between short sleep cycles and coronary pathology include sympathetic nervous system hyperactivity, increased blood pressure increase or reduced glucose tolerance. Finally, sleep and fatigue have traditionally been linked. Fatigue can have a physical etiology but is also associated with depression. Sleep alterations are also considered an important risk factor for psychological dysfunction and also mental illness. However, despite the noted repercussions of sleep dysfunction, studies investigating interventions to improve sleep have been limited in number. Benefits of exercise programs on sleep habits have been controversial with some have finding positive effects, whereas others did not find any significant effect. It is possible that the dose or intensity of exercise programs may have an important influence in the outcomes. It is our opinion that based on the multi-system repercussions of different sleep dysfunctions, evaluation of sleep habits should be considered fundamental in the context of rehabilitation and should be included as part of the clinical history of each patient attending physical therapy.

Journal of Bodywork & Movement Therapies (2011) 15, 262–267

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REVIEW

Consideration of sleep dysfunction in rehabilitation

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KEYWORDS
Sleep dysfunction;
Physical therapy;
Rehabilitation;
Pain;
Sleep apnea

Summary The physiology of sleep is not completely understood but it is widely accepted that sleep is important to the human body in the recovery of metabolic and neurological processes. This paper summarizes the effects of sleep dysfunction on different systems and considers implications in the context of rehabilitation. When sleep is experimentally completely or partially curtailed important brain functions are impacted leading to psychological and neurological disturbances. Increased cortisol levels, reduction of glucose tolerance, and increased sympathetic nervous system activity have also been identified in healthy subjects under such conditions. Several studies show that 50–80% of patients with chronic pain suffer from sleep dysfunction. It has been suggested that on the one hand pain can cause sleep dysfunction and on the other hand that sleep dysfunction can aggravate pain. The physiologic mechanism behind this interaction is not completely clear; although most authors describe the relationship between pain and sleep dysfunction as aberrant processing of tactile-cutaneous sensory inputs at the meso-encephalic level and in the trigeminal nucleus both when asleep and awake. Decreased duration of sleep also increases heart rate, blood pressure and sympathetic activity magnifying the individual's response to stressful stimuli. Possible causal mechanisms for the established connection between short sleep cycles and coronary pathology include sympathetic nervous system hyperactivity, increased blood pressure increase or reduced glucose tolerance. Finally, sleep and fatigue have traditionally been linked. Fatigue can have a physical etiology but is also associated with depression. Sleep alterations are also considered an important risk factor for psychological dysfunction and also mental illness. However, despite the noted repercussions of sleep dysfunction, studies investigating interventions to improve sleep have been limited in number. Benefits of exercise programs on sleep habits have been controversial with some have finding positive effects, whereas others did not find any

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significant effect. It is possible that the dose or intensity of exercise programs may have an important influence in the outcomes. It is our opinion that based on the multi-system repercussions of different sleep dysfunctions, evaluation of sleep habits should be considered fundamental in the context of rehabilitation and should be included as part of the clinical history of each patient attending physical therapy.

Introduction

The physiology of sleep is not completely understood but it is widely accepted that sleep is important for recovery of normal metabolic and neurological **activity** (Shapiro and Flannigan, 1993). For instance, the REM phase of sleep significantly impacts memory and learning. Hence, any pathology or behaviour altering normal sleeping habits may have an important impact on health status. The structure of sleep has been studied for many years and the conclusion is that sleep is not a homogeneous phenomenon. It is distributed in two phases: REM and non-REM phases, which are electro-physiologically differentiated:

Non-REM phase

This phase is characterized by a high voltage-low frequency electroencephalogram and a cortical synchronization with both sleep time and visible K complexes. Muscle tone is progressively reduced in the deepest phases of the sleep with the exception of the diaphragm tone, which is maintained independently of the phase of sleep. Authors define the non-REM as a phase of brain inactivity and relative regulation of an active body (Carscadon and Dement, 1994). It is divided into four steps, numbered 1 to 4 depending on depth, going from a shallow sleep in the phase 1 to the deepest sleep in the phase 4. The non-REM phase is controlled by the ascending reticular activating system and by the supraquiasmatic nucleus. This phase represents a decrease of the basal metabolism and is associated with decreased O_2 consumption, CO_2 production, heart rate, blood pressure, body temperature, and respiratory rate (Rosenberg-Adamsen et al., 1996).

REM phase

This phase is characterized by a low voltage-high frequency electroencephalogram, accompanied by rapid and coordinated ocular movements and muscle atony (Shapiro and Flannigan, 1993; Dement and Kleitman, 1957). Carscadon and Dement (1994) identified an inhibition of the spinal motoneurons that may explain the observed reduction in muscle tone.

It should be noted that no consensus exists for a definition of normal sleep in terms of duration or length of REM and non-REM phases. What has been shown is that sleep is a cyclic process that repeats each 90 min, where the non-REM phase takes around 80% of the duration and the REM phase usually accounts for the remaining 20% (Carscadon and Dement, 1994). In addition, although duration of normal sleep has been established as around 7.5 h/day (Carscadon and Dement, 1994); some authors have defined sleep dysfunction as less than 6 h per day (Buysse et al., 1989). The current paper summarizes the effects of sleep dysfunction on different physiological systems and presents considerations in the context of rehabilitation.

Effects of sleep dysfunction on different body systems

Pathological modifications of the architecture, quality and quantity of sleep are called "sleep dysfunctions" and these occur in all age-groups. Most of the studies conducted on healthy subjects have focused on curtailed sleep with effects on the duration and composition of sleep architecture. Studies into complete or selective restriction of sleep have found important effects on brain function leading to psychological and neurological dysfunctions (Horne, 1985), changes in behavioural and psychological performance (Horne, 1985; Bonnet, 1986; Gillberg and Akersted, 1994), somnolence (Bonnet, 1986), and concentration difficulties (Horne, 1985). In addition, mood and life attitude are affected with irritability, lack of vitality, anxiety and confusion reported (Agnew et al., 1967; Horne, 1985). Physiological effects including increased cortisol levels, reduced glucose tolerance, and increased sympathetic nervous system activity (Spiegel et al., 1999) have been found in healthy subjects as a result of complete or partial sleep restriction. Tochibuko et al. (1996) reported increased blood pressure and sympathetic activity in individuals sleeping only 3.6 h.

Sleep dysfunction and pain

The relationship between sleep and pain is complex (Smith and Haythornthwaite, 2004). Traditionally pain has been considered a state characterized by hyper-vigilance state, whereas sleep is considered a state with reduced vigilance. The interest in the relationship between pain and sleep has been identified in the literature as early as 1934 when Copperman et al. (1934) demonstrated the effect of sleep dysfunction on the nociceptive process. Later studies (Walter et al., 1960; Smith and Haythornthwaite, 2004) have demonstrated an apparent bidirectionality in this relationship with pain causing sleep dysfunction and sleep dysfunction aggravating pain. More recent studies have demonstrated that changes in the nociceptive process result from sleep disturbances appear particularly in subjects with selective REM phase restriction (Older et al., 1998; Lentz et al., 1999; Arima et al., 2001; Onen et al., 2001). The physiologic mechanism related to these processes is not completely clear although most authors describe it as an aberrant processing of tactile-cutaneous sensory inputs at the meso-encephalic level and in the

trigeminal nucleus both when asleep and awake (Lavigne et al., 2005, pp.1246–1255). Several studies have shown that 50–80% of patients with chronic pain also experience sleep dysfunctions (Pilowsky et al., 1985; Atkinson et al., 1988; Morin et al., 1998; Smith et al., 2000). The most studied pathologies in the context of sleep cycles have been fibromyalgia syndrome, low back pain and whiplash (Menefee et al., 2000; Schlesinger et al., 2001). Menefee et al. (2000) identified a positive correlation between pain intensity and severity and sleep dysfunction.

A number of studies have also investigated serotonin production and its role in sleep and the pain. Kundermann et al. (2004) demonstrated that serotonergic dysfunction was related to increased thermal pain sensitivity, while Wei et al. (2008) found that serotoninergic receptors in the spinal cord have a complex role in the control of sleep-restriction induced cutaneous hypersensitivity. However, at this time understanding of the mechanisms underlying the association between serotonergic dysfunction, pain and sleep remains limited (Ohayon, 2009).

Headaches have also been associated with sleep dysfunction (Alberti, 2006) and numerous studies have examined this relationship (Ødegård et al., 2010). A relationship has been reported between headaches, low sleep efficiency, frequent waking and reduction of the low waves of sleep in the tracing during or at the end of the REM phase (Chervin and Zallek, 2001; Dexter and Weitzman, 1970; Manzoni et al., 1981) Up to 55% of patients with headaches present with primary sleep disorders such as apnea or restless legs syndrome (Spierings et al., 1996). Patients diagnosed with sleep apnea also usually suffer morning migraines (Idiman et al., 2004).

However, it is not clear whether pain causes or contributes to these sleep abberations. Nevertheless, it seems clear that when pain and sleep interact, the biological capacity and behaviour of the individual is compromised causing a decrease in quality of life.

Sleep disturbances and hemodynamic alterations

Sleep and arterial rigidity

The associations between sleep disorders and cardiovascular and neurological control has important clinical implications. Various studies have shown that sleep restriction increases heart rate, blood pressure and sympathetic activity predisposing the individual to an inadequate response to stressful stimuli (Tofler et al., 1990; Krachman et al., 1995; Masahiko et al., 2000). It is postulated that the renin-angiotensin system is activated causing endothelial vasoconstriction (Willich et al., 1987).

Coronary pathology

The possible connection between sleep duration and its effect on coronary artery disease has been widely investigated and it has been found that sleeping less than 7–8 h per night increases the incidence of cardiac related death (Schwartz et al., 1999; Ayas et al., 2003; Gangwisch et al., 2006; Wingard and Berkman, 1983; Kripke et al., 1979; Sehdev and Hutchins, 2001). Mechanisms for the correlation between short sleep and coronary pathology may include sympathetic hyperactivity, increased blood pressure or reduced glucose tolerance. Indicating the complexity of the associations, Spiegel et al. (1999) and Tochibuko et al. (1996) found an increase in blood pressure with brief sleep restriction but a decrease in blood pressure with long sleep restriction.

Sleep dysfunctions and fatigue

In the context of sleep dysfunction, fatigue deserves special attention due to its possible multi-factorial etiology. Fatigue can be defined as a distressing, persistent, subjective sense of tiredness or exhaustion that is not proportional to physical or emotional activity and interferes with daily activities and functioning. Indicating the likely complicated interaction of sleep dysfunction and fatigue, several studies have reported relationships between sleep alterations and depression (Bianchi et al., 2005), sleep alterations and fatigue (Girgrah et al., 2003) and fatigue and depression (Huang and Lin, 2009). When dealing with physical fatigue several studies have found a greater psychological rather than musculoskeletal component (Sehdev and Hutchins, 2001; Bianchi et al., 2005). Schaefer (1995) suggested a possible interaction between sleep, fatigue and fibromyalgia. Fatigue is one of the 5 criteria indicating clinical remission in patients with rheumatoid arthritis (Pincus et al., 2007).

Sleep disturbances and musculoskeletal function

The psychological and physiological effects resulting from sleep alteration on musculoskeletal function have been described yet remain controversial. Martin (1981) suggested a cause-and-effect relationship between sleep dysfunction, psychological effects and musculoskeletal function changes. It has been suggested that the greatest effect of sleep disturbances would be a reduction in high-intensity physical exercise tolerance (Martin, 1981). Evidence suggests that athletes are concerned about the effects of inadequate restful sleep on their physical performance (Leger et al., 2005), although the effects of sleep restriction on physical performance (e.g. anaerobic power, muscle strength, stamina, heart rate, ventilation and oxygen consumption) are not clearly understood (Souissi et al., 2003).

Rodgers et al. (1995) found that a 48-h sleep restriction period caused a considerable reduction in performance in physical activities that required from 30% to 45% of VO_2máx without affecting the anaerobic power. Souissi et al. (2003) proved that the length of restriction of sleep period could be important as the peak-power was not affected after 24 h of sleep restriction; however, 26 h of sleep restriction did significantly affect significantly the peak-power.

Sleep disturbances, cognitive and psychological alterations

It seems that prolonged sleep restrictions have a relevant effect on cognitive and emotional function (Pilcher and Huffcutt, 1996). Different studies conducted on healthy subjects found progressive cognitive function deterioration (e.g., lack of concentration or memory) related to sleep dysfunction (Dinges et al., 1997; Van Dongen et al., 2003).

Among the different cognitive functions, memory has most often been the subject of study (Bell-McGinty et al., 2004; Mu et al., 2005; Lim et al., 2007). Other cognitive alterations, e.g., verbal learning (Thomas et al., 2000; Drummond et al., 2005), divided attention (Drummond et al., 2001), decision making processes (Venkatraman et al., 2007) or emotional response to images (Michael and Lisa, 2008) have also been studied but to a lesser extent.

Sleep alterations are also considered an important risk factor for psychological dysfunction and mental illness (Chang et al., 1997; Koren et al., 2002; Argoff, 2007). For instance, people with schizophrenia usually have long periods of weakness due to decreased duration of sleep whereas people with obsessive symptoms require less sleep (Chang et al., 1997). People suffering from depression have precocious waking with a subsequent difficulty falling sleep again, while subjects with anxiety have problems in getting to sleep.

It has been shown that serotoninergic system is involved in the regulation of sleep and wakefulness (Cifariello et al., 2008). In particular, REM-phase sleep depends on the decrease of serotoninergic tone within brain stem structures. Sleep restriction also induces an activation of serotoninergic neurons due to prolonged wakefulness. Further, the common neurobiological mechanisms resulting from sleep restriction suggest that sleep loss in insomniac or depressed patients might be an endogenous compensatory process (Adrien, 2002).

In addition, poor sleep has also been associated with emotional stress. This has been shown in the form of depression, hostility, fatigue and confusion (Atkinson et al., 1988). Sleep alterations in patients with chronic pain have also been connected with a modification of sensitivity to pain, which may become a perpetuating factor in the cycle connecting chronic pain with sleep alterations and depression (Moldofsky and Scarisbrick, 1976).

Nevertheless, the way in which sleep restriction affects cognitive function is treated differently by different authors, probably due to discrepancies between studies.

Sleep apnea

Sleep apnea obstructive syndrome (SAOS) is produced by an intermittent and repetitive occlusion of the superior airway during sleep, causing a complete (apnea) or partial (hypopnea) interruption of the airflow. It is one of the more studied sleep dysfunctions due to its multiple repercussions in different body systems. In fact, sleep apnea is an example of sleep alteration with a great quantity of associated pathologies. The prevalence of SAOS ranges from 4 to 6% in males and is reported as 2% in females (Young et al., 1993; Marín et al., 1997).

Apneas and hypopneas have a variable duration and affect cardiorespiratory homeostasis in different ways. Its repetition during sleep, sometimes several hundred times in one night, and day after day for years, gives rise to important disturbances in the central nervous system, myocardial and brain perfusion and the systemic and pulmonary blood circulation. Diurnal hyper-somnia, snoring and a spousal report of apnea pauses are the 3 main symptoms. Definitive diagnosis is based on polysomnographic monitorization or on nocturnal cardiorespiratory polygraphy. The lack of sleep has also been associated with behaviour and personality disorders (depressive syndrome, irritability or paranoia), lack of memory, intellectual deterioration and diminished motor ability and perceptive skills. Further, obstructive apneas also cause important alterations in intrapulmonary gas exchange increasing the risk of cardiovascular (Krieger et al., 1989; Hung et al., 1990) and systemic hypertension (Palomäki, 1991). Similarly, these patients often also present with a greater incidence of cardiac arrhythmia (sinus bradycardia, sinus blockade, auricle-ventricular jamming) and nocturnal sudden death (Shepard, 1994).

Considerations in the context of rehabilitation

Despite the repercussion of sleep dysfunctions, studies that have investigated interventions for improving sleep are few and far between (Page et al., 2006). Although no definitive evidence is currently available, non-pharmacological interventions have shown positive findings in promoting high-quality sleep and daytime functioning (Page et al., 2006). For instance, it has been identified that exercise programs improve sleep habits in obese patients with mild to moderate sleep apnea (Barnes et al., 2009) and that they improve central sleep apnea in patients with chronic heart failure (Yamamoto et al., 2007). Further, Tai Chi exercises enhanced sleep stability in patients with chronic heart failure (Yeh et al., 2008). On the contrary, moderate-intensity walking or low-intensity yoga were not effective in improving sleep quality (Elavsky and McAuley, 2007). It is possible that dose or intensity of exercise programs have an important influence in the outcomes.

Finally, different hands-on techniques may be also used for improving clinical implications of sleep disturbances. In fact, oropharyngeal exercises significantly reduced severity and symptoms in individuals with sleep apnea obstructive syndrome (Guimarães et al., 2009). No further scientific evidence related to hands-on techniques and sleep changes is available.

Based on the systemic repercussions of different sleep dysfunctions reviewed in the current paper, evaluation of sleep habits should be considered a fundamental clinical competency in contemporary physical therapy (Coren, 2009). In fact, questions on sleep dysfunction should be included in the clinical history of each patient attending a physical therapy clinic allowing the therapist to tailor management to also this possible aspect of a patient's presentation.

Buysse et al. (1989) developed "The Pittsburgh Sleep Quality Index" to assess the quality of sleep in psychiatric conditions. Clinicians may also use this Index in their patients in relation to sleep. Some key questions can be recommended: 1) For how long do you sleep at night? 2) Do you usually wake up during the night? 3) Do you need much time to get to sleep? 4) Do you feel rested when you wake up in the morning? In our clinical practice these 4 questions help us, as clinicians, to provide an orientation with regard to the quality of sleep in our patients with chronic pain.

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Articulo II:

Valenza MC, Valenza G, Gonzalez-Jimenez E, Isabel-de-la-Llave-Rincon A, Arroyo-Morales M, Fernandez-de-las-Peñas C. Alteration in Sleep Quality in patients with mechanical insidious neck pain and whiplash-associated neck pain. American Journal of Physical Medicine & Rehabilitation. 2012 91,1:

Abstract

OBJECTIVE: This study aimed to determine differences in sleep quality between patients with mechanical neck pain, patients with whiplash (WAD) pain, and healthy controls and to determine the relationship between the intensity of ongoing pain, disability, and sleep quality.

DESIGN: Nineteen patients with mechanical neck pain (4 men, 15 women; age, 40 ± 16 yrs), 22 with WAD (4 men, 18 women; age, 38 ± 15 yrs), and 18 comparable controls (4 men, 14 women; age, 41 ± 13 yrs) completed the Pittsburgh Sleep Quality Index to assess sleep quality. A numerical pain rate scale (0-10) and the Neck Disability Index (0-50) were collected for assessing neck pain and disability.

RESULTS: Significant differences in sleep quality ($P < 0.001$), sleep latency ($P = 0.005$), sleep efficiency ($P = 0.002$), sleep disturbances ($P < 0.001$), use of sleeping medication ($P < 0.001$), daytime dysfunction ($P < 0.001$), and total Pittsburgh Sleep Quality Index score ($P < 0.001$) but not for sleep duration ($P = 0.096$) were found; patients with mechanical neck pain and WAD pain exhibited higher scores in all components compared with healthy controls. Seventeen (77%) patients with WAD and 13 (68%) with mechanical neck pain reported poor sleep quality (Pittsburgh Sleep Quality Index score, >8). Significant positive correlations between mean intensity of ongoing pain with sleep quality ($rs = 0.693$; $P < 0.001$); sleep duration ($rs = 0.433$; $P = 0.044$); sleep efficiency ($rs = 0.644$; $P = 0.001$) and total Pittsburgh Sleep Quality Index score ($rs = 0.643$; $P = 0.001$) were found in patients with WAD pain; the higher the intensity of ongoing pain, the worse the sleep quality.

CONCLUSIONS: Sleep disturbances are a common finding in individuals with neck pain and are associated with the intensity of ongoing pain in WAD. It seems essential to address the ongoing cycle of pain and sleep disturbances as an integral part of the treatment of patients with neck pain.

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ORIGINAL RESEARCH ARTICLE

Alteration in Sleep Quality in Patients with Mechanical Insidious Neck Pain and Whiplash-Associated Neck Pain

ABSTRACT

Valenza MC, Valenza G, González-Jiménez E, De-la-Llave-Rincón AI, Arroyo-Morales M, Fernández-de-las-Peñas C: Alteration in sleep quality in patients with mechanical insidious neck pain and whiplash-associated neck pain. Am J Phys Med Rehabil 2012;91:584–591.

Objective: This study aimed to determine differences in sleep quality between patients with mechanical neck pain, patients with whiplash (WAD) pain, and healthy controls and to determine the relationship between the intensity of ongoing pain, disability, and sleep quality.

Design: Nineteen patients with mechanical neck pain (4 men, 15 women; age, 40 ± 16 yrs), 22 with WAD (4 men, 18 women; age, 38 ± 15 yrs), and 18 comparable controls (4 men, 14 women; age, 41 ± 13 yrs) completed the Pittsburgh Sleep Quality Index to assess sleep quality. A numerical pain rate scale (0–10) and the Neck Disability Index (0–50) were collected for assessing neck pain and disability.

Results: Significant differences in sleep quality ($P < 0.001$), sleep latency ($P = 0.005$), sleep efficiency ($P = 0.002$), sleep disturbances ($P < 0.001$), use of sleeping medication ($P < 0.001$), daytime dysfunction ($P < 0.001$), and total Pittsburgh Sleep Quality Index score ($P < 0.001$) but not for sleep duration ($P = 0.096$) were found; patients with mechanical neck pain and WAD pain exhibited higher scores in all components compared with healthy controls. Seventeen (77%) patients with WAD and 13 (68%) with mechanical neck pain reported poor sleep quality (Pittsburgh Sleep Quality Index score, >8). Significant positive correlations between mean intensity of ongoing pain with sleep quality ($r_s = 0.693$; $P < 0.001$); sleep duration ($r_s = 0.433$; $P = 0.044$); sleep efficiency ($r_s = 0.644$; $P = 0.001$) and total Pittsburgh Sleep Quality Index score ($r_s = 0.643$; $P = 0.001$) were found in patients with WAD pain; the higher the intensity of ongoing pain, the worse the sleep quality.

Conclusions: Sleep disturbances are a common finding in individuals with neck pain and are associated with the intensity of ongoing pain in WAD. It seems essential to address the ongoing cycle of pain and sleep disturbances as an integral part of the treatment of patients with neck pain.

Key Words: Sleep, Pain, Cervical Spine, Whiplash

Neck pain constitutes a significant health care problem and can have an insidious (mechanical) or traumatic (whiplash-associated [WAD] neck pain) onset. A systematic review reported 1-yr prevalence for neck pain ranging from 16.7% to 75.1% with a mean of 37.2%.[1] The incidence rate of WAD varies across different studies and countries, but it may be as high as 677 per 100,000 habitants.[2] In addition, the economic burden associated with the management of neck pain is second only to low back pain in annual workers' compensation costs in United States.[3]

Sleep disturbances are considered an essential element of a conceptual model for sleep-related problems in patients with pain. In fact, several studies have demonstrated that individuals with chronic pain present sleep disturbances.[4,5] Bigatti et al.[6] found that almost 95% of women with fibromyalgia syndrome have poor sleep quality,[6] whereas Theadom et al.[7] reported that poor sleep quality had significant implications for health-related quality-of-life in this pain syndrome.[7] Other studies have shown that sleep disorders were also present in patients with chronic low back pain and that worse sleep quality was associated with a higher impact on daily life.[8] It seems that poor sleep quality is related to pain intensity and psychologic distress, at least, in temporomandibular disorders.[9] Therefore, it is likely that sleep quality can be altered in patients with neck pain of insidious or traumatic onset affecting their quality-of-life.

It has been suggested that mechanical insidious neck pain and WAD-associated neck pain exhibit difference in nociceptive processing.[10] Scott et al.[11] concluded that mechanical insidious neck pain reflects segmental local sensitization because mechanical pain hypersensitivity is restricted to the neck region, whereas WAD can reflect an augmented central pain processing mechanism because pressure hypersensitivity is present in pain-free distant areas (widespread).[11] It is possible that patients with WAD neck pain also show different pattern of sleep quality than do patients with mechanical insidious neck pain. In fact, Marty et al.[8] suggested that sleep disturbances differ according to the pain syndrome with which they are associated.[8] To the best of the authors' knowledge, no study has previously investigated sleep quality in individuals with an insidious (mechanical) or traumatic (WAD) onset of neck pain.

Therefore, the aims of the current study were (1) to determine differences in sleep quality between patients with mechanical neck pain and those with WAD neck pain compared with healthy controls and (2) to determine the relationship between the intensity of ongoing pain, disability, and sleep quality in patients with neck pain.

METHODS

Participants

In this study, patients with insidious or traumatic onset of neck pain recruited from a regional hospital were included. To be included in the insidious mechanical neck pain group, patients should have generalized neck and shoulder pain, with symptoms provoked by neck postures, neck movement, or palpation of the cervical musculature. Exclusion criteria of these patients included (1) history of whiplash injury, (2) history of cervical surgery, (3) diagnosis of cervical radiculopathy or myelopathy, (4) diagnosis of fibromyalgia syndrome, or (5) age younger than 18 or older than 65 yrs. The medical history of each patient was solicited from their primary care physician to assess the presence of any exclusion criteria or "red flags" (infection, osteoporosis).

To be included in the traumatic neck pain group, patients should report neck pain as a result of a motor vehicle accident. They were eligible if they met the Quebec Task Force Classification of WAD II, that is, neck complaints and musculoskeletal signs without evidence of conduction loss on neurologic examination.[12] Patients were excluded if they experienced (1) concussion or loss of consciousness during the accident, (2) head or upper quadrant injury during the accident, (3) history of repetitive whiplash, (4) previous diagnosis of primary headache, (5) psychiatric condition, (6) diagnosis of fibromyalgia, or (7) had a current claim for litigate or compensation.

Finally, healthy subjects without history of neck/shoulder pain in the previous year, neck surgery or fracture, or neurologic disorders who responded to a local advertisement were also included.

The control group was searched for comparable subjects in terms of age and sex. The protocol was approved by the local human research committee and conducted after the declaration of Helsinki. All subjects signed an informed consent before their inclusion in the study.

Demographic and Clinical Data

Demographic data including age, sex, body mass index, past medical history, and location and nature of the symptoms were collected. An 11-point numerical pain rating scale (0, no pain; 10, maximum pain) was used to assess the current level of neck pain. The numerical pain rating scale has been

demonstrated to be a reliable instrument to assess pain intensity.[13]

Patients also completed the Neck Disability Index (NDI) to measure self-reported disability. The NDI consists of ten questions measured on a 6-point scale (0, no disability; 5, full disability).[14] The numeric score for each item is summed for a score ranging from 0 to 50, where a higher score reflects greater disability. The NDI has been demonstrated to be a reliable and valid tool for the assessment of neck disability.[15,16] A systematic review found that most studies investigating the reliability of the NDI reported intraclass correlation coefficients ranging from 0.50 to 0.98, suggesting that the NDI has sufficient support and usefulness to be the most commonly used self-report measure for neck pain.[17]

Assessment of Sleep Quality

In the current study, the Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality.[18] The PSQI is the most commonly used standardized questionnaire for the comprehensive assessment of sleep quality. The PSQI appraises sleep quality over a 1-mo period through a standardized questionnaire differentiating between "good" and "poor" sleepers. The PSQI consists of 19 self-rated questions and 5 questions answered by bedmates or roommates. The 19 questions are categorized into seven components (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleeping medication use, and daytime dysfunction) graded on a score ranging from 0 to 3. PSQI items use varying response categories that include recording usual bed time, usual wake time, number of actual hours slept, and number of minutes to fall asleep, as well as forced-choice Likert-type responses. The sum of the scores for the components yields one global score, which ranges from 0 to 21, where a higher score indicates worse sleep quality. Buysse et al.[19] have reported that the PSQI has good internal consistency ($\alpha = 0.83$) and test-retest reliability ($r = 0.85$).[19] A total score greater than 8.0 has been found to be indicative of poor sleep quality.[20] In the current study, we considered total global score, the scores on each component and also the distribution of the responses on each component of the PSQI.[21]

Statistical Analysis

Data were analyzed using the SPSS version 17.0. The Kolmogorov-Smirnov test was used to analyze the normal distribution of the variables ($P > 0.05$). Differences in demographic and clinical features between both groups of patients and healthy controls were compared using an analysis of variance for continuous data and χ^2 tests of independence for categorical data. For the first objective, a one-way analysis of variance test was used to analyze the differences in the total global score and the score on each component among the three groups (the Bonferroni test was applied as post hoc analysis). In addition, χ^2 tests were used to analyze the differences in the distribution of the responses on each component of the PSQI among the three groups. Pain scores, duration of symptoms, and NDI did not follow normal distribution ($P = 0.007$); therefore, for the second objective of the study, the nonparametric Spearman rho (r_s) test was used to analyze the association between intensity of ongoing pain, duration of symptoms, and NDI with the scores on each component of the PSQI and the global PSQI score in either neck pain group. The statistical analysis was conducted at a 95% confidence level. A P value less than 0.05 was considered statistically significant.

RESULTS

Nineteen patients with mechanical insidious neck pain (4 men, 15 women) aged 19–56 yrs (mean, 40 ± 16 yrs), 22 patients with WAD (4 men, 18 women) aged 18–55 yrs (mean, 38 ± 15 yrs), and 18 comparable controls (4 men, 14 women) aged 18 to 52 yrs (mean, 41 ± 13 yrs) were included. No significant differences in sex ($P = 0.879$) and age ($P = 0.332$) were found among the groups. Patients with mechanical insidious neck pain showed a longer duration of the symptoms compared with those with WAD neck pain ($P = 0.001$), but nonsignificant differences in the intensity of ongoing pain ($P = 0.451$) and NDI scores ($P = 0.336$) between groups were found. A significant positive association between mean intensity of ongoing pain and NDI score was found in both patients with mechanical neck pain ($r_s = 0.533$; $P = 0.033$) and with WAD ($r_s = 0.830$; $P = 0.003$); the higher the pain intensity, the higher the self-reported disability. Table 1 summarizes the demographic and clinical data of patients with insidious neck pain, WAD, and healthy controls.

The analysis of variance revealed significant differences in the total PSQI score among the three groups ($F = 27.670$; $P < 0.001$). Post hoc analysis found that patients with insidious neck and WAD neck pain exhibited higher scores ($P < 0.001$) than did the healthy controls. No significant differences ($P = 0.778$) between mechanical and WAD neck pain individuals were found. Seventeen (77%) patients with WAD and 13 (68%) with mechanical neck pain reported poor sleep quality (PSQI score, >8). In addition, significant differences for sleep quality ($F = 23.763$, $P < 0.001$), sleep latency ($F = 5.866$, $P =$

TABLE 1 Demographic and clinical data of patients with insidious (mechanical) or traumatic (WAD) onset of neck pain and healthy subjects

	Healthy Controls (n = 18)	Mechanical Neck Pain (n = 19)	WAD Neck Pain (n = 22)	Significance
Sex (male/female)	4/14	4/15	4/18	$\chi^2 = 0.25$; $P = 0.88$
Age, yrs	41 ± 13	40 ± 16	38 ± 15	$F = 4.61$; $P = 0.33$
BMI, kg/cm^2	26.3 ± 3.3	27.8 ± 3.9	27.3 ± 3.2	$F = 1.96$; $P = 0.34$
Pain duration	—	10.8 ± 8.3 mos	22 ± 8 days	$F = 12.26$; $P = 0.001$[a]
NPRS (0–10)	—	6.2 ± 1.5	6.9 ± 1.6	$F = 1.46$; $P = 0.45$
NDI (0–50)	—	23.0 ± 8.6	26.8 ± 9.6	$F = 0.98$; $P = 0.34$

Data are expressed as mean ± SD.

[a]Statistically significant difference between groups.

BMI, body mass index; NDI, Neck Disability Index; NPRS, numerical pain rating scale; WAD, whiplash-associated.

0.005), sleep efficiency ($F = 6.952$, $P = 0.002$), sleep disturbances ($F = 13.121$, $P < 0.001$), use of sleeping medication ($F = 10.387$, $P < 0.001$), and daytime dysfunction ($F = 22.930$, $P < 0.001$) but not for sleep duration ($F = 2.448$, $P = 0.096$) were also found (Table 2). Post hoc analysis revealed that both patient groups exhibited higher scores in all components of the PSQI compared with controls ($P < 0.01$) and that patients with WAD neck pain showed worse sleep quality compared with those with mechanical neck pain ($P < 0.001$).

Differences were also evident in the percentage of patients reporting worse sleep quality ($\chi^2 = 34.707$, $P < 0.001$), worse sleep latency ($\chi^2 = 11.051$, $P = 0.047$), less sleep efficiency ($\chi^2 = 19.668$, $P = 0.003$), worse sleep disturbances ($\chi^2 = 22.710$, $P = 0.001$), higher use of sleeping medication ($\chi^2 = 30.679$, $P < 0.001$), and daytime dysfunction ($\chi^2 = 37.832$, $P < 0.001$). Tables 3 and 4 summarize the number of patients with either insidious or traumatic onset of neck pain and healthy subjects reporting each answer.

Finally, significant positive correlations between the mean intensity of ongoing pain with sleep quality ($r_s = 0.693$; $P < 0.001$), sleep duration ($r_s = 0.433$; $P = 0.044$), sleep efficiency ($r_s = 0.644$; $P = 0.001$), and total PSQI score ($r_s = 0.643$; $P = 0.001$, Fig. 1*A*) were found in patients with traumatic onset neck pain (WAD); the higher the intensity of ongoing pain, the worse the sleep quality; the less the sleep duration, the worse the sleep efficiency and the higher the sleep disturbances (global PSQI score). On the contrary, no significant associations between intensity of ongoing pain and sleep quality ($r_s = 0.282$; $P = 0.243$); sleep duration ($r_s = 0.294$; $P = 0.221$); sleep efficiency ($r_s = 0.292$; $P = 0.226$), and total PSQI score ($r_s = 0.141$; $P = 0.566$; Fig. 1*B*) were found in individuals with mechanical insidious neck pain. In addition, no significant associations between the duration of pain symptoms and any of the subscales of the PSQI were found in either neck pain group ($P > 0.120$). No significant association between PSQI score and NDI score in individuals with either mechanical ($r_s = 0.228$; $P = 0.189$) or

TABLE 2 PSQI scores on each component and global total score in patients with insidious or traumatic onset of neck pain and healthy controls compared with published normative and insomniac data

	Mechanical Neck Pain (n = 19)	WAD Neck Pain (n = 22)	Healthy Controls (n = 18)	Normative Data (n = 52)[18]	Insomniacs (n = 45)[18]
Sleep quality[a,b]	1.5 ± 1.0	2.4 ± 0.8	0.7 ± 0.6	0.4 ± 0.5	2.0 ± 0.9
Sleep latency[a]	1.5 ± 0.9	1.5 ± 1.0	0.6 ± 0.8	0.5 ± 0.7	1.4 ± 1.0
Sleep duration	1.3 ± 0.9	1.2 ± 1.0	0.7 ± 0.5	0.3 ± 0.5	1.5 ± 1.2
Sleep efficiency[a]	0.9 ± 0.8	1.1 ± 1.1	0.1 ± 0.3	0.1 ± 0.3	1.5 ± 1.3
Sleep disturbances[a]	1.9 ± 0.5	1.6 ± 0.5	0.9 ± 0.7	1.0 ± 0.4	1.4 ± 0.6
Use sleeping medication[a]	1.5 ± 1.3	1.6 ± 1.3	0.1 ± 0.4	0.1 ± 0.3	1.2 ± 1.3
Daytime dysfunction[a]	2.0 ± 0.9	2.1 ± 0.7	0.6 ± 0.7	0.4 ± 0.5	1.4 ± 1.0
Global PSQI score[a]	10.2 ± 3.8	11.5 ± 3.9	3.7 ± 2.0	2.8 ± 1.7	10.4 ± 4.6

Data are expressed as mean ± SD.

[a]Both patient groups exhibit higher scores than healthy controls (analysis of variance, $P < 0.001$).

[b]Significant differences between patients with mechanical neck pain and WAD neck pain ($P < 0.001$).

PSQI, Pittsburgh Sleep Quality Index; WAD, whiplash-associated.

TABLE 3 Number of patients with insidious (mechanical) or traumatic (WAD) onset of neck pain and healthy subjects reporting sleep quality, sleep latency, sleep efficiency, and daytime dysfunction perception

	Very Good	Good	Bad	Very Bad
Sleep quality				
Mechanical neck pain (n = 19)[a]	3	6	8	2
WAD neck pain (n = 22)[a,b]	1	1	8	12
Healthy controls (n = 18)	6	11	1	0
Sleep latency				
Mechanical neck pain (n = 19)[a]	3	6	7	3
WAD neck pain (n = 22)[a]	3	6	7	7
Healthy controls (n = 18)	10	5	3	0
Sleep disturbances				
Mechanical neck pain (n = 19)[a]	9	3	15	1
WAD neck pain (n = 22)[a,b]	0	10	12	0
Healthy controls (n = 18)	5	9	4	0
Daytime dysfunction				
Mechanical neck pain (n = 19)[a]	0	8	4	7
WAD neck pain (n = 22)[a,b]	0	4	12	6
Healthy controls (n = 18)	10	6	2	0

[a]Significant different distribution compared with healthy control group ($P < 0.001$).
[b]Significant different distribution compared with mechanical neck pain ($P < 0.01$).
WAD, whiplash-associated.

WAD (r_s = 0.229; P = 0.470) neck pain was also found.

DISCUSSION

In the current study, we found that sleep disturbances is a common finding in patients with mechanical (insidious onset) or WAD (traumatic onset) neck pain. In fact, 77% patients with WAD and 68% with mechanical neck pain reported poor sleep quality (PSQI score, >8). In addition, the intensity of ongoing pain was associated with sleep quality in patients with WAD but not in those with

TABLE 4 Number of patients with insidious (mechanical) or traumatic (WAD) onset of neck pain and healthy subjects reporting sleep duration, habitual sleep efficiency, and use of sleeping medication

	Sleep Duration			
	>7 hrs	6–7 hrs	5–6 hrs	<5 hrs
Mechanical neck pain (n = 19)	3	9	5	2
WAD neck pain (n = 22)	7	6	6	3
Healthy controls (n = 18)	6	11	1	0
	Sleep Efficiency			
	>85%	84%–75%	74%–65%	<65%
Mechanical neck pain (n = 19)[a]	7	7	5	0
WAD neck pain (n = 22)[a]	9	6	3	4
Healthy controls (n = 18)	16	2	0	0
	Use of Sleep Medication			
	None	<1 per wk	1–2 per wk	>2 per wk
Mechanical neck pain (n = 19)[a]	6	5	1	7
WAD neck pain (n = 22)[a,b]	8	0	6	8
Healthy controls (n = 18)	17	0	1	0

[a]Significant different distribution compared with healthy control group ($P < 0.001$).
[b]Significant different distribution compared with mechanical neck pain ($P < 0.01$).
WAD, whiplash-associated.

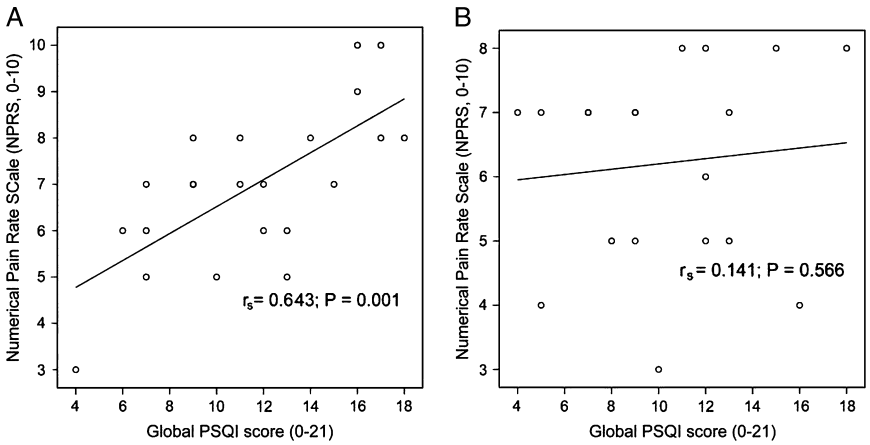

FIGURE 1 *Scatter plots of relationships between mean intensity of ongoing pain and PSQI score in patients with traumatic onset of neck pain (A) or insidious onset of neck pain (B). Some points are overlapping. A positive linear regression line is fitted to the data within the WAD group (A). WAD, whiplash-associated; PSQI, Pittsburgh Sleep Quality Index.*

mechanical neck pain; the higher the intensity of ongoing pain, the worse the sleep quality. No association between sleep quality and neck disability was found.

Current results are similar to those previously found in other chronic pain conditions. In our study, the mean PSQI score was 10 ± 3.2 for patients with mechanical neck pain and 11.5 ± 3.9 for those with WAD neck pain. This score is very similar to the PSQI score showed by patients with chronic low back pain (mean, 10.9 ±7.9),[8] with fibromyalgia syndrome (mean, 11.2 ± 3.9),[6] or with heterogeneous benign, chronic pain (mean, 11.5 ± 4.3).[5] In addition, PSQI scores reported by patients with neck pain was also very similar to those published for individuals with insomnia,[18] supporting the presence of sleep disturbances in these patients. Finally, we should note that the PSQI score of our control group was similar to normative published data[18]; therefore, we can conclude that our control group showed normal PSQI values and that most of our patient group exhibited sleep disturbances. The current results suggest that sleep disorders are frequently associated with chronic pain syndromes; nevertheless, these disturbances differ according to the syndrome with which they are associated.[8] In fact, the current study demonstrated that patients with WAD showed worse sleep quality than did those with mechanical neck pain.

We also found that higher intensity of ongoing pain, but not self-reported neck disability, was associated with worse sleep quality and more sleep disturbances in patients with a traumatic onset of neck pain but not in those with an insidious (mechanical) onset pain. In agreement with current results, a relationship between pain intensity and sleep quality has been also reported in chronic low back pain.[22] In addition, Menefee et al.[23] found that pain intensity was related to sleep quality and sleep latency but not to the remaining components of PSQI in individuals with degenerative spinal disease or postlaminectomy syndrome who presented to a tertiary care outpatient patient pain center. On the contrary, Chapman et al.[24] did not find a relationship between mean pain intensity and sleep quality in a sample of veterans presenting to a pain clinic. One possible reason may be the fact that patients with insidious neck pain presented with chronic pain, whereas those with WAD presented with acute pain; however, this hypothesis is not supported by the results of the current study because no significant association between the duration of pain symptoms and sleep quality was found. Future studies should investigate the relationship between the onsets of pain and sleep disturbances.

Whether cause or consequence, sleep disorders associated with neck pain must be taken into account in the overall management of these patients in the same way as pain. It seems essential to address sleep disturbances as an integral part of the evaluation and treatment of patients with neck pain. In fact, a recent study has demonstrated that insufficient sleep at 16 yrs predicted the presence of insidious neck pain in both girls (odds ratio, 4.4; 95% CI, 2.2–9.0) and boys (odds ratio, 2.2; 95% CI, 1.2–4.1).[25]

Nevertheless, the mechanisms underlying the relation between pain and sleep disorders are complex and little understood.[26] For instance, pain may be considered as activator of the central nervous

system areas responsible for wakefulness, at the same time diminishing the effectiveness of areas responsible for sleep initiation (latency) and maintenance (lack of fragmentation).[27] Furthermore, decreased sensitivity of mu and delta opioid receptors or reduced endorphin secretion may occur in patients with worse sleep quality because prolonged deprivation of rapid eye movement sleep may render the serotoninergic system unable to mediate the analgesic effects of opioid systems.[28] It seems that sleep modulation and pain regulation share a common neurobiologic process with pain. The fact that pain was associated with self-reported disability and sleep quality but that sleep quality was not associated with disability reflects the complexity of this process. Another possible mechanism involved in this process is the presence of posttraumatic stress, particularly in patients with WAD. Sterling and Chadwick[29] found that posttraumatic stress was associated with greater same-hour pain and associated with fear of pain. It is possible that posttraumatic stress seen in patients with WAD contribute to impaired sleep and nightmares in these subjects.

There exist a few limitations to the current study. First, the cross-sectional nature of the study does not permit establishing a cause-and-effect relationship between neck pain and sleep disturbances. Second, the sample size was small, which may explain the lack of significance in some outcomes. It is possible that some correlational analyses, particularly those related to the NDI, were likely underpowered because of the small sample size. In addition, we do not know whether the reported sleep disturbances can be different between men and women because the current study included a greater number of women. Third, the findings of our study cannot be generalized to the general neck pain population because patients evaluated in a regional hospital service probably represent only a fraction of the overall neck pain population. Fourth, we did not collect data on catastrophizing posttraumatic stress, anxiety, posttraumatic stress disorder, fear, uncomfortable sleep position caused by restricted neck mobility, or potential medication adverse effects that could also be related to sleep disturbances. Future longitudinal studies with larger sample sizes and including all of these related outcomes are required to further confirm a relationship between neck pain symptoms and sleep disturbances.

CONCLUSIONS

Sleep disturbances is a common finding in patients with mechanical (insidious onset) or WAD (traumatic onset) neck pain. Seventy-seven percent of patients with WAD and 68% with mechanical neck pain reported poor sleep quality (PSQI score, >8). The intensity of pain but not self-reported disability was associated with sleep quality in WAD but not mechanical neck pain; the higher the intensity of pain, the worse the sleep quality. It seems essential to address the vicious cycle of pain and sleep disturbances as an integral part of the evaluation and treatment of patients with neck pain.

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Articulo III:

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Abstract

Our aim was to estimate the frequency of sleep apnea, non-restorative sleep, and insomnia and their association with demographic factors, lifestyle behaviors and co-morbid conditions in an at-risk population in Spain. A total of 1009 individuals with suspected Obstructive Sleep Apnea Syndrome (OSAS) completed a questionnaire and personal interview including demographic data, lifestyle behaviors, sleep-wake schedule, diurnal and nocturnal symptoms and also co-morbid conditions. Laboratory tests included lung function test, echocardiography, arterial blood analysis, total blood counts, and standard polysomnography for diagnosing sleep apnea. The frequency of OSAS, insomnia and non-restorative sleep was 88.5%, 16.76%, 59.72%, respectively. The frequency of OSAS was lower in females than in males (OR 0.33, 95% CI 0.20–0.56) whereas the frequency of insomnia was higher (1.95, 1.29–2.95). People in the 61–70 year group exhibited higher frequency of OSAS (3.81, 1.51–9.58) and also insomnia (1.85, 1.08–4.32), whereas the obese exhibited higher probability of OSAS (1.80, 1.15–2.81). OSAS was associated with snoring (7.95, 1.57–24.58), nocturia (1.80, 1.12–2.89), daily fatigue (1.89, 1.12–3.17), apathy (0.53, 0.30–0.89), memory loss (0.44, 0.26–0.73), and hypertension (2.60, 1.41–4.78). Insomnia was associated with esophageal reflux (1.78, 1.21–2.61), awakening (3.39, 2.19–5.22), apathy (1.68, 1.11–2.55), and memory loss (1.58, 1.06–2.35). Non-restorative sleep was associated with nocturia (1.43, 1.01–2.05), gastro-esophageal reflux (2.08, 1.31–3.31), diaphoresis (3.31, 1.88–5.83), awakening (1.41, 1.01–2.02), daily fatigue (2.09, 1.47–2.97), memory loss (2.23, 1.40–3.54), irritability (2.26, 1.59–4.03) and headache (2.57, 1.65–4.00). The frequency of sleep-related breathing disorders was high in our sample. Different factors seem to be associated with OSAS, insomnia or non-restorative sleep.

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ORIGINAL ARTICLE

Epidemiology of sleep-related complaints associated with obstructive sleep apnea, insomnia and non-restorative sleep in an at-risk population in Granada, Spain

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Abstract

Our aim was to estimate the frequency of sleep apnea, non-restorative sleep, and insomnia and their association with demographic factors, lifestyle behaviors and co-morbid conditions in an at-risk population in Spain. A total of 1009 individuals with suspected Obstructive Sleep Apnea Syndrome (OSAS) completed a questionnaire and personal interview including demographic data, lifestyle behaviors, sleep-wake schedule, diurnal and nocturnal symptoms and also co-morbid conditions. Laboratory tests included lung function test, echocardiography, arterial blood analysis, total blood counts, and standard polysomnography for diagnosing sleep apnea. The frequency of OSAS, insomnia and non-restorative sleep was 88.5%, 16.76%, 59.72%, respectively. The frequency of OSAS was lower in females than in males (OR 0.33, 95% CI 0.20–0.56) whereas the frequency of insomnia was higher (1.95, 1.29–2.95). People in the 61–70 year group exhibited higher frequency of OSAS (3.81, 1.51–9.58) and also insomnia (1.85, 1.08–4.32), whereas the obese exhibited higher probability of OSAS (1.80, 1.15–2.81). OSAS was associated with snoring (7.95, 1.57–24.58), nocturia (1.80, 1.12–2.89), daily fatigue (1.89, 1.12–3.17), apathy (0.53, 0.30–0.89), memory loss (0.44, 0.26–0.73), and hypertension (2.60, 1.41–4.78). Insomnia was associated with esophageal reflux (1.78, 1.21–2.61), awakening (3.39, 2.19–5.22), apathy (1.68, 1.11–2.55), and memory loss (1.58, 1.06–2.35). Non-restorative sleep was associated with nocturia (1.43, 1.01–2.05), gastro-esophageal reflux (2.08, 1.31–3.31), diaphoresis (3.31, 1.88–5.83), awakening (1.41, 1.01–2.02), daily fatigue (2.09, 1.47–2.97), memory loss (2.23, 1.40–3.54), irritability (2.26, 1.59–4.03) and headache (2.57, 1.65–4.00). The frequency of sleep-related breathing disorders was high in our sample. Different factors seem to be associated with OSAS, insomnia or non-restorative sleep.

Key words: insomnia, non-restorative sleep, Obstructive Sleep Apnea Syndrome.

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INTRODUCTION

It seems that sleep disturbances are associated with greater daytime sleepiness, deterioration of physical-psychological performance, impaired quality of life,[1] cognitive deficits,[2,3] psychological changes,[4,5] and risk of motor vehicle accidents.[6] Obstructive Sleep Apnea Syndrome (OSAS) is the most common form of sleep disturbance (called sleep-related breathing disorders) and characterized by repetitive cessation of breathing during sleep which is accompanied with sleep fragmentation, nocturnal hypoxemia, an excessive daytime sleepiness (Epworth Sleepiness Scale >10) and an Apnea-Hypopnea Index (AHI) of 5 or higher.[7]

Obstructive Sleep Apnea Syndrome is also associated with snoring, nocturnal respiratory arrest, repeated nocturnal awakening, non-restorative sleep, diurnal fatigue, and altered concentration. Other sleep disturbances commonly seen are non-restorative sleep, that is, a report of persistently feeling un-refreshed upon awakening in the presence of normal sleep duration occurring in the absence of a sleep disorder;[8] and insomnia defined as a subjective perception of dissatisfaction with the amount and/or quality of sleep including difficulty in initiating or maintaining sleep or early awakening with inability to fall asleep again.[9]

The prevalence of sleep disturbances has been conducted in several countries: United Kingdom,[10] Denmark,[11] Greece,[12] Australia,[13] United States,[14] China,[15] India,[16] Thailand,[17] and Korea.[18] All these studies have reported high prevalence of snoring and non-restorative sleep in the general population. Netzer *et al*. compared the prevalence of symptoms and risk of OSAS between USA and Europe,[19] and found that OSAS was more prevalent ($P < 0.001$) in USA (35.8%) than in Europe (26.3%), and in men than in women (37.9% vs. 27.8%, respectively; $P < 0.005$).[19] Nevertheless, the prevalence of sleep disturbances differs by region[20] and by country.[21,22] Therefore, it is important to conduct epidemiological studies in different regions in one country.

In Spain, few studies investigating the prevalence of sleep disturbances have been conducted. Marin *et al*. estimated that 0.8% of women and 2.2% of men exhibited the minimal criteria for diagnosis of OSAS.[23] Ohayon investigated the prevalence of non-restorative sleep in seven European countries (France, UK, Germany, Italy, Portugal, Spain, and Finland) and found that UK and Germany showed the highest prevalence of non-restorative sleep (16.1%, and 15.5%, respectively), whereas Spain exhibited the lowest (2.4%).[24] No epidemiological studies have recently estimated the frequency of sleep disturbances and their association with socio-demographic factors, lifestyle habits and co-morbidity in a Spanish population. Therefore, the objective of the current study was to estimate the frequency of OSAS, non-restorative sleep and insomnia and their association with socio-demographic factors, lifestyle behavior and co-morbid conditions in a specific at-risk population in Granada, a southern region of Spain.

METHODS

A cross-sectional observational study was conducted. One thousand and nine ($n = 1009$) participants, 804 men and 205 women, referred to the Sleep Laboratory of Hospital San Cecilio, Granada, Spain between January 2008 and December 2010 with suspected OSAS were included. Each participant completed a questionnaire and personal interview. The study protocol was approved by the human research committee and conducted following the declaration of Helsinki. All subjects signed an informed consent prior to their inclusion in the study.

In the questionnaire, participants answered general questions related to personal data and health information, as well as lifestyle behaviors, for example, smoking and alcohol consumption. The questionnaire included the Epworth Sleepiness Scale, which is used for assessment of subjective daytime sleepiness during face-to-face interviews.[25,26] It consists of an eight-item questionnaire that requires the patient to rate their likelihood of dozing-off in various situations on a 4-point Likert scale (0: not at all likely to doze; 3: very likely to doze). Total score ranges from 0 to 24 with scores > 10 indicating significant daytime sleepiness.[25,26]

During the interview, they were questioned in the presence of their most closely-related person, preferably their spouse/partner. Participants and their partners answered questions about clinical characteristics of OSAS and other sleep disorders, such as snoring, cessation of breathing during sleep, and daytime somnolence, and also informed about co-morbid conditions diagnosed by their medical doctor: cardio-pulmonary pathology, diabetes, hypertension, depressive symptoms, menopause, metabolic syndrome, chronic obstructive pulmonary disease. Any co-morbid condition was recorded when patients had a medical diagnosis.

Anthropometric data were measured by a trained nurse and consisted of: weight, height, age, sex, and abdominal and neck circumference. Weight was measured in light clothes on a portable scale. Neck circumference was measured just below the laryngeal prominence using standardized methods.[27]

Medical laboratory tests included lung function test, arterial blood gas analysis, echocardiography and total blood counts. In addition, participants underwent two nights of standard polysomnography for diagnosing OSAS and Continuous Positive Airway Pressure (CPAP) titration separately, including nasal and oral flow with a thermistor, thoracic and abdominal respiratory movements with a strain gauge, and arterial oxygen saturation with a finger oximeter. They went to bed at their chosen time and all woke up naturally without an alarm on both nights. Data were stored in real time on Personal Computer Memory Card International Association (PCMCIA) cards. The equipment was retrieved the next morning.

Apnea was defined as complete cessation of airflow for at least 10 s. Hypopnea was defined as a reduction of respiratory signals for at least 10 s associated with oxygen desaturation of 4%. Detailed protocol for central scoring of sleep stages, arousals, and respiratory events has been described.[28]

In the current study, self-report insomnia and non-restorative sleep, and presence of OSAS were the dependent variables.

Statistical analyses

We first estimated demographic data, frequency of sleep disturbance symptoms, and presence of co-morbidity conditions according to the presence of each dependent variable (OSAS, insomnia, and non-restorative sleep). Bivariate logistic regression models were conducted to estimate the measure of association. A multivariate analysis was performed using the variables statistically significant within the bivariate analysis. Variables were eliminated, one at each step, according to their significance in the model used (Wald statistic) and considering the model's goodness-of-fit with regard to the previous step. The effects of interaction among the variables included in the final model were also examined. The adjusted odds ratio (OR) for each factor is reported. Estimates were made by incorporating the sampling weights, using the "svy" (survey command) functions of the STATA program, which enabled us to incorporate the sampling design into all statistical calculations (adjusted OR, logistic regression). The statistical significance was set at two-tailed $\alpha < 0.05$.

RESULTS

Demographics and clinical features

Of the 1008 participants, 893 suffered from OSAS, 169 from insomnia and 602 non-restorative sleep. Therefore, the frequency of OSAS, insomnia and non-restorative sleep was 88.5%, 16.76% and 59.72%, respectively. A significant association between the presence of OSAS and insomnia (OR 1.65, 95% CI 1.04–2.07) was found: subjects with OSAS exhibited a higher frequency of insomnia than those without OSAS.

The frequency of OSAS was significantly higher ($P < 0.01$) in males (91.10%) than in females (82.18%), whereas the frequency of insomnia and non-restorative sleep was significantly higher ($P < 0.01$) in females (29.41% and 67.16%, respectively) than in males (13.56%, 57.91% respectively). The frequency of OSAS and insomnia showed the highest value in participants in the 61–70 years group (93.99% and 25.68%, respectively). We also found that participants with a body mass index (BMI) ≥ 30 also showed a greater frequency of OSAS (92.11%) than those with a BMI < 30 (83.90%). Further, non-smokers and participants consuming alcoholic drinks occasionally were more likely to suffer insomnia (20.86%, 22.22% respectively) than smokers (11.90%) or those consuming alcoholic drinks daily (14.89%). Table 1 summarizes the frequency of OSAS, insomnia and non-restorative sleep according to the socio-demographic variables.

Nocturnal and diurnal symptoms

Participants with OSAS were more likely to snore (90.33%) and to experience nocturia (92.42%) than those without OSAS (53.33% and 85.81%, respectively). We found that individuals suffering from insomnia were more likely to present with several nocturnal symptoms (diaphoresis: 26.38%; self-reported asphyxia: 24.30%; nocturia: 21.80%; gastro-esophageal reflux: 29.82%; awakening: 26.20%; nightmares: 30.39%) than those individuals without insomnia (diaphoresis: 13.84%; self-reported asphyxia: 13.81%; nocturia: 11.13%; gastro-esophageal reflux: 11.87%; awakening: 6.60%; or nightmares: 13.78%). Similarly, participants reporting non-restorative sleep suffered higher frequency of nocturnal symptoms (diaphoresis: 91.49%; self-reported asphyxia: 81.98%; nocturia: 69.55%; gastro-esophageal reflux: 86.50%; awakening: 72.80%; nightmares: 91.16%) than those with a restorative sleep (diaphoresis: 50.13%; self-reported asphyxia: 51.10%; nocturia: 48.84%; gastro-esophageal reflux: 49.80%; awakening: 45.77%; nightmares: 52.91%). The frequency of these nocturnal symptoms during sleeping time according to the presence of OSAS, insomnia or non-restorative sleep is shown in Table 2.

Table 1 Demographic and clinical data of the sample to the presence of obstructive sleep apnea syndrome (OSAS), insomnia or non-restorative sleep

Variable	Categories	*n*	OSAS	Insomnia	Non-restorative sleep
Sex[†‡§]	Male	804	91.10%	13.56%	57.91%
	Female	205	82.18%	29.41%	67.16%
Age[†‡]	18–30 years	62	80.39%	15.69%	62.75%
	31–40 years	159	87.42%	19.38%	57.86%
	41–50 years	260	83.46%	16.67%	57.20%
	51–60 years	283	93.64%	15.14%	63.38%
	61–70 years	183	93.99%	25.68%	59.56%
	71–80 years	62	91.94%	18.75%	57.81%
Smoking habit[‡]	Smoker	353	89.17%	11.90%	58.36%
	Ex-smoker	321	90.88%	18.07%	61.88%
	Non-smoker	326	88.58%	20.86%	60.43%
Alcohol consumption[‡]	No drink	445	89.16%	19.06%	54.26%
	Occasionally	27	96.15%	22.22%	65.39%
	Daily	524	89.44%	14.89%	55.56%
Obesity[†]	BMI < 30	356	83.90%	18.82%	57.58%
	BMI ≥ 30	626	92.11%	15.81%	61.92%

[†]Significant differences ($P < 0.01$) for sleep apnea. [‡]Significant differences ($P < 0.01$) for insomnia. [§]Significant differences ($P < 0.01$) for non-restorative sleep. BMI, body mass index.

Table 2 Prevalence of nocturnal symptoms during sleeping time according to the presence of obstructive sleep apnea syndrome (OSAS), insomnia or non-restorative sleep

Variable	Categories	*n*	OSAS	Insomnia	Non-restorative sleep
Snoring†	No	15	53.33%	13.33%	46.67%
	Yes	979	90.33%	17.06%	60.53%
Diaphoresis[‡§]	No	773	89.57%	13.84%	50.13%
	Yes	235	88.41%	26.38%	91.49%
Self-reported Asphyxia[‡§]	No	724	89.83%	13.81%	51.10%
	Yes	284	87.94%	24.30%	81.98%
Nocturia[†‡§]	No	476	85.81%	11.13%	48.84%
	Yes	532	92.42%	21.80%	69.55%
Gastro-esophageal reflux[‡§]	No	733	89.81%	11.87%	49.80%
	Yes	275	87.96%	29.82%	86.50%
Awakening[‡§]	No	485	90.02%	6.60%	45.77%
	Yes	523	88.63%	26.20%	72.80%
Nightmares[‡§]	No	827	89.28%	13.78%	52.91%
	Yes	181	89.39%	30.39%	91.16%

†Significant differences ($P < 0.01$) for sleep apnea. [‡]Significant differences ($P < 0.01$) for insomnia. [§]Significant differences ($P < 0.01$) for non-restorative sleep.

Individuals with OSAS were less likely to experience diurnal symptoms (apathy: 85.04%; irritability: 85.52%; memory loss: 85.22%) than those without sleep apnea (apathy: 90.91%; irritability: 90.85%; memory loss: 91.20%). On the contrary, the presence of diurnal symptoms was more prevalent in participants with insomnia (daily fatigue: 21.44%; headache: 23.64%; apathy: 31.64%; irritability: 27.30%; concentration difficulty: 30.77%; memory loss: 29.38%; libido loss: 37.14%) or non-restorative sleep (fatigue: 74.55%; headache: 82.48%; apathy: 90.88%; irritability: 90.1%; concentration difficulty: 90.13%; memory loss: 87.85%;

Table 3 Prevalence of diurnal symptoms during sleeping time according to the presence of obstructive sleep apnea syndrome (OSAS), insomnia or non-restorative sleep

Variable	Categories	*n*	OSAS	Insomnia	Non-restorative sleep
Daily fatigue[‡§]	No	453	88.64%	11.04%	41.72%
	Yes	555	89.84%	21.44%	74.55%
Headache[‡§]	No	732	89.67%	14.21%	51.23%
	Yes	275	88.28%	23.64%	82.48%
Musculoskeletal pain	No	956	89.35%	16.42%	59.37%
	Yes	52	88.46%	23.08%	67.31%
Psychiatric symptoms					
Apathy[†‡§]	No	733	90.91%	11.91%	48.16%
	Yes	235	85.04%	31.64%	90.88%
Irritability[†‡§]	No	715	90.85%	12.45%	47.34%
	Yes	293	85.52%	27.30%	90.10%
Cognitive alterations					
Concentration difficulty[‡§]	No	774	90.21%	12.53%	50.65%
	Yes	234	86.32%	30.77%	90.13%
Memory loss[†‡§]	No	687	91.20%	10.92%	40.65%
	Yes	321	85.22%	29.38%	87.85%
Loss of libido[‡§]	No	973	89.12%	16.03%	58.85%
	Yes	35	94.29%	37.14%	85.71%

†Significant differences ($P < 0.01$) for sleep apnea. [‡]Significant differences ($P < 0.01$) for insomnia. [§]Significant differences ($P < 0.01$) for non-restorative sleep.

loss of libido: 85.71%) than in those without insomnia (fatigue: 11.04%; headaches: 14.21%; apathy: 11.91%; irritability: 12.45%; concentration difficulty: 12.53%; memory loss: 10.92%; loss of libido: 16.03%) or with restorative sleep (daily fatigue: 41.72%; headache: 51.23%; apathy: 48.16%; irritability: 47.34%; concentration difficulty: 50.65%; memory loss: 40.65%; libido loss: 58.85%). The frequency of diurnal symptoms according to the presence of OSAS, insomnia or non-restorative sleep is shown in Table 3.

Co-morbid conditions

Hypertension, diabetes and cardiac pathology were associated with the presence of OSAS: participants with apnea exhibited higher frequency of these co-morbid disorders than those participants without OSAS ($P < 0.01$). Additionally, participants with insomnia or non-restorative sleep were more depressed (31.62% and 88.46%, respectively) than those without insomnia or non-restorative sleep (12.27%, 51.10% respectively). Finally, a lower proportion of participants with insomnia (7.58%) suffered from hyper-uremia as compared with those without insomnia (17.41%). Frequency of OSAS, insomnia, or non-restorative sleep related to co-morbid chronic diseases is summarized in Table 4.

Variables associated with the presence of OSAS, insomnia or non-restorative sleep

Table 5 summarizes the results of the multivariate analysis with the adjusted OR of those variables that were associated with the presence of OSAS, insomnia or non-restorative sleep. The analysis showed that female gender decreased the probability of reporting OSAS (OR 0.33, 95% CI 0.20–0.56), but increased the probability of reporting insomnia (OR 1.95, 95% CI 1.29–2.95). In addition, using the 18–30 year group as the reference category, participants within the 51–60 year (OR 3.59, 95% CI 1.55–8.31) and 61–70 year (OR 3.81, 95% CI 1.51–9.58) group reported significantly higher frequency of OSAS, and those within the 61–70 year group reported significantly higher frequency of insomnia (OR 1.85, 95% CI 1.08–4.32). We also found that obese participants (BMI ≥ 30) exhibited higher probability of OSAS (OR 1.80, 95% CI 1.15–2.81).

Table 4 Prevalence of co-morbid conditions according to the presence of obstructive sleep apnea syndrome (OSAS), insomnia or non-restorative sleep

Variable	Categories	*n*	OSAS	Insomnia	Non-restorative sleep
Depression[‡§]	No	774	90.23%	12.27%	51.10%
	Yes	234	86.21%	31.62%	88.46%
Chronic obstructive pulmonary disease	No	984	89.24%	16.87%	60.22%
	Yes	24	91.67%	12.50%	41.67%
Metabolic syndrome[†]	No	972	88.91%	16.77%	60.14%
	Yes	36	100%	16.67%	60.14%
Hypertension[†]	No	670	86.43%	15.22%	60.09%
	Yes	338	94.96%	19.82%	59.17%
Diabetes[†]	No	919	88.49%	16.10%	59.69%
	Yes	89	97.73%	23.60%	60.67%
Cardiac pathology[†]	No	924	88.66%	16.23%	59.80%
	Yes	84	96.39%	22.62%	59.52%
Hyper-uraemia[‡]	No	942	88.87%	17.41%	60.15%
	Yes	66	95.45%	7.58%	54.55%
Hypercholesterolemia	No	882	88.79%	16.55%	60.27%
	Yes	126	83.90%	18.82%	57.58%

[†]Significant differences ($P < 0.01$) for sleep apnea. [‡]Significant differences ($P < 0.01$) for insomnia. [§]Significant differences ($P < 0.01$) for non-restorative sleep.

Table 5 Variables significantly associated with a higher likelihood of presenting obstructive sleep apnea syndrome (OSAS), insomnia and non-restorative sleep

Variable	Categories	OSAS	Insomnia	Non-restorative sleep
Sex[†]	Female	0.33 (0.20–0.56)	1.95 (1.29–2.95)	NS
Age[‡]	31–40 years	NS	NS	NS
	41–50 years	NS	NS	NS
	51–60 years	3.59 (1.55–8.31)	NS	NS
	61–70 years	3.81 (1.51–9.58)	1.85 (1.08–4.32)	NS
	71–80 years	NS	NS	NS
Obesity[§]	BMI ≥ 30	1.80 (1.15–2.81)	NS	NS
Nocturnal symptoms				
Snoring[¶]	Yes	7.95 (2.57–24.58)	NS	NS
Nocturia[¶]	Yes	1.80 (1.12–2.89)	NS	1.43 (1.01–2.05)
Diaphoresis[¶]	Yes	NS	NS	3.31 (1.88–5.83)
Gastro-esophageal reflux[¶]	Yes	NS	1.78 (1.21–2.61)	2.08 (1.31–3.31)
Awakening[¶]	Yes	NS	3.39 (2.19–5.22)	1.41 (1.01–2.02)
Diurnal symptoms				
Daily fatigue[¶]	Yes	1.89 (1.12–3.17)	NS	2.09 (1.47–2.97)
Apathy[¶]	Yes	0.52 (0.30–0.89)	1.68 (1.11–2.55)	NS
Memory loss[¶]	Yes	0.44 (0.26–0.73)	1.58 (1.06–2.35)	2.23 (1.40–3.54)
Irritability[¶]	Yes	NS	NS	2.62 (1.59–4.03)
Co-morbid conditions				
Hypertension[¶]	Yes	2.60 (1.41–4.78)	NS	NS
Headache[¶]	Yes	NS	NS	2.57 (1.65–4.00)

Reference categories: [†]Male; [‡]18–30 years; [§]BMI (body mass index) < 30; [¶]No. NS, not stated.

The analysis revealed a significant association of OSAS with snoring (OR 7.95; 95% CI 1.57–24.58) and nocturia (OR 1.80, 1.12–2.89). Insomnia was significantly associated with the presence of gastro-esophageal reflux (OR 1.78, 95% CI 1.21–2.61) and awakening (OR 3.39, 95% CI 2.19–5.22). Further, non-restorative sleep was related to higher frequency of nocturia (OR 1.43, 1.01–2.05), diaphoresis (OR 3.31, 1.88–5.83), gastro-esophageal reflux (OR 2.08, 1.31–3.31), and awakening (OR 1.41, 1.01–2.02).

In relation to diurnal symptoms, daily fatigue was associated with OSAS (OR 1.89, 1.12–3.17) and non-restorative sleep (2.09, 1.47–2.97); apathy was associated with OSAS (0.53, 0.30–0.89) and insomnia (1.68, 1.11–2.55); memory loss was associated with OSAS (0.44, 0.26–0.73), insomnia (1.58, 1.06–2.35), and non-restorative sleep (2.23, 1.40–3.54); whereas irritability was only associated with non-restorative sleep (2.26, 1.59–4.03). Finally, hypertension was co-morbid with OSAS (OR 2.60, 1.41–4.78), and headache with non-restorative sleep (OR 2.57, 1.65–4.00).

DISCUSSION

This is the first epidemiological study to investigate sleep disorders in a specific Spanish population referred to a hospital. Our study demonstrated a high frequency of OSAS (88.5%), insomnia (16.7%), and non-restorative sleep (59.7%), data slightly superior than previous studies conducted in different countries.[10–18] A previous study conducted in Zaragoza, a northeast region of Spain, estimated a prevalence rate ranging from 1% to 2% of apnea.[23] Ohayon reported that the prevalence of non-restorative sleep in a general population representative of seven European countries was 10.8%.[24] Higher frequency of sleep disturbances in the current study may be related to the fact that our sample size was derived from a specialized unit in a hospital; whereas previous studies included data from the general population. In contrast, others have reported higher prevalence rate (27.6%) of insomnia symptoms in the Italian population.[29] It seems that the prevalence of sleep disturbances varies by region and country depending on cultural differences on sleeping habits, differences in bedtime and wake-up hours, or differences in climatology and hours of light.[20–22] Further, differences in prevalence may be also explained by sample biases and different diagnostic approaches. Nevertheless, our study is the first one including an objective diagnosis of OSAS with polysomnography.

The frequency of OSAS was positively associated with men, older age, obesity and snoring, which is consistent with previous studies.[10–22] Marin *et al*. also found that individuals with OSAS in Zaragoza were men, older and obese.[23] A theoretical interaction between these three factors may be that obesity tends to increase the size of the neck (neck obesity), which has been implicated in upper airway obstruction during sleep.[30] In such circumstances, obese people will snore more frequently.[31] In fact, differences in obesity rates between USA and Europe has been proposed as one the main factors related to differences in OSAS apnea prevalence between both countries.[19] This is consistent with the fact that obesity is the most common predisposing factor for suffering from OSAS.[32] Nevertheless, the association between OSAS and obesity (OR 1.8) in our study was lower than expected, probably because two thirds of our sample was obese.

The frequency of OSAS was more prevalent in men, which is in accordance with previous studies.[19,23,33] Netzer *et al*. reported that men exhibited higher scores of OSAS as caused by snoring and sleep apnea, supporting the relationship between male gender, apnea, and snoring.[19] Redline *et al*. specifically investigated gender differences in sleep disturbances and have reported a male : female ratio for OSAS of 2:1.[34] Importantly, the occurrence of snoring is a predictor of subsequent diagnosis of hypertension.[35] In fact, individuals with sleep disordered breathing are at increased risk for cardiovascular diseases, such as hypertension, angina, myocardial infarction, and stroke.[36] In our study, we found that hypertension was a highly co-morbid condition in subjects with OSAS supporting this relationship. Finally, some diurnal symptoms, for example, daily fatigue, apathy or memory loss, and nocturia (nocturnal symptom) were also more prevalent in participants with OSAS, which is consistent with previous studies.[37,38]

Insomnia was associated with females and the elderly, gastro-esophageal reflux and awakening as nocturnal symptoms, and apathy and memory loss as diurnal symptoms in agreement with previous data.[24,39,40] A study suggested that concentration difficulty and memory loss was highly present in older people with excessive daytime sleepiness, which may be related to insomnia.[41] Additionally, non-restorative sleep was associated with nocturia, diaphoresis, esophageal reflux, and awakening as nocturnal symptoms, and daily fatigue, memory loss and irritability as diurnal symptoms. Current results are very similar to those previously reported by Ohayon who also found that participants with non-restorative sleep reported more frequent irritability, physical, and mental

fatigue as compared to those with normal sleep, and also consulted a physician twice as frequently for their sleeping difficulties than did participants with insomnia.[24] Finally, headache was more frequent in individuals with non-restorative sleep, confirming that sleep can be a trigger factor for headache.[42]

Although strengths of our study include a large sample size, the employment of personalized surveys, and an objective assessment of OSAS by polysomnography, there are also a number of significant limitations. First, we included a population derived from a specific regional hospital; therefore, current results should not be extrapolated to the general population. Second, since this was a cross-sectional study, we cannot determine cause and effect relationships between OSAS, insomnia or non-restorative sleep with their associated symptoms. Finally, information obtained from personal interviews may be subject to recall errors or a tendency of individuals to give socially desirable responses in the survey, particularly regarding lifestyle habits. Despite these limitations, our findings provide additional insight into some clinical aspects of sleep-related breathing disorders in a specific Spanish population for which there is little information at a population level. Therefore, data from our study are a valuable tool for evaluating the effectiveness of the campaigns promoting breathing health care among people.

The current study has shown that OSAS, insomnia, and non-restorative sleep were highly prevalent sleep-related breathing disorders in a specific at-risk population in Granada, a southeast region of Spain. Current results show some similarities in risk factors for these sleep-related breathing disorders with previous studies, but also exhibit different factors associated with OSAS, insomnia or non-restorative sleep. In fact, these differences may be crucial for a proper distinction between these sleep disorders.

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Resumen

Introducción: El síndrome metabólico se está convirtiendo en uno de los principales problemas de salud pública del siglo XXI. Se considera que la aparición del syndrome metabólico está determinada por la interacción de factores genéticos, ambientales y nerviosos centrales (disfunción de los centros hipotalámicos de hambre y saciedad) que generan dos alteraciones metabólicas importantes: la resistencia a la acción de la insulina y la obesidad visceral. La relación de este síndrome, que concentra en la actualidad al mundo científico, con las alteraciones del sueño sigue siendo un punto sin esclarecer. Aunque se ha teorizado sobre la relación causa efecto, se desconoce aún su interrelación convirtiéndose su estudio en un objetivo primario de la investigación epidemiológica. Muestra y métodos: Se reclutaron 1016 sujetos que acudieron al servicio de Fisiología Respiratoria del Hospital Universitario "San Cecilio" de Granada (España) por sospecha de Apnea de Sueño. Resultados: Se encontró una correlación significativa ($p < 0,001$) entre los valores de apneas hipopneas y los valores de saturación de Oxigeno nocturna con las diferentes alteraciones metabólicas asociadas al síndrome metabólico (Hipertensión, Diabetes y Obesidad). Por el contrario, no se encontraron diferencias estadísticamente significativas test (t-Student) en la mayoría de las variables entre el grupo NO-Apnea y el grupo Apnea moderada. Conclusiones: Los sujetos con apnea de sueño poseen significativamente más riesgo de desarrollar síndrome metabólico, y por lo tanto de presentar patología cardiovascular. Estos sujetos deben ser evaluados en este sentido para reducer la morbimortalidad asociada a estas patologías.

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Original

Factores de riesgo para el síndrome metabólico en una población con apnea del sueño; evaluación en un grupo de pacientes de Granada y provincia; estudio GRANADA

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Palabras clave: *Apnea del sueño. Síndrome metabólico. Factores de riesgo.*

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RISK FACTORS FOR METABOLIC SYNDROME IN A POPULATION WITH SLEEP APNEA; EVALUATION IN A POPULATION OF GRANADA; THE GRANADA STUDY

Abstract

Introduction: **The Metabolic Syndrome is one of the first health problems in the public health of the century. It's consider that the beginning of the syndrome is determined by numerous factors that developed two main metabolic disturbances: the insulin resistance and the central obesity. This relationship is concentrating the scientific world. As the cause-effect relationship has to be answered, the epidemiologic research has focused on without results.**

Material and methods: **1,016 subjects were recruited in the sleep disorders laboratory in San Cecilio Hospital with sleep apnea suspicion.**

Results: **Significant correlation (p < 0,001) was found between sleep apnea severity and nocturnal saturation values and the different metabolic disturbances related to the metabolic syndrome (Hypertension, Diabetes and obesity). By the contrary, we doesn't found significant differences between No-Sleep apnea group and moderate sleep apnea group in the majority of the variables.**

Conclusions: **Subjects with sleep apnea have significantly more possibilities to develop metabolic syndrome, and cardiovascular pathology. These subjects had to be evaluated in this sense to reduce the impact associated to this pathology.**

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Key words: *Sleep apnea. Metabolic syndrome. Risk factors.*

Introducción

El sueño, definido en el plano de la conducta por la suspensión normal de la conciencia y desde un punto de vista electrofisiológico por criterios de ondas encefálicas específicas, consume un tercio de nuestra vida[1]. Por ello, en los últimos años las patologías del sueño y sus repercusiones clínicas comprenden un objetivo prioritario para la comunidad científica.

El Síndrome de Apnea del Sueño (SAS), también llamado Síndrome de Apneas-Hipoapneas del sueño (SAHS)[2], es tras el insomnio el trastorno del sueño más común. Su prevalencia se ha estimado en torno a un 5% en la población adulta[3]. Sin embargo, muchos autores refieren que estas cifras se incrementaran debido al aumento de los valores de obesidad a nivel mundial[4-5].

Se caracteriza por un cuadro de episodios repetidos de obstrucción de la vía aérea superior acompañado por esfuerzo respiratorio inefectivo y apneas. Ello se acompaña habitualmente por respiraciones amplias de recuperación llamadas hiperapneas durante el sueño (AHI), que provocan constantes desaturaciones de la oxihemoglobina y despertares transitorios.

Las alteraciones del sueño han sido en los últimos años un punto de gran interés para la comunidad científica. Su enorme prevalencia en los países desarrollados y su interrelación con gran cantidad de patologías sistémicas[6,7], es objetivo de primer orden para la investigación en salud.

Recientemente, la interacción entre la Apnea de sueño (AS) y la disfunción metabólica han sido objeto de numerosas investigaciones. En particular la AS, ha sido asociada de manera independiente a la Resistencia insulínica, sugiriendo que la AS[8] puede jugar un rol determinante en el desarrollo de la diabetes tipo II y el llamado síndrome metabólico, que, como síndrome, es una constelación de obesidad, resistencia a la insulina, hipertensión y dislipemia.

Las relaciones entre el sueño y el desarrollo del síndrome metabólico se han demostrado tanto en sujetos sanos como enfermos. Por una parte, la privación parcial de sueño dá lugar a cambios similares a los propios del síndrome metabólico. Por otra, se ha sugerido que el síndrome de apnea del sueño es una manifestación del síndrome metabólico.

En 1998 Wilcox y cols.[9] ya teorizaron sobre esta relación patológica entre apnea del sueño y SM, e incluso le dieron el nombre de síndrome Z.

Y aunque es objeto de gran cantidad de investigaciones al respecto, los investigadores aun no han desentrañado el origen de su interrelación.

Mientras los criterios para diagnosticar diabetes mellitus tipo 2, obesidad, e hipertensión arterial son claros, no ocurre lo mismo con el SM. Diferentes grupos de investigadores han desarrollado las definiciones existentes y los criterios clínicos para el SM. Actualmente se reconocen las del Grupo Europeo para el estudio de la Resistencia a la Insulina (EGIR), la OMS[10], y grupos del NCEP ATP III[11]; todos coinciden en que los componentes básicos del SM son: obesidad, resistencia a la insulina, dislipidemia e hipertensión arterial.

Sin embargo, emplean diferentes parámetros para medir estas alteraciones. Según estos criterios, se ha estimado la prevalencia del SM en diferentes poblaciones y se han hecho comparaciones entre estos estudios[12-17].

La hipoxia intermitente característica de la SA se asocia con cambios anatómicos en el sistema nervioso central (con consecuencias cognitivas)[18], con reestructuración cardiovascular y respuesta anormal a estimulación simpática[19], y con resistencia a la insulina, aun en ausencia de obesidad y de hiperactividad simpática[20].

Las últimas décadas se han desarrollado diferentes estudios sobre diferentes tipos de disfunción metabólica en sujetos con SA[21]. Sin embargo, muy poca de esta literatura ha caracterizado a los sujetos en términos de la alteración del sueño. Existe gran cantidad de artículos que se han centrado en la evidencia clínica de la contribución independiente de la AS para el desarrollo o agravamiento del síndrome metabólico. Sin embargo, el síndrome metabólico y sus componentes (en concreto la obesidad y la resistencia insulínica) pueden tener un efecto causal en el desarrollo de la AS, proponiéndose así que la AS pudiese ser un síndrome metabólico en sí y un componente del SM[22].

El objetivo de este estudio es caracterizar a una población con desordenes del sueño en función de sus alteraciónes endocrionometabólicas, en concreto, aquellas relacionadas con el síndrome metabólico. Se trata de uno de los primeros estudios desarrollados en población española con este tipo de características en las que confluyen dos grandes pandemias, las alteraciones del sueño y las alteraciones metabólicas.

Muestra

Se incluyeron 1.016 sujetos en el estudio, 811 hombres y 205 mujeres, derivados al servicio de Fisiología respiratoria y Laboratorio del Sueño del Hospital Universitario San Cecilio de Granada. Se solicito la participación a todos los sujetos derivados entre enero 2008 y diciembre 2010 por sospecha de Síndrome de Apnea de Sueno.

Metodología

Cada sujeto completó un cuestionario y una entrevista personal. El protocolo del estudio fue aprobado por el Comité Ético del Hospital San Cecilio (Granada) y se dirigió respetando la declaración de Helsinki en el desarrollo de estudios realizados en humanos. Todos los sujetos firmaron un consentimiento informado previo a la participación en el estudio.

En el cuestionario los participantes respondían cuestiones de tipo general relacionadas con datos personales e información de estilos de vida, como de su consumo de tabaco y alcohol. El formulario incluía el

Tabla I
Descripción demográfica de la muestra por grupo de RDI

Características	*Total (n = 1.016)*	*Grupo NOAS (n = 115)*	*Grupo Apnea 1 (n = 159)*	*Grupo Apnea 2 (n = 742)*	*p*
Sexo (% hombres)	79,8	62,1	75,5	82,9	0,000
Edad media (media ± DS)	51,08 ± 12,8	45,99 ± 12,4	47,73 ± 11,9	52,48 ± 12,7	0,000
IMC (media ± DS)	32,672 ± 8,9	30,225 ± 5,189	30,373 ± 4,84	33,473 ± 9,87	0,000
Epworth (media ± DS)	11,91 ± 5,22	10,46 ± 4,83	11,16 ± 5,1	12,29 ± 5,26	0,001
Tabaquismo (% fumadores habituales)	35,2	36,9	32,7	35,9	0,342
Alcohol (% ingesta diaria)	52,7	58,8	49	52,3	0,519
Sat O_2 ≤ 90 (media ± DS)	19,28 ± 24,8	5,11 ± 14,2	8,88 ± 16,35	23,23 ± 26,01	0,000

cuestionario Epworth de somnolencia (ES) que está validado para la medida de la somnolencia durante las entrevistas[23,24].

Consiste en un cuestionario de 8 items en el que el paciente tiene que cuantificar en una escala linkert su posibilidad de quedarse dormido en diferentes situaciones. La puntuación total puede ir de 0 a 24, y una puntuación mayor de 10 indica una somnolencia significativa.

Durante la entrevista, se solicitó a los sujetos la presencia de una persona cercana, preferiblemente su pareja. Los sujetos respondieron a las cuestiones sobre sus síntomas clínicos relacionados con el diagnostico de AS (ronquido, despertares, somnolencia…) y sobre las comorbilidades relacionadas (hipertensión, diabetes, hipotiroidismo…). Todas la comorbilidades fueron registradas bien por diagnostico referido por el sujeto, bien a través de la medicación prescrita.

Las mediciones antropométricas y las pruebas de laboratorio fueron desarrolladas por una enfermera entrenada. Además, a los sujetos se les realizó una polisomnografía nocturna domiciliaria.

Análisis estadístico

Se diseñó una base de datos en Microsoft Excel XP para almacenar la información de la población en estudio, la cual contó con las variables definidas anteriormente. Posteriormente, se evaluó la información digitalizada para evitar posibles inconsistencias. El análisis estadístico se realizó con el software SPSS versión 15.0 para Windows. Los análisis se realizaron estratificando a los sujetos por severidad de AHI. Se calculó el promedio, la desviación estándar y los rangos de los factores de riesgo.

Se llevó a cabo estadística descriptiva y análisis de la varianza para verificar la existencia de significación estadística entre los factores considerados.

Resultados

Características de la muestra

De los 1.016 sujetos, 901 fueron diagnosticados como apneicos (AHÍ > 10) y 115 como no apneicos. Las características de la muestra final (tabla I) se han mostrado asociadas a la presencia o no de apnea y en el último caso a la severidad de ésta, quedando la muestra distribuida en tres grupos: No apneicos, Grupo Apnea 1 (11 > AHI < 30) y Grupo Apnea 2 (AHÍ ≥ 31).

Con una alta prevalencia de diagnóstico de apnea en hombres (91,10%) respecto a las mujeres (82,18%) (P < 0,01). Además, en el caso de los hombres el porcentaje se encontró significativamente asociado a la severidad de la AS (75,5 *vs* 82,9) (P < 0,001).

La edad media de la muestra también se mostró significativamente asociada a la pertenencia, o no, a grupo AS y a la Severidad de la AS (45,99 ± 12,4 *vs* 47,73 ± 11,9 *vs* 52,48 ± 12,7) (P < 0,001).

El Índice de Masa Corporal (IMC) mostró diferencias significativas entre los grupos apnea severa y no apnea (30,373 ± 4,84 *vs* 33,473 ± 9,87) (P < 0,001).

Sin embargo, respecto al consumo diario de tabaco y alcohol, no se encontraron diferencias significativas entre los grupos (P < 0,342 y P < 0,519).

Relación entre factores de riesgo de síndrome metabólico y AS

Para el análisis estadístico se analizó la prevalencia de cada uno de los factores de riesgo para el Síndrome Metabólico descritos por la Federación Internacional de Diabetes[25] asociados a los grupos: No Apnea, Apnea moderada y Apnea Severa (tabla II).

La hipertensión se mostro como el factor de riesgo más prevalente (33,3%) y como el que mostró mayor prevalencia asociado a la Apnea y a su severidad (P < 0,001).

Tabla II
Prevalencia de componentes del síndrome metabólico por índice RDI

Características	*Total (n = 1.016)*	*Grupo NOAS (n = 115)*	*Grupo Apnea 1 (n = 159)*	*Grupo Apnea 2 (n = 742)*	*p*
Hipertensión (%)	33,3	18,4	23,1	37,7	0,000
Diabetes (%)	8,8	2,9	6,1	10,2	0,071
Hipercolesterolemia (%)	12,4	11,7	12,9	12,8	0,581
Dislipidemia (%)	5,8	1,9	5,4	6,6	0,276
Obesidad (%) IMC ≥ 30	61,7	44,7	47,6	67	0,000
Síndrome metabólico (%)	3,5	0	2	4,1	0,090

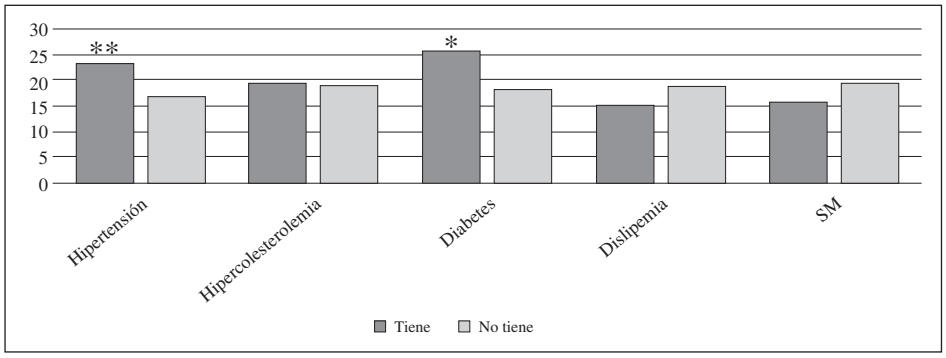

*Fig. 1.—Tiempo nocturno de saturación O_2 ≤ 90 asociados a los distintos factores de riesgo del síndrome metabólico. Se muestra el tiempo de saturación O_2 nocturno < 90. Valores expresados en %. *(p < 0,05); **(p < 0,001).*

Sin embargo el resto de los factores de riesgo, aunque se presentaron como más prevalentes en el grupo Apnea severa, no llegaron a la significación estadística. Tan solo el porcentaje de sujetos con IMC > 30 se mostró asociado de manera significativa a la Severidad de la Apnea (47,6 % *vs* 67%) (P < 0,001).

Una de las consecuencias asociadas a los episodios de apneas intermitentes y asociado de gran manera a los factores de riesgo cardiovascular, son los episodios de hipoxia intermitente.

Se analizó la asociación entre los diferentes factores de riesgo para el desarrollo de Síndrome Metabólico con el porcentaje de tiempo de sueño en que el sujeto saturó con valores por debajo de 90 O2 (fig. 1).

La hipertensión y la diabetes se mostraron significativamente asociadas a valores de saturación más bajos (P < 0,001 y P < 0,05) respectivamente.

Discusión/conclusión

Estudios previos ya han demostrado que la apnea del Sueño se encuentra asociado de manera independiente con gran numero de factores de riesgo cardiovascular como la hipertensión[26,27], la resistencia insulínica, la alteración de la tolerancia a la glucosa[28,29] y la dislipemia[30,31,32], en diferentes poblaciones.

Sin embargo, los estudios que se han desarrollado hasta el momento no han sido capaces de determinar el mecanismo de asociación entre la AS y el Síndrome Metabólico, teniendo en cuenta que este síndrome agrupa a diversas alteraciones[33] que también se encuentran asociadas a la AS.

Los datos existentes hasta el momento, han sido obtenidos en estudios de corte prospectivo o retrospectivo, pero sin seguimiento ni con perfiles de sujetos controlados. Por lo tanto no han sido capaces de reflejar la relación entre la AS y el Síndrome Metabólico. El número poblacional y las herramientas de medición, han permitido aumentar la calidad de estudios previos en una población de riesgo, como los sujetos con AS severa.

Permitiendo además, cotejar una población extensa con cada una de las alteraciones endocrinometabolicas asociadas con el síndrome metabólico.

En este estudio, uno de los primeros en incluir población española con AS, se demuestra que la AS está asociada a mayor prevalencia de hipertensión, hipocolesterolemia, diabetes, dislipemia y obesidad. Encontrando una significación estadística entre grupos entre la apnea de sueño severa y obesidad e hipertensión. Sin embargo, se han encontrado valores de prevalencia muy similares entre grupos en los valores de hipocolesterolemia. Estudios similares[34] han encontrado diferencias significativas (p < 0,001) sin embargo sus grupos muestrales, aun siendo menos numerosos, poseían grupo AS y Grupo control emparejados por IMC, lo que en nuestro estudio no ha sido posible replicar.

Los grandes estudios epidemiológicos que han demostrado que el síndrome de apnea obstructiva del sueño precede y predice la hipertensión arterial son el Wisconsin Sleep Cohort Study[35] y el Sleep Heart Health

Study[36]. En nuestro estudio, la hipertensión se ha mostrado como el factor de riesgo más prevalente en nuestra muestra (33%), estos valores correlacionan con otros estudios de corte similar. De hecho, al menos 30% de los pacientes hipertensos sufre síndrome de apnea obstructiva del sueño[37,38], este porcentaje puede aumentar hasta el 70% o más si la hipertensión arterial es resistente.

Investigaciones recientes han mostrado una alta prevalencia de diabetes tipo II en sujetos con AS sin embargo la relación de causalidad queda sin aclarar en la mayoría de estos. En nuestro estudio la diabetes ha mostrado una prevalencia del 8,8% sobre la muestra global, mostrando una tendencia a su incremento junto al grupo de mayor severidad pero sin alcanzar significación estadística ($p = 0,071$) y una asociación estadísticamente significativa asociada a bajos niveles de saturación ($p > 0,005$). Nuestros resultados han mostrado una alta relación de la diabetes asociada a los valores de saturación nocturna, estos resultados se encuentran en la línea de Iiyory y cols.[39], en un modelo con ratones sin obesidad, describen que la hipoxemia intermitente es causa de resistencia a la insulina[40], lo que explica por qué la severidad de la hipoxemia es el parámetro polisomnográfico que mejor se asocia con intolerancia a la glucosa en pacientes con síndrome de apnea obstructiva del sueño[41].

Este estudio buscaba responder a la asociación entre prevalencia de factores de riesgo de síndrome metabólico y severidad de Apnea de Sueño. En nuestro estudio hemos encontrado la asociación entre algunos de ellos y el grupo de mayor apnea, sin embargo, otros estudios han encontrado asociación incluso en el grupo de AHÍ leve[42]. Una diferencia con nuestro estudio es la selección de nuestros sujetos, ya que todos ellos acudían al servicio por sospecha de apnea de sueño, dificultando esta asociación. Otros autores ya han referido que las alteraciones del sueño, no únicamente la apnea, implican gran cantidad de factores de riesgo asociados tradicionalmente al síndrome metabólico[43].

El sueño tiene un papel fundamental en la regulación del equilibrio energético. Las alteraciones metabólicas y la Apnea de Sueño presentaron en nuestra muestra una importante asociación que debe, sin duda, ser investigada en mayor profundidad. Sin duda, un mejor conocimiento de la relación entre AS y las alteraciones metabólicas pueden tener importantes repercusiones en la salud pública.

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Articulo V:

Valenza MC, Valenza G, Muñoz-Casaubon T, Botella-Lopez M, Puentedura EJ, Arroyo-Morales M, Fernandez-de-las-Peñas C. Apnea del Sueño y Arritmias Ventriculares. Revista Iberoamericana de Arritmologia 2012 ;12 (2)208-318

Resumen

Introducción: La asociación entre las alteraciones cardiovasculares y la apnea del sueño (AS) ha sido extensamente descrita. Sin embargo, la relación entre la AS y las arritmias ventriculares (AV) han sido poco exploradas. El objetivo de este artículo es revisar la bibliografía disponible y discutir el impacto pronóstico de esta asociación. Método: Revisión bibliográfica sistemática de los últimos 15 años en Medline, incluyendo ensayos clínicos y revisiones que relacionaran AS y AV en humanos, en idioma ingles y español. Resultados: La bibliografía ha mostrado una clara asociación entre las AV y la AS. En estudios sobre sujetos con patologías del ritmo cardíaco se encontró una prevalencia de hasta el 60% de AS, mientras que en estudios sobre sujetos con AS se ha encontrado un incremento de tres veces el riesgo de padecer extrasístoles ventriculares respecto a sujetos sin AS (OR 3.40; 95% CI 1.03-11.20, p=0.004). Conclusiones: La AS y las AV se encuentran interrelacionadas, sin embargo, diferentes hipótesis deben aún ser esclarecidas en esta relación. La importancia de esta relación merece ser estudiada de manera más profunda y sus consecuencias clínicas deben implicar de manera especial a los agentes sanitarios que intervienen en el cuidado de estos pacientes.

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Apnea del Sueño y Arritmias Ventriculares

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Resumen

Introducción: La asociación entre las alteraciones cardiovasculares y la apnea del sueño (AS) ha sido extensamente descrita. Sin embargo, la relación entre la AS y las arritmias ventriculares (AV) han sido poco exploradas. El objetivo de este artículo es revisar la bibliografía disponible y discutir el impacto pronóstico de esta asociación.

Método: Revisión bibliográfica sistemática de los últimos 15 años en Medline, incluyendo ensayos clínicos y revisiones que relacionaran AS y AV en humanos, en idioma ingles y español.

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Palabras clave: arritmia ventricular, apnea del sueño

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Sleep Apnea and Ventricular Arrhythmias

Abstract

Introduction: The association between cardiovascular alterations and sleep apnea (SA) has been extensively described. However the relationship between SA and ventricular arrhythmias (VA) has not been explored in detail. This article aims to review the available literature on this association and discussing the impact forecast of this association.

Method: Systematic review of the literature for the last 15 years; using Medline and including studies assessing on SA and VA association in humans, both in English and Spanish.

Results: Our systematic reviewed showed a clear association between SA and VA. In studies on subjects with cardiovascular disease and heart rhythm disorders, the prevalence of SA was found up to 60%, while in studies of subjects with SA, we found three times increased the risk of developing ventricular ectopy in comparison to subjects without SA (OR 3.40; 95% CI 1.03 - 11.20, p = 0. 004).

Conclusions: SA and VA are associated; however the intrinsic mechanisms of this association require further clarification. The importance of this association deserves further studies in order to bring light to the clinical consequences. Special emphasis should be given to those health care practitioners taking care of these patients.

Key Words: sleep apnea, ventricular arrhythmia

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INTRODUCCIÓN

El sueño, definido en el plano de la conducta por la suspensión normal de la conciencia y desde un punto de vista electrofisiológico por criterios de ondas encefálicas específicas, consume un tercio de nuestra vida[1]. Por ello, en los últimos años las patologías del sueño y sus repercusiones clínicas se han destacado como un objetivo prioritario por gran parte de la comunidad científica.

El síndrome de Apnea del Sueño (AS), también llamado síndrome de Apneas-Hipoapneas del Sueño es uno de los trastornos del sueño de mayor prevalencia, oscilando en la población general entre un 1 a 2%[2], y se caracteriza por un cuadro de episodios repetidos de obstrucción de la vía aérea superior, acompañada por esfuerzo respiratorio inefectivo y apneas seguidas habitualmente por respiraciones amplias de recuperación (llamadas hiperpneas) durante el sueño, que provocan constantes desaturaciones de la oxihemoglobina y despertares transitorios.

La **apnea** definida como la interrupción completa del flujo inspiratorio superior a 10 segundos, puede diferenciarse en función de su origen: si se mantiene el esfuerzo ventilatorio durante este tiempo, la apnea se considerará de origen *obstructivo*, y si no existe este esfuerzo se considerará como de origen central.

Una **hipoapnea** es un episodio de definición más compleja consistente en la obstrucción parcial de las vías aéreas superiores y que produce una clara disminución del flujo aéreo en boca-nariz de duración igual o superior a 10 segundos. Se acompaña de un despertar transitorio y/o desaturación cíclica de la oxihemoglobina. Un índice de apnea e hipoapnea (IAH) (número de apneas+ número de hipoapneas por hora de sueño) superior a 5 por hora se considera patológico.

Si observamos de cerca el efecto del sueño "normal" encontramos un predominio de la modulación parasimpática y un aumento de la estabilidad eléctrica miocárdica, de este modo podemos entender que la alteración del sueño provocada por la AS puede provocar un desequilibrio de estos mecanismos regulatorios.[3] De hecho, ya ha sido descrita la relación entre la AS y alteraciones cardiovasculares como la hipertensión, enfermedad coronaria, accidente cerebrovascular (ACV) y fallo cardíaco congestivo[3,4,5,6,7]; además de asociarse a somnolencia, disfunción neuro-cognitiva y patologías psiquiátricas. A pesar de estas asociaciones y manifestaciones clínicas, y de ser considerada entre los grandes síndromes del milenio, la AS continúa siendo una de las patologías más sub-diagnosticadas (oscilando las cifras entre un 20–30% en función del escenario clínico)[6,8 ,9,10,11,12,13].

Las alteraciones del ritmo y de la conducción cardíaca son muy frecuentes en la consulta cardiológica y se encuentran presentes en casi un 40% de la totalidad de los pacientes atendidos y en 1 de cada 5 de los que consultan por primera vez[14]. Estudios previos han demostrado el aumento de la incidencia de las arritmias cardíacas en pacientes con AS obstructiva. El objetivo de nuestro trabajo fue realizar una revisión sistemática de la literatura que analice la asociación entre AS y AV.

Metodología de búsqueda

Se ha revisado la literatura de manera sistemática para determinar al asociación entre AS y AV, utilizando los términos "sleep apnea" "obstructive sleep apnea" "sleep disordered breathing" asociados a los términos "ventricular arrhythmias", "ventricular fibrillation", "ventricular tachycardia", "ventricular extrasystoles", "non-sustained ventricular contraction", "premature ventricular contraction" y "ventricular extra beats". Se realizó una búsqueda en Medline imponiendo como límite una antigüedad inferior a 15 años y la inclusión tan solo de ensayos clínicos y revisiones. La búsqueda ha sido duplicada de manera paralela e independiente por dos investigadores (MV y AB) y se han valorado las discrepancias para mayor fiabilidad de los resultados obtenidos. Además se

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revisaron las referencias de los artículos seleccionados como
método de revisión secundario a los resultados obtenidos.

Mecanismos de asociación entre apnea del sueño y arritmia cardíaca

Los mecanismos que vinculan la AS y las arritmias cardíacas continúan siendo objeto de especulación y debate continuo. Uno de los mecanismos potenciales de asociación es la interrelación entre el efecto proarrítmico de los episodios intermitentes de hipoxia nocturna, isquemia miocárdica y el aumento de la actividad simpática, lo que conlleva un incremento de las concentraciones plasmáticas de catecolaminas[15,16]. Sin embargo, las especulaciones sobre los diferentes mecanismos de asociación tan solo han sido confirmadas parcialmente.

En el 2008 nuestro grupo publicó una editorial[17] que describe gran parte de los mecanismos que enumeramos a continuación (Figura 1):

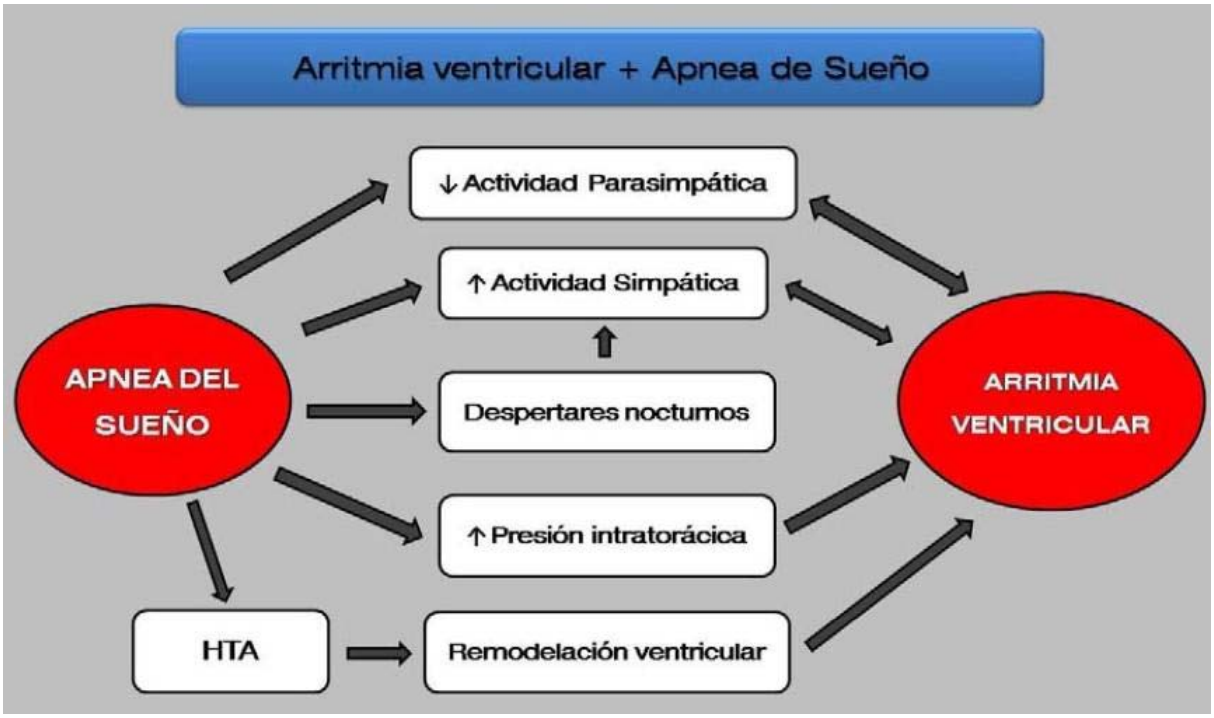

Figura 1: Descripción de los mecanismos de interacción entre apnea del sueño y arritmia ventricular. Interrelación entre AS y AV.

1. Alteración del sistema nervioso autónomo

Las alteraciones autonómicas han sido descritas en pacientes con AS como un aumento del tono simpático y/o una reducción del tono parasimpático. En los estudios de Aydin[18] y Jo[19] se demostró una disminución de la sensibilidad barorefleja, una reducción de la respuesta vagal y una alteración de los componentes parasimpáticos de la variabilidad de la FC (VFC) relacionada con la apnea (P <0.01 y P <0.01). Sin embargo, si bien la mayoría de los estudios valoraron la VFC para detectar alteraciones autonómicas, estos resultados no pudieron ser reproducidos por nuestro grupo. Recientemente hemos publicado nuestra experiencia en una serie de pacientes con apnea del sueño severa en quienes, si bien los parámetros clásicos de VFC resultaron normales[20], al valorar los mismos casos utilizando *Asimetría de la Frecuencia Cardíaca*, los parámetros de aceleración y desaceleración se encontraron profundamente alterados, sugiriendo una profunda alteración autonómica[21]. Las diferencias entre nuestros trabajos [20,21] y las publicaciones previas, pueden estar dadas por las diferentes metodologías de

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registro. En nuestro caso, usamos registros de 10 minutos durante el día, mientras que en estudios previos, se incluyeron registros durante la noche, donde la influencia de las apneas sobre la VFC, es mucho mayor.

2. Incremento persistente del tono simpático

Ha sido intensamente descrita la asociación entre el aumento del tono simpático y el incremento de la ectopía ventricular[22]. Mehra[23] publicó en el 2009 un estudio epidemiológico con 2911 pacientes portadores de AS, y encontró una relación entre el aumento del tono simpático mediante registro de la variabilidad cardiaca y la prevalencia de ectopía ventricular compleja (OR, 1.58; 95% CI, 1.28–1.96 ($p < 0.001$)).

3. Apnea del sueño y alteraciones de la repolarización ventricular

Algunos autores reportaron aumento del QT y la dispersión del QT en sujetos con AS obstructiva, mientras que otros no han encontrado esta relación[24,25,26]. En los estudios de Harbison [27], Voight[28] y Barta y col[29] los intervalos QTc nocturnos, QRd y QTcd no mostraron diferencias entre grupos con y sin AS obstructiva ($p = 0.121$). Sin embargo en estudios similares como el de Nakamura y col[30] encontraron que el QTcd en sujetos con AS obstructiva fue mayor durante las horas de sueño (65±14.6 ms) que durante las horas de vigilia (57 ±13.5 ms, ($P < 0.0001$).

4. Relación entre apnea e hipertensión arterial

La relación entre AS e hipertensión arterial ha sido ratificada en numerosos estudios tanto de corte transversal como epidemiológico [6,12] llegando las cifras incluso al 50 %[31]. La relación entre hipertensión y arritmias ventriculares[32,33] también ha sido probada [16,34]. En un estudio epidemiológico desarrollado en más de 30000 sujetos se evidenció la presencia de extrasístoles ventriculares asociadas a un aumento de muerte súbita en el 25% en pacientes hipertensos, aun sin patología coronaria[35,36].

5. Aumento de la presión intratorácica

La presión intratorácica es uno de los primeros reflejos del desarrollo patobiomecánico ligado a la AS. El mecanismo de producción de la AS obstructiva que incluye el colapso de la vía aérea asociado al esfuerzo inspiratorio ineficaz, resulta en un aumento de la presión intratorácica[37].

Este aumento de presión intratorácica generaría un aumento de la presión transmural cardíaca, provocando un aumento de la tensión en la pared ventricular y sobrecarga del trabajo ventricular, lo que puede desencadenar AV[38,39]. Estos cambios de presión se producen de manera brusca en los sujetos con AS, y además suelen asociarse con hipoxemia intermitente, contribuyendo así a incrementar la frecuencia de las AV[40].

Bradley[41] evidenció un incremento de la carga ventricular ($p < 0.05$). En realidad Bradley afirma que hubo un aumento de la presión VI transmural asociado a caída de la presión arterial sistólica e índice cardíaco en estos pacientes comparados con los sanos.

6. Despertares frecuentes

Los despertares frecuentes se encuentran asociados con las alteraciones en la arquitectura y cantidad de sueño asociados a la AS, lo que se traduce en una reducción de la duración del sueño. Estudios previos refieren que esta reducción significativa del tiempo de sueño, aumentaría la actividad nerviosa simpática aumentando significativamente el número de extrasístoles ventriculares que ocurren durante los periodos de vigilia[42,43,44]. Aunque no existe un acuerdo en la comunidad científica sobre todos estos factores, sí existe un reconocimiento general sobre el carácter multifactorial de los mecanismos que relacionan la AS con las alteraciones cardiovasculares. Veremos a continuación los datos pertinentes en la relación entre AS y AV.

Arritmia ventricular en pacientes con AS

La relación entre AS y AV está en un estadío de definición menos avanzado que la

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asociación entre AS y fibrilación auricular o bradiarritmias. El conocimiento de la interrelación entre la AS y las arritmias cardíacas provienen en su mayor parte de un número relativamente escaso de estudios desarrollados en pacientes referidos para evaluación o tratamiento por patología cardiaca o derivados a laboratorios del sueño [28,30,45,46]. Sin duda, esto implica una dificultad adicional al intentar extrapolar estos hallazgos a la población general. Guilleminault [48], publicó un estudio demostrando que el 20% de 400 pacientes con AS obstructiva tenían frecuentes extrasístoles ventriculares. Algunos pacientes mostraron episodios de taquicardias ventriculares no sostenidas, que ocurrieron únicamente durante el sueño. Este patrón se opone a la prevalencia diurna habitual de las extrasístoles ventriculares en sujetos que no tienen apnea[47,48]. Además, encontraron una prevalencia de un 20% de arritmias ventriculares nocturnas asociadas a los episodios de mayor desaturación. En este estudio, las extrasístoles ventriculares y la taquicardia ventricular nosostenida se asociaron con episodios de desaturación de O2 severas, de lo que se podría suponer que la AS obstructiva actúa como un desencadenante de AV a través de la hipoxia intermitente[49,50]. El Sleep Heart Study, que incluyó 6,441 sujetos mayores de 40 años que fueron evaluados por sospecha de AS, demostró un aumento significativo en la prevalencia de fibrilación auricular, taquicardia ventricular no-sostenida y extrasístoles ventriculares nocturnas en sujetos con apnea severa comparados con sujetos sin apnea [54,51] (4.8 versus 0.9% (p < 0.003)).(Figura 2)

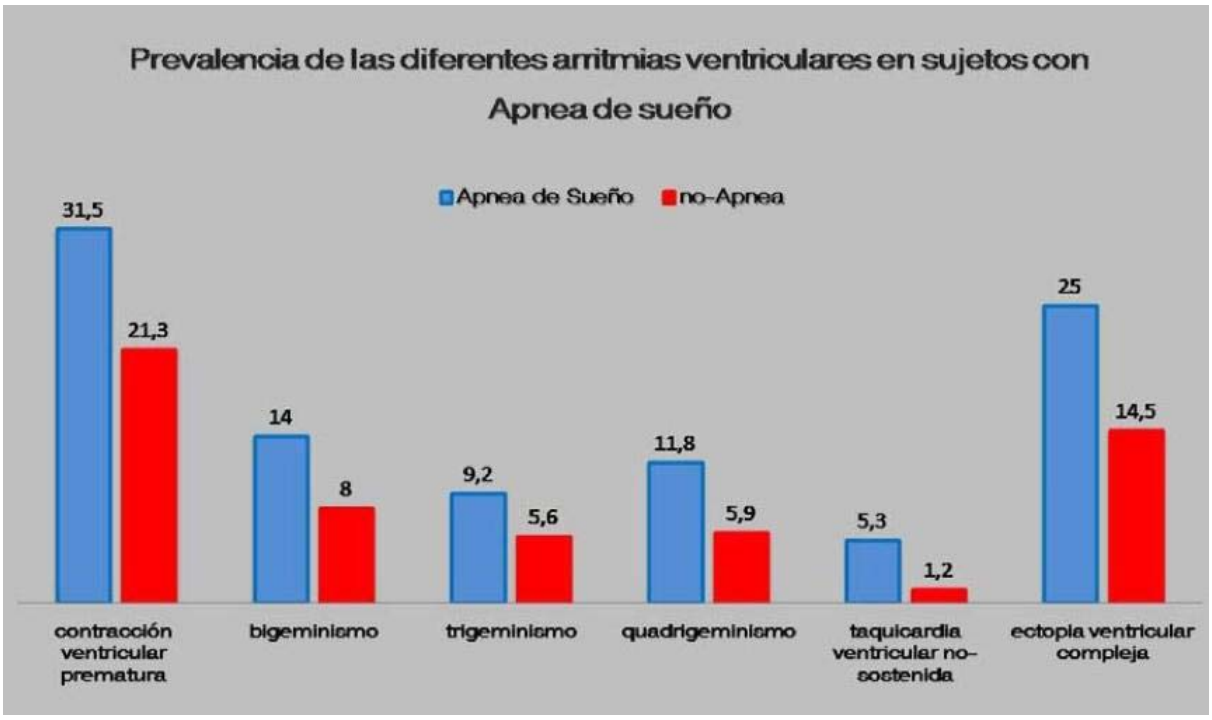

Figura 2: Descripción de la prevalencia encontrada de alteraciones del ritmo ventricular en sujetos de mediana edad con y sin apnea del sueño. Modificado de Mehra y col54. Prevalencia de las diferentes AV en sujetos con y sin AS (modificado Mehra 2006)

Un sub-estudio del Sleep Heart Health Study[22] en el que se evaluó un número mayor de pacientes, también mostró una asociación significativa entre AS y AV, contribuyendo así a incrementar la frecuencia de las AV (OR 3.40; 95% CI 1.03-11.20, p=0.004)[54].

Koshino y col[55] estudiaron 35 pacientes con AV encontrando una prevalencia del 60% de AS. En este grupo un 26% tenían AS moderada y un 34% AS severa.

Gami y col[52] demostraron que los pacientes con AS tienen mayor frecuencia de

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muerte súbita durante la noche (entre las 12 AM y 6 AM (RR 2.57, 95% CI 1.87-3.52, p=0.01)). Se ha teorizado sobre si estos picos de muerte súbita en pacientes con AS pueden ser atribuidos a hipoxia intermitente, a hipertensión arterial o a las alteraciones autonómicas durante el sueño[52]. La prevalencia de AS se estima en más de un 50% en pacientes con fallo cardíaco sintomático y con una fracción de eyección izquierda (FEVI) deprimida, con disfunción sistólica asintomática o con disfunción diastólica[53,54,55]. Este hecho debe permitirnos reflexionar sobre la alta prevalencia de AS en pacientes con deterioro de la FEVI. Uno de cada dos pacientes con insuficiencia cardíaca (con o sin deterioro de la FEVI) presenta AS. Como demuestra Bradley[56] en una excelente revisión recientemente publicada, contrariamente a lo que el sentido común indicaría, la AS obstructiva es también altamente prevalente en pacientes con insuficiencia cardíaca congestiva. Los mecanismos de AS central en pacientes con insuficiencia cardíaca son obvios y se relacionan con la desensitización de los núcleos centrales vinculados al hipoflujo constante. Sin embargo, la AS obstructiva es menos sencilla de explicar. En primer lugar, existe un edema de las vías aéreas superiores. Pero, como señala Bradley, el mecanismo principal es la redistribución de flujo nocturno que ocurre en pacientes con fallo congestivo. El decúbito facilita la redistribución del flujo corporal total hacia el tórax y el cuello, incrementando el edema de las vías respiratorias altas durante el sueño. Nuestro grupo ya ha demostrado que la prevalencia de AS en pacientes con cardiodesfibriladores implantables (CDI) es de por lo menos un 20%. En nuestro estudio retrospectivo de 147 pacientes con CDI, encontramos que la AS se asoció más frecuente con terapias apropiadas (31% vs. 17%; p=0.09) y que el tiempo transcurrido hasta la primer terapia apropiada fue más breve en pacientes con AS (8 vs. 12 meses; p= 0.12)[57]. El sesgo que añade la naturaleza retrospectiva de nuestro estudio puede hacer que nuestros valores estén infraestimando la prevalencia real de esta asociación. Grimm y col. en un estudio prospectivo, evaluaron una población similar encontrando una prevalencia muy superior (62% (44% AS central, 18% AS obstructiva))[58] .

El estudio de Zeidan-Shwiri[59], uno de los más recientes, ha demostrado una sorprendente incidencia de arritmias ventriculares fatales durante las horas de sueño en sujetos con AS (OR 5.6, 95% CI 2.0-15.6, P = .001). Estos resultados son similares a los observados por Serizawa[60], que mostraron que las terapias adecuados del CDI en sujetos con fallo cardiaco y fracción de eyección ≤35% ocurren con más frecuencia en sujetos con AS que en sujetos sin AS (43% vs 17%, P-.029) y que la AS estaba asociada a mayor incidencia de terapias del CDI desde la medianoche a las 6 am[65]. Los mecanismos fisiopatológicos involucrados en esta asociación ya han sido postulados previamente en este artículo, pero en base a los estudios de los últimos años podemos añadir ciertos detalles:

1. La AS se asocia de manera significativa con un aumento de la incidencia de eventos cardiovasculares no-fatales (infarto de miocardio no-fatal, ACV, insuficiencia coronaria, revascularización) (OR: 3.17, 95% CI 1.12- 7.51, p>0.05)[56]. Esto puede representar un incremento del riesgo post- IM asociado a arritmias y riesgo a largo plazo mediado por un deterioro de la función ventricular[9].

2. La AS podría deteriorar la FEVI.

Se ha teorizado sobre si este efecto podría estar mediado por la presión negativa intratorácica, la hipoxia intermitente alterando la contractilidad cardíaca, un aumento de la presión arterial pulmonar o isquemia cardíaca. Este deterioro de la función ventricular izquierda puede llevar a cambios humorales y celulares que pueden predisponer a muerte súbita. El tratamiento con presión positiva continua (CPAP) ha mostrado mejorar la FEVI en un grupo de 24 pacientes con AS durante un periodo de un mes (25.0 ± 2.8 a 33.8 ± 2.4%, P<0.001)[61].

3. Las extrasístoles ventriculares son comunes en los pacientes hipertensos con hipertrofia ventricular izquierda (RR 8.9, p < 0.01)[34,62]. La hipertensión se asocia significativamente con AS [5,10,17,63].

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4. La hipoxia intermitente es una consecuencia de la AS. En una situación aguda, los episodios hipóxicos severos pueden provocar extrasístoles ventriculares[64], como un desencadenante potencial para arritmias ventriculares más complejas. En una situación crónica, el estrés oxidativo repetido puede inducir remodelamiento ventricular que predisponga a la arritmia[65].
5. La alteración del control autonómico ha sido ampliamente demostrada en sujetos con AS[18,19] Su efecto deletéreo sobre la variabilidad de la FC y sobre el acoplamiento de los *inputs* cardiacos y ventilatorios fue reportada en varias publicaciones. La fluctuación de la actividad autónoma causada por la AS, puede tener también efectos sobre los cambios latido a latido de la repolarización ventricular, que podrían predisponer a AV[66].
6. La elevación crónica del tono simpático que ha sido observada en sujetos con AS[67] representa una alteración mayor ligada al aumento del riesgo de muerte súbita[68].

AS, insuficiencia cardíaca y AV: Consideraciones finales

Sabemos que tanto la apnea de origen central como la de origen obstructivo se encuentran presentes con gran frecuencia en sujetos con patologías cardiacas, sobre todo en sujetos con fallo cardiaco congestivo[69].
Javaheri[74] encontró una asociación entre las apneas de tipo central y extrasístoles ventriculares en pacientes con fallo cardíaco congestivo y bajos niveles de PaCO2 (PaCO2 b35 mm Hg) comparándolos a sujetos con valores de CO2 normales.

Lafranchi[57] encontró una incidencia elevada de arritmias ventriculares en sujetos con fallo cardiaco y con AS de tipo central severa (55%). Además encontró un aumento de episodios de taquicardias ventriculares sostenidas asociadas con mayor severidad de AS central (P=0.05).

Leung[70] reportó un estudio en sujetos con Cheyne-Stokes y AV encontrando un patrón de asociación entre AS central y extrasístoles ventriculares. En su experimento, aplicó una dosis baja de CO2 inhalado para eliminar las AS de origen central produciéndose una reducción significativa de las AV (de 4.7 ± 3.8 a 3.3 ± 4.0 extrasístoles ventriculares por minuto, P =.048).

En el estudio de Mehra y col en hombres mayores de 40 años con AS (MrOS Sleep Study)[23] encontraron una asociación entre AS y AV, interpretando la prevalencia de episodios de AS obstructiva como un indicador de AV. Sin embargo, los estudios que han abordado esta cuestión han abierto el debate sobre como se desarrolla la relación de causalidad entre las apneas de tipo central, las arritmias ventriculares y la patología cardíaca de base.

En cuanto a las implicaciones terapéuticas del CPAP y la AV, tan solo algunos estudios han reportado algunos resultados, siendo los mismos muy controvertidos. En un estudio aleatorizado y controlado realizado de la Universidad de Ohio coordinado por Khayat y col[71.39], se evidenció una mejoría de la FEVI en pacientes ingresados por insuficiencia cardíaca.

Se obtuvo una muestra de pacientes diagnosticados con AS durante el ingreso; el grupo control se trató con medidas convencionales y el grupo intervención se trató con autoPAP además de las medidas convencionales. En este grupo se evidenció un incremento de la función sistólica, persistiendo la significación estadística tras ajustar por posibles factores de confusión (4.6% (p = 0.03)). En el estudio de Javaheri [72] se sometió a sujetos con fallo cardíaco y AS a tratamiento con CPAP, una sola noche, tras esto se evidenció una reducción de extrasístoles ventriculares por minuto de 66± 117 a 18±20, P=0.055.

CONCLUSIONES

Los estudios que han profundizado en la relación entre AS y AV han evolucionado desde la publicación de casos clínicos, a estudios observacionales con grandes grupos muestrales hasta la última generación de ensayos clínicos. Aunque los datos que asocian al AS y la AV aún son limitados, la asociación es clara y se ha demostrado reiteradamente en diferentes escenarios clínicos. En la actualidad, nuestro

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grupo está categorizando las extrasístoles ventriculares en pacientes con AS, en cuanto a su morfología, sitio de origen, intervalo de acoplamiento, densidad y pausas compensadoras. Una mayor comprensión sobre esta asociación es necesaria para emprender alternativas de tratamiento racionales.

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CONCLUSIONES

1. La producción científica que vincula las alteraciones del sueño con gran cantidad de patologías de alta prevalencia en Fisioterapia, justifica la necesid0ad de su conocimiento por la disciplina.
2. Las alteraciones de la cantidad, calidad y arquitectura del sueño se encuentran significativamente relacionadas con el perfil de dolor en sujetos con cervicalgia.
3. Las alteraciones de sueño como, apnea de sueño, sueño no reparador e insomnio se encuentran significativamente asociadas a perfiles clínicos y sintomáticos en la población granadina.
4. Los factores de riesgo cardiovascular, en concreto, los factores de riesgo para el desarrollo del Síndrome Metabólico se encuentran relacionados con la severidad de la Apnea de Sueño y con los valores de desaturación nocturnos.
5. La apnea de sueño y la arritmia ventricular se encuentran interrelacionados por los valores de desaturación nocturnos, las alteraciones del sistema nervioso simpático y por la presión intratorácica generada en los episodios de Apnea.

En conclusión, Las alteraciones del sueño y su interrelación con patologías y síntomas frecuentes justifican la necesidad de su conocimiento. El dolor, tanto agudo como crónico se han mostrado como generadores de alteraciones del sueño que pueden condicionar la respuesta de los pacientes a las propuestas terapéuticas. Las alteraciones del sueño tienen una gran prevalencia en nuestra sociedad y se muestran asociados a diferentes perfiles sintomáticos en el grupo poblacional estudiado en esta tesis.

CONCLUSSIONS

1. The scientific production that related sleep disorders and various pathologies, that are very common on physiotherapy practice, justify the need of knowledge in this area.

2. Disturbances on sleep quantity, architecture and quality are significantly related to pain profile in subjects with neck pain.

3. Sleep disturbances like sleep apnea, insomnia and non-restorative sleep are significantly related to clinical and symptomatic profiles in a Granada population.

4. Cardiovascular risk factors, concretely, risk factors for metabolic syndrome are related to sleep apnea severity and nocturnal saturation values.

5. Sleep apnea and ventricular arrhythmias are related to nocturnal saturation values, to the sympathetic nervous system and the intrathoracic pressure generated by apnea episodes.

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