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Is melatonin's sleep related deficiency associated responsible of static diseases including cancer?

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Abstract:

***Background**: Melatonin is well-known for its regulation of circadian rhythm. It is produced by stimulation of pineal gland by darkness and inhibited by light. Disturbance of Melatonin production by lack of night sleep is responsible of many diseases including cancer. Therefore, we hypothesized that if we maintain melatonin to normal by overcoming the civilization life or by creation of lenses that can keep our photoreceptor senseless, the non-communicable diseases including cancer will disappear. Therefore the objective of this study was to evaluate the relationship between lack of melatonin resulting from short night sleep hours and non-communicable diseases. **Methodology**: In this study 286 Saudi adult volunteers living in the city of Hail, KSA, were randomly selected to participate regardless of age and sex. A purposeful questionnaire was designed to collected information regarding sleep habits, frequencies of exposure to disease and other personal characteristics. **Results**: This study investigated 286 individuals, their age ranging from 16 to 72 years old with a mean*

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age of 33 years. The males' females' ratio was 1.71: 1:00. About 73.8% of the study subjects were found to sleep for less than 6 hours per day. Notably, 62.6% of the study group was found to sleep after 1:00 am, and only 53.4% of them awake before sunrise. Depression, non-communicable diseases and other factors were identified among numerous participants. ***Conclusion:*** *Habitual sleep disturbances are prevalent in Saudi Arabia. The high frequencies of disorders that are associated with night sleep disorders are most probably attributed to lack of Melatonin, which requires deep future research.*

Key words: Melatonin, non-communicable diseases, Cancer, Saudi

INTRODUCTION

Circadian rhythm (biological clock) is a daily cycle of biological activity in human based on a 24-hour period and influenced by variations in the environment, such as alterations of sleeping and awaking. In humans, the internal clock is located within the brain's hypothalamus and pineal gland, which releases melatonin in response to the information it receives from photoreceptors in the retina [1].

Melatonin is well-known for its regulation of circadian rhythm. It is produced by stimulation of pineal gland by darkness and inhibited by light [2]. Melatonin is a small, highly conserved indole with numerous receptor-mediated and receptor-independent actions. Receptor-dependent functions include circadian rhythm regulation, sleep, and cancer inhibition. The receptor-independent actions relate to melatonin's ability to function in the detoxification of free radicals, thereby protecting critical molecules from the destructive effects of oxidative stress under conditions of ischemia/reperfusion injury (stroke, heart attack), ionizing radiation, and drug toxicity, among others. Melatonin has numerous applications in physiology and medicine [3].

Disturbance of circadian clocks by genetic and/or environmental factors seems to precipitate in many disorders, including cancer [4].

Now a days there is a very high prevalent of prolonged exposure to the light due to dramatic movement of life style towards civilians in mostly all nations. Consequently, we hypothesized that the high prevalence of non-communicable diseases including cancer is due to lack of melatonin production due to night sleep. Consequently, these observations suggest that restore of normal melatonin hold potential prevention as well as treatment of various diseases including cancer. Therefore, to evaluate the relationship between lacks of melatonin resulting from short night sleep hours and non-communicable diseases. To assess the relationship between lack of melatonin and quality of life including success, satisfaction and depression.

METHODOLOGY

In this study 286 Saudi adult volunteers living in the city of Hail, KSA, were randomly selected to participate regardless of age and sex. A purposeful questionnaire was designed to collected information regarding sleep habits, frequencies of exposure to diseases and other personal characteristics. Each participant was consented before inclusion. The collected data was analyzed using SPSS program.

RESULTS

In this study 286 volunteers have responded to complete the questionnaire, their age ranging from 16 to 72 years old with a mean age of 33 years. Of the 286 participants, 180/286 (63%) were males and 106/286(37%) giving males' females' ratio of 1.71: 1:00.

Of the 275 respondents to sleep hours, 203/275 (73.8%) were used to sleep for less than 6 hours per day and the remaining 72/272(26.2%) were found to sleep for more than 6 hours per day. Of the 281 respondents to sleeping time, 176/281 (62.6%) sleep late after 1:00 am, 68/281(24.2%) sleep relatively late (between 10:00pm to 12:00 am, and 37/281(13.2%). Regarding age, most of those with < 6 hours were found in age group 26-35 followed by age ranges, 36-45 and <25 years constituting 64/203 (31.5%), 61/203(30%) and 60/203(29.6%), respectively. Regarding occupation, employees represented the highest proportion followed by students constituting 91/203(44.8%) and 36/203(17.7%) in this order, as indicated in Table 1. The description within each group is shown in Fig 1.

Table 1. Distribution of sleeping hours per 24 day by demographical characteristics

Variable	Categories	Sleeping hours per day			
		< 6 hours	**>6 hours**	**Total**	**P value**
Sex	Males	130	46	176	
	Females	72	26	98	
	Total	202	72	274	
Age in years					
	< 25	60	21	81	
	26-35	64	16	80	
	36-45	61	24	85	
	46-55	16	5	21	
	56+	2	4	6	
	Total	203	70	273	
Occupation					
	Students	36	13	49	
	Employees	91	21	112	
	Other jobs	59	31	90	
	unemployed	17	5	22	
	Total	203	70	273	

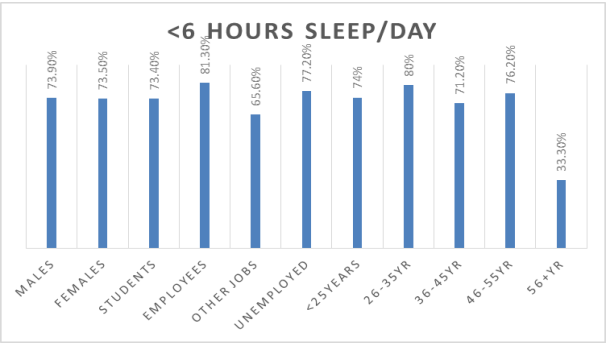

Figure 1. Showing demographic characteristics by sleep shortage (less than 6 hours per 24 hours day)

Table 2. Summarizes the distribution of sleeping hours per 24hours day by sleep time and duration of the habit in years. Of the 202 subjects used to sleep for less than 6 hours, 140/202(69.3%) start their sleep between 1:00 am to 5:00 am and 41/202(20.3%) start their sleep between 10:00 pm to 12:00 pm. Of the 191 subjects used to sleep for less than 6 hours, 67/191(35%), 51/191(26.7%) and 53/191(18.3%) were in this habit for durations of <5 years, 6-10 and 16-20 years respectively as indicated in Table 2.

Table 2. Distribution of sleeping hours per 24hours day by sleep time and duration of the habit in years.

Variable	Categories	Sleeping hours per day			
		< 6 hours	>6 hours	Total	P value
Sleep time	1:00 to 5:00 am	140	29	169	
	6:00 to 10:00 pm	21	15	36	
	10:00 to 12:00 pm	41	24	65	
	Total	202	68	270	
Duration					
	< 5 years	67	20	87	
	6-10	51	18	69	
	11-15	20	7	27	
	16-20	35	14	49	
	21+	18	8	26	
	Total	191	67	258	

In regard to the relationship between shortage of sleep and frequency or having static disease, of the 17 individuals who have disease frequency of more than 3 times per month, 14/17 (82.3%), used to sleep for less than 6 hours per day, as indicated in Table 3. Notably, the frequency of all other static diseases was higher among those sleep for less than 6 hours compared to those sleep more than 6 hours and the different was statistically significant $P < 0.005$, as shown in Fig 2, Table 3.

Table 3. Distribution of sleeping hours per 24hours /day by Diseases

Variable	**Categories**	**Sleeping hours per day**			
		< 6 hours	>6 hours	Total	P value
Episodic diseases	Frequency/moth				
	<3 times	181	59	240	
	≥3 times	14	3	17	
	Total	195	62	257	
Static diseases					
Diabetes	Present	13	6	19	
	Absent	190	66	256	
Hypertension	Present	12	5	17	
	Absent	191	67	258	
Tumors	Present	4	3	7	
	Absent	199	69	268	
Rheumatoid	Present	12	5	17	
	Absent	190	67	257	
Allergy	Present	11	1	12	
	Absent	192	71	263	
Kidney disease	Present	2	1	3	
	Absent	198	71	269	
Lung disease	Present	1	0	1	
	Absent	201	71	272	
Liver disease	Present	4	0	4	
	Absent	199	72	271	
Heart disease	Present	4	1	5	
	Absent	199	71	270	
Other diseases	Present	22	5	27	
	Absent	176	64	240	

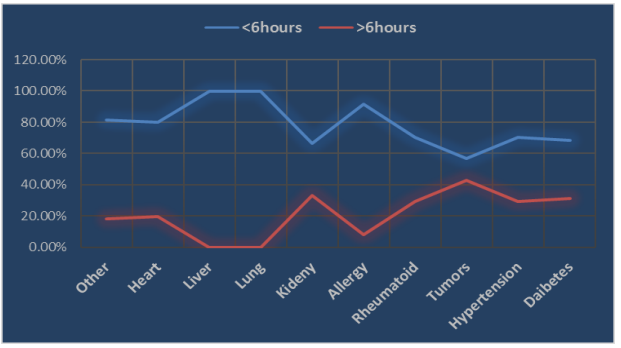

Figure 2, Description of the study population by Sleep durations per day and proportion of diseases.

The distribution of daily sleeping time by demographical characteristics and duration of habit continuity in years was summarized in Table 4, as well as, the distribution of daily sleeping time by diseases was also summarized in Table 5.

Table 4. Distribution of daily sleeping time by demographical characteristics and duration of habit continuity in years

Variable	Categories	Daily sleeping time				
		1:00 to 5:00am	6:00 to 10:00 pm	10:01to 12:00 pm	Total	P value
Sex	Males	100	23	53	176	
	Females	76	13	16	104	
	Total	176	36	68	280	
Age in years						
	< 25	47	12	22	81	
	26-35	57	9	15	81	
	36-45	57	12	18	87	
	46-55	15	0	8	23	
	56+	0	4	3	7	
	Total	176	37	66	279	
Occupation						
	Students	28	9	12	49	
	Employees	81	11	26	118	
	Other jobs	52	12	26	90	
	unemployed	15	5	2	22	
	Total	176	37	66	279	
Duration of habit						
	< 5	58	14	16	88	
	6-10	48	2	13	69	
	11-15	16	8	9	27	
	16-20	31	5	12	48	
	21+	10	4	13	27	

Table 5. Distribution of daily sleeping time by diseases

Variable	Categories	Sleeping hours per day				
		1:00 to 5:00am	6:00 to 10:00 pm	10:01to 12:00 pm	Total	P value
Episodic disease	Frequency/month					
	<3 times	158	29	59	246	
	≥3 times	12	2	3	17	
		170	31	62	282	
Static diseases						
Diabetes	Present	13	1	6	20	
	Absent	163	36	62	261	
Hypertension	Present	13	2	3	18	
	Absent	163	35	65	263	
Tumors	Present	4	3	0	7	
	Absent	172	34	68	274	
Rheumatoid	Present	15	1	2	18	
	Absent	161	36	65	262	
Allergy	Present	9	2	1	12	
	Absent	167	35	67	269	
Renal disease	Present	2	2	0	4	
	Absent	172	35	67	274	
Lung disease	Present	1	0	0	1	
	Absent	175	37	66	278	
Liver disease	Present	4	0	0	4	
	Absent	172	37	68	277	
Heart disease	Present	4	0	1	5	
	Absent	172	37	67	276	
Other diseases	Present	22	2	6	30	
	Absent	150	32	61	243	

DISCUSSION

The internal or biological clock which is located in the suprachiasmatic nuclei of the anterior hypothalamus is controlled by clock genes and environmental factors which are capable to synchronize the clock to 24h. Rhythm desynchronization (shiftwork and night work, trans-meridian flights, aging, some psychiatric diseases, blindness, etc) arises when the internal clock does no longer function in harmony with the astronomical time i.e. our watch. The circadian system comprises of three major components, which are the clock, the retino-hypothalamic tract and melatonin which is secreted by the pineal gland and considered as the arrow of the clock. Both

light and melatonin present a phase response curve suitable for the treatment of sleep circadian complaints [5].

The present study evaluated the deficiency of melatonin that associated with natural sleep pattern. In recent years, melatonin (N-acetyl-5-methoxytryptamine) has received a pronounced deal of consideration as a potential therapeutic strategy for the prevention of stress-related illnesses. Melatonin is well-known for its special effects on oxidative stress pathways [6,7]. It is well established that melatonin acts as an antioxidant through free radical scavenging properties as well as by its role in triggering numerous antioxidant enzymes [8,9].

Consequently, and as shown in the findings of this study the proportions of static diseases were higher among all those sleep late. Melatonin disturbances have been associated with many static diseases including; neurodegenerative diseases [10], Parkinson's disease [11] diabetic kidney disease [12], Alzheimer's disease [13], cancer [14], etc. Melatonin has been proved to inhibit tumor development under *in vivo* as well as *in vitro* circumstances. There are six mechanisms by which melatonin could utilize its oncostatic properties: (a) via direct pro-apoptotic actions; (b) via antioxidant actions; (c) by decreasing the uptake of important factors involved in tumor growth signaling molecules; (d) by improving the immune system; (e) through anti-angiogenic effects [15], (f)activates various pathways involved in apoptosis [16]. Melatonin may possibly be used as a novel onco-static adjuvant agent [17].

Usual circadian rhythms are synchronized to a regular 24 hour environmental light–dark cycle, and the suprachiasmatic nucleus and the hormone melatonin have essential roles in this process. Desynchronization of circadian rhythms, as happens in chrono-biological disorders, can yield severe disturbances in sleep patterns. According to the International Classification of Sleep Disorders, circadian

rhythm sleep disorders (CRSDs) involve delayed sleep phase syndrome, advanced sleep phase syndrome, non-24 hour sleep–wake disorder, jet lag and shift-work sleep disorder. Disturbances in the circadian phase position of plasma melatonin levels have been recognized in all of these disorders. There is convincing evidence to associate endogenous melatonin as an important mediator in CRSD pathophysiology, though further research including large numbers of patients will be required to clarify whether the disruption of melatonin secretion is a causal factor in CRSDs [18].

Nevertheless, there were some limitations in this study of these, it didn't involve and analytical measurements, for melatonin or its associated factors.

However, habitual sleep disturbances are prevalent among Saudi population, as indicated in the finding of the present study. The bulk introduction of lighting devices according to the concept of "maximum coverage area" and multistoried buildings of cities offered intensification to light pollution, which turn into a problem for astronomers, ecologists and hygienists. Analysis of modern lighting devices and installations has shown that about 30-45% of the luminous flux becomes the light pollution. Night lighting of cities causes both direct and indirect damage to the environment. Light pollution affects the human hormonal system, causing different health disorders, such as insomnia and depression as a consequence. The light pollution through the ganglion cells of the retina affects the synthesis of melatonin by the pineal gland (epiphysis) and contributes to its calcification, which significantly affects the human psyche. Now a days, several countries have been paying much state thoughtfulness to this problem through delivery of national documents and change of the concept of the designing of lighting devices and installations. The essence of this concept-to shine with a preset quality of light only in the right place at the specified time

interval. This decreases the light pollution, and increases the environmental safety of lighting [19]. However, this is a technical solution to reduce the light pollution. Another part of the solution is the enhancement of the individual life style to be more close to the nature which can be achieved by raising the awareness of population.

In conclusion: Habitual sleep disturbances are prevalent in Saudi Arabia. The high frequencies of disorders that are associated with night sleep disorders are most probably attributed to lack of Melatonin, which requires deep future research.

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