RELATIONSHIP OF SLEEP DURATION AND QT INTERVAL IN OBESE AND NON-OBESE MEDICAL STUDENTS

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ABSTRACT

BACKGROUND

Sleep deprivation has become a major concern in the modern era. It is found to have an inverse relation with obesity increasing cardiovascular diseases. This study was done to correlate effects of sleep deprivation & obesity with QT interval.

OBJECTIVES

1. To assess sleep deprivation in medical students.
2. To measure QT interval and QTc in obese and normal weight medical students.
3. To correlate these QT interval and QTc values with sleep deprivation and obesity.

METHODOLOGY

In this cross sectional study by simple random sampling 30 obese and 30 normal weight individuals were selected based on Quetelet Index. They were further sub- grouped into Group A with 2-4 hrs., Group B with 4-6 hrs. and Group C with 6-8 hrs. of sleep duration, respectively. Electrocardiography was recorded and QT & QTc was measured. The mean and standard deviations were calculated and by 2 tailed t-test for equality of means, significance was established.

RESULTS

The QT interval measured in Group A has a mean 363±25.1 in normal weight whereas 374±31.6 in obese which is increased. In all groups QTc interval was within normal limits though more in obese individuals. But in group A obese 431±31.6 which shows borderline QTc prolongation (≥430-451ms in men). Thus severe sleep deprivation contributes to obesity and prolongs QTc interval to pathologically.

CONCLUSIONS

Our study concludes that sleep deprivation has significant correlation with QTc interval. Mild to moderate sleep deprivation affects obese more than normal weight & Severe sleep deprivation with obesity may lead to borderline QTc prolongation.

KEYWORDS

Sleep deprivation, Obesity, QT prolongation, Medical students.

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INTRODUCTION: Sleep disorders and excessive stress have become major concern as health risks in the modern industrialized society. Chronic sleep deprivation leads to physical and mental exhaustion thus contributing to rise in cardiovascular diseases.(1)

It has been observed that inadequate sleep patterns with respect to quality & quantity could contribute to early metabolic abnormalities leading to obesity, affecting neuro-endocrine regulation of metabolism & autonomic activity.(2) Nocturnal sleep patterns may be a factor for contributing epidemic of obesity. The importance of prevention of obesity is relevant particularly at a young age. Especially REM sleep has been associated with regulation of nervous system development and training. NREM sleep reflects growing integration of whole brain with somatic restoration and regulation of pituitary release of growth hormone and glucose metabolism. An inverse association was found between amount of sleep and risk of obesity. Hence sleep deprivation and duration of less than 7 hrs even in adolescent age group had its impact in adulthood.(2)

Obesity has been reported as the cause of QT interval prolongation. Delayed repolarization of ventricular myocardium leads to QT interval prolongation which is associated with ventricular arrhythmia and sudden cardiac death.(3) There was significant association between BMI and electrocardiographic values such as P-wave and QTc dispersion which were increased.

Thus from the above, we see a probable correlation between sleep deprivation leading to obesity and QT and QTc interval.(4) Although there is evidence of changes in QT interval during night, there are very few data examining the physiological effects of sleep deprivation and QT interval.(5)

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AIM: To study the relationship between sleep duration and QT interval in obese and normal weight medical students.

OBJECTIVES:

1. To assess sleep deprivation in medical students.
2. To measure QT interval and QTc in obese and normal weight medical students.
3. To correlate these QT interval and QTc values with sleep deprivation and obesity

MATERIALS AND METHODS: Ethical clearance and informed consent was obtained from all the subjects before carrying out the research. This was Cross sectional study with sample size of 30 obese and 30 normal weight individuals.

Based on inclusion criteria individuals with sleep duration of 2-8 hours, aged 18-25 yr. were selected from the study group (i.e. undergraduate and post graduate students of Sri Manakula Vinayagar Medical College and Hospital, Puducherry) using a questionnaire and they were classified as GROUP A (with sleep duration of 2-4 hrs.), GROUP B (with sleep duration of 4-6 hrs.) and GROUP C (with sleep duration of 6-8 hrs.). Individuals with qualitative sleep disturbances & sleep disorders, cardiac disease, alcohol, smoking/drug intake, having Diabetes mellitus, Hyperthyroidism & Renal disease were excluded from study.

Body mass index (BMI) was calculated and the subjects were categorized as obese and normal weight based on "The International classification of underweight, overweight and obesity" according to their BMI. Based on this classification, those subjects with BMI $\geq$ 30 kg/m^2 were grouped as obese and those with BMI $\geq$18.5 kg/m^2 $\leq$24.99 kg/m^2 as normal weight. Using simple random sampling, 30 obese and 30 normal weight individuals were selected from the above population (with a minimum of 5 in each group). A written consent was obtained from these 60 subjects. Then, electrocardiogram was recorded in each of these subjects and thereby QT interval was calculated in each individual and it was corrected to QTc by Bazett's formula.

BMI was measured, blood pressure & ECG were recorded as explained. For the assessment of obesity, height and weight measurements were taken on each subject using Quetelet Index BMI were calculated for each subject using BMI=Weight/Height (m)^2.

Height and Weight was measured with subjects in light clothes and without shoes using standard apparatus & weight was measured on a weighing machine. A measuring tape was fixed to the wall and the subject was made to stand with heels, buttocks, shoulders and occiput touching the vertical tape. The head was held erect with the external auditory meatus and the lower border of the orbit in one horizontal plane.

Initially subjects were asked to rest for 15 min. Then, Blood pressure was measured in the right arm of the seated subjects with a sphygmomanometer, using the auscultatory method and people with blood pressure $\geq$130 mm of Hg systolic or $\geq$85 mm Hg diastolic were excluded.

Electrocardiogram(ECG) was recorded using a standard 12 lead conventional ECG lead. Frontal plane leads consists of standard limb leads I, II, III and aVR, aVL and aVF & the horizontal plane chest leads consists of leads V_1 to V_6.

The bipolar standard leads I, II and III are placed on the right arm, left arm and left leg according to Einthoven's basis & the chest leads record electrical activity from six chest leads V_1 to V_6 placed at different places on the chest.

Electrocardiograms were recorded and calibrated on thermosensitive paper at a speed of 25 mm/s on a graph paper as small squares 1mm sq. measuring 0.04s. The horizontal axis and the vertical axis represents time in seconds (s) and amplitude in millivolt (mv).The normal electrocardiographic complexes include P wave, QRS complex, R wave and T wave. The QT interval is measured from the earliest onset of the QRS complex to the terminal portion of the T wave where it meets the baseline. QT interval was measured by computerized measurements from limb lead II.[6] RR interval is the interval between an R wave and the next R wave. The RR interval from the preceding cardiac cycle is measured from the peaks of the R waves to correct the QT interval for heart rate (QTc).QT intervals were corrected with Bazett's formula.[7]

QTc = QT/R-R$^{1/2}$, which was also done by the computer.

OBSERVATIONS AND RESULTS: This is a cross sectional study ECG was recorded on 60 subjects who were randomly selected and divided into obese and normal weight based on BMI. They were grouped based on their sleep duration into 3 groups:-

Group A- 2-4 hrs of sleep (severe sleep deprivation).
Group B- 4-6 hrs of sleep (moderate sleep deprivation).
Group C- 6-8 hrs of sleep (mild sleep deprivation).

QT interval and QTc interval values measured by standardised ECG machine were tabulated. The mean and standard deviation were calculated for each group. By using 2 tailed t-test for equality of means, significance were estimated for each group. The intergroup relations were estimated using Dunnett T3 and significance was established and tabulated. They were quantified based on European regulatory guidelines to stratify baseline QTc prolongation (ms) in men:

Normal QTc prolongation $\leq$ 430ms, Borderline - 431-450ms & Abnormal QTc prolongation $\geq$451ms.[8,9]

		Number of subjects	Mean ± Standard Deviation	Significance (2-tailed)
Group A 2-4 hrs.	Normal weight	10	363±25.1	>0.05**
	Obese	8	374.4±31.6	>0.05**
Group B 4-6 hrs.	Normal weight	12	338.6±31.5	>0.05**
	Obese	11	343.9±40	>0.05**

Group C 6-8hrs.	Normal weight	8	354.5±30.3	>0.05**
	Obese	11	341.7±19.6	>0.05**

Table 1: Comparison of QT interval with sleep duration in normal weight and Obese subjects

(Significant <0.05) * (Not Significant >0.05) **

The table 1 shows the QT interval mean and standard deviation of obese and normal weight individuals in three groups. We observe that the mean of QT interval in severely sleep deprived individual Group A is slightly increased compared to that in Group B or C even though they are normal weight. But, all the QT intervals are within the normal QTc in men i.e. ≤430ms as per European regulatory guidelines. Secondly we also observe that obese subjects have slightly longer QT duration than normal weight in all three groups but statistically not significant.

		Normal weight	Obese
Group A (2-4hrs)	Group B (4-6hrs)	>0.05**	>0.05**
	Group C (6-8hrs)	>0.05**	>0.05**
Group B (4-6hrs)	Group A (2-4hrs)	>0.05**	>0.05**
	Group C (6-8 hrs)	>0.05**	>0.05**
Group C (6-8hrs)	Group A (2-4hrs)	>0.05**	>0.05**
	Group B (4-6hrs)	>0.05**	>0.05**

Table 2: P value of QT interval in between groups

(Significant <0.05) * (Not Significant >0.05) **

The table 2 shows that the intergroup correlation QT interval between sleep duration, normal weight and obesity is statistically insignificant.

		Number of subjects	Mean ± Standard Deviation	Significance (2-tailed)
Group A 2-4 hrs.	Normal weight	10	404±21.0	<0.05*
	Obese	8	431±26.1	<0.05*
Group B 4-6 hrs.	Normal weight	12	365±37.5	<0.05*
	Obese	11	400±24.3	<0.05*
Group C 6-8hrs.	Normal weight	8	382±31.5	>0.05**
	Obese	11	392±26.7	>0.05**

Table 3: Comparison of QTc interval with sleep duration in normal weight and Obese subjects

(Significant <0.05) * (Not Significant >0.05) **

Table 3 we observe that QTc value is more in obese individuals compared to normal weight and is significant for moderate & severe sleep deprivation. But in severely sleep deprived individuals QTc duration is 431±26.1 which contributes to borderline QTc prolongation.

		Normal weight P value	Obese P value
Group A (2-4hrs)	Group B (4-6hrs)	<0.05*	>0.05**
	Group C (6-8hrs)	>0.05**	<0.05*
Group B (4-6hrs)	Group A (2-4hrs)	<0.05*	>0.05**
	Group C (6-8hrs)	>0.05**	>0.05**
Group C (6-8hrs)	Group A (2-4hrs)	>0.05**	<0.05*
	Group B (4-6hrs)	>0.05**	>0.05**

Table 4: P value of QTc intervals in between groups

(Significant <0.05) * (Not Significant >0.05) **

Table 4 shows intergroup relations and their P value. Comparison of QTc of Group A with Group C QTc is statistically significant in obese which implies sleep duration is important contributor QTc prolongation but not with Gp A & Gp B. similarly observed with Gp C & Gp A in normal weight individuals. Hence, this shows that sleep deprivation is an added risk factor for QTc prolongation in obese & normal weight subjects. Greater sleep deprivation it affects QTc prolongation proportionately.

DISCUSSION: The impact of sleep on arrythmogenesis has been recognized widely. Autonomic nervous system seems to play a key role in this complex and poorly defined interaction. Surges in cardiac muscle sympathetic nerve activity which are part of physiology of rapid eye movement (REM) sleep contribute to nocturnal arrhythmias and heightened parasympathetic tone in non-REM sleep has also been implicated in tachyarrhythmias and bradyarrhythmias. Thus sleep deprivation which affects phases of REM and NREM sleep indirectly does affect heart rate and QT intervals.[5]

Obesity group showed a near inverse linear relationship between weight and reported sleep time. The relationship between obesity and insufficient sleep has only emerged in the past 5 yrs. In a pioneering study by Van Cauter and colleagues it was found that sleep restricted to only 4 hrs per night for 1 week led to endocrine and metabolic changes associated with diabetes and weight gain in young healthy men and these effects were reversible with normal sleep time.

Insufficient sleep could be leading to a cascade of disorders. It is of particular interest now to determine the mechanisms by which acute or chronic sleep loss alters this complex metabolic machinery. While insufficient sleep has often been associated with elderly population, the increasing demands and lifestyles of modern society have imposed restricted sleep on our youth on a trajectory towards obesity

and the metabolic syndrome which could be altered if sleep loss is playing a role in this epidemic.

There are also neural interconnections linking sleep and metabolic homeostasis. A lack of sleep may perturb the homeostatic co-ordination of these pathways that trigger energy conservation. Increase in leptin levels in individuals depressed their appetite but enhanced their consolidated sleep and leptin deficient animals exhibited increased sleep fragmentation and periods of micro-sleep during active period.[10]

Sleep restriction is more common in modern society that may play a role in rapid increase in the prevalence of diabetes and obesity. Sleep plays a role in the 24 hour pattern of glucose concentrations. During sleep which is a fasting glucose level, glucose remains fairly constant. During early part of nocturnal sleep, glucose increases by an average of 20% but returned to baseline levels in morning. In summary, glucose utilization appears lowest during non-REM sleep and highest during wake with intermediate levels during REM sleep. After sleep deprivation, plasma glucose levels were higher in mid-morning to late afternoon despite similar insulin levels and decreased daytime insulin action, suggesting decreased daytime insulin action. This is due to absence of slow wave sleep and growth hormone secretion in the beginning of the night.[8,11]

In partial sleep deprivation conditions, the rate of glucose clearance was approximately 40% lower and acute insulin response to glucose (AIR_G) was 30% lower compared to sleep extension condition may be associated with the hypothalamic-pituitary axis. During sleep loss, there is increase in growth hormone in night time and increase in evening cortisol levels. Increase in growth hormone levels reduced muscular glucose uptake. Increase in cortisol levels reduced insulin sensitivity on the following morning. Decreased AIR_G may be attributed to changes in sympatho-vagal balance that indicated increased sympathetic nervous activity which inhibits pancreatic function.[11]

Appetite is regulated by two opposing sets of neuronal circuitry-appetite stimulating and inhibiting in arcuate nucleus of hypothalamus. Leptin secreted by adipose tissue decreased appetite and promotes feeling of satiety. Ghrelin secreted by stomach stimulates appetite. Mean leptin levels were 18% lower and, mean ghrelin levels were 28% higher in partial sleep restriction. Hunger was 24% higher and appetite was increased. Thus ghrelin is more increased with acute short time sleep and leptin is increased with chronic sleep loss plays important role in increasing appetite and promoting obesity.[11] Reduced leptin increased propensity to snacks contributing obesity & orexin neurons in hypothalamus regulate arousal, waking and feeding behaviour.[12] A number of studies have observed an association between sleep duration and body mass index(BMI). Short sleep duration have been associated with increased prevalence of obesity as seen in Wisconsin sleep cohort study which observed lowest BMI at an average bedtime of 7.7hrs per night. Analysis of data from National Health and Nutrition Examination survey observed that every hour increase in sleep duration was associated with a 50% reduction in risk of obesity.[11]

Prolongation of heart rate corrected QT (QTc) interval increased the risk of sudden cardiac death(SCD) which is independent of other known risk factors. Hence QTc prolongation should be considered an independent predictor of SCD in adult patients. The European regulatory guidelines to stratify baseline QTc prolongation into gender specific groups in men:

QTc prolongation (ms): Normal 430ms, Borderline 431-450ms, Abnormal >450 ms.

Thus the length of QTc is just a marker for severity of subclinical cardiac disease as prolonged QTc is proarrhythmic and contributes to SCD.[9]

The QT interval is affected by many things –heart rate, autonomic nervous tone, sympathomimetics, electrolytes especially calcium, drugs, age, (male) sex, hypercholesterolemia, fibrinogen, BMI and even sleep. QT measurement can help to recognize life threatening problems before they happen. Of these BMI and sleep deprivation have a strong association with QT and QTc intervals.[4] Ozer O et al clearly demonstrated that even one night of sleep deprivation significantly increased QT max, QTd & cQTd in healthy young adults despite remaining within normal limits.[6]

The present study examined the effects of sleep duration on QT and QTc intervals in normal weight and obese subjects. This present study also supports the hypothesis that sleep deprivation propentiates obesity and increases QTc intervals. The influence of imbalanced sympathetic activity on heterogeneity of repolarization in the myocardium resulting in QT interval prolongation and increase in incidence of ventricular arrhythmias which is also responsible for increased risk of sudden cardiac death. In healthy humans physical and psychological stresses induce ventricular arrhythmias and sympathetic imbalance which manifests as prolongation of QTc. This increases the risk of sudden cardiac deaths in subjects of coronary heart disease although they had been healthy at baseline. The association with total mortality might demonstrate that autonomic imbalance is an indicator of poor health in general and sleep deprivation aggravates this autonomic balance. Thus, QTc prolongation is predictive of mortality and is derived from a simple non-invasive diagnostic method.

SUGGESTIONS: Further studies on "Effects of different stages of REM and NREM in men and women influenced by sex" is recommended. Also, measurement of insulin, leptin, ghrelin and orexins in association with sleep deprivation may contribute to further explaining of glucose-homeostatic mechanisms that are altered in sleep deprivation.

CONCLUSION: This was a cross- sectional study conducted in medical students who are acutely sleep deprived to study the effects on QTc interval in Obese & non- Obese students. It was found that severe sleep deprivation (2-4 hr) is a compounding factor with obesity in pathologically prolonging QTc interval to 431±32 ms (Borderline 431-450 ms). In all

other groups the QTc interval was more in obese than normal weight individuals. Thus our study are in agreement with other studies whish have shown a strong association between sleep deprivation, obesity & QTc prolongation. Hence severe sleep deprivation is a potential risk factor which propentiates obesity & prolongs QTc interval which is a co- morbid condition for cardiovascular diseases & death.

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