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Sleep Loss: Risk Of Obesity And Type 2 Diabetes

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Abstract: ***Sleep is a complex behavioral state that occupies one-third of the human life span; although viewed as a passive condition, sleep was considered to be primarily important for restoration of brain function. Recent evidence has shown that sleep also modulates metabolic, endocrine and cardiovascular systems. Sleep loss as a consequence of voluntary bedtime restriction is a common phenomenon in modern society. Studies revealed that consistent restriction of sleep duration at night results in metabolic changes which contributes to development of obesity and insulin resistance. Laboratory studies in healthy volunteers have shown that experimental sleep restriction s associated with an adverse impact on glucose homeostasis, insulin sensitivity decreases rapidly and markedly without adequate compensation in beta cell function, resulting in an elevated risk of diabetes. Sleep curtailment is also associated with a dysregulation of the neuroendocrine control of appetite, with a reduction of the satiety factor, leptin, and an increase in the hunger-promoting hormone, ghrelin. Thus, sleep loss may alter the ability of leptin and ghrelin to accurately signal caloric need, acting in concert to produce an internal misperception of insufficient energy availability thereby increasing excessive food intake resulting in increased body mass index.***

Keywords: Diabetes, Energy expenditure, Ghrelin, Glucose tolerance, Leptin, Obesity, Sleep deprivation

I. INTRODUCTION

The planet earth exists in two parts which forms the 24 hours daily cycle which are 12 hours daylight and 12 hours night. Most creatures adapt by being active during the day and inactive at night (Walter, 2011).Sleep is a complex behavioral state that occupies one-third of the human life span; although viewed as a passive condition, sleep was considered to be primarily important for restoration of brain function. Sleep is a measure of the quantitative and qualitative amount of sleep (Shittu *et al.*, 2014) recent evidence has shown that sleep also modulates metabolic, endocrine and cardiovascular systems (Trenell, 2007; Boethel, 2002; Knuston, 2008). Sleep is a natural process controlled by the human brain and it restores body functions. It is commonly believed that sleep is a period when the body and brain shuts down from its metabolic activities but electroencephalograms (EEG) show that the brain is quite active during the period of sleep, thus sleep can also be referred to as a periodic state of rest in which the brain responsiveness to the environment is suspended. It is now clear that it is a period of intense brain activity involving higher cortical functions with considerable physiologic activity, to the extent that the brain is considered more active during sleep than wakefulness (Chadwick, 2001; Dahl, 1998; Zee and Turek, 1999). There is a growing epidemic of obesity and diabetes mellitus affecting not only adults but even children. Obesity is one of the major causes of non-communicable chronic diseases (WHO, 1998) one of the most interesting findings that are becoming available is the relationship between sleep deprivation, weight gain and diabetes. Recent research suggests that untreated Obstructive Sleep Apnea (OSA) which occurs as a result of recurrent blockage of the upper airway during sleep predisposes to insulin resistance, diabetes mellitus, visceral fat accumulation and obesity The importance of sleep to overall health and well-being is becoming increasingly appreciated, and the lack of adequate education in the area of sleep is a concern that has only recently gained recognition (Davis and Parker, 2004). The cause of sleep loss is mostly work related and the contemporary lifestyle (Jolanta, 2010).

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This review focuses on the evidence linking sleep loss with Obesity and Type 2 Diabetes. Sleep loss in this context means sleep duration that is less than 6 hours per night.

II. SLEEP PHYSIOLOGY

Sleep is a state of semi-consciousness in which the brain is relatively more responsive to internal than external stimuli. The predictable cycling of sleep and the reversal of relative external unresponsiveness are features that assist in distinguishing sleep from other states of unconsciousness. The brain gradually becomes less responsive to visual, auditory, and other environmental stimuli during the transition from wake to sleep, which is considered by some to be stage I of sleep. Both homeostatic factors and circadian factors interact to determine the timing and intensity of sleep (Tarokh *et al.*, 2012). The homeostatic process is the mechanism that enhances increase in sleep drive as a result of sleep debt accumulated during waking hours. It enables the body and mind to rejuvenate and restores alertness (Davis *et al.*, 2000).

SLEEP STAGES

Sleep is characterized by two main stages of sleep which are Rapid eye movement sleep (REM) and Non-Rapid eye movement sleep (NREM). Rapid-eye-movement (REM) sleep also called paradoxical sleep. It is characterized by small amplitude, fast-EEG waves, no postural tension and rapid eye movements.

NON-RAPID EYE MOVEMENT (NREM) SLEEP

Non-rapid eye movement (NREM) sleep also called Slow-wave sleep (SWS) is characterized by the presence of slow wave EEG activity as shown in figure 2. It is characterized by deep sleep. During NREM sleep the blood pressure, breathing and metabolic rate are all depressed significantly. Bodily movements do not occur during non-REM sleep. It is referred to as slow wave sleep because during this period the brain waves are very strong and of a very low frequency (i.e. slow); while non-REM sleep is sometimes referred to as dreamless sleep, dreams and even nightmares can occur during non-REM sleep. These are not associated with movement and are not remembered as they are not consolidated to memory during this sleep phase. NREM sleep is subdivided into four different stages which are:

Stage 1 - This is the beginning of slow wave sleep which is accompanied by slowing of the heart rate and relaxation of the muscles. In addition, under the closed eyes lid the eyes may roll about slowly. Stage 1 sleep usually lasts several minutes and gives way to stage 2 sleep. NREM stage 1 sleep serves a transitional role in sleep-stage cycling. Aside from newborns and those with narcolepsy and other specific neurological disorders, the average individual's sleep episode begins with NREM stage 1. This stage usually lasts 1 to 7 minutes in the initial cycle, constituting 2 to 5 percent of total sleep, and is easily interrupted by a disruptive noise. Brain activity on the EEG in stage 1 transitions from wakefulness (marked by rhythmic alpha waves) to low-voltage, mixed-frequency waves. Alpha waves are associated with a wakeful relaxation state and are characterized by a frequency of 8 to 13 cycles per second (Carskadon and Dement, 2005).

Stage 2 - It is characterized by waves of 12-14Hz called sleep spindles that occur in periodic bursts. If awakened during these first two stages of sleep, many subjects deny that they have been asleep, even though they failed to respond to signals while in those stages. Stage 2 sleep lasts approximately 10 to 25 minutes in the initial cycle and lengthens with each successive cycle, eventually constituting between 45 to 55 percent of the total sleep episode. An individual in stage 2 sleep requires more intense stimuli than in stage 1 to awaken. Brain activity on an EEG shows relatively low-voltage, mixed-frequency activity characterized by the presence of sleep spindles and K-complexes. It was hypothesized that sleep spindles are important for memory consolidation and the report of the study showed that individuals who learn a new task have a significantly higher density of sleep spindles than those in the control group (Gais et al., 2002).

Stage 3 - is defined by the appearance of large amplitude, very slow waves also called Delta waves about one per second. Sleep stages 3 and 4 are collectively referred to as slow-wave sleep (SWS), most of which occurs during the first third of the night. Each has distinguishing characteristics. Stage 3 lasts only a few minutes and constitutes about 3 to 8 percent of sleep. The EEG shows increased high-voltage, slow-wave activity.

Stage 4 - The last NREM stage is stage 4, which lasts approximately 20 to 40 minutes in the first cycle and makes up about 10 to 15 percent of sleep. The arousal threshold is highest for all NREM stages in stage 4. This stage is characterized by increased amounts of high-voltage, slow-wave activity on the EEG (Carskadon and Dement, 2005).

REM SLEEP

REM sleep is characterized by the presence of rapid eye movements during sleep. It is defined by the presence of desynchronized (low-voltage, mixed-frequency) brain wave activity, muscle atonia, and bursts of rapid eye movements (Carskadon and Dement, 2005). "Sawtooth" wave forms, theta activity (3 to 7 counts per second), and slow alpha activity also characterize REM sleep. This type of sleep is less restful than slow wave sleep and is associated with dreaming. During the initial cycle, the REM period may last only 1 to 5 minutes; however, it becomes progressively prolonged as the sleep episode progresses (Carskadon and Dement, 2005). The brain is extremely active during REM sleep. The electroencephalogram shows pattern of brain wave activity similar to those that occur during waking hours. Due to this feature of REM sleep, it is often referred to as paradoxical sleep as it is a paradox that one can be asleep and yet the brain is incredibly active. Dreaming is most often associated with REM sleep. Loss of muscle tone and reflexes likely serves an important function because it prevents an individual from "acting out" their dreams or nightmares while sleeping (Bader et al., 2003).

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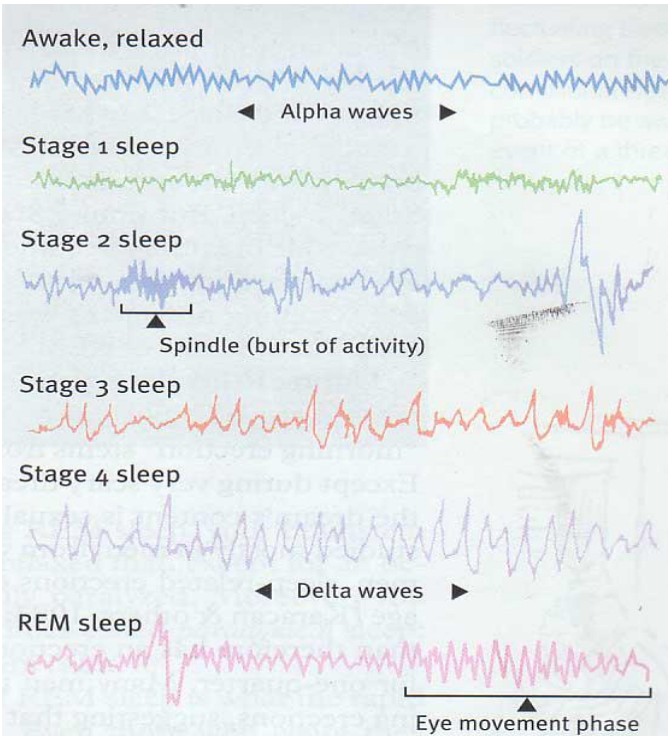

Source: www.sinancanan.net

Figure 2: EEG of brainwave activity during different sleep stages

III. SLEEP AND GLUCOSE METABOLISM

Blood levels of glucose are tightly regulated within a narrow range to avoid hypoglycemia and hyperglycemia as both conditions have adverse life threatening consequences. Glucose metabolism is critical to normal physiological functioning, glucose acts both as a source of energy and as a source of starting material for nearly all types of biosynthetic reactions. Glucose metabolism is a function of glucose tolerance and insulin sensitivity.

Glucose tolerance refers to the ability to metabolize exogenous glucose and return to baseline normal glucose level in the blood. This is maintained by disposing exogenous glucose via insulin mediated and non insulin mediated mechanisms. Glucose tolerance can be examined after ingestion of a carbohydrate-rich meal or after intravenous injection or infusion of glucose. Normal glucose tolerance depends on the ability of the pancreatic beta cells to produce insulin.

Insulin sensitivity refers to the responsiveness of insulin dependent cells or tissues to insulin secretion by the pancreatic beta cells. As insulin sensitivity declines, insulin secretion increases to maintain normal glucose levels. Diabetes results when the pancreatic beta cells fail to compensate for the decreased insulin sensitivity (Carol and Silvana, 2011). Glucose tolerance is dependent on the balance between glucose production by the liver and glucose utilization by insulin-dependent tissues, such as muscle and fat, and non-insulin dependent tissues, such as the brain. Reduced insulin sensitivity, or insulin resistance, occurs when higher amounts of insulin are needed to reduce blood glucose levels after the administration of the same amount of exogenous glucose.

In normal, healthy individuals, glucose tolerance varies across the day such that plasma glucose responses to exogenous glucose are markedly higher in the evening than in the morning, and glucose tolerance is at its minimum in the middle of the night (Van *et al.,* 1997). The reduced glucose tolerance in the evening is at least partly due to a reduction in insulin sensitivity concomitant with a reduction in the insulin secretory response to elevated glucose levels.

The further decrease in glucose tolerance during the night is dependent on the occurrence of sleep. Indeed, a variety of mechanisms intervene to maintain stable glucose levels during the extended overnight fast associated with sleep (Van *et al*., 1997). Overall, glucose utilization is greatest during wake and lowest during non-REM (Stages 2, 3, and 4) sleep, with intermediate levels during REM sleep (Scheen *et al.*, 1996). In the first half of the night, glucose metabolism is slower, partly because of the predominance of slow-wave sleep that is associated with a marked reduction in cerebral glucose uptake, (Nofzinger *et al.*, 2002; Maquet, 2000) and may also be because of the reduction in peripheral glucose utilization. These effects are reversed during the second half of the night, when light non-REM sleep and REM sleep are dominant and awakenings are more likely to occur. These major modulatory effects of sleep on glucose regulation can also be observed when the sleep period occurs during the daytime (Van *et al.*, 1991).

IV. SLEEP LOSS IN RELATION TO RISK OF TYPE 2 DIABETES

Sleep quantity and quality is reported to be associated with an increased morbidity and mortality (Kripke *et al.*, 2002; Enstrom *et al.*, 1986).Diabetes is one of the debilitating chronic diseases that are increasing at an alarming rate worldwide (Morkad *et al.*, 2001). It has been observed over time that due to the time demanding nature of work and other life activities in modern societies, sleep duration has been curtailed to less than 6 hours per night; for example a survey study from 1960 found sleep duration to be 8 to 9 hours (Kripke *et al*, 1979), while another survey in 1995 observed it to be 7 hours. Recent studies also indicate that a greater percentage of adult Americans report sleeping 6 hours or less as at 2004 than in 1985 which shows a progressive sleep loss; similarly in Nigeria, the average sleeping duration of employed adults is less than 6 hours. Thus, the increase in the prevalence of diabetes appears to be mirrored by a decrease in average sleep duration in the U.S. There are quite a number of evidence which establishes the connection between sleep loss and diabetes.

Studies have demonstrated that experimental restriction of sleep to less than 4 hours per nights for six nights resulted in an impaired glucose tolerance in young healthy adults (Spiegel *et al.*, 1999). Sleep deprivation results in impaired glucose metabolism which leads to diabetic conditions (Gottlieb *et al.*, 2005; Knuston *et al.*, 2007)

V. EXPERIMENTAL STUDIES LINKING SLEEP LOSS TO TYPE 2 DIABETES

Karine Spiegel *et al.*, 2004 did the first thorough investigation of the effects of sleep loss on glucose metabolism in 11 healthy young men (aged 18–27 years) whose sleep was restricted to 4 h for six consecutive nights, with a subsequent recovery period of six nights with 12 h of sleep opportunity. During an intravenous glucose tolerance test, sleep restriction versus subsequent sleep extension was associated with impaired glucose tolerance, as shown by a 40% reduction in the glucose disposal rate caused by reduced glucose effectiveness (non-insulin-dependent glucose uptake), and with a reduced acute insulin response. Subsequent analysis of these data also showed a significant decrease in insulin sensitivity after sleep loss (Vanhelder *et al.*, 1993). Furthermore, the peak blood glucose response to a breakfast meal was increased by 0·8 mmol/L after the nights of sleep restriction. These results were corroborated and extended in several methodologically sound laboratory studies in healthy men and women, which showed decreases in glucose tolerance and insulin sensitivity after sleep restriction to roughly 4 h per night for 14 nights, (Youngstedt and Kripke, 2004; Thomas *et al.*, 2000; Vgontas *et al.*, 1999; 2004) and after sleep fragmentation for two nights (Tasali *et al.*, 2008). Increased markers of insulin resistance have also been noted in adolescents after their sleep was restricted to 4 h for three consecutive nights (Flint *et al.*, 2007). Although an impairing effect of short sleep duration on insulin sensitivity, as shown by increased hepatic glucose production (Spiegel *et al.*, 2005) and reduced peripheral glucose disposal was recorded fairly consistently in all the studies mentioned above, results on the effect of sleep loss on β-cell insulin secretion are much less consistent (Vanhelder *et al.*, 1993, Vgontas *et al.*, 1999; 2004; Tasali *et al.*, 2008; Flint *et al.*, 2007).

The first detailed laboratory study done by Spiegel *et al.*,1999 using healthy young men subjecting them to 6 nights of 4 hours sleep duration and afterwards 12 hours sleep duration for 7 nights (sleep recovery). Glucose tolerance test carried out after each phase showed a 40% decrease in the intravenous glucose tolerance test (ivGTT) during the first phase; also 30% decrease in acute insulin response to glucose (AIR_G) and 30% decrease in insulin sensitivity (SI). Disposition index which is given as a product of AIR_G x SI is a marker of diabetes risk that is used in genetic studies (Palmer *et al.*, 2006). Individuals with normal glucose tolerance have a constant DI because beta cell function sufficiently to compensate for insulin resistance with increased insulin release (Bergman *et al.*, 2002). Type 2 diabetes occur when the pancreatic beta cells do not sufficiently compensate for insulin resistance which results in hyperglycemia; low DI values represent a high risk of type 2 diabetes and DI value of 2000 and above is typical of individual with normal blood glucose level (Xiang *et al.*,2006). The result from the findings is shown in Table 1.

	12hr for 6 days (fully rested)	4hr for 6days (sleep restriction)
K_G	2.40 + 0.41	1.45 + 0.31
AIRg	548 + 158	378 + 136
S_G	2.6 + 0.2	1.7 + 0.2
SI	6.73 + 1.24	5.41 + 0.60
DI	2897 + 404	1726 + 395

Glucose tolerance (k_G),
Acute insulin response to glucose (AIR_g)
Glucose effectiveness (S_G)
Insulin disposition index (DI)
Source: Kristen and Eve, 2008.

Table 1: Results of intravenous glucose tolerance tests in healthy males while fully rested and after sleep restriction

Findings from animal studies also showed that sleep deprivation in mice led to altered cell function in the pancreas, an organ that plays an important role in regulating blood sugar. Endocrine cells in the pancreas produce hormones including insulin which helps in the regulation of glucose level in the blood. It was also noted that age was also an important factor in the body system response to sleep deprivation. The mice study showed that the degree of cellular stress was significantly higher in older mice than in younger mice; although all mice experienced negative changes to glucose metabolism, sleep deprivation appeared to magnify the impairment of the body ‘s reaction to cell stress in older mice weakening a protective response that is already challenged by age.

A study by Nedeltcheva and colleagues, 2012 has provided the first evidence of a modulating effect of dietary intake on the consequences of sleep loss on glucose metabolism. In this study of obese patients on a hypocaloric weight-loss regimen, 14 days of sleep restriction to 5·5 h, compared with 8·5 h of sleep opportunity, reduced 24 h serum insulin concentrations with no effect on glucose homoeostasis. This finding suggests that sleep restriction results in a state of increased insulin economy under hypocaloric conditions.

Circadian rhythm desynchronisation which means sleeping out of phase of habitual sleeping times has likewise been shown to adversely affect glucose metabolism. In a carefully designed experimental study by Scheer *et al.*, 2009, healthy adults underwent a 10- day laboratory protocol that required them to eat and sleep at all phases of the circadian cycle, which was achieved by scheduling of a recurring 28 h day. In the test session taking place during the final period of circadian misalignment, average blood glucose concentrations increased by 6%, despite a concurrent 22% increase in circulating insulin concentrations.

Kuhn *et al.*,(1969) reported in a study examining the impact of 72–126 hours of total sleep deprivation on oral glucose tolerance found that levels of glucose were markedly higher throughout the test when subjects were sleep deprived. Since then, a large body of evidence has accumulated to indicate that sleep has major modulatory effects on glucose regulation (Van *et al.*, 1991). It may therefore be somewhat surprising that only within recent years has the possibility been considered that recurrent sleep loss may be associated with adverse metabolic effects. An explanation for this inconsistency may be that nearly all early studies used the paradigm of acute total sleep deprivation, a condition that is necessarily of short duration in humans and invariably followed by sleep recovery. Alterations evidenced during acute total sleep deprivation are readily corrected after sleep recovery and therefore the possibility that sleep loss may

result in long-term adverse effects on glucose tolerance appeared unlikely. However, as pointed out elsewhere, there are differences in the EEG and hormonal effects of acute total as compared to recurrent partial sleep deprivation (Spiegel *et al.*, 2005). For example, after recovery from total sleep deprivation, slow-wave sleep and Growth hormone levels rebound (Spiegel *et al.*, 2005; Spiegel *et al.*, 2000), whereas during recurrent sleep restriction, slow-wave sleep and Growth hormone levels were not higher than it was at baseline. During total sleep deprivation, thyroid stimulating hormone (TSH) levels were more than doubled, whereas after 3–5 days of partial sleep deprivation, TSH levels were markedly depressed (Allan *et al.*, 1994; Van *et al.*, 1994; Spiegel *et al.*, 1999).

Another study carried out by Najafan *et al.*, 2013 on individuals in a baseline survey of a community based program entitled "Isfahan healthy heart program". It was observed that participants who reported sleeping 6 hours or less compared to those sleeping 7-8 hours per night were at higher risk of diabetes mellitus. He concluded that sleep duration of 5 hours or less in individuals less than 60 years is associated with an increased prevalence of diabetes mellitus (Najafan *et al.*, 2013).

Another research study conducted by researchers at the university of Chicago Medical Center shows that loss of slow wave sleep in healthy young adults significantly increases their risk of type 2 diabetes by impairing their ability to regulate blood sugar levels. They studied nine lean healthy volunteers, five men and four women between the ages of 20 and 31. The subjects spent two consecutive nights in the sleep laboratory where they were monitored while they slept undisturbed. The same subjects were next studied for three consecutive nights during which their sleep was disturbed by sounds administered through speakers whenever they showed signs of entering into slow-wave sleep. This study found that after only three nights of interrupted slow-wave sleep, young healthy subjects became less sensitive to insulin, resulting in reduced tolerance to glucose and increased risk for type 2 diabetes (Tasali *et al.*, 2008).

These alterations in glucose metabolism may be associated with the hypothalamic-pituitary axis. Under normal conditions, glucose tolerance and insulin sensitivity begin to improve during the latter part of the night, reflecting a delayed effect of low cortisol levels during the evening and early part of the night (Plat *et al.*, 1996). Disturbances in the secretory profiles of the counter-regulatory hormones, growth hormone (GH) and cortisol, may partially contribute to the alterations in glucose regulation observed during sleep loss. Previously it was reported that 6 days of sleep restriction were associated with an extended duration of elevated night time growth hormone concentrations and with an increase in evening cortisol levels (Spiegel *et al.*, 1999). An extended exposure of peripheral tissues to higher growth hormone levels may induce a rapid decrease in muscular glucose uptake adversely affecting glucose regulation. Also, increase in level of cortisol in the evening is likely to result in reduced insulin sensitivity on the following morning (Plat *et al.*, 1999). The reduction in AIRg may be attributed to measured changes in sympathovagal balance that indicated increased sympathetic nervous activity, which inhibits pancreatic function (Spiegel *et al.*, 1999).

Another study recruited age- and weight-matched groups of healthy normal-weight habitual short sleepers (<6.5 hours per night) and normal sleepers (7.5-8.5 hours per night). During an intravenous glucose tolerance test, the glucose tolerance was similar for the two groups, however the short sleepers secreted an average of 50% more insulin during both the first and second phases of response resulting in a 40% lower insulin sensitivity (Mander *et al.*, 2001). Thus, there seems to be no healthy adaptation to sleep loss in terms of carbohydrate metabolism since larger amounts of insulin were secreted in order to achieve the normal glucose tolerance.

These two studies of partial sleep deprivation suggest possible mechanisms by which sleep loss could lead to impaired glucose tolerance and eventually type 2 diabetes. After only a week of sleep restriction, subjects were unable to metabolize the glucose at rates observed in healthy young individuals. Subjects who reported having being short sleepers for at least 6 months, on the other hand, had glucose tolerance rates similar to healthy long sleepers, but they had to secrete more insulin to achieve this glucose profile. Increasing levels of insulin could lead to insulin resistance, a risk factor for type 2 diabetes. Thus, over long periods of time as short sleepers age, the risk of developing type 2 diabetes and obesity may increase.

VI. EPIDEMIOLOGICAL STUDIES OF SHORT SLEEP DURATION AND GLUCOSE METABOLISM

Multiple cross-sectional epidemiological studies have suggested an association between short sleep duration and diabetes; several prospective epidemiological studies have suggested that short sleep actually plays a causative role in diabetes. Epidemiological data increasingly suggests that short sleep duration or chronic partial sleep deprivation may increase the risk of type II diabetes. In a large cohort of nurses (Nurse Health Study with more than 70,000 respondents), self-reported short (5 hours or less) and long duration of sleep (9 hours or more) was associated with symptomatic diabetes with a relative risk of 1.34 for short (1.04–1.72) and long 1.35 for long (1.04–1.75) sleepers (Ayas *et al.*, 2003) . A Swedish study with more than 2000 people followed for over 10 years revealed that short duration of sleep (< 5 hours) and difficulty initiating and maintaining sleep were associated with higher incidence of diabetes in men (but not in women) even after adjusting for confounding factors like age, BMI, snoring, depression, and hypertension (Mallon *et al.*, 2005) The landmark observations of Spiegel *et al.*, 1999 led to a number of epidemiological studies examining the relationships between sleep duration and sleep disturbances and diabetes risk (Zizi *et al.*, 2010).

A large, cross-sectional, community-based study of the cardiovascular consequences of sleep-disordered breathing carried out by Gottlieb *et al.*, 2005 assessed the relationship between reported sleep duration and impaired glucose tolerance or type 2 diabetes in more than 1,400 men and women who had no history of insomnia. After adjustment for age, sex, and race, the prevalence of impaired glucose

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tolerance and type 2 diabetes was higher in those who reported sleeping 6 hours or less per night (Gottlieb *et al.*, 2005). Another study by Ayas *et al.*, (2003) on nurses followed 70,000 non –diabetic women for 10years compared with nurses who slept 7 to 8 hours per 24 hours, those who slept 5 hours or less had a relative risk of diabetes even after controlling for many co variables such as body mass index, shift work, hypertension, exercise, and depression.

Francesco et al., 2010 reported a similar study in a review to associate sleep loss/disturbance to type 2 diabetes. Duration of sleep was assessed by self-reported habitual sleep duration using questionnaires (Björkelund et al., 2005).The study followed 2,649 Japanese men for 8 years. Those who had difficulty going to sleep and staying asleep, which are both likely to result in shorter sleep duration, had higher age-adjusted risks of developing type 2 diabetes, with hazard ratios of 2.98 and 2.23 respectively.

Björkelund et al., 2005 followed 6,599 non-diabetic Swedish men for an average of 15 years. Self-reported difficulty sleeping predicted the development of diabetes with an odds ratio of 1.52 even after controlling for age, body mass index at screening, changes in body mass index at follow-up, baseline glucose level, follow-up time, physical activity, family history of type 2 diabetes, smoking, social class, and alcohol intake (Nilsson *et al.*, 2004).

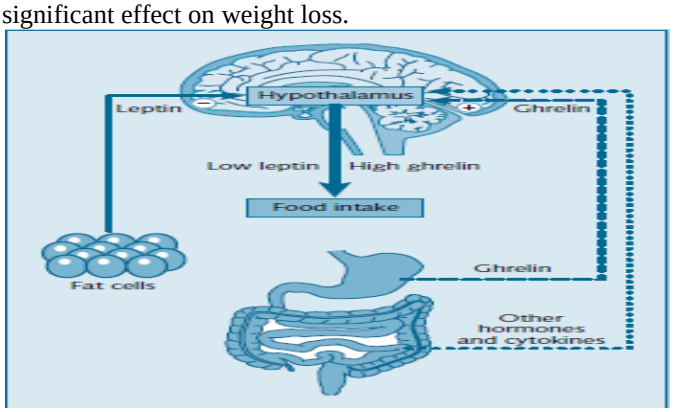
VII. SHORT SLEEP DURATION AND OBESITY

Obesity is a global public health problem (Kopelman, 2000). Report from WHO estimated that in 2005, less than one billion worldwide were overweight and less than 300 million were Obese. The report forecast that the number of overweight individuals will reach 1.5 billion by 2015. Many observational and epidemiological studies have shown a relationship between obesity and sleep deprivation. The common reason for this relationship is the fact that sleep restriction affects the regulation of appetite hormones like Ghrelin and Leptin.

Leptin is a 16 kDa, 167 amino acid, secreted protein that is primarily produced by adipose tissue. The rate of leptin secretion and its plasma concentration are correlated with total fat mass. Excessive weight gain is associated with adipose tissue expansion and high circulating leptin levels. It has been proposed that, in obesity, a defect in the transport mechanism of leptin into the central nervous system may occur, resulting in the observed leptin resistance. Therefore, low leptin levels in states of energy deficit are a greater biological signal than high leptin levels (Leibel, 2002). Weight loss results in leptin deficiency and, interestingly, adaptations to reduced body weight are reversible with low-dose leptin administration Leptin circulates bound to a soluble receptor (Rosenbaum *et al.*, 2002; 2005). As well as food intake and changes in energy balance, leptin levels are regulated by several factors including negative regulation by the sympathetic nervous system (Chin-Chance *et al.*, 2001). Levels of leptin, but not its soluble receptor, show circadian changes; they are low during the day but rise in the night during sleep (leptin levels peak at about 2 AM). The diurnal leptin pattern has been reported to change concurrently with body temperature and plasma insulin and glucose levels. In obese individuals, there is a sharper rise in leptin levels during the night compared with the rise in lean individuals (Yildiz *et al.*, 2004).

Ghrelin is a 28-amino acid peptide hormone synthesized by the stomach (Kojima and Kangawa, 2005). It circulates as active and inactive forms. Active ghrelin is acylated and lipophilic, and therefore can cross the blood–brain barrier. Acute administration of small doses of ghrelin, either systemically or directly into the brain, dramatically increases food intake in rats (Tschop *et al.*, 2000; Wren *et al.*,2000).Chronic systemic administration of ghrelin to rodents results in weight gain and increased fat mass. In addition, ghrelin appears to have an effect on energy expenditure. Calorimetry has suggested that administration of ghrelin causes an increase in respiratory quotient in rodents, but ghrelin negatively correlated with energy expenditure in humans (Wren *et al.*, 2000).

Other associations that were found with ghrelin levels included high-density lipoprotein (HDL) cholesterol, creatinine levels, and alcohol intake (Taheri *et al.*, 2004). Short sleep duration was associated with low leptin (with a predicted reduction in leptin of 15.5% for habitual sleep of 5 h vs. 8 h), and high ghrelin (with a predicted increase in ghrelin of 14.9% for nocturnal/polysomnographic sleep of 5 h vs. 8 h), independent of BMI (Taheri *et al.*, 2004). These relationships remained following correction for multiple possible confounding factors including age, sex, BMI, morningness–eveningness tendencies, self-reported exercise, and sleep-disordered breathing (Taheri *et al.*, 2004; Young *et al.*, 2005). These hormone changes are usually observed in reaction to food restriction and weight loss, and are typically associated with increased appetite. The hormone changes observed with sleep duration require comparison with changes after calorie restriction, and similar changes in leptin to those observed with sleep loss have been reported with both acute and long-term calorie deficits (Chin-Chance *et al.*, 2000). For example, in a study of 50 overweight and obese female volunteers (aged 18–50 years; BMI 25–32 kg/m2; who were put on a calorie-restricted diet over 3 weeks, the women lost approximately 3.9% of their BMI ($p<0.001$) and this was associated with a 13.6% increase in levels of ghrelin ($p<0.01$) (Taheri, 2004). Therefore, high circulating ghrelin and low circulating leptin provide powerful signals to the hypothalamus to promote food intake (Fig. 3). The fact that gastric bypass surgery is associated with low ghrelin levels suggests that lowering ghrelin levels by ensuring adequate sleep may have a significant effect on weight loss.

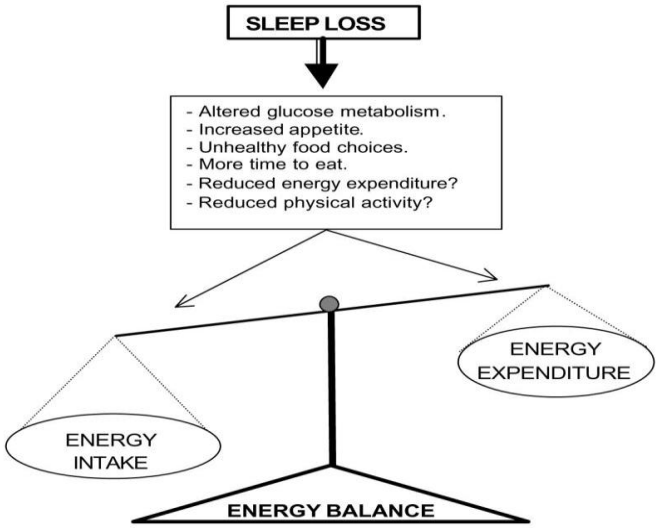


Source: Taheri et al., 2004

Figure 3: Leptin and ghrelin in appetite regulation

VIII. SLEEP LOSS, ENERGY BALANCE AND OBESITY

Lack of energy balance most often causes overweight and obesity. Energy balance means that the energy intake is equal to energy output. Energy intake is the amount of energy or calories obtained from food and drinks consumption while energy output is the amount of energy the body uses for metabolic activities such as digestion, breathing and physical activities. Thus when energy input equates energy output, the weight remains the same; when energy intake is greater than energy output, it results to weight gain; when energy output is greater than energy intake, it results in weight loss. Energy balance is tightly regulated by ghrelin and leptin which conveys information from the body to the brain centers that control energy intake and expenditure (St-Onge *et al.*, 2012). Overweight and obesity results over time when energy input outweighs energy output which results in a positive energy balance. Various studies have shown that consistent sleep restriction results in decrease in the level of Leptin and increase in the level of ghrelin which promotes hunger (St-Onge *et al.*, 2011). Fig.4 shows the connection between sleep loss and energy balance (energy expenditure and energy intake).



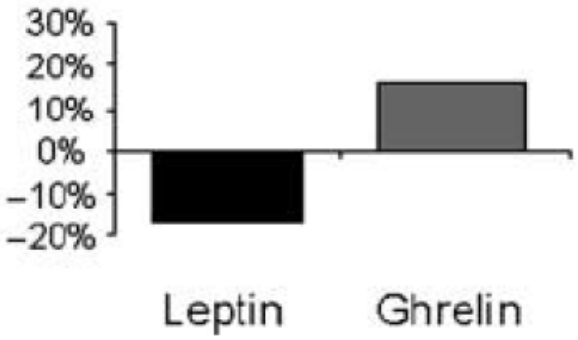
Source: Kristen, 2007

Figure 4: Schematic representation of potential pathways through which sleep loss may lead to a positive energy balance in which energy intake is greater than energy expenditure

According to Bass *et al.*, 2010 and Laposky *et al.*, 2008, Sleep influences energy metabolism and one function of sleep as earlier stated in chapter two is to conserve energy. One of the mechanisms known to associate insufficient sleep and obesity is positive energy balance. Sleep restriction could affect endogeneous process related to energy balance such as impairment in glucose metabolism and up regulation of appetite (Kristen, 2007). Sleep restriction could also affect exogenous factors such as food choice, reduction in physical activity or energy expenditure.

IX. EXPERIMENTAL STUDIES LINKING SHORT SLEEP TO OBESITY

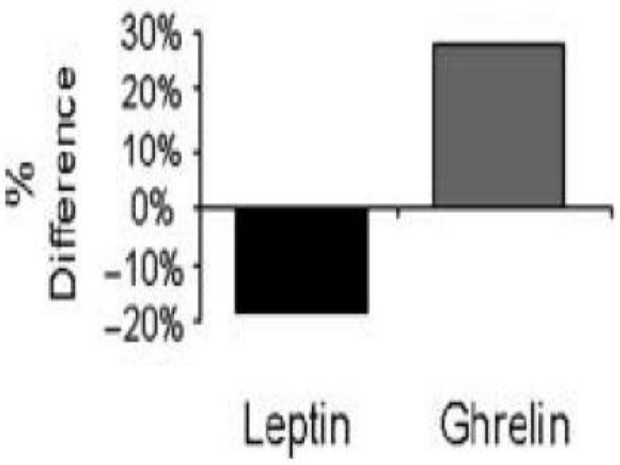
In the Wisconsin Sleep Cohort Study(WSCS) done by Taheri *et al.*, 2004, it was stated that the link between short sleep duration and obesity could be mediated by alterations in circulating leptin and ghrelin levels, two opposing hormones in appetite regulation as shown in Fig. 3 (Taheri *et al.*, 2004; Zigma *et al.*, 2003). The result of the study showed that individuals who slept less than 8 hours had an increased BMI proportional to decreased sleep duration. A decrease in sleep duration from 8 hours to 5 hours was accompanied with 15.5% decrease in the level of leptin and 14.9% increase in ghrelin as shown in Fig. 5.



Source: Taheri et al., 2004

Figure 5: Percent difference in levels of leptin and ghrelin comparing short sleep (5hours) to longer sleep (8 hours) conditions

A similar study by Spiegel *et al.*, 2004 also showed corresponding decrease in the level of Leptin and increase in the level of Ghrelin comparing sleep duration of 4 hours and 10 hours of which the subjects received equal amount of caloric intake. The result obtained showed a percentage decrease of 18% in leptin level and 28% increase in Ghrelin level when sleeping 4 hours compared with 10 hours sleep duration as shown in Fig.10.



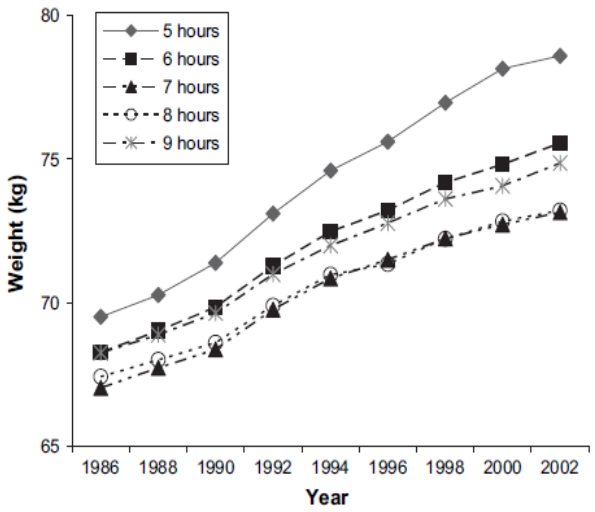
Source: Spiegel et al., 2004

Figure 6: Percent difference in levels of leptin and ghrelin comparing short sleep (4hours) to longer sleep (10 hours) conditions

X. EPIDEMIOLOGICAL STUDY LINKING SHORT SLEEP TO OBESITY

A meta-analysis of 45 cross sectional studies including 604,509 adults and 30,002 children confirmed the relationship between short sleep (generally fewer than 5 hours per night in adults and fewer than 10 hours per night in children) and obesity (Cappuccio *et al.*, 2008). According to most studies, short sleepers experience greater weight increase over time (Hasler *et al.*, 2004; Patel *et al.*, 2006; Chaput *et al.*, 2008; Lopez *et al.*, 2008; Gunderson *et al.*, 2008; Hairson *et al.*, 2010). Short sleepers (fewer than five to six hours) gained 2kg more in a 6-year study (Patel *et al.*, 2006). In addition, subjects had a 35% and 31% greater chance of gaining more than 5kg in 6 years and gaining more than 15kg in 16years respectively (Patel *et al.*, 2006; Chaput *et al.*, 2008). However there is a gender dependent variability among the studies of short sleep associated with weight gain, for instance, a large study including 35,247 subjects found that lean men, but not lean women who slept fewer than five hours had increased odds of becoming overweight within one year (Watanabe *et al.*, 2010). In contrast, in a cohort of 3576 elderly subjects, women, but not men who slept fewer than five hours had a higher risk of gaining 5kg in two years (Lopez *et al.*, 2008).

A study was carried out by Patel *et al.*, 2006 on middle aged women in a Nurse Health Cohort study which took place for a period of 12 years. A detailed questionnaire was completed based on their medical history and lifestyle which includes their habitual sleep duration. Follow up questionnaire were administered every 2 years to update their information on potential risk factors and to identify newly diagnosed illness. Also, participants were asked their current weight on each biennial questionnaire. The result obtained from the study is summarized in the graphical representation shown in Fig. 7.The result showed that those who reported sleeping less than 5 hours had the highest body mass index with highest risk of obesity compared to the other time duration reported; the graphical representation in Fig.7 showed that those who reported sleeping for less than 5 hours had a significant increase in their weight gain compared to the other sleep durations reported.



Source: Patel et al., 2006

Figure 7: Mean age-adjusted weight of the Nurses' Health Study cohort from 1986 to 2002 as a function of habitual sleep duration in 1986

XI. CONCLUSION

Sleep loss is a major problem to the maintenance of good health which has been ignored overtime. The consequence of sleep loss goes beyond daytime fatigue or weakness but poses a risk of a number of health problems which includes Obesity and Type 2 Diabetes. Thus, sleep should be taken as one of life important physiological activity and irrespective of our busy daily schedules, ample time should be dedicated to sleep per night as it has been stated by the National sleep foundation that adults should sleep for a minimum of six hours per night. Adequate sleep is restorative mentally, physically and emotionally. It facilitates learning, helps concentration and retention of information, and gives the brain much needed rest from daily stress. Sleep is thus essential to the maintenance of good health.

The following tips are helpful in getting good sleep:

- ✓ Ensure your bed is comfortable enough and pillows at a comfortable height if necessary.
- ✓ Ensure the room is cool, well ventilated, and free of any disturbance such as noise.
- ✓ Incorporate a period of exercise into each day.
- ✓ Avoid stimulants before bedtime.

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