

Obesity and circadian system

Abstract

Obesity, an epidemic health concern that related with high levels of worldwide morbidity and mortality levels, showed marked increase to last years. Studies focus on the factors leading such rise to make effective and long lasting interventions intended for obesity. Decreased nightly sleep duration, compared to the past century, is considered as one of these factors and studies emphasize the relation between changing sleep patterns and obesity and accompanying health disorders as impaired glucose metabolism, cardiovascular diseases, type 2 diabetes mellitus, hypertension those also have high prevalences. This literature review is prepared with the articles those taken from Pubmed and Science Direct especially were published after 2010 to comply with the aim of demonstrating the association of sleep with obesity and mentioned health disorders, basic mechanisms underlying this association and factors affecting the functioning of these mechanism.

Keywords: sleep, sleep loss, obesity, obesity comorbidities, circadian system, hormones, metabolism, sleep induced changes

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Abbreviations: NPY, neuropeptide y; BMI, body mass index; SWS, slow wave sleep; NREM, non-rapid eye movement; RVLM, rostral ventrolateral medulla; TSH, thyroid stimulating hormone

Introduction

Obesity, a chronic inflammatory state, is one of the most significant health problem that characterized by abnormal fat accumulation in the body and increasing ratio among fatty and lean body masses thereby rising body mass index (BMI). According to world health organization (WHO) statistics in 2014, 1.9 billion adults were overweight (BMI > 25 kg/m²) and 600 millions of them were obese (BMI > 30 kg/m²). Obesity can be handled as an epidemic and life threatening issue with its folding rates from the past to the present and accompanied health disorders such as type 2 diabetes mellitus, cancer, cardiovascular diseases, atherosclerosis, hypertension, hypertriglyceridemia etc. This issue with its comorbidities became a global concern due to its doubling prevalence rates between 1980 and 2014 independent from the welfare or development level of country or age, sex, and race.¹ In the same way, TURDEP statistics in 2010 represents the increased percentages of obese and overweight individuals compared to 1997 and 1998 in Turkey.² Changing life styles and consumption patterns, reasoned from industrialization, leads increasing rates of obesity. Along with industrialization, physical works has reduced whereas the time people spent on sitting works has increased. This change in working style leads people to have more sedentary life routines that can be illustrated as one of the main reason of obesity. In addition to alterations on working styles, extension of working times also affect the diet and life patterns. Increasing working hours reduce the chance for consumption of home made foods and cause people to consume packaged, ready to consume food that found to be responsible from increasing daily energy intake and rising obesity levels related with abdominal fat accumulation.³ Besides, increasing mass media marketing blaze the trail to consumption of high energy dense food having poor nutritional values that especially responsible for childhood obesity⁴ because of child's vulnerability to marketing.⁵

Increasing worldwide focus on obesity is reasoned from its rising and life threatening comorbidities rather than obesity itself. So,

any issue on the basis of metabolism, hormones or nervous system which have considered as being precursor or risk factor of obesity and its comorbidities have began to studied to detect causes and thereby making well functioning interventions to prevent such health problems. Herein, another crucial and recently quite under investigated issue about development of obesity is changing sleep patterns that can be seen among all age groups as independent from, sex, race and socioeconomic status.

The relation between sleep and obesity and accompanied health disorders has become one of the recently most studied issue owing to changing sleep patterns along with the time has occurred simultaneous with rising prevalence of obesity.⁶ Statistics revealed 6.8 hours of nightly sleep for Western Societies as lower than past centuries.⁷ In behavioural risk factor surveillance system study conducted in 12 state of USA, approximately 35% of adults have been reported as sleep less than 7 hours without any difference related with gender.⁸ In addition, increasing percentage of short sleepers (less than 7 hours) have been reported among American adolescents.⁹ Sleep has been investigated within its several components, such as sleep durations, sleep patterns (timing, regularity), sleep architecture and sleep quality, those revealing metabolic, hormonal and neural effects as a result of human and animal experiments. Because of strong relationship being detected between obesity and sleep variables with the contribution of many conducted correlational or experimental researches, the need for adding sleep intervention to obesity prevention programs has been defended.¹⁰ Decreased sleep hours from the past to the century¹¹ and changing sleep patterns in terms of time and regularity have led alterations on energy intake¹² changing food patterns¹³⁻¹⁵ and meal timing¹⁶ and also alterations on bodily circadian mechanism those have found to be precursor of obesity related hormonal¹⁷ and metabolic changes,^{18,11} unhealthy eating behaviours¹⁹ and thereby increase in obesity indicators²⁰ both for adults⁶ and children.^{14,15} Studies also revealed strong relationship between changes in such mentioned sleep variables and rising levels of chronic diseases as diabetes mellitus, cardiovascular diseases and hypertension.^{7,21} The purpose of this review to agglomerate evidences support the role of sleep variables and circadian clock in the development of obesity and metabolic diseases and lighten intermediary factors on mentioned relationships to inspire government in the development of well functioning health

policies on such interceptible area for prevention and treatment of obesity and metabolic diseases those take a big cost from national health budget.

Discussion

Sleep duration and obesity

It has been indicated that nightly sleep durations have been declined historically from childhood ages to adolescence although it varies among sex, race and socioeconomic status Keyes et al.⁹ One of the recent research on sleep durations has revealed that the average nightly sleep duration has reduced by 1.5 hours compared to past century.¹¹ Such change in sleep durations over the centuries has been thought to leading obesity by several aspects such as increasing energy intake,¹² changing food patterns,^{13,14} increasing choice of sugary and more energy dense foods and beverages,¹⁵ changes in meal timing,¹⁶ and changes in hormones,¹⁷ and metabolism.¹⁸

Most of the studies has detected the U-shaped relationship between sleep duration and basic obesity measures like waist-hip circumferences, body mass index, body weight and body fat deposition that means both short and long durations of nightly sleep leads rising obesity levels from the aspects of measured obesity indicators. A recently conducted experiment among childrens aged from 8 to 10 revealed significant relation in terms of increased BMI and body fat deposition both for short and long time sleepers and found increasing waist circumferences only related with short sleep durations as independent from caloric intake and physical activity level,¹⁴ while another study examining adults found increase in BMI scores related with both short and long sleep durations only for female participants and found L shaped relation for males meaning only short sleep durations have been found as related with rising BMI scores.⁶ Increase in caloric intake especially those from fat, increasing portion sizes, and late time nightly eatings and increasing total number of meals have been found as significantly correlated with body weight increase during sleep restriction days particularly among females and African American people¹⁶ in contrast to NHANES being conducted between 2005 and 2010 among American people has found increase on energy intake after 20:00 hours despite of stable 24 hours calories amount across short and long sleepers.¹⁹ The change in dietary patterns is seen as another touchstone mediating the obesity and sleep relationship. A study completed by examining the long term (200 days) sleep and related diet habits of Danish school children demonstrated every 15 minutes sleep restriction as responsible from 0.3 increase on percentage of sugar sweetened beverages and 1.2 increase on percentage of additional sugar to diet among the total daily caloric intake in addition to indication of increasing 134 calories in daily caloric intake during short sleep period compared to long sleep period.¹⁵

Sleep patterns and obesity

The times people spent on screening, social media and working affect not only sleep durations but also its regularity and timing. In a study, sleep patterns determined by sleep times on weekend and weekdays have been associated with waist and hip circumferences and BMI for children and adolescents.²⁰ In the study revealing variability in sleep durations as highly correlated with higher BMI scores and low self reported physical activity status for both sexes, the positive association between sleep timing variability (sleep regularity) and obesity related health problems such as diabetes and coronary heart diseases also have been mentioned for both male and female adults.²¹

Late meal times presented as one of the peacemakers in the relation of sleep timing and obesity. Late sleep times probably leads delay on meal times proposed as related with weight loss effectiveness.²² In a study that aimed to look on relation between elevated BMI and sleep timing, late sleepers had demonstrate tendency toward cumulative caloric intake as taking most of the calories at dinner and after 8 pm that resulted in consumption of 248 more calories in comparison with early sleepers. Besides, sleep timing induced food patterns among late sleepers as higher fast food and full energy beverages consumption accompanied by lower fruits and vegetables consumptions have been related with rising obesity levels.²³ Late sleep times also affect breakfast frequencies²⁴ as one of the predictor of metabolic syndrome²⁵ and lead increase caloric intake in nighthours which have been proved as disrupt the circadian clock as another obesity pathway that will be mentioned later.

Sleep architecture and obesity

The American Academy of Sleep divides sleep into four categories as three stages of non-rapid eye movement (NREM) sleep namely N1, N2, N3 also called as slow wave sleep (SWS) and rapid eye movement (REM) sleep. In recent years increasing attention have started through sleep architecture due to several studies that found sleep stages, particularly N3 sleep and REM sleep as associated with body weight,²⁶ glucose metabolism,²⁷ changing brain signals, metabolic rate and hunger.²⁸ In a study that found N3 sleep duration and its percentage in total sleep duration as important in terms of insulin secretion, increasing parasympathetic activity in N3 sleep have been found related with improving insulin secretions in obese and overweight adolescents while the N2 sleep negatively correlated with insulin sensitivity.²⁹ In one of the previous research that has revealed decreased percentage of REM and stage 2 sleep in spite of increased SWS percentage in total sleep duration after sleep restriction, stage 2 sleep has been found as positively related with increased RMR and inversely related with desire for salty and sweet foods and REM sleep showed inverse associations with hunger rates, fat and carbohydrate intake.²⁸ In a study revealing the effect of REM sleep on energy and hunger mechanism, REM sleep deprived rates have demonstrated decreased weight in spite of upregulation of neuropeptide Y (NPY) and downregulation of proopiomelanocortin (POMC) in hypothalamic arc as favoring hyperphagia.³⁰ Tasali et al.²⁷ have reported decreased glucose tolerance and increased risk of type 2 diabetes mellitus with stable insulin secretion in spite of lowered insulin sensitivity as a result of experimental SWS suppression without any interference with total sleep time.²⁷

Sleep quality and obesity

Decreasing sleep quality is another aspect of view which have been found as correlated with increasing obesity measures like bodily fat depositions, weight and waist-hip ratio²⁰ and impaired glucose homeostasis in terms of its mediation in sleep and obesity affair. One of the laboratory study that performed as exposing rats to sleep fragmentation by disturbing the wake-sleep cycles, thereby corrected sleep quality, in addition to sleep restriction (4 hour sleep per night for eight nights), found weight and metabolic responses being given to sleep fragmentations similar to those obtained by the effect of sleep restriction. To data obtained from aforementioned study, the blood insulin were lower while the glucose was higher as response to intravenous glucose tolerance test in both groups, compared to the values reported before the experiment. In addition to rising plasma glucose and decreasing plasma insulin levels displaying the impact

of sleep quality on the development of hyperglycemia, decreasing corticosterone levels and similar body weight change have been recorded with no observed change in energy intake as a result of sleep restriction and sleep fragmentation³¹ in contrast to the Wang et al.³² those had explained the relation between decreasing sleep quality and body weight from the aspect of increasing energy intake as an obesogenic behaviour reasoned from leptin resistance and also found low sleep quality as responsible for growing visceral and subcutaneous bodily fat depots³². Another study tested the impact of sleep duration and sleep quality on glucose homeostasis and glucose tolerance had found 1 hour increase in sleep quality related with improvement on both peripheral and hepatic insulin sensitivity and one percent decline in insulin secretion.³³

Circadian rhythm and obesity

Circadian clock: The circadian rhythm has become another important issue as an obesity pathway because of its effects on energy balance and glucose metabolism being proved by several researches. The circadian system is an endogenous 24hours repetitive mechanism work on regulating bodily hormonal, neural and metabolic activities within the external cues such as daytime light exposure and food availability as most important ones to catch optimal physical homeostasis level for survival. In mammals there present two main administrator of circadian clock namely, the Master Clock, located in subrachiasmatic nucleus in front of the hypothalamus, ensure homeostasis between environmental cues and physiology and the Slave clock, the name given to all peripheral circadian oscillators, work through the neural and hormonal informations from Master clock. Every hormonal and metabolic activities have their own diurnal circadian rhythm as basically depending on the signals received from Master Clock. Imbalance on external cues especially the light-dark cycle regulated by the light received from retino-hypothalamic tract, leads circadian disruption and misalignment on secretion of bodily hormones and enzymes which reveals serious metabolic consequences.

There present a study revealed the increasing BMI levels reasoned from long term increase in cortisol levels as a precursor of metabolic syndrome, obtained from hair sample of shiftworker subjects whose circadian timing has been disrupted due to the mismatch between external light and its normal bodily cycle.³⁴ Increasing energy intake caused by misalignment on circadian timing caused by sleep restriction is another supposed peacemaker of obesity and circadian disruption.³⁵ A recent study that has eliminated the effect of sleep restriction by comparing two groups those exposed to changing sleep times and those having stable sleep times in addition to sleep restriction (5hours a day) on both groups in 8 consecutive days after 3 days of ten hour sleep to examine the metabolic consequences of circadian disruption have found decreasing insulin sensitivity and increasing inflammation as up to 2 times higher compared to start conditions for male participants in circadian misaligned group³⁶. Fluxional metabolic rates over circadian disruption is another appointed intermediary conduce toward obesity. In the study that subjects underwent sleep restriction for 3 weeks and circadian disruption by changing the initial optimal sleep hours at the baseline, declines in the resting metabolic rates and increase in the postprandial plasma glucose levels due to loss of pancreatic insulin secretion have been observed.³⁷ In another study, the circadian rhythm measured by wrist temperature, has been found as valid predictor of future weight loss in response to diet intervention. To same study, low fragmentations and high amplitude of circadian rhythm was related with higher weight loss ensured by diet intervention.³⁸

As mentioned before, food working through Gut Clock³⁹ which is proposed as the other controller of satiety and hunger except Master clock in humans and also regulating the secretory peak periods of digestive system³⁵ is another crucial external cue even can take place of light on the basis of regulation of Master clock to influence Slave clock thus peripheral tissue and organ functionings. By this view changing meal times appear as another causative agent of obesity due to imbalance between internal and external rhythm. In a study examine the effect of light at night on body weight, mice those exposed to dim or bright light during nighthours have been found as have increased body weight and impaired glucose tolerance compared to the those under the normal, 12hours light and 12hours dark cycle although their daily caloric intake and physical activity levels did not differ in total. In addition, the observed difference among the meal timing of bright and dim light exposed mice (more food consumed during nighthours) compared the normal light cycle housing group proved the influence of meal timing disruption on weight gain.⁴⁰ As cited in Verga et al.³⁵ the adipose tissue also has its own diurnal circadian rhythm also regulates secretions from adipocytes. Lipoprotein lipase, the enzyme responsible from fat digestion, reaches fever pitch after meal intake and if mismatch occurs between fat taken through the meal and lipoprotein lipase levels, due to the misaligned circadian clock of adipose tissue fat components are carried out and reveal toxic effect to other body structures particularly muscle and liver. So, the food consumption during the peak plasma levels of LPL which is also coincide with lighthours has been suggested.³⁵

Molecular circadian clock: In addition to circadian rhythm regulated by external stimuli both central and peripheral clocks has diurnal rhythmicity controlled by 8 basic proteins, namely, CLOCK (circadian locomotor output cycle kaput), BMAL1 (brain and muscle ARNT like protein 1), two CRY (cryptochrome 1,2), three PER (period 1,2,3) and REV-ERB, acting as negative or positive translational/transcriptional feedback loops to maintain the circadian control of gene expressions. While the primary loop, BMAL1-CLOCK complex, act as positive loop by stimulating the transcription of PER and CRY, both REV-ERB and PER-CRY complex work as negative loop with their inhibitory actions.^{41,42} Although the molecular circadian clock has its own rhythmicity regulated via the interaction of mentioned translational/transcriptional feedback loops also external cues like sleep and food availability can leads alterations on gene expressions. Previous human and murine studies have emphasized the impact of sleep on occurrence of unfavorable metabolic alterations reasoned by changing genetic expression of circadian clock. Completed researches on mice those mutated to disruption or removal of clock gene components illustrates the mediating role of circadian system on metabolic changes related with obesity. The pancreas related BMAL1 and CLOCK mutant mice have been reported as vulnerable to diabetes mellitus with reduced insulin secretion, impaired glucose tolerance and deformity of pancreatic beta cells accompanied by functional defects.⁴³ Furthermore the pancreas specific BMAL1 knockout mice study has illustrated the role of BMAL1 on normal insulin secretion via ensuring normal beta cell functioning over preveing against circadian disruption and its protective role against accumulation of reactive oxygen species that thought as responsible from diabetes mellitus due to reduced glucose stimulated insulin secretion.⁴⁴ Increasing CRY activity has been found beneficial for type 2 diabetes mellitus with enhancing fasting glucose levels and insulin sensitivity via its modulating role on transcriptional regulators of hepatic gluconeogenesis.⁴⁵ In another study, that indicates the effect of clock proteins on regulation of circadian rhythm and metabolism, REV-

ERB knockout mice have demonstrated altered circadian rhythm and reduced output on lipid metabolism.⁴⁶ Besides, skeletal muscle specific BMAL1 knockout mice show impaired muscle glucose metabolism characterized by disrupted glucose stimulated insulin intake and reduced levels of insulin dependent glucose transporters.⁴⁷

Changing energy expenditure and feeding times are thought to be possible paths in terms of mediation between metabolic changes related with obesity and genes based circadian disruption. In a study examining the adipose tissue specific BMAL1 deprivation, the clock debarred mice became corpulent because of changing food intake times and increasing feeding induced by rising concentrations of polyunsaturated fatty acids (PUFA) secreted from adipocytes that regulate feeding by working as appetite regulator in hypothalamic neurons.⁴⁸ In one of the recent study on circadian rhythm related gene in which the 721 subjects have CRY2 gene variants and 722 have MTNR1B gene variants were compared in terms of energy expenditure measurements, representing metabolic rate, and effect of preferred macronutrient pattern on those measures has been examined via applying two year diet intervention, the CRY2 and MTNR1B genes have been found related with changes in energy expenditure measurements as response to two year diet intervention and dietary fat intake has found

as indicator of the effect of those circadian rhythm related genes on detected changes on energy expenditure.⁴⁹ Additionally, recent studies also have emphasized the circadian rhythmicity of adipose related gene expressions as another potential link between obesity and circadian mechanism that has been found as inducing several metabolic syndrome components.⁵⁰ By Gimble et al.⁵¹ the glucocorticoid induced leucine zipper, the gene expressed oscillations in terms of circadian biology of adipose tissue, has been reviewed as one of the potential paths between obesity and circadian contrivance because of its crucial roles on adipogenesis and osteogenesis.⁵¹ Hormonal changes also can be given as another incontrovertible obesity inducing manner resulted by suppressed expressions of circadian rhythm related genes. In a study, the human participants exposed to sleep deprivation for one night displayed the increase in amplitude of melatonin rhythm because of the suppression of BMAL1 expression⁵² which have been commented as related with glucose metabolism in turn.⁴¹ Furthermore BMAL1 knockout mice have been shown as prone to obesity with reduced insulin sensitivity due to disrupted diurnal rhythm of insulin action.⁵³ In the light of all these reviewed findings, the circadian mechanism seems to be one of the vital impressive factors on obesity originating from sleep affairs (Table 1).

Table 1 Represent sleep deprivation induced circadian disruption and its obesity related outcomes

References	Sample number	Aim of the study	Results
Leproult et al. ³⁶	26 healthy adults	Determining adverse metabolic consequences of sleep deprivation induced circadian misalignment	Waned insulin sensitivity after sleep restriction both in circadian aligned and misaligned groups Increased inflammation and decreased insulin sensitivity in circadian misaligned males as independent from sleep deprivation.
Ackerman et al. ⁵²	12 young males	Determining effects of sleep deprivation on circadian mechanism	Sleep loss induced BMAL1 suppression Alterations on melatonin secretion rhythmicity and core peripheral circadian clock oscillators
Buxton et al. ³⁷	11 young people 10 older people	Determining the relationship between sleep loss combined circadian disruption and impaired glucose metabolism and obesity.	Decreased resting metabolic rates Decreased insulin secretion
Marcheva et al. ⁴³	33 shift workers 89 day workers	Determining the relationship between metabolic syndrome and circadian disruption	Increased cortisol and BMI levels

Sleep and hormones

There present several studies have proved the reciprocal impact of sleep and hormones on each other. While the circadian rhythms and sleep variables like sleep quality and sleep cycles have impact on diurnal hormone regulation, hormones also can affect circadian rhythmicity and thereby sleep variables by working as internal cues regulating circadian system. To support, in a previous meta analysis orexin has been reported as sleep wake cycle regulators⁵⁴ in addition to its known role on appetite mechanism. As previously discussed each hormone has its own daily rhythmicity and fluctuates with the influence of light and dark cycle and feeding behaviour as most important circadian system regulators. Kim et al.⁵⁵ has reported insulin resistance, obesity, hormonal and metabolic imbalance as considerable consequences of impaired hormonal rhythms induced by sleep impairment and sleep disturbances and has reviewed daily fluctuation of sleep related hormones, namely, human growth hormone, TSH, leptin, ghrelin, melatonin and insulin as increasing level of GH during sleep, high melatonin levels in night, maximum level of TSH during middle of night and also maximum level of cortisol in middle of night with its peak level in the morning.⁵⁵

Melatonin is a hormone secreted by pineal gland in response to darkness to prepare body for sleep and regulate waking and sleeping cycles.⁵⁶ In a previous study, the daily intraperitoneal melatonin injection for a week to 96 hours sleep deprived rats has been found as protective against memory impairment and oxidative stress in the brain, induced by sleep deprivation, on the occasion of role of melatonin on decreasing lipid and DNA peroxidation markers and also decreasing neural cell death ensured by its antioxidant and anti-inflammatory effects on body.⁵⁷ In another study, sleep restricted mice (4 hour sleep a day for eight experimental days) those demonstrate decreased glucose tolerance and HDL cholesterol levels despite of increased insulin resistance, total cholesterol and triglycerides level have responded positively to intraperitoneal melatonin and piromelatin, a melatonin agonist discarding as beneficial on sleep maintenance and emotional disorders, in form of improved such metabolic dysfunctioning symptoms.⁵⁸ Melatonin also has effects on carbohydrate metabolism via stimulating pancreatic glucagon secretion in addition to its inhibitory effect on insulin.⁵⁹ Besides, detection of negative correlation between BMI score and urinary 6-HMS, a melatonin metabolite, has proved the role of melatonin on weight maintenance in addition to its negative relation with degree of sleep disorders also revealed

by same study that conducted to examine the effect of melatonin supplementation on weight control among postmenopausal women.⁶⁰ Furthermore, in a study that reviewed melatonin to regulate glucose homeostasis via suppression of hepatic gluconeogenesis with activation of hypothalamic arc and enhance insulin resistance, nightly light exposure has been reported as impair glucose metabolism via repressed melatonin secretion that cause circadian disturbance.⁴¹ Due to the cited roles of melatonin on both sleep and weight maintenance, sleep curtailment in night conducting light exposure that display causative role on interruption of the nightly melatonin secretions give rise the potential role of melatonin on sleep loss induced obesity.

Human Growth Hormone secretions peak just after the sleep onset especially in NREM sleep. In a study, mice have been applicated growth hormone releasing hormone agonist showed beter performance in maze and thereby proves the research hypothesis that growth hormone therapy is beneficial in protection againt neurocognitive deficits leading by intermittent hypoxia as a cause of obstructive sleep apnea which is reported as related with suppression of growth hormone secretion during sleep.⁶¹ Additionally, in another previous study, growth hormone has diluted the detrimental effects of sleep deprivation on brain areas vulnerable to sleep disorders, especially hippocampus, with its role on prevising brain related cell proliferation.⁶² In another previous study, growth hormone deficient children have exhibited reduced sleep time accompanied with reduced sleep efficiency. Growth hormone therapy also reported as has impact on sleep architecture in the same study⁶³ as well as the influence of sleep stages on sleep related growth hormone secretion, such as deprivation on stage 3 which is also known as slow wave sleep, and stage 4 that lead supression of growth hormone peak during sleep.⁶⁴ In one of the study represented the effects of sleep on growth hormone secretion, participants display monophasic growth hormone oscillation in the normal sleep condition (8.5hours a day) while in the sleep curtailment condition, in the form of 4.5hours a day, biphasic oscillation of growth hormone secretion has been observed which extend the period of oscillation for 50minutes without any difference in total secreted amount compared to normal condition. Such change in nightly growth hormone secretion has been related with increased free fatty acid amount during sleep restriction.⁶⁵ It has been reviewed that growth hormone defends towards hypoglycemia by acting as counter regulatory hormone against the hepatic and peripheral effects of insulin during sleep, leading extended time of fasting, to keep blood glucose level stable or ensure minimal fall through the agency of such aforementioned proven effect of growth hormone on free fatty acid release.⁶⁶ On the strengths of highlighted direct metabolic effects of growth hormone and interrelation with sleep, this hormone attracts attention in terms of sleep and obesity relation.

Both human and animal studies, have reported alterations on thyroid functions as one of the endocrine change subsequent to sleep restriction. In a cross-over study conducted with 15 healthy normal weight men those underwent to 2 consequent night of sleep restriction and 2 normal sleep night respectively, increasing thyroxin (T4) and triiodothyronine (T3) levels accompanied with blunting nightly Tiroid Stimulating Hormone (TSH) have been reported in the condition of sleep restriction.⁶⁷ Likewise, increased peripheral activity of T4 and T3 and central hypothyroidism has been observed in sleep deprived wistar rats.⁶⁸ As a contrary to such studies put forth increasing thyrothropic axis activity, in a recent study 14days exposure to sleep restriction (4.5 hour a day) has resulted as decreased THS and T4 activity in females.⁶⁹

Although the thyroid function activity affected by sleep varies with sex and either the sleep restriction is acute or chronic,⁶⁷ sleep related alterations in thyrothropic axis activity has found associated with glucose metabolism. In a study comparing the type2 diabetic patients, and prediabetic patients, having impaired glucose tolerance, and healthy individuals in terms of thyroid hormones, increased levels of thyroid hormones has been observed in those with type 2 diabetes mellitus and impaired glucose tolerance. Increased insulin resistance has found as positively related with increased levels of thyroid hormones in the same set of experiment⁷⁰ as consistent with the finding that patients with hypothyroidism and subclinical hypothyroidism have displayed higher insulin resistance and decreased insulin stimulated glucose transport compared to euthyroid subjects.⁷¹ As well as, the decreasing insulin stimulated glucose transport and rising insulin resistance have been also observed among patients with hyperthyroidism.⁷² Such findings indicate the thyrothropic axis activity as potential pathological mechanism lies under alterations on glucose metabolism.

Cortisol is a steroid hormone secreted by adrenal glands in response to stressfull conditions, morning awakening and physical activity in exercise level.⁷³ This hormone has daily diurnal rhythm as rising in middle of night and reaching the peak level during morning awakening hours.⁵⁵ Like that occurs in other hormones, sleep curtailments and deteriorations disrupt the normal diurnal rhythm of cortisol that particularly results in elevated cortisol levels reasoned from increasing hypothalamic pituitary adrenal axis (HPA) activity that induced by stress. In a study subjects exposed to four days of 4.5hours sleep a day, cortisol levels that been expected to peak during awakening, has reached their maximum 2hours earlier in addition to 23 percent higher levels in the evening and early night.⁶⁵ As well as elevated evening and afternoon cortisol levels has been observed in participants subjected to sleep restriction⁷⁴ as consistent with the finding that higher serum cortisol levels obtained from those exposed to sleep disruption.⁷⁵ Such increasing levels of cortisol have detrimental effects as weight gain, impaired blood glucose levels, immune system supression, cardiovascular diseases and gastrointestinal problems⁷³ due to its crucial role on glucose metabolism and energy regulation. In a study that has detect elevated levels of cortisol in response to acute sleep deprivation whereas decreased levels as a result of chronic circadian misalignment, rising plasma levels of pro-inflammatory and anti-inflammatory proteins namely, tumor necrosis factor alpha (TNF- α), interleukin-10 (IL-10) and C-reactive protein (CRP) has been found as related with alterations on cortisol levels induced by sleep deprivation and circadian misalignment.⁷⁶ In the study examined the patients with type 2 diabetes mellitus, elevated cortisol levels has been discovered as related with hig fasting plasma glucose, high cholesterol levels and high prevalence of ischemic heart disease.⁷⁷ Elevated cortisol levels also has been reported as predictor of greater weight gain in hospitalized anorexic adolescents.⁷⁸ In addition to crucial impacts of cortisol levels on body and metabolism, it also affects the sleep architecture and sleep duration. High morning cortisol levels has been recorded as negatively correlated with both nightly sleep duration and slow-wave sleep whereas it has revealed positive association with stage 2 sleep⁷⁹ and also with stage 1 and REM sleep.⁸⁰ In another recent study, high morning cortisol levels has exhibited possitive correlation with insomnia symptoms in children.⁸¹ So, cortisol levels influence metabolism with the mediation of its role on both sleep duration and quality as well as its direct affects.

Recent researches has underlined adipokines, adipocyte derived

hormones that have roles on regulation of insulin resistance, inflammation⁸² and also appetite and energy balance regulation mechanism,⁶⁶ in terms of their sleep induced changes acting as matter for obesity and comorbid disorders. Alterations on adipokine secretions induced by sleep loss has been reported as create chronic sub-inflammatory state that leads impairment on glucose metabolism by causing insulin resistance and type 2 diabetes mellitus.⁸³ Hayes et al.⁸² has found sleep curtailment as associated with increase in both leptin and visfatin levels, adipokines reported as related with inflammation and insulin resistance those being accepted as among biomarkers of obesity. Besides, in the same study each one hour reduction in REM sleep also has been found related with respectively %15 and %31 increase in leptin and visfatin levels.

Sleep duration has also been found to modify the circulating concentrations of orexigenic and anorexic hormones that play central role in appetite and energy regulation mechanism. In a previous study elevated leptin and decreased ghrelin levels has been observed in the subjects those demonstrated high BMI levels as a result of less sleep habits.¹⁷ In another study elevated ghrelin levels among participants subjected to acute sleep restriction has been related with increase in caloric intake, especially from sweets, snacks and carbohydrates with any alteration on leptin levels.⁸⁴ Besides in the study that has compared obese and normal weighted adolescents in terms of changes in sleep loss induced metabolism-relevant hormones, orexin, leptin and ghrelin, and also BMI levels, among those sleep less than 8hours obese participants exhibit lower sleep times than normal weighted subjects and leptin, ghrelin and orexin levels that accompanied with increased nightly snack intake were higher in both obese and normal weighted subjects those sleep less than 8hours which is considered as short for the age group of studied subjects(10-15years).⁸⁵ Decrease in leptin and increase in ghrelin levels those lead increase in energy need and hunger respectively has been reported as a response of body to changing energy balance as elevated need for caloric intake that induced by increase in wake time due to sleep curtailment⁸⁶ in contrast to the finding that 8 day sleep restricted subjects have demonstrate increased caloric intake compared to normal sleepers without any alteration on ghrelin and leptin levels or energy expenditure rates caused by sleep curtailment.⁸⁶

In addition to those mentioned sleep related hormonal changes, both animal and human studies being completed in this field has suggested incontrovertible associations between sleep loss or impairments and problems with glucose metabolism. In a study it has been reported that healthy, normal weight participants had demonstrate reduction in glucose tolerance that caused by decrease in insulin sensitivity with elevated concentrations of C peptide those stated by elevated insulin and glucose peak response to breakfast accompanied with

blunted glucagon responses after 2 days of sleep restriction as 4hours per night compared to 2 nights of regular sleep to 8hours per night.⁸⁷ Another study that subjected healthy men and women to 5 week of sleep restriction in conjunction with circadian misalignment as 5hours of sleep per night with libitum food intake opportunity, has detected reduced intravenous and oral insulin sensitivity for both sexes as suggesting the detrimental effects of sleep impairments on glucose metabolism.⁸⁸ In the study that Barf and coworkers have investigated the effects of acute and chronic sleep disturbance and sleep restriction on glucose homeostasis in rats, subjects demonstrate reduced insulin and increased glucose responses to intravenous glucose tolerance test (IVGT) without any difference between sleep restriction or sleep disturbance conditions. Besides, subjects exhibit hyperglycemia as a response to both sleep restriction and sleep disturbance with the difference that acute changes in sleep has not been found related with any alterations on insulin response while chronic conditions have caused such change.³¹ The reduced insulin secretion with no alteration on plasma glucose levels and hypothalamic insulin receptors has been reported in wistar rats that subjected to 4 days of sleep disturbance.⁸⁹ The optimal glucose homeostasis has been observed for 7.5-8.5hours of sleep in the study that has revealed u-shaped relation between glucose homeostasis and total sleep duration.²⁹ In contrast Byberg and coworkers have not pointed any relation between total sleep time and insulin secretion or insulin sensitivity besides to unchanged plasma fasting glucose levels. However they have reported such change as 2% increase in both periferal and hepatic insulin sensitivity and 1% decrease in insulin secretion for 1 hour increase in sleep quality rather than sleep duration. Additionally, in the same study, increase in sleep duration has been found related with reduced HbA1c levels as 0.3mmol/mol decrease per each one hour increase in total sleep time and increase in sleep duration also has found related with 25% decrease in impairment of glucose metabolism in the measurements that have been adjusted for waist circumferences of subjects.³³ In another previous study that participants exposed to 4days of sleep restriction, insulin sensitivity that measured by frequently sampled intravenous glucose test (FSIGT) has been reported as 23% lower in sleep restricted participants than normal sleepers. The findings of the same study as quite high insulin and glucose responses given to breakfast and increased fasting plasma insulin levels that observed after sleep restriction proves the hypothesis that sleep restriction leads insulin resistance and diabetes mellitus. In addition to such shown impaired glucose metabolism, those mentioned alterations on insulin levels has been found correlated with increased free fatty acid levels which leads several obesity related metabolic impairments in turn.⁶⁵ In consideration of all mentioned studies hormonal alterations appear as one of the important liable agent in the wake of relevance at issue (Table 2).

Table 2 Represents sleep related hormonal alterations

Hormones	References	Outcomes
Melatonin	Tan et al. ⁴¹	Suppression of nocturnal melatonin secretion via exposure of light at night
	Broussard et al. ⁶⁵	Biphasic oscillation of growth hormone in sleep restricted groups, which is monophasic in normal sleepers and 50 minutes delay in oscillation as a result of sleep restriction that found to be related with increased plasma free fatty acid levels.
	Rodrigues et al. ⁶⁵	Sleep deprivation led increased peripheral T3 and T4 activity and hypothyroidism in Wistar rats
TSH	Schmid et al. ⁶⁷	Sleep restriction produced attenuated TSH secretion and increased T3 and T4 secretion in human participants.
	Kessler et al. ⁶⁹	Decreased TSH and T4 activity in female participants who underwent 14 days of sleep restriction

Table Continued...

Hormones	References	Outcomes
Cortisol	Broussard et al., ⁶⁵ Wolkow et al., ⁷⁴ Song et al. ⁷⁵	Increased cortisol levels, particularly at night, in sleep deprived participants.
	Wright et al. ⁷⁶	Sleep restriction and circadian misalignment induced fluctuation in cortisol levels have found as related with increase in TNF- α , IL-10 and CRP levels
Adipokines	Hayes et al. ⁸²	Decrease in sleep hours has reported as related with increased leptin and visfatin levels those thought as antecedents of obesity and insulin resistance.
	Padilha et al. ⁸³	Impaired glucose metabolism and type 2 DM have reported as a result of alterations on TNF- α and IL-6 that stemming from sleep restriction
Leptin & Ghrelin	Broussard et al. ⁶⁵	Acute sleep restriction has resulted in stationary leptin levels but increased ghrelin levels that illustrated positive association with increased caloric intake from deserts and snacks
	Fue et al. ⁸⁵	Increased leptin and ghrelin levels in participants aged between 10 and 15 and sleep less than 8 hours at night showed associations with snack intakes at nights
	Calvin et al. ⁸⁶	Sleep restricted participants have demonstrated stationary leptin and ghrelin levels and energy expenditure in spite of increased caloric intake
	Taheri et al.	After sleep restriction participants have demonstrated weight gain with increased leptin and decreased ghrelin levels.
Insulin	Eckel et al. ⁸⁸	Decreased oral and intravenous insulin sensitivity in human participants exposed to 5 hours of night sleep for 5 weeks.
	Koren et al. ²⁹	The U-shaped relationship has been detected between sleep duration and glucose metabolism and 7.5-8.5 hours of sleep has been reported as optimal for ace glucose homeostasis.
	Schmid et al. ⁶⁷	Sleep restriction in healthy normal weighted participants has resulted in increased C-peptide and insulin levels and escalated glucose response to breakfast that arising from impaired glucose metabolism and insulin resistance.

Sleep and metabolism

The extent of change in energy expenditure to contribute weight gain as a result of sleep restriction has been demonstrated by several researches with its possible paths as change in components of energy expenditure⁹⁰ increased fatigue and altered thermoregulation¹¹ and increased opportunity of time to eat.⁹¹ Benedict et al.⁹⁰ had reported %5 decrease in resting metabolic rate and %20 decrease in postprandial energy expenditure after sleep deprivation in subjects exposed to one night total sleep deprivation and one night of regular sleep conditions in a crossover design. There were no difference in terms of caloric intake between conditions while decreased core body temperatures, fancied as long term weight gain contributor, after sleep deprivation has been reported.⁹⁰ As it reversed, another crossover designed study that conducted with adolescents boyshas demonstrated negative energy balance after sleep deprivation conditions in two paths which are increased energy expenditure due to increased spontaneous physical activity accompanying increased wakefulness and decreased caloric intake as a result of decreased motivation of eating.⁹² In a study has been conducted with 14 healthy young women, after 4 nights of sleep restriction participants has demonstrated net weight gain as a result of increased caloric intake contrariwise to stable energy expenditure components like resting energy expenditure (REE), thermic effect of food (TEF) and Physical activity levels (PAL). Additionally, sleep loss has been found as cause increased glucose induced thermogenesis (GIT), triiodothyronine (T3) and thyroxine (T4) levels as conversely related with the percentage of bodily fat mass whose high levels lead weight gain by inhibiting increase in thermogenesis.⁹³ One of the recent study have indicated the role of increased food intake rather than alterations on energy metabolism in terms of short sleep induced weight gain among non-obese premenopausal healthy women those expressed stable postprandial thermogenesis and substrate oxidation

after 3 consecutive night of 4hours of sleep.⁹⁴ Calvin et al.⁸⁶ have reported stable activity energy expenditure (AEE), physical activity level (PAL) and circulating leptin and ghrelin levels in study subjects being exposed to 8 nights of sleep curtailment that has brought about 559 additional calories and resulted in 677 net increase in caloric intake in comparison with normal sleep condition.⁸⁶ In another study those underwent 4hours of sleep condition have demonstrated stable total energy expenditure (TEE) and resting metabolic rates (RMR) on the contrary intake of additional 300 calories especially from fat accompanying increased hunger and appetite rates compared with habitual 9 hour of sleep condition.⁹⁵ Insufficient sleep has been found to favor weight gain by increasing caloric intake especially after dinner, considered as inflicted by retardation on melatonin onset caused by circadian disruption, in spite of increased energy expenditure.⁹⁶ As reviewed by Chaput et al.⁹¹ rising energy intake reasoned from increased opportunity for time to eat accompanying short sleep times and rising levels of activities paired with the times expended as awake such as video games, television viewing, music listening and cognitive working that lead additional caloric intake increase the energy consumption while in another side energy expenditure tend to decrease as a result of low levels of physical activity including exercise and spontaneous daily physical activity due to sleep loss induced fatigue and decrease in nonexercise activity thermogenesis that comprises motions like stance allocation and fidgeting etc.⁹¹ In a longitudinal study, sleep related decreasing physical activity levels with the mediation of too much television viewing has been reported as responsible from childhood obesity.⁹⁷

Sleep and neural changes

In the study that subjects have been kept under 5.5 and 8.5hours of nightly sleep conditions in random order, increased consumption of snacks that have high content of carbohydrate without any change in

amount of meals has been indicated to favor obesogenic environment with stable energy expenditure components in short sleepers in laboratory conditions with add libitum food access.⁹⁸ In the same way, less than 8 hours of sleep have been found related with 475 or more additional calories those from snacks and tendency toward consumption of foods high in fat and low in carbohydrate content among adolescents.⁹⁹

Sleep loss related such snacking behaviour forms the non-homeostatic part of feeding that is stimulated by environmental, reward related, emotional and cognitive cues that processed in specific parts of brain mainly, striatum, some parts of prefrontal cortex and limbic system and explain the changes in food intake related with sleep restriction in addition to homeostatic changes in feeding behaviour including alterations on peripheral hunger and bodily hormones related with satiety and appetite.^{100,101} Recent studies discourse the effect of sleep loss on hedonic processes related to the some parts in the brain that enhance the drive to eat. In a study, total sleep deprivation led participants to show increased activation in right anterior cingulate cortex, the part of frontal cortex responsible from evaluation of the rewarding quality of food, in reply to food images as independent from caloric content in spite of same hunger ratings and same fasting plasma glucose before the scanning with those under normal sleep condition. Such finding emphasize the effect of prolonged wakefulness in terms of alterations on reward modulatory brain systems.¹⁰² In another study, participants under sleep restriction showed higher activation in insula, medial prefrontal cortex and orbitofrontal cortex, the brain parts related with hedonic functions, in response to unhealthy foods in comparison with healthy foods. In the same study sleep restricted participants demonstrated tendency toward consuming high fat diet that thought to activating the brains dopaminergic system like sugary foods with the mediation of mesoaccumbens dopaminergic pathway¹⁰³ that reported as highly activated in REM sleep.¹⁰⁴ Baldo et al.,¹⁰⁰ has reported 10 days of sleep deprivation in rats as resulted in transcriptional changes in opioid striatal system and hypothalamic energy-sensing system genes in the fashion of upregulation of proenkephalin (ENK), prodynorphin (DYN), seen combined in depressed mood, and Neuropeptide Y (NPY) and downregulation of cocaine- and amphetamine-regulated transcript (CART) as favoring increase in palatable food intake and hedonic taste reactivity that brought answer to snacking behaviour coming with sleep loss.¹⁰⁰

Sleep, hypertension, cardiovascular disease and diabetes mellitus

Several researches have indicated sleep duration as a risk factor for rising hypertension, type2 diabetes mellitus and cardiovascular disease incidences. To a study conducted with urban African population, increased nightly sleep duration led increase in both systolic and diastolic blood pressure and after a certain level each hour of sleep led %0.30 and %0.50 decrease for systolic and diastolic blood pressure respectively in females, while only day time napping over a half hour lower the blood pressure in male participants.¹⁰⁵ In the Nurses' Health Studies conducted with women between 1986 and 2000 five or less than five hours of nightly sleep has been reported as related with increased risk for prevalence of hypertension with the mediation of high levels of BMI in participants younger than 60 years. Such detected relation between hypertension prevalence and nightly short sleep duration that ruled out the 60 years older participants have been interpreted as resulted by increased sympathetic nervous system activation due to sleep losses especially for middle aged participants

while the main reason of hypertension incidences in participants older than 60 years is age related loss of arterial deference.¹⁰⁶ In one of the recent research that detected U-shaped relationship between sleep duration and hypertension for all age and sex groups, high prevalences of hypertension have been reported among female those in age groups that younger than 45 and older than 65 years and sleep less than 6 hours and also in those aged between 45 and 65 years and sleep 10 or more hours, while such increased risk have been recognized for male those sleep 10 or more hours at ages younger than 45 and sleep less than 6 hours between ages of 45 and 65.¹⁰⁷ In addition to sleep restriction induced increase in sympathetic nervous system activity, increased salt intake and reduced renal salt-fluid excretion as a stress response to sleep restriction act as another possible path in terms of sleep related hypertension by creating chronic renal overload.¹⁰⁸ Sleep loss related elevations of CRP levels⁷⁶ also has been reported as related with increased hypertension prevalence.⁷

Perry et al.¹⁰⁹ has reported sleep restriction related with cardiovascular impairment with the mediator of increased renal sympathetic nervous system activity (rSNA) accompanying decrease in Angiotensin,¹⁻⁷ a bioactive peptide act as a component of renin-angiotensin system (RAS) and responsible from activation of peripheral vasodilator mechanisms by its stimulating effect on vasodilator prostaglandins and NO release.¹⁰⁹ In another study, sleep restriction caused downregulation of gamma aminobutyric acid receptors (GABA_A) in paraventricular nucleus (PVN), the nuclei involve central neurons responsible from cardiovascular system control besides those in rostromedial medulla (RVL), have been found as responsible from increase in rSNA in rats as contributing cardiovascular alterations.¹¹⁰ Beside, in a previous research, each one hour increase in sleep duration has been reported as protective against cardiovascular disease with approximately 33% decrease in probability of coronary artery calcification that characterized with accumulation of calcified plaques to the arteries and act as future predictor of development of coronary diseases.¹¹¹ As mentioned before, short sleep duration have been reported as related with impaired glucose metabolism and type2 diabetes mellitus with the mediation of reduced glucose tolerance,⁸⁷ reduced insulin sensitivity,⁸⁸ hyperglycemia,³² and impaired glucose regulation.³³ The possible paths mediating the relationship between type2 diabetes mellitus and sleep loss has been reviewed as elevated evening cortisol levels as a stress response to sleep restriction that causing impaired glucose metabolism and inhibitory effect of increased sympathetic tone on pancreatic action. In addition, sleep loss related melatonin suppression have been reported as another mediator of increased sympathetic nervous activation that acting as the common pathology under sleep loss related hypertension, cardiovascular diseases and type 2 diabetes mellitus.⁷

Conclusion

Human and animal studies demonstrates u shaped relationship between sleep and obesity, type2 diabetes mellitus, impaired glucose metabolism, cardiovascular diseases, and hypertension those thought to be induced by sleep related impaired circadian rhythm, hormonal, metabolic and neural alterations as basic mechanisms. However, experimental and laboratory studies being conducted in this field, have revealed conflicting findings in terms of the extents of alterations on such potential explanatory mechanisms. Several researches indicates the altered parameters of hunger and appetite on the hormonal basis, particularly as increase in leptin and decrease in ghrelin¹⁷ while some others demonstrated antipodean⁶⁶ or no alterations

in both hormones⁸⁷ although increased caloric intake is common denominator for all. Similarly, findings about sleep induced changes in energy expenditure components show discrepancy in completed studies. While a previous study have found sleep loss as favoring weight gain with decrease in energy expenditure components despite of stable caloric intake¹⁰² in some others, stable energy expenditures and increased caloric intake of sleep restricted participants was indicated to beat a path for positive energy balance.^{93–95} In contrast, in another study sleep loss that accompanied with decrease in caloric consumption an increase in energy expenditure has been reported as favor negative energy balance.⁹²

As stated, researches had revealed conflicting results in terms of the extent and direction of functions of basic mechanisms underlying the relationship between sleep and mentioned health disorders. Referring to the literature, several factors play decisive role for the extent of the influence of sleep loss or disturbance on health disorders.¹¹² In a study that participants underwent sleep restriction for 5 nights as 4 hour sleep per night, men have exhibited greater caloric intake than women and the differences have been detected between food patterns of African Americans and Whites as a result of sleep loss as supporting the sex and race differences.¹² In the same way, the study being conducted with participants aged between 6-18years, while short sleep durations have been detected as a risk factor for obesity in girls for all age groups, such risk detected in boys aged between 13-18 and tend to decrease in boys those ages between 6 and 12years.¹¹³ Sleep architecture also plays an important role for sleep loss induced health outcomes. The effect of sleep restriction varies as depending on whether which stage of sleep is influenced from intervention.²⁸ To recent studies, SWS have been related with glucose metabolism²⁹ while stage 2 sleep have reported as associated with energy expenditure and taste related request for food²⁸ and REM sleep also with appetite related hormones.³⁰

Indicating the late sleep times as another determinant, Spaeth et al.¹¹⁴ found late bedtimes to space greater caloric intake during sleep restriction conditions¹² as like another study found late bedtimes as strongly related with increased waist-hip circumferences, bodily fat deposition and BMI levels as independent from sleep duration.²⁰ Furthermore, both genotype and phenotype variables also act as indicator for effects of sleep loss. Bandin et al.¹¹⁵ has reported circadian impairments in those have CLOCK 3111 C allele that had found to related with obesity, while CLOCK 311T allele carriers demonstrated more vigorous circadian rhythm status.¹¹⁵ In another study conducted as two experimental sleep restriction condition as 5 night of 4hours of sleep with 60days interval, while participants demonstrated different responses to sleep restriction in terms of weight gain and caloric intake, such responses have revealed stability across conditions on the individual basis as supporting the genetic and phenotype differences as important indicators for sleep loss related outcomes.¹¹⁴ Because sleep loss acts as stress factor that actuate the HPA axis activity as bodily response to stressful conditions, the evaluation of such response and sleep related emotional distress with the light of individual differences like sex, race, sleep pattern, genotype and phenotype will shed light on future studies.

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Conflict of interest

Author declares that there is no conflict of interest.

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