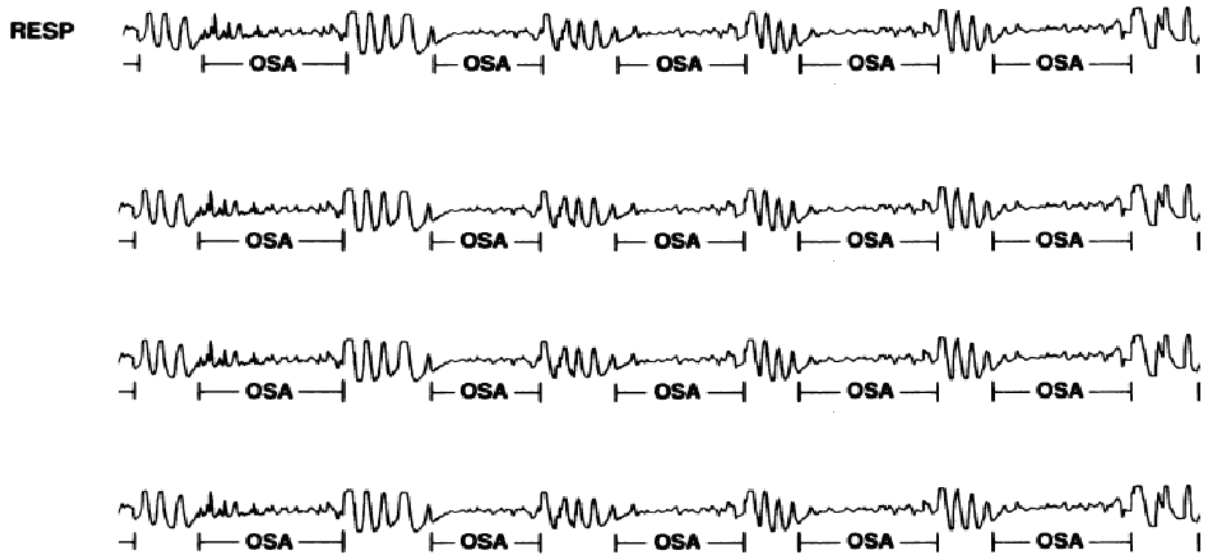
Obstructive Sleep Apnea

Cause or consequence?



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June 2010

Biomedical Sciences

RuG Groningen

Index

Abstract

Obstructive sleep apnea (OSA) is a common disorder in the western world. OSA patients suffer from repetitive collapses of the upper airway tract during sleep, resulting in hypoxemia and arousal from sleep. 2-7% of general adult population is found to suffer from OSA. Incidence of OSA in the obese population exceeds these numbers by far; the numbers increase up to 30% and even as far as 70% in obese diabetic individuals. The idea that there is a correlation between OSA and obesity is a commonly shared idea since years. But what is the chicken and what is the egg in this story?

Some researchers say crenialfacial abnormalaties cause the upper airways to collapse during the night. During the day, the activation of mucles that dilate the airways would protect the airway against collapsing. Though not all researchers support these hypothesis, they all agree on the idea that fat deposition in the neck region makes one vulnerable for the development of OSA. Fat depositioning in the upper airway region would promote changes is muscle orientation and alter the firing rate of neurons of the dilatory mucles. Neckcircumference correlates with prevalence of OSA; a neck circumference of 43 cm or more increases the risk on OSA significantly. Some, though not all, studies found a wider neck in OSA patients compaired with BMI matched non-OSA patiets. Besides, weight loss is associated with a decrease in OSA severity and vice versa. But OSA severity appears to be not the only factor correlating with neck circumference. The same accounts for other obesity associated factors. Recently the proposed direct causal relationship between fat depositioning in the neck region and the development of OSA is questioned and a reverse relationship is proposed.

Short sleep duration is associated with an increase in BMI. OSA patients, because of the frequent arousal from sleep, both adequate sleep duration and sleep quality are reduced. Indeed increased weightgain in OSA patients has been found compaired with non-OSA patients. Besides that, an increase in both calloric intake and fat deposition in OSA patients compaired with non-OSA patients is seen, making OSA patients more susceptible for weight gain. This is caused by several factors. First of al, repetitive waking causes activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis promoting a chronic state of inflammation in the body. Besides that, both sleep restriction and sympathetic nervous activation causes upregulation of leptin levels but in the same time, the body becomes insensative for leptin, deminishing its restriction on caloric intake. Ghrelin is also elevated due to sleep restriction and seems to cause an increase in caloric intake. All these changes together induce insulin resistance. Treatment of OSA using continous positive airway pressure appears to normalize all impaired values noted above and promotes weight loss, suggesting OSA causes obesity.

Whether obesity causes OSA or vice versa is hard to say; for both statements plausible evidence is present. But regarding all evidence presented in this review, I would say OSA causes obesity. But before conclusions can be drawn, more research should be performed.

List of Abbrevations

AHI	-	Apnea Hypopnea Index
BMI	-	Body mass index
CPAP	-	Continuous positive airway pressure
EDS	-	Excessive daytime sleepiness
IL	-	Interleukin
NPY	-	neuropeptide Y
OSA	-	Obstructive Sleep Apnea
TNF-a	-	Tumor Necrocis Factor alfa

Introduction

Obstructive sleep apnea (OSA) is a common disorder in the western world. OSA patients suffer from repetitive collapses of the upper airway tract during sleep, resulting in hypoxemia and arousal from sleep (Pillar and Shehadeh, 2008; Vgontzas, 2008). Consistent results on its prevalence do not exist. Some researchers say 4-5% of middle-aged men and 2-3% of middle-aged women suffer from OSA (Pillar and Shehadeh, 2008), while others say between 17-24% of a general male population and 5-9% in general female population meets the criteria of OSA (Vgontzas, 2008). All researchers however are consistent on its prevalence in obese individuals; OSA is among obese individuals a very common disorder. The numbers increase up to 30% in obese individuals (Pillar and Shehadeh, 2008) and even as far as 70% in obese diabetic individuals (Brooks et al, 1994). Some even speak of a prevalence of 58-98% in morbidly obese populations. Fact is that OSA prevalance has increased over the last centuries in parallel with the rise in obesity (Donohue, 2010).

The idea that there is a correlation between OSA and obesity is a commonly shared idea since years. But what is the chicken and what is the egg in this story (Pillar and Shehadeh, 2008)? On one hand, obesity is known to be the most important reversible risk factor for the development of OSA (Shah et al, 2009; Malhotra et al, 2002). But on the other hand, a roughly estimated 50% of all OSA diagnosed individuals are not obese (Mortimore et al, 1998). In this review, I shall focus on the OSA syndrome and obesity and their common features. Following I will present the evidence suggesting obesity causes sleep apnea. But I will also strive to question the common thought that obesity causes obstructive sleep apnea and present data that may argue against this common thought. Data suggesting the opposite, that OSA causes obesity is accumulating.

Obstructive sleep apnea

Obstuctive sleep apnea is a chronic condition defined as the cessation (apnea) or reduction (hypopnea) of airflow for at least 10 seconds during sleep as a result of obstruction of pharyngeal airways, despite thoracical and abdominal respiratory muscle effort. A hypopnea is defined as a reduction in oronasal airflow by 25 to 50%, associated with either arousal or a decrease in oxygen saturation (Punjabi, 2008). An arousal is a sudden cortical activation and does not necessarily result in behavioral waking (Ekstedt et al, 2004). Both apnea and hypopnea result in hypoventilation, hypoxemia and hypercapnia. The patient has to arouse or even wake up to resume breathing, which results in sleep fragmentation and activation of the sympathetic nervous system (Pillar and Shehadeh, 2008; Al Lawati et al: 2009). The frequent arousal caused by hypoxemia results in reduced sleep efficiency and a non-refreshing nature of sleep. Besides that, a significant reduction of approximately 50% of slow wave sleep (stage 3 and 4) is observed in OSA sufferers (Sergi et al, 1999). Duration of REM sleep is reduced as well (Pillar and Shehadeh, 2008).

The severity of OSA is usually represented by the apnea-hypopnea index (AHI) value which is as much as the number of apneas plus hypopneas per hour of documented sleep. An AHI below 5 is considered normal (Guilleminault et al, 1993), but whether everybody has apneas or hypopneas during sleep or the majority of people has an AHI of 0 is not documented. If the AHI reaches levels between 5 to 15 events per hour and oxygen saturation stays above 85%, it is divined as mild OSA. Moderate OSA corresponds with 15 to 30 events per hour, whereas severe OSA is diagnosed if the events per hour rise above 30, or arterial oxygen saturation drops below 65% (Al Lawati et al, 2009; Pillar and Shehadeh, 2008 and Purvin et al, 2000). This definition however is not universally used; different studies use different definitions for OSA. Ancoli-Israel devines OSA as an AHI of 10 or more per hour in his studies (Ancoli-Israel et al, 1991). Besides that, different studies devine OSA severity different; Harris considers OSA mild if the AHI reaches between 5 and 20, moderate between 20 and 40, and above 40 he calls OSA severe (Harris et al, 2010).

The amount of apneas per hour and the oxygen saturation is usually measured using an overnight polysomnogram. In this test multiple physiological signs of sleep are measured simultaneously, such as electroencephalogram, electrooculogram, electromyogram, oronasal airflow, oxyhemoglobin saturation and respiratory muscle effort (Punjabi, 2008; Donohue, 2010). The overnight polysomnogram comes with some difficulties. First of all, polysomnography requires an overnight stay in a sleep laboratory. This is a time consuming and costly procedure and will never give a complete correct diagnosis, considering the laboratory is not the normal sleep environment of the patients. This is partly solved by making a polysomnogram at home (Pillar and Shehadeh, 2008), or by letting people sleep in the laboratory for two or more nights in order to overcome the 'first-night' effect (Punjabi, 2008). It has been noted that standardization of this procedure is very difficult and untill now not successfull. Comparisons between studies from different laboratories should be made extremely careful (Punjabi, 2008). The difficulties of standardization might explain at least a part of the enormous variation seen in the epidemiology of OSA. According to Punjabi, who compared a lot of

Being a premenopausal woman seems to decrease the risk on developing OSA. In this population the prevalence is as low a 0,6%. Postmenopausal women in contrast, have a risk at developing OSA that lies close, though still lower then, to the risk in age-mathed men.

(Bixler et al, 2001).

epidemiological studies on this subject, one of the most reliable estimations of OSA prevalence comes from Young and Bixler. They estimated a 3-7% OSA with Excessive Daytime Sleepiness (EDS; one of the major physiological consequences of obstructive sleep apnea) prevalence for adult Caucasian men, and 2-5% for adult Caucasion women in the general population (Young et al, 1993; Bixler et al, 2001).

The incidence of OSA increases with age. Studies on elderly persons (between 65 and 99 years of age) reported an OSA incidence of 70% among men and 56% among women. Sleep apnea was defined as an AHI of 10 or more per hour in this study (Ancoli-Israel et al, 1991). In comparison to individuals of 20 to 44 years of age, individuals above 65 have an increased risk on a AHI greater that or equal to 10 events per hour of 6.6 concerning men (Bixler et al, 2001).

Comparison of these results with other etnic groups suggest a somewhat higher prevalance in Asian, Indian, Hispanic and Afro-Americans in comparison with Caucasians. What causes these differences is unknown. The cause could be directly genetic or from ethnic-related characteristics such as upper airway structure (Pillar and Shehadeh: 2008). Punjabi states that differences in craniofacial morphology may cause some of the variation found in OSA prevalence among different ethnical groups (Punjabi, 2008)

Treatment of OSA consists of continuous positive airway pressure (CPAP). Via a mask, a machine blows pressured air into the nostrils, hereby keeping the airways open (Donohue: 2010). CPAP is proven to have a positive effect on daytime sleepiness in moderate and severe OSA patients (Vgontzas: 2008). Randomized trials have shown benefits of CPAP in severe OSA patients considering subjective sleepiness, objective tests of sleepiness, quality of life, driving performance and depression scores (Vgontzas: 2008). But these are very optimistic results. Other studies found no changes in subjective sleepiness, or even worsening of night time symptoms. The effects of CPAP on more complex problems associated with OSA is not systematically studied, and the results that do exist are inconsistent (Vgontzas: 2008). Later in this review I shall present more data on the effectiveness of CPAP treatment regarding several comorbidities of OSA.

Although the prevalence of OSA is over 4% in a mixed population, only 1,6% is diagnosed as such by their physicians and only 0,6% are actually treated for OSA, according to the Sleep Heart Health Study (Pillar and Shehadeh, 2008). Fact is that, although more and more recognized as a cause of medical morbidity and mortality, OSA is still under-diagnosed by physicians and under-recognized as an important disorder (Pinjabi, 2008). An early diagnoses of OSA is important, since frequent arousal is not the only feature associated with OSA. OSA sufferers usually suffer from loud snoring, dry mouth, morning headaches, heartburn, noctoria, daytime sleepiness (EDS), impaired work performance, sexual disfunction in men and decrements in health-related quality of life (Pillar and Shehadeh, 2008; Punjabi, 2008). But the worst is yet to come. The fragmented sleep results in decreased neurocognitive function. OSA is therefore associated with a high rate of deadly car accidents. George found a 2 to 10 fold

OSA patients seem to suffer from hippocampal damage and cognitive deficits as a result of metabolic and hypoxic insults. A significant reduction of grey matter in the cornu ammonis 1 region in the hypocampus has been reported. This region is associated with learning and memory, both functions seem te be impaired in OSA patients.

(Fung et al, 2007)

increase in risk of causing a motor vehicle accident in OSA patients compaired with the general population (George, 2007). Other side effects of OSA are cardiovascular complications such as systemic and pulmonary hypertension, arrhythmias, myocardial infarction and strokes (Pillar and Shehadeh, 2008) and abnormalities in glucose metabolism (Punjabi, 2008). Besides this, OSA is more frequently seen in patients with hypothyroidism, diabetes and gastro-esophageal reflux. The most striking OSA associated disorder found so far, is obesity. Prevalence of OSA in obese subjects reach the 30% level and even as high as 60-98% in morbidly obese persons. Besides, 60-90% of all OSA sufferers are overweight, indicating a strong link between these two disorders.

Obesity

Obesity is defined as a body mass index (BMI) of 30 kg/m² or more. A BMI above 40 kg/m² is considered as morbidly obese. In the United States, one in three adults is obese (Ogden et al, 2006). In Great-Brittain obesity levels reach as high as 25% in adult population (Harris et al, 2010). In the Netherlands 11% of adult men and 12% of adult women are considerd obese (Obesitas vereniging Nederland). Obesity has reached the statuts of a pandemic (Roth et al, 2004) and its prevalance is ever rising (Ogden et al, 2006). First obesity was only seen in industrialized contries, now it is even seen in developing countries. Not only adults develop obesity; its prevalance in children is rising as well. For the first time in history, the number of overfed people has overtaken the number of underfed people (Newmen, 2004).

Obesity has been associated with a stunning increase in mortality risk (figure 1) (Roth et al, 2004). The increase in mortality ratio is mostly due to the complications associated with obesity, such is diabetes mellitus type II and cardiovascular diseases.

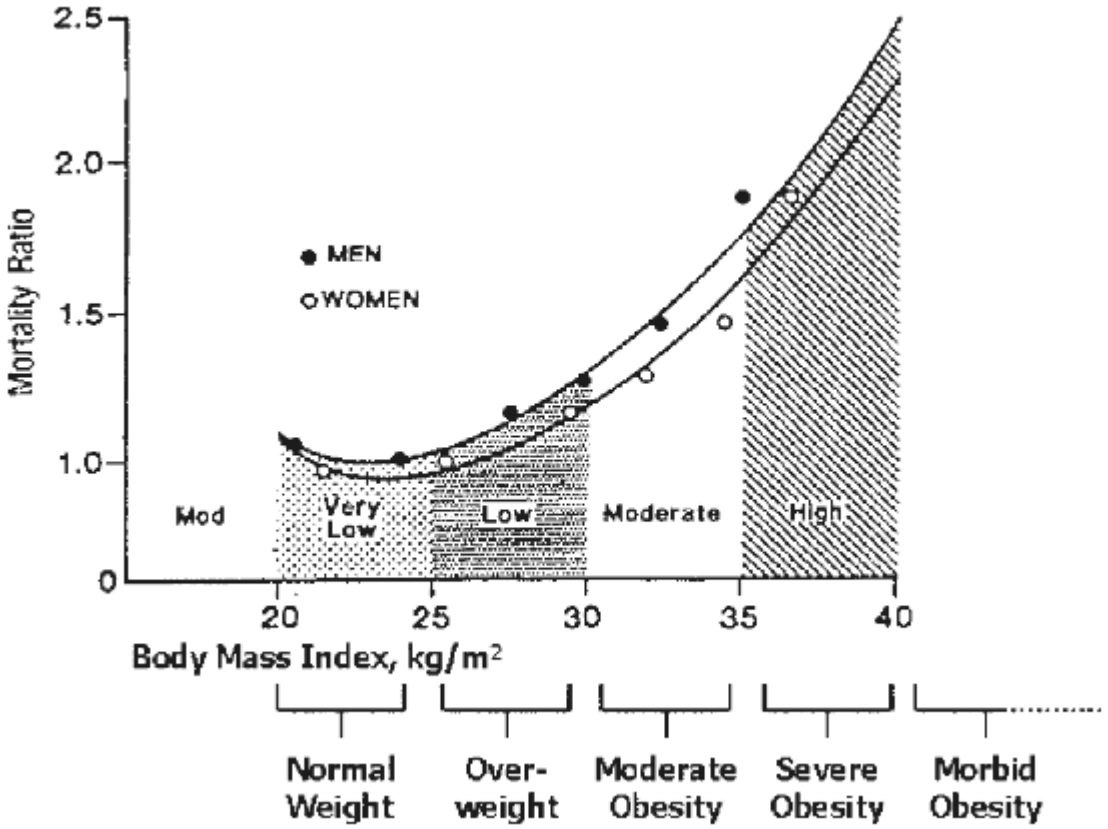

Figure 1: Risk of mortality

Risk of mortality in both men and women increases with BMI. The curves are J-shaped, showing an increase in mortality risk on the low end of BMI as well.

(extracted from Rothe et al, 2004)

Overfeeding causes a disbalance on the energybalance of the body, resulting in excessive fat accumulation. Fat can be stored both visceral and subcutanous. Visceral fat, being the 'bad' fat, and subcutanous fat, being the 'good' fat, resulting in apple or pear shapes respectivily (Roth et al, 2004).

Visceral fat is metabolically active fat producing a variety of molecules, such as leptin (a satiety factor), resistin (which heightens resistance to insulin), and adiponectin (a hormone which heightens insulin sensitivity). All these hormones are only produced in the fat tissue and are all upregulated in obese subjects. Serum and plasma leptin concentrations have been shown to correlate with BMI and percentage of body fat (Schwartz et al, 1996). Leptin, being able to cross the blood-brain barrier, signals to the brain about the energy stores of the body and thereby regulating long term energy balance. Accumulating evidence however indicate that leptin is also produced by the stomach and is thereby able to regulate short-term energy balance and food intake as well (Sobhani et al, 2000).

Another peripheral factor regulating energy balance in the body is ghrelin. This hormone is secreted by the stomach and is concidered an appetite-stimulatory factor (Klok et al, 2006). In obese subjects, ghrelin levels have been shown to be decreased (Tschop et al, 2001). Both ghrelin and leptin can cross the blood-brain barrier and bind to hypothalamic receptors. Here they influence central factors regulating energy balance such as Neuropeptide Y (NPY). In obese subjects, in which the energy balance is positive, one would expect decreased levels of ghrelin and increased levels of leptin to restore energy balance. The opposite is true, as read above. This might be due to the development of leptin resistance (Klot et al, 2006). Obese subjects therefore are no longer sensetive for the influence of this hormone and energy balance becomes more disturbed. It has been hypothesized that this resistance is due to disturbed transport accros the blood-brain barriere. Decreased leptin levels in the cerebrospinal fluid have indeed been found in obese subjects compaired with lean individuals (Schwartz et al, 1996).

Other factors produced by the fat tissue, are inflammatory proteins such as Tumor Necrocis Factor alfa (TNF-a) and interleukins. Being obese therefore is said to be a chronic state of inflammation. It has been shown that the adipose tissue of obese people has a higher density of macrophages hosted then fat tissue in non obese subjects (Xu et al, 2003). This chronic inflammation state is a very important contributor to the insulin resistance often seen in obese individuals (Perseghin et al, 2003). Insulin resistance is devined as the decreased responce of peripheral tissue to insulin action. Type II Diabetes Mellitus often results from insulin resistance (Xu et al, 2003).

If the fat tissue is already heavely loaden with fat, additional fat might be deposited as metastatic fat. This is very dangerous fat since it can compromise or damage the deposition site. One example is the impairment of insulin secretion of ß-cells in the pancreas due to metastic fat diposition (Unger et al, 2002).

Obesity is not just a risk factor for insulin resistance, high prevalance of cardiovascular diseases such as hypertension, cardiac ischemia and stroke (Piorier et al, 2006), chronic kidney disease and diabetes mellitus type II are commonly seen in obesity patients (Katchunga et al, 2010). As noted above, OSA and obesity are to disorders commonly seen together as well. In the next chapters, I will futher discuss the relationship between these to disorders and try to find out what causes what.

Does obesity cause OSA?

Epidemiologically the association between OSA and obesity is well documented. Neck circumference and, though less convincing, waist/hip ratio have been reported to correlate with OSA severity (Sergi et al, 1999). But whether obesity causes OSA or OSA causes obesity is still under debate. Mechanistically, several obesity related effects have been suggested to contribute to the development of OSA (Pillar and Shehadeh, 2008).

Airway anatomy

Patency in the pharyngeal airways can be described using a 'balance of pressures' concept. The size of the upper airways depends on this balance with on the one side the forces that would collapse the airway (extraluminal pressure and the negative pressure in the airways during inhalation) and the forces that maintain airway patency on the other side (the contraction of dilator mucles). It has been suggested that the evolution of speech led to the loss of rigid support of the hyoid bone, making pharygneal patancy depending largely on muslce activity. The dependency on muscle activity makes the pharyngeal airways vulnerable for collapse, especially in individuals with a small upper airway (Fogel et al, 2004).

Several studies have found differences in the upper airways of OSA patients compaired to non-OSA patients. Cistulli has found several skeletal and soft tissue structural differences in OSA sufferers compaired with non-OSA sufferers during wakefulness, using radiography, CT and MRI (Cistulli: 1993). He found features such as retrognathia, enlarged tongue, tonsollar hypertrophy and decreased posterior airway space, which can all lead to a narrow upper airway. Smaller pharyngeal airways, resulting in a reduced luminar space, is commonly seen in OSA patients. A reduced lumen makes the airway more vulnerable for collapse. Miles and colleagues found that the length of the mandibular body (the lower jaw bone) is the craniofacial measure associated with the highest increase of risk on developing OSA (Miles et al: 1996). All these anatomical predispositions are during wakefullness overruled by protective mechanisms. These mechanisms maintain pharyngeal airway patency by increasing the activity of dilator mucles. During sleep, these mechanisms fail, resulting in apneas and hypopneas (Fogel et al, 2004).

There have been a limited amount of surgical trails adjusting crenialfacial abmormalities. This surgery, such as Uvulopalatopharyngoplasty or Expansion sphincter pharyngoplasty, seem to have a decreasing effect on AHI though no significant changes have been reported so far (Sundaram et al, 2009). It should be noted that all these studies were methodologically far from optimal and more and better controlled studies should be performed since results are promising. A very recent study does prove that multilevel surgery on the crenialfacial area is associated with a decrease in AHI. Results vary widely among subjects however (Kezirian et al, 2010).

Other studies however, state that no skeletal differences were observed thus far is OSA sufferers (Pillar and Shehadeh, 2008). It is even stated that patients with smaller upper airways due to anatomic abnormalities do not suffer from OSA (Vgontzas, 2008). Crenialfacial differences or not, excess fat accumulation seems to induce OSA by altering crenialfacial differences. Increases in body weight can alter crenialfacial features and upper airway mechanics in several ways (Punjabi, 2008). First of all, direct deposition of fat within the airway luminal walls may increase the extraluminal pressure, shifting the balance of pressures towards airway collapse. This results in a reduction of the upper airway luminal size (Fogel et

al, 2004). Another argument making obesity guilty of causing OSA, comes from its effect on pharyngeal muscles. In non-OSA subjects, the inspiratory dilator phasic upper airway muscles (the genioglossus being the best studied), activated during inspiration, counteract the collapsing influence of negative airway pressure and extraluminal pressure. Other muscles, such as the tensor palatini, are also thought to play a role in the maintenance of airway patency. These are tonic muscles and show a constant level of activity throughout the respiratory cycle. The effect of sleep on these two types of muscles play an important role in OSA (Pillar and Shehadeh, 2008). It has been shown that during sleep, the activity of muscles with a primarily tonic activation pattern (e.g. the tensor palatini) decrease. They are found to reach levels of 20-30% of waking values during stage 4 sleep. Fat deposition is thought to interfere with neural compensatory mechanisms that maintain airway patency during sleep by altering firing rate of the neurons in the ventral medulla controlling this pathway (Puljabi, 2008 and Fogel et al, 2004). Fat deposition within the muscles of the upper airways cause altered muscle structure or decreased upper airway muscle protective force (Pillar and Shehadeh, 2008). Fat deposition can also alter muscle orientation in this region, making ditalor muscles less able to maintain airway patency (Foge et all, 2004).

Fatty tissue deposition on the chest wall and on the latheral walls of upper airways, contributes to a reduced functional residual capacity due to a diminished chest wall compliance and an oval shaped pharnix. A reduced functional residual capacity of the lungs seems to reduce is size of the upper airways (Pillar and Shehadeh, 2008). Decrease in functional residual capacity also results in a decrease in the stabilizing caudal tractions of the upper airways (Punjabi, 2008). An oval shaped pharyngeal airway results in a relatively high airway pressure. The oval shaped airway reduces the ability of the muscles to dilate the pharynx. Thus being obese makes one anatomically predisposed for upper airway collapse and thereby the development of OSA.

Neck circumference

Crenialfacial abnormalaties or not, most researchers agree that fat deposition in the neck region makes one vulnerable for the development of OSA. Fact is, that airway size always decreases with the increase of body fat (Pillar and Shehadeh, 2008). It has been shown that weight, waist circumference and neck circumference correlate with prevalence of OSA (Soriano-co et al, 2010). Several studies have found no relation between the severity of OSA and BMI (Martinez-Rivera et al, 2008; O'Keeffe and Patterson, 2004). Neck circumference and abdominal fat seem to be far more indicative as OSA predictors (Harris et al, 2010). A neck circumference of 43 cm or more seems to increase the risk on OSA significantly (Gregg et al, 2000). The circumference of the neck is usually measured to estimate the upper body subcutanous fat amount (Preis, 2010).

If fat deposition in the neck region is indeed the most important riskfactor for the development of OSA and not being obese as such, several criteria have to be met. First of all, obese people suffering from OSA have to have a bigger neck circumference then non-OSA suffering obese. Soriano-co has studied this variable but has not found a significant difference in neck circumference between OSA and non-OSA suffering obese populations (figure 2)(Soriano-co et al, 2010). He did however, found a higher central adiposity ratio and fat mass in OSA sufferers compaired with non-OSA suffers. The fact that neck circumference was not significantly different, might be due to the low number of participants in this studie (26 morbidly obese women), since in an other study there were found significant differences.

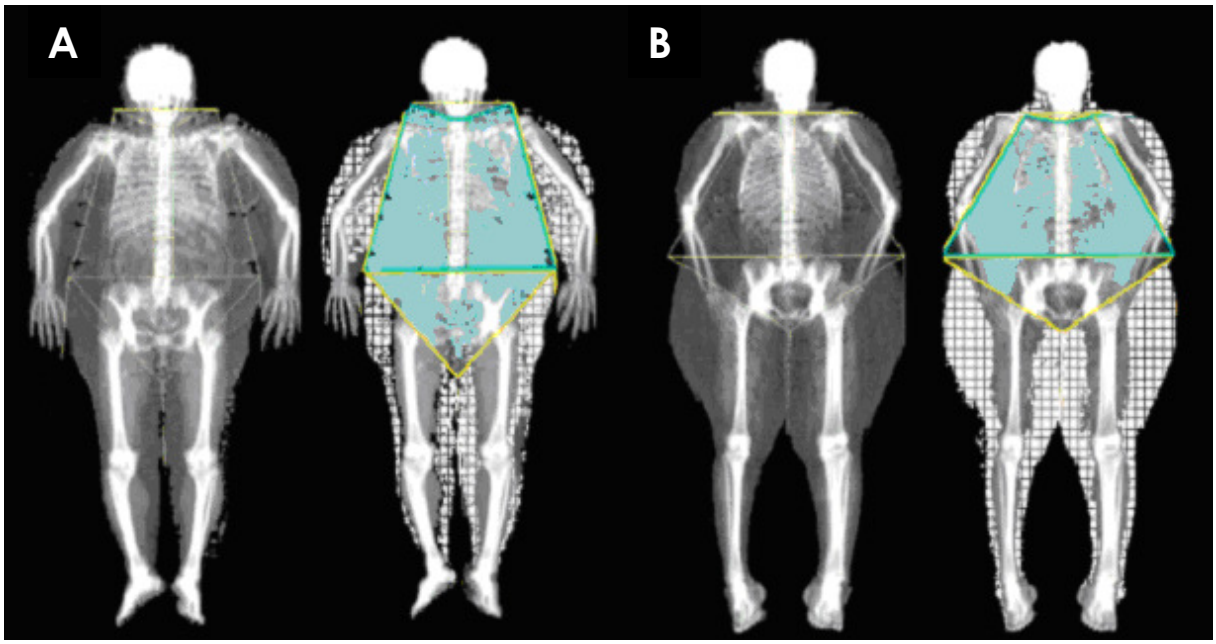

Figure 2: ***Fat deposition might influence OSA development***

	A	B
Total mass (kg)	141	124
Fat mass (kg)	65.2	58.6
BMI (kg/m²)	45.9	42.8
Central adiposity ratio	1.11	0.99
AHI	20.8	0.6
Neck circumference (cm)	44.45	41.96

This picture shows DXA scans of the obese women with similar body weights and BMI but different central adiposity rates (trunk/non-trunck % body fat) and AHI.
(Extracted from Soriano-Co et al, 2010)

670 people were studied in a study that revealed that obese patients with sleep apnea had fatter necks than equally obese nonapneic snorers, though abdominal circumferences were similar (Hoffstein and Mateika, 1992). Onat et al found a significant 1.4 cm wider neck in OSA suffering men, with a mean neck circumference of 40.1 cm, compared with age and BMI matched controles (Onat et al, 2009). This studie also found that neck circumference is an indicator of central obesity, suggesting Soriano-co simply had a too small study population to find significant differences in neck circumference. Sergi even found a significant difference of 5 cm between the mean neck circumference of obese OSA sufferers compaired with obese non-OSA sufferers. In this study, in which 27 obese subjects participated, neck circumference accounted for 74% of the variability in AHI (Sergi et al, 1999).

Second, a fat neck should be related with sleep apnea, even in non-obese subjects. Roughly estimated, 50% of all OSA sufferers are not obese (if stated as a BMI > 30 kg/m²). Mortimore showed that non-obese OSA sufferers have a 10% greater neck tissue volume then there non-OSA suffering counterparts. They also had 27% more neck tissue volume attributed to fat. This fat was localized anterolateral of the upper airway (Mortimore et al, 1998).

It has been stated that a short and fat neck is a very characteristic sign in OSA patients (Dancey et al, 2003). Dancey has investigated the influence of gender differences in fat deposition on the prevalence of OSA. It is well known that OSA is more frequently seen in men compaired with women, especially pre-menopausal women. Men also tend to store fat abdominal, while women have more subcutanous fat. Dancey has found differences in neck circumference between the genders, with men having the biggest necks. Difference in neck circumference between men and women explains only 20% of the variation in AHI. Katz investigated both external neck circumference, BMI and internal circumference of the pharnyx and found that these variables accounted for 39% of AHI variability (Katz et al, 1990).

Third, a decrease is neck circumference has to be followed by a decrease in OSA severity and vice versa. As read above, obesity is considerd the most important reversible risk factor for OSA. Many researchers therefore say weight loss might decrease OSA severity. Yee et al have investigated the effect of weight loss on OSA severity and neck circumference. They found that a loss of approximately 10% weight in obese OSA sufferers resulted in a significant decrease of AHI of 16 incidences per hour (mean of 87 subjects) and a decrease in neck circumference. It should be noted that waist circumference and sagittal height also decreased (Yee et al: 2007). Other studies found similar, though far less dramatic results. Carter and Watenpaugh showed a reduction of AHI after weightloss and an increase in AHI after weight gain. Whether neck circumference changed was not measured (figure 3) (Carter and Watenpaugh, 2008).

> The gaining and loosing of weight has different effects on men compared to women. Men with more than 10 kg weight gain had 5.2-fold the odds of increasing their AHI by more than 15 events per hour. In contrast, women how gained that amount of weight, had but 2.5-fold the odds of a similar increase in their AHI.
>
> *(Punjabi, 2008)*

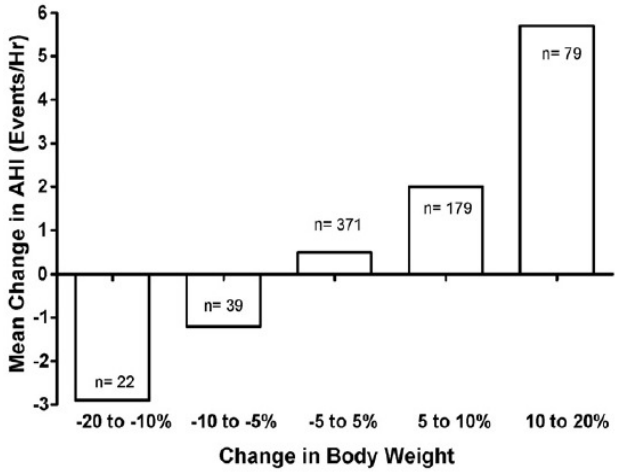

Figure 3: Changes in body weight alter AHI

(Extracted from Longitudinal Study of Moderate Weight Change and Sleep-Disordered Breathing).

Weight gain was also shown to increase OSA severity in several cohort studies such as the Sleep Heart Health Study. In this study, a weight gain of 10% corresponded with an increase in OSA severity of 32%. A 10% weight loss, resulted in a 26% reduction of AHI. Neck circumference was again, not measured (Peppard et al, 2000). Several studies on surgical weight loss also show a decrease in AHI. Measures where performed on patients before and after jejenoileal surgery (Haman et al, 1982) and gastic bypass surgery (Peiser et al, 1984). And again no measures of neck circumference where performed.

Surgery in which fat in the neck is removed, should have a positive effect on OSA, considered all above. Data on this subject however, is hard to find. In one article the removal of subcutaneous fat in the neck region of obese OSA patients was evaluated, but not regarding to AHI. This study focused on fat removal in the neck region for tracheotomy (Gross et al, 2002). The removal of fat in the neck region has been reported to be a surgical option allready performed for the treatment of OSA (Terris, 1999). But in this study as well, there was no attention to whether OSA severity changed or not. More research regarding this subject should be performed.

Neck circumference appears to correlate with other factors as wel, indepentant of BMI or waist circumference. Preis showed recently that neck circumference independantly contributed to cardiometabolic risk (Preis et al, 2010). Besides that, neck circumference is found to be a powerfull marker for visceral adipose tissue (VAT) and correlates positively with insulin resistance (Yang et al, 2010). A positive correlation was found between cholesterol as well as triglycerides and neck circumference as wel (Ben-Noun and Laor, 2006). Ben-Noun also showed that changes in both systolic and diastolic bloodpressure correlate with changes in neck circumference (Ben-Noun and Laor, 2004).

These are all valid and interesting data indicating obesity might cause OSA. However, critical readers must have noted that, as read above, neck circumference correlates not strictly to OSA severity but to a lot of obesity associated features. On top of that, confincing results indicating neck circumference is the most important riskfactor for the development of OSA are lacking. Yang has stated that neck circumference is a powerfull marker for VAT and, with increasing BMI, stays a powerfull marker. Waist circumference however, becomes less and less indicative for VAT with risings BMI, probably due to the increasing amount of subcutanous fat (Yang et al, 2010). So the correlation of neck circumference and not waist circumference with OSA might be due to the fact that visceral fat is the actual correlation with OSA. Soriano-cos results showed indeed a higher central adiposity ratio in OSA sufferers compaired with non-OSA suffers (Soriano-co et al, 2010). The more recent the studies on this subject, the more they question whether this correlative evidence should be considered as direct causal evidence. In recent studies, the effect of decreased sleep caused by OSA on e.g. leptin levels, insulin resistance, sympathetic nerve activity and sleep related hormones are mentioned as possible effectors on weight gain.

Does OSA causes obesity?

Recently, the aim of the studies has shifted to more physiological differences between OSA sufferers and non-OSA sufferers. More and more evidence accumulates suggesting that OSA causes weight gain and even obesity. Luutikäinen found in a follow-up study that having sleep problems increased the risk on major weight gain in women. Baseline BMI had a neglegible effect on this association (Lyytikäinen et al, 2010). People suffering from OSA have been reported to gain significant more weight than non-OSA sufferers. Phillips reported an average 5.2 kg weight gain in OSA patients, compaired with a 0.5 kg weight gain in non-OSA sufferers in one year (Phillips et al, 2000). Tehari has found in his study that a dose-response relationship excists between sleep duration and high BMI (Tehari et al, 2004). An U-shaped curvilinear relationship was found in which both extremely long sleep duration and short sleep duration correlated with high BMI (figure 4). It has been hypothesized that OSA patients spend more time in bed to compensate for their fragmented sleep, but even after controlling for AHI the U-shaped curvilinear relationship remained visible. Though this is a nice correlation suggesting OSA causes weight gain, an explanation it is not. It has been found however, that over the past decades the increase in obesity prevalence is associated with a decrease of self reported sleep in these decades. Short sleep duration is even found to be indipendantly associated with weight gain (van Cauter et al, 2008). According to van Cauter, adequate sleep duration and quality are important the normal functioning of hormonal processes, daily metabolic processes and appetite regulation. As read above, OSA decreases sleep quality and therefor might impair with both metabolic and hormonal processes and appetite regulation. In this chapter I shall attand these factors.

The relationship between BMI and sleep duration differs between men and women. In women, a U-shaped curve was found, while in men a monotonic trend towards higher BMI with shorter sleep duration has been reported.

(Tehari et al, 2004).

Caloric intake and physical activity

The first and most simple explenation why OSA could cause obesity lies in EDS as seen in OSA patients. Exessive daytime sleepiness would logically lead to less physical activity during the day, resulting in less energy expenditure and thereby increase of weight. Basta et al investigated this in a large study involving 1106 adults with AHI of more then 5. They found that physical activity decreased with increasing sleepiness. Epworth sleepiness scorese strongly correlated with Log AHI suggesting that more severe OSA correlates with less physical activity (Basta et al, 2008). Vasquez also investigated the phisical activity in OSA sufferers and found indeed a reduction if the AHI increased. OSA sufferers with an AHI above 50 exspendid 224.58 kilocalories less than OSA sufferers with an AHI below 50. But this was not the only interesting finding in this studie. She also found significant differences regarding to dietary intake in OSA sufferers. Female OSA sufferers with a AHI over 50 on average consumed 88,16 gram more cholesterol, 21.96 gram more protein, 27.75 more gram fat per day than OSA sufferers with an AHI below 50 (Vasquez et al, 2008). These differences in dietary intake remained significant even after adjusting for daytime sleepiness and BMI. The decreased energy expenditure in severe OSA suffererers however, was no longer significant after adjustment for BMI. These data indicate that OSA increases energy intake and thereby promotes weight gain. A role for OSA in energy intake has indeed been hypothesized; 'fatigue and short sleep duration influence dietary intake via alterations in neuroendocrine

control of feeding behavior' (Vasquez et al, 2008). So if this is true, OSA patients should have different serum levels of at least one food intake regulating hormone, independent of BMI. Indeed this has been found. More and more evidence accumulates showing changes in the serum levels of several hormones induced by OSA, indicating a role for OSA in the development of obesity.

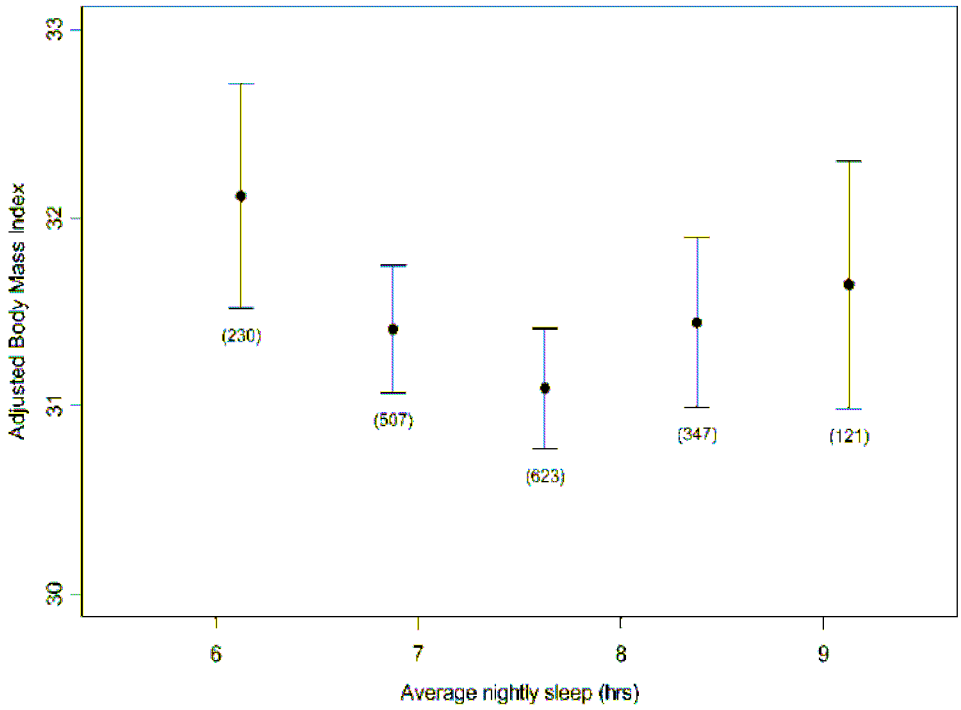

Figure 4: Relation between average nightly sleep and BMI

Mean BMI and average nightly sleep after adjustment for age and sex are plotted in the figure. A higher BMI correlates with a shorter average nightly sleep. A longer average nightl sleep correlates also with a higher BMI. A little over 7.5 hours of sleep correlates with the lowest BMI.

(extracted from Tehari et al, 2004)

Sympathetic nervous system and the hypothalamic-pituitary-adrenal axis

Repetitive episodes of hypopnea, apnea, hypercepnia and waking cause activation of chemoreceptors and other mechanisms, causing activation of the sympathetic nervous system and activation and disruption of the hypothalamic-pituitary-adrenal axis (Henley et al, 2009; Lanfranco et al, 2010). The constant activation of the sympathetic nervous system causes great fluctuations in bloop pressure during the night. If an OSA patient resume breathing, the venous return increases with results in increased cardiac output. This in combination with severely vasoconstricted peripheral vasculature resulting from HPA-axis activity, results in surges in blood pressure. At the end of an apnoeic event (mostly in stage 2 sleep), blood pressure can be as high as 250/110 mmHg (Narkiewicz et al, 2003). During daytime, OSA patients also show high sympathetic nerve activation which explains the high

prevalance of hypertension in OSA patients (Vgontzas. 2008). Grassi et al have confirmed these results in their study (Grassie et al, 2010). They also found that OSA is linked to a high sympathetic nerve activity not only in obese subjects, but also in non-obese subjects (figure 5).

Constant waking has been associated with changes in the circadian pulsatile cortisol release. The cortisol system activity has been find to be maximal during sleep (Henley et al, 2009). The changed patterns of pulsatile cortisol release has a great influence on insulin sensitivity and the vasculature. Cortisol therefore is likely to play a key role in the development of Diabetes Mellitus type II and cardiovascular diseases in OSA sufferers. Not only cortisol, but activation of the sympathetic nervous system increases insulin resistance as well (Grossie et al, 2010). The incidence of OSA in obese diabetes mellitus type II patients have been reported to be as high as 70% (Brooks et al, 1994).

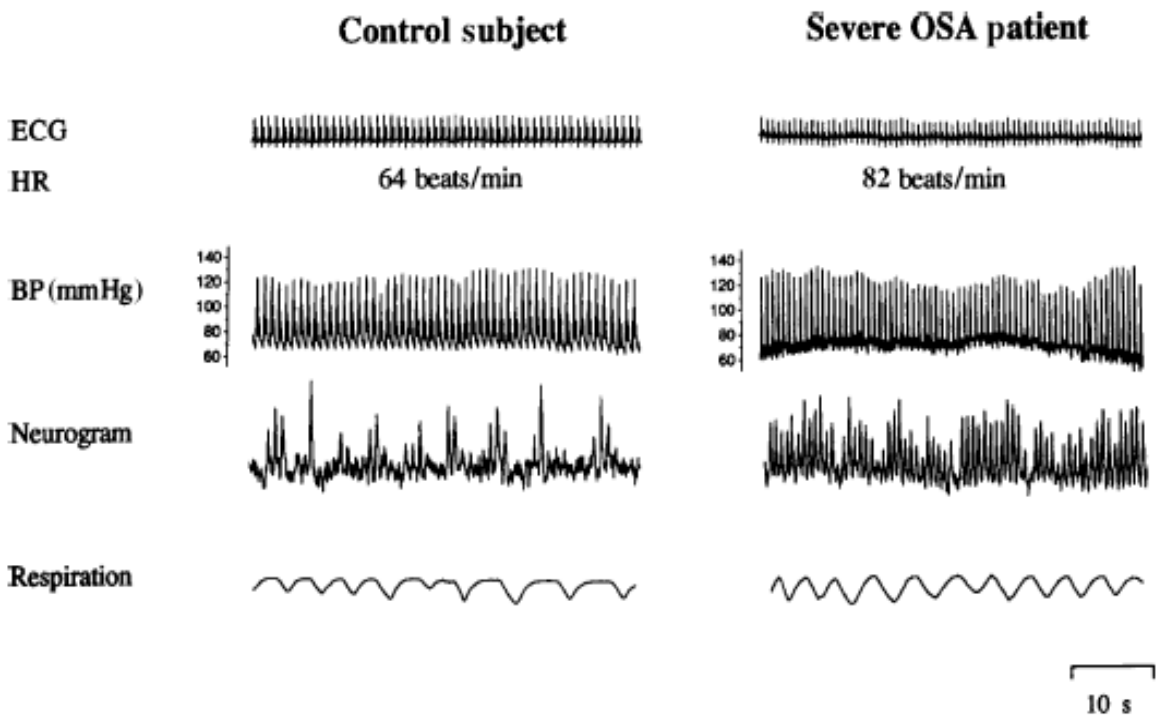

Figure 5: electroenchephalogram, blood pressure, neurogram and respiration recordings of a severe OSA patient and a control subject

The OSA patient shows an elevated heartbeat, increased blood pressure varriability and neuron activitie compaired with the control subject. Respiration is impaired in the OSA patient as wel.

Extracted from Narkiewicz and Somers, 2003.

Leptin

Phillips et al have hypothesized that high sympathetic nerve activation would activate adipocyte ß-receptors which in turn would decreases apidocyte leptin secretion in OSA patients. Decreased levels of leptin therefore would increase food intake en thereby predisposing OSA patient to excessive weight gain (Phillips et al, 2000). They found however, higher levels of leptin in OSA patients compaired with control subjects even after adjusting for percentage of body fat. Serum leptin levels appear to strongly correlate with OSA severity (e.g. Ulukavak Ciftci et al, 2005). High levels of leptin, which are also seen in non-OSA suffering obese patients, should reduce food intake and thereby decrease body weight. Phillpes hypothesized that, as seen in obesity, OSA patients develop leptin resistance which makes them insensitive for high levels of this hormone and making weight control difficult.

Not only high sympathetic nervous system activity, but sleep restriction as well has been found to increase serum leptin levels (Simpson et al, 2010). OSA patients have been found to have higher serum leptin levels than their sex and BMI matched controles (figure 5) (Vgontzas et al, 2000). These higher levels might be due to the low quality of sleep in OSA patients, but it has also been shown that OSA patients have more visceral fat than non-OSA patiets (Vgontzas et al, 2000). Visceral fat produces leptin and may therefore be the cause of the high leptin levels found in OSA patients. Besides, the amount of visceral fat is highly correlative to the severity of OSA (figure 5).

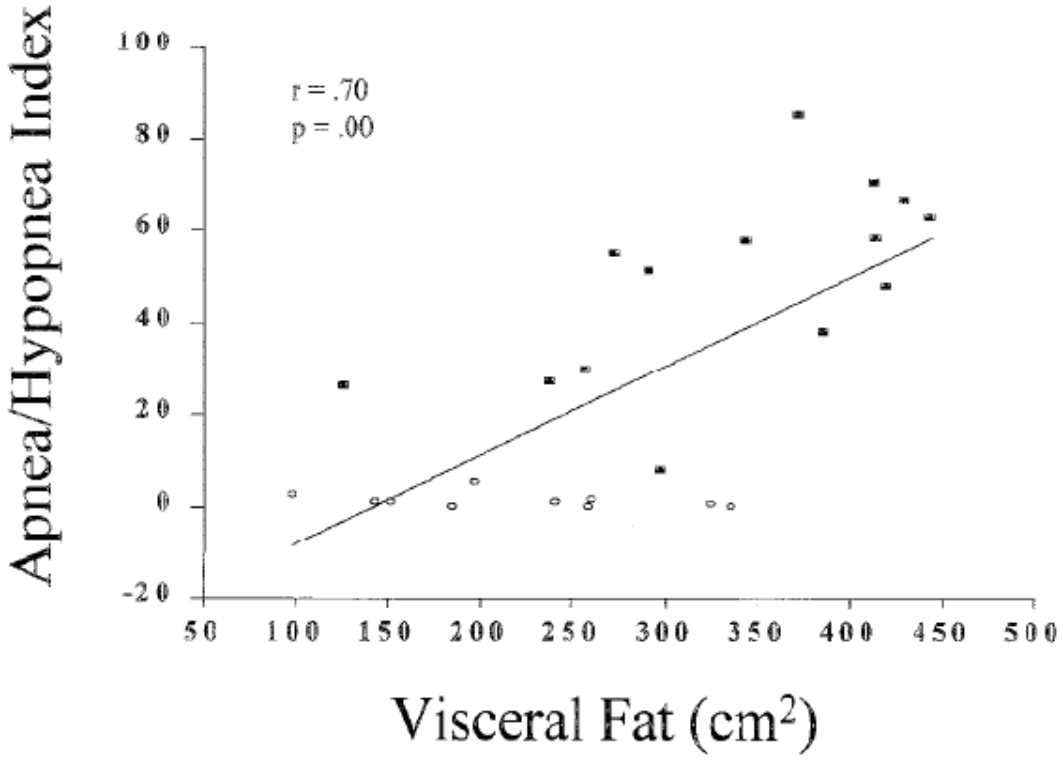

Figure 5: The relation between AHI and visceral fat.

A higher amount of visceral fat correlates with greater OSA severity.

(Extracted from Vgontzas et al, 2000)

In a study in lean mice in which intermittent hypoxia was induced, a increase in serum leptin levels was found as well. In these mice leptin was the only upregulated gene affecting glucose uptake. Blood glucose levels had dropped but insulin levels had remained the same. In obese mice in which hypoxia was induced however, an increase in serum insulin levels was found. Long term intermittent hypoxia in obese mice led to time-dependent increase in fasting serum insulin levels and worsened glucose tolerance (Polotsky et al, 2003). So not only increased cortisol levels, but sleep restriction by itself as well can alter insulin sensitivity. These findings indicate the development of insulin resistance in OSA patiets is caused by OSA independent of obesity. Indeed OSA has been found to be an independent risk factor for insulin resistance (Vgontzas, 2008; Lanfranco et al, 2010).

An explenation for the high leptin levels found in OSA patients might be the downregulation of the adipocyte b3-receptor downregulation as a result of sympathetic activation (Phillips et al, 2000). This results in insensitivity for leptin, making weight gain possible even though leptin levels are high and rising.

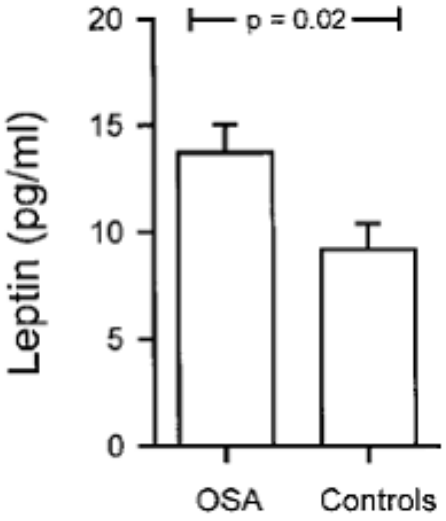

Figure 5: Serum Leptin levels in Obese and OSA patiensts

Serum leptin levels are significantly increased in OSA patients compaired with obese controls.

(Extracted from Phillips et al, 2000)

Ghrelin

Ghrelin is another hormone that has been found elevated after sleep deprivation (Tehari et al, 2004). In a recent study of patients with OSA and BMI matched control subejcts, ghrelin levels were shown to be significantly elevated in patients with OSA (Harsch et al, 2003). This indicates that elevated levels of ghrelin in OSA patients are due to their short sleep duration. The elevated serum ghrelin levels may contribute to the increased caloric intake seen in OSA patients (Pillar and Shehdeh, 2008). Other studies however have not found these elevated ghrelin levels in OSA patients (Ulukavak Ciftci et al, 2005).

Systemic inflammation

Alexandros Vgontzas, who has published over 100 articles about sleep apnea, was the first stating that OSA induces systamic inflammation. He found that the inflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6) and Tumor Necrosis Factor alfa (TNF-a) are involved in physiological sleep regulation and there secretion showed circadian patterns (Vgontzas,

2008). IL-6 secretion is found to increase even in modest sleep restriction. OSA, independantly of obesity, is associated with increased plasma levels of IL-1, IL-6 as well as TNF-a. (Vgontzas et al, 2000). There was however a positive correlation to BMI. Furthermore, they are positvely correlated with the degree of nocturnal sleep disturbance and the degree of hypoxia. Vgontzas states that elevated levels of these inflammatory cytokines results in EDS. It is said that these cytokines can cross the blood-brain bariere and act via peripheral autonomic afferent nerves to promote sleepiness (Romero et al, 1996). There is even evidence suggesting TNF-a impairs with insulin action (Vgontzas, 2008).

It has even been found that at least a part of the cardiovascular diseases associated with OSA, can be explained by high cytokine levels. IL-6 promotes the production of C-reactive protein. This protein plays an important role in plaque formation, repture and vascular thromobis thereby increasing the risk for myocardial ishemia and infarction (Libby et al, 2002).

The elevation of these inflammatory proteins in OSA patients leads to a chronic low-grade inflammation state in these patients. It has been hypothesized that this chronic state of inflammation decreases the primary weightloss effect of the adrenergic system and further promoting fat accumulation (Kuo et al, 2007).

High serum level concentrations of leptin and TNF-a in OSA patients regardless of BMI may be due to the relative high percentage of visceral fat in OSA patients. It has been hypothesized that the high percentages of visceral fat are caused by high sympathetic activity. So high sympathatic activity may cause fat storage according to Greenfield. He even states that high leptin levels stimulate sympathetic nerve activity, as well as high insulin levels (Greenfield and Campbell, 2008). It appears that all effects found to be caused by OSA evaluated above are intertwined and stimulate each other in their functions. In obese subjects however, insulin and leptin resistance occure, making the sympathetic nervous system at least partly invulnerable for these substances. In OSA patients, the sympathetic nervous system is stimulated by due to the apnea and hypapnea events during the night, regardless of its vulnerability to leptin and insulin.

It has been speculated that NPY plays a key role in this process. NPY is released as a result of sympathetic nervous system activation. NPY levels in OSA patients have barely been studied. The studies that did investigate serum NPY levels indeed found an increase of peripheral NPY in OSA patients independed of obesity (Barceló et al, 2005). NPY has been shown to have a vasoconstrictory effect as well as causing vascular hypertrophy and smooth muscle cell proliferation(Barceló et al, 2005). NPY therefore might contribute to the vasculair diseases commonly seen in OSA patients.

So to make a long story short: repetitive wakening during the night, whether it is due to anatomic abnormalities or not, results in activation of sympathetic nervous system and the hypothalamic-pituitary axis. The body therefore comes in a chronic stress state with elevated levels of IL-1, IL-6 and TNF-a. Besides, repetitive wakening causes changes in endocrine hormone release such as leptin, ghrelin and insulin. Al these concequences together result in elevated visceral fat deposition, increased caloric intake, insulin resistance and predispose OSA patients to cardiovascular diseases.

Animal studies have suggested a link between sleep and metabolism. In rats, chronic complete sleep deprivations increased both food intake and energy expenditure (Tehari et al, 2004). These rats lost weight and eventually even died. The kind of diet these rats were on,

seemed to influence the caloric intake in sleep deprived rats. Caloric intake remained normal if the rats were fed protein-rich diets, but increased 250% in calorie-rich diet fed rats. Sleep deprivation therefore may not only increase appetite through ghrelin and other mechanisms, but may also increase preference for lipid-rich, high-calorie diets (Tehari et al, 2004). The elevated calorie intake found by Vasquez may thus be due to sleep deprivation.

CPAP

If OSA really causes obesitiy though all the mechanisms stated above, treatment of OSA with CPAP should normalize all impaired values noted above and promote weight loss. Indeed positive results have been found. CPAP makes collapse of the upper airway allmost impossible so apneac and hyponeac event will barely occure during the night, making repatative wakening unnecessary and therefore should undo all changes indicated above as a results of OSA.

Treatment with CPAP has been shown to significantly reduce AHI values as well as Epworth Sleepiness Scale (Henley et al, 2009). AHI droped from an avarege 60.2 to 4.2 after three months of CPAP treatment. Besides that, CPAP has been shown to increase oxygen saturation and keep it above 90% in all sleep stages (Somers et al, 1995).

It has been shown that treatment with CPAP remarkably decreases nocturnal sympathetic nerve activation and blunt blood pressure surges. Not only in the night, but also during day time sympathetic nerve activation is decreased after treatment with CPAP (Somers et al, 1995). In a beautifull designed study comparing CPAP treatment with sham CPAP treatment in BMI matched OSA patients showed a significant reduction in diastolic blood pressure (Lam et al, 2010). Besides, a decrease in visceral fat deposition and subcutanous fat deposition has been reported, toghether with a significant decrease in body weight after 6 or more months of CPAP treatment(Chin et al, 1999). In a study including 13 OSA patients, visceral fat deposition reduced significantly from an average of 236 cm^2 to 182 cm^2. The same study showed a significant decrease in serum leptin levels in OSA patients using CPAP after only 3 to 4 days. After a month of CPAP treatment, leptin levels where still significantly reduced, even without weight changes being reported (Chin et al, 1999). In a study of 30 obese OSA patients, plasma ghrelin levels rapidly decreased with CPAP therapy (Harsch et al, 2003). Barceló et al found that NPY levels decreased significant after 12 months of therapy with CPAP in both obese and non-obese OSA patients, regardless of changes in BMI (Barceló et al, 2005). It has even been shown that insulin sensitivity improves after 3 months of treatment with CPAP (Lanfranco et al, 2010). Insulin sensitivity was markedly improves after 3 months, but not after 2 days, of CPAP treatment in OSA patients. Patients with lower BMI showed a greater inprovement than patiets with higher BMI (Harsch et al, 2003). Up untill now, no significant changes in IL-1, IL-6 and TNF-a have been reported due to treatment with CPAP (Drummond et al, 2009; Arias et al, 2008).

Recently it has been found that treatment with CPAP is beneficial for cardiovascular diseases. It has been shown that four months of CPAP treatment reverses atherioscleroses independend of bloop pressure changes. After four weeks of treantment a decresase in arterial stiffness has been reported (Turgut Celen and Peker, 2010).

These results all indicate that indeed CPAP can normalize all impared values and promote weight loss. It should however be noted that not all findings are as positive. No significant changes where found in systolic blood pressure after three months of CPAP treatment in

Henleys follow-up study (Henley et al, 2009). Besides, Chin et al, who did find significant changes is body fat, weight and leptin levels, have not been able to report significant changes in either serum insulin levels of serum cortisol levels in obese OSA patients using CPAP (Chin et al, 1999). Weight loss as consequence of CPAP treatment has not been reported by every study investigating this either (Barceló et al, 2005).

Discussion

In this review I have tried to describe all evidence collected over the years on whether obesity causes sleep apnea or sleap apnea causes obesity. For both statements plausible evidence is present.

Fat accumulation in the neck and upper body region change the structure and pressures involved in inhaling and exhaling in the phagyrneal airways. During night time, when muscle tension in phagyrneal airways decrease, these pressure changes making the airways suspectible for collapse, resulting in apneaic and hypopnic events. Besides, nerve activity in the pagyrneal airways seem to be impaired due to fat accumulations. Agreement on the role of crenialfacial differences in the unset of OSA has not been reached yet, but researchers do agree that fat accumulation in the neck region plays an important role. So obesity seems a plausible cause for the development of OSA.

OSA however, appears to be able to induce obesity. Repetative waking during the night activates both sympathetic nerves and the HP-axis. Cortisol levels are elevated and so are inflammatory peptides, causing a chronic state of inflammation. Besides, ghrelin is upregulated and leptin resistance has occured. All these factors induce either increased caloric intake or increased fat accumulation, making the OSA patient susceptible for the development of obesity.

Both weight loss, surgical or not, and CPAP have been found to reduce OSA severity. One pointing in the direction of obesity causing OSA, the other in the direction of OSA causing obesity.

If you would ask me, I would say OSA causes obesity. Of course, OSA does not comes out of the blue; crenialfacial abnormalities such as a large neck, could predispose individuals to OSA. OSA impairs with sleep, in my opinion one of the most important factors in homeostatic and circadian processes throughout the body. A lot of hormones and other processes have been shown to change with sleep restriction or repetative waking. Most of which have not even been reported here.

But before a conclusion can be drawn about what causes what, I would like to see some additional evidence. First of all, I would like to see a study in which fat tissue will be removed in the phagyrneal airways and the AHI is evaluated. Next, artificial placement of fat into the phagyrneal airways in animal models might produce nice evidence suggesting fat accumulation in the neck causes OSA. The fact that animals barely sleep on there backside might be a limitation in this study. To prove that OSA causes obesity, caloric intake should be evaluated in patients on CPAP. A marked reduction would insinuate that OSA indeed causes obesity. Besides, the effects of CPAP treatment in lean OSA patients has barely been investigated. No significant differences have been shown on behalf of the inflammatory proteins so far. Evidence indicating a reduction of the chronic inflammatory state of OSA patients would be nice.

In conclusion, OSA and obesity share a lot of features making it hard to identify one cause. Fact is however that these disorders have overlapping prevalances. Besides, OSA has been shown to worsen obesity and vice versa. So what was first; the chicken or the egg? Additional evidence is should be provided before this question can be answered.

References

Adamantidis A and Lecea L de (2008). Sleep and metabolsim: shared circuits, new connections. Trends in Endocrinology and Metabolsim 19: 362-370.

Al Lawa NM, Patel SR and Ayas NT (2009). Epidemiology, Risk Factors, and Consequences of Obstructive Sleep Apnea and Short Sleep Duration. Progress in Cardiovascular Diseases, 51: 285-293.

Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R and Kaplan O (1991). Sleep-disordered breathing in community-dwelling elderly. Sleep. 14: 486–495.

Arias MA, García-Río F, Alonso-Fernández A, Hernanz A, Hidalgo R, Martínez-Mateo V, Bartolomé S, Rodríguez-Padial L (2008). CPAP decreases plasma levels of soluble tumour necrosis factor-alpha receptor 1 in obstructive sleep apnoea. ur Respir J. 32: 1009-15.

Barcelo A, Barbe F, Llompart E, Durán-Cantolla J, Ladaria A, Bosch M, Guerra L and Agustí AGN (2005). Neuropeptide Y and Leptin in Patients with Obstructive Sleep Apnea Syndrome Role of Obesity. American journal of respiratory and critical care medicine, 171: 183-187.

Basta M, Lin HM, Pejovic S, Sarrigiannidis A, Bixler EO and Vgontzas AN (2008). Lack of Regular Exercise, Depression, and Degree of Apnea are Predictors of Excessive Daytime Sleepiness in Patients with Sleep Apnea: Sex Differences. Journal of Clinical Sleep Medicine, 4: 19-25.

Ben-Noun LL and Laor A (2004). Relationship between changes in neck circumference and changes in blood pressure. Am J Hypertens. 2004 May;17(5 Pt 1):409-14.

Ben-Noun LL and Laor A (2006). Relationship between changes in neck circumference and cardiovascular risk factors. Exp Clin Cardiol. 11(1):14-20.

Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A and Kales A (2001). Prevalence of sleep-disordered breathing in women: effects of gender. American Journal of Respiratory and Critical Care Medicine 163: 608–613.

Brooks B, Cistulli PA, Borkman M, Ross G, McGhee S, Grunstein RR, Sullivan CE and Yue DK (1994). Obstructive sleep apnea in obese noninsulin-dependent diabetic patients: effect of continuous positive airway pressure treatment on insulin responsiveness. Journal of Clinical Endocrinology & Metabolism 79: 1681–5.

Van Cauter E, Spiegel K, Tasali E and Leproult R (2008). Metabolic consequences of sleep and sleep loss. Sleep Med. 9(1):S23-8.

Carter R and Watenpaugh DE (2008). Obesity and obstructive sleep apnea: Or is it OSA and obesity? Pathophysiology 15: 71–77.

Cistulli PA (1996). Craniofacial abnormalities in obstructive sleep apnoea: implications for treatment. Respirology 1: 167–174.

Dancey DR, Hanly PJ, Soong C, Lee B, Shepard J Jr and Hoffstein V (2003). Gender Differences in Sleep Apnea: The Role of Neck Circumference. Chest 123; 1544-1550.

De Stefano A and Comi D (1999). Sleep Apnea in Moderate-Severe Obese Patients. Sleep and Breathing 3: 47-52.

Donohue DA (2010). Treating obstructive sleep apnea with CPAP. Nursing Management (Springhouse) 41(7); 49−50.

Drummond M, Winck J, Guimarães J, Santos AC, Almeida J and Marques J (2009). Long term effect of autoadjusting positive airway pressure on C-reactive protein and interleukin-6 in men with obstructive sleep apnoea syndrome. Arch Bronconeurmol 45(12): 577-584.

Ekstedt M, Akerstedt T and Söderström M (2004). Microarousals During Sleep Are Associated With Increased Levels of Lipids, Cortisol, and Blood Pressure. Psychosomatic Medicine 66: 925–931.

Fogel RB, Malhotra A and White DP (2004). Sleep 2: Pathophysiology of obstructive sleep apnoea/hypopnoea syndrome. Thorax 59: 159-163.

Fung SJ, Xi MC, Zhang JH, Sampogna S, Yamuy J, Morales FR, Chase MH (2007). Apnea promots glutamate-induced exitotoxicity in hippocampal neurons. Brain Res. 1179: 42-50.

George CFP (2007). Sleep Apnea, Alertness, and Motor Vehicle Crashes. American Journal of Respiratory and Critical care medicine 176: 954-956.

Grassi G, Facchini A, Trevano FQ, Dell'Oro R, Arenare F, Tana F, Bolla G, Monzani A, Robuschi M and Mancia G (2005). Obstructive Sleep Apnea−Dependent and −Independent Adrenergic Activation in Obesity. Hypertension 46: 321-325.

Greenfield JR and Campbell LV (2008). Role of the Autonomic Nervous System and Neuropeptides in the Development of Obesity in Humans: Targets for Therapy? Current Pharmaceutical Design 14: 1815-1820.

Gross ND, Cohen JI, Andersen PA and Wax MK (2002). 'Defatting' Tracheotomy in Morbidly Obese Patients. Laryngoscope 112: 1940-1994.

Guilleminault C, Stoohs R, Clerk A, Cetel M and Maistros P (1993). A cause of excessive daytime sleepiness. Chest 104: 781–7.

Harman EM, Wynne JW and Block AJ (1982). The effect of weight loss on sleep-disordered reathing and oxygen desaturation in morbidly obese men. Chest. 82: 291-294.

Harris AT, Morell D, Bajaj y and Martin-Hirsch DP (2010). A discussion of airway and respiratory complications along with general considerations in obese patients. International Journal of Clinical Practice 64: 802–806

Henley DE, Russell GM, Douthwaite JA, Wood SA, Buchanan F, Gibson R, Woltersdorf WW, Catterall JR and Lightman SL (2009). Hypothalamic-pituitary-adrenal axis activation in obstructive sleep apnea: the effect of continuous positive airway pressure therapy. J Clin Endocrinol Metab 94(11):4234-42.

Hoffstein V and Mateika S (1992). Differences in abdominal and neck circumferences in patients with and without obstructive sleep apnea. Eur Respir J 5:377–81.

Katchunga P, Hermans MP, Manwa B, Lepira F, Kashongwe Z, M'buyamba-Kabangu JR (2010). Hypertension, insulin resistance and chronic kidney disease in type 2 diabetes patients from South Kivu, DR Congo. Nephrol Ther. [Epub ahead of print]

Katz I, Stradling J, Slutsky AS, Zamel N amd Hoffstein V (1990). Do patients with obstructive sleep apnea have thick necks? Am Rev Respir Dis. 141: 1228-31.

Kezirian EJ, Malhotra A, Goldberg AN and White DP (2010). Changes in Obstructive Sleep Apnea Severity, Biomarkers, and Quality of Life After Multilevel Surgery. Laryngoscope 120: 1481-1488.

Kuo LE, Kitlinska JB, Tilan JU, Li L, Baker SB and Johnson MD (2007). Neuropeptide Y acts directly in the periphery on fat tissue and mediates stress-induced obesity and metabolic syndrome. Nat Med 13: 803-11.

Lam JCM, Lam B, Yao TJ, Lai AYK, Ooi CG, Tam S, Lam KSL and Ip MSM (2010). A randomised controlled trial of nasal continuous positive airway pressure on insulin sensitivity in obstructive sleep apnoea. Eur Respir J 35: 138-145.

Lanfranco F, Motta G, Minetto AM, Baldi M, Balbo M, Ghigo E, Arvat E and Maccario M (2010). Neuroendocrine Alterations in Obese Patients with Sleep Apnea Syndrome. International Journal of Endocrinology [Epub ahead of print].

Libby P, Ridker PM and Maseri A (2002). Inflammation and atherosclerosis. Circulation 105(9):1135–143.

Lyytikäinen P, Lallukka T, Lahelma E and Rahkonen O (2010). Sleep problems and major weight gain: a follow-up study. International Journal of Obesity. [Epub ahead of print].

Malhotra A, White DP. 2002. Obstructive sleep apnoea. Lancet. 360:237–45.

Martinez-Rivera C, Abad J, Fiz JA. Usefulness of truncal obesity indices as predictive factors for obstructive sleep apnea. Obesity 2008; 16:113-118.

Miles PG, Vig PS, Weyant RJ, Forrest TD and Rockette HE Jr (1996). Craniofacial structure and obstructive sleep apnea syndrome–a qualitative analysis and meta-analysis of the literature. American Journal of Orthodontics and Dentofacial Orthopedics 109:163–172.

Mortimore IL, Marshall I, Wraith PK, Sellar RJ and Douglas NJ (1998). Neck and Total Body Fat Deposition in Nonobese and Obese Patients with Sleep Apnea Compared with That in Control Subjects. Am J Respir Crit Care Med 157: 280–283.

Narkiewicz K and Somers VK (2003). Sympathetic nerve activity in obstructive sleep apnoea. Acta Physiol Scand 177: 385–390.

Newman C (2004). Why are we so fat? National Geographic. August:46–61.

O'Keeffe T and Patterson EJ. Evidence supporting routine polysomnography before bariatric surgery. Obes Surg 2004; 14:23-26.

Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ and Flegal KM (2006). Prevalence of overweight and obesity in the United States, 1999-2004. JAMA. 295:1549-55.

Onat A, Hergenç G, Yüksel H, Can G, Ayhan E, Kaya Z and Dursunoğlu D (2009). Neck circumference as a measure of central obesity: Associations with metabolic syndrome and obstructive sleep apnea syndrome beyond waist circumference. Clin Nutr. 28: 46-51.

Peiser J, Peretz L, Ovnat A and Charuzi I (1984). Sleep apnea syndrome in the morbidly obese as an indication for weight reduction surgery. Ann Surg. 199: 125-129.

Peker Y, Svensson J, Hedner† J, Grote L and Johannsson G (2006). Sleep apnoea and quality of life in growth hormone (GH)-deficient adults before and after 6 months of GH replacement therapy. Clinical Endocrinology 65: 98–105.

Peppard PE, Young, T, Palta M, Dempsey J and Skatrud, J (2000). Longitudinal Study of Moderate Weight Change and Sleep-Disordered Breathing. JAMA, 284: 3015-3021

Perseghin G, Petersen K and Shulman GI (2003). Cellular mechanism of insulin resistance: potential links with inflammation. Int J Obes Relat Metab Disord. 27: S6 –11.

Phillips BG, Kato M, Narkiewicz K, Choe I and Somers VK (2000). Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. Am J Physiol Heart Circ Physiol 279: H234–H237.

Pillar G and Shehadeh N (2008) Abdominal Fat and Sleep Apnea; The chicken or the egg? Diabetes Care, 31: S303–S309.

Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH; American Heart Association; Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism (2006).Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 113: 898-918.

Polotsky VY, Li J, Punjabi NM, Rubin AE, Smith PL, Schwartz AR and O'Donnell CP (2003). Intermittent hypoxia increases insulin resistance in genetically obese mice. J Physiol. 552: 253-64.

Preis SR, Massaro JM, Hoffmann U, D'Agostino RB Sr, Levy D, Robins SJ, Meigs JB, Vasan RS, O'Donnell CJ and Fox CS (2010). Neck Circumference as a Novel Measure of Cardiometabolic Risk: The Framingham Heart Study. J Clin Endocrinol Metab. [Epub ahead of print].

Punjabi NM (2008). The Epidemiology of Adult Obstructive Sleep Apnea. Proceedings of the Amarican Thoracic Society, 5: 136-143.

Purvin VA, Kawasaki A, Yee RD (2000). Papilledema and Obstructive Sleep Apnea Syndrome. Arch Ophthalmol.118:1626-1630.

Romero LI, Kakucska I, Lechan RM and Reichlin S (1996). Interleukin-6 (IL-6) is secreted from the brain after intracerebroventricular injection of IL-1b in rats. Am J Physiol. 270: R518–R524.

Schwartz MW, Peskind E, Raskind M, Boyko EJ and Porte D Jr (1996). Cerebrospinal fluid leptin levels: relationship to plasma levels and to adiposity in humans. Nat Med 2: 589–593.

Sergi M, Rizzi M, Comi N, Resta O, Palma P, Stefano A and Comi D (1999). Sleep Apnea in Moderate-Severe Obese Patients. Sleep and breating 3: 47-52.

Shah N and Roux F. (2009). The relationship of obesity and obstructive sleep apnea. Clinics in Chest Medicine, 30:455-465

Simpson NS, Banks S and Dinges DF (2010. Sleep restriction is associated with increased morning plasma leptin concentrations, especially in women. Biol Res Nurs (Epud ahead of print).

Sobhani I, Bado A, Vissuzaine C, Buyse M, Kermorgant S, Laigneau JP, Attoub S, Lehy T, Henin D, Mignon M and Lewin MJ (2000). Leptin secretion and leptin receptor in the human stomach. Gut 47: 178–183.

Somers VK, Dyken ME, Clary MP and Abboud FM (1995). Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 96: 1897–1904.

Somers VK, Dyken ME, Clary MP and Abboud FM (1995). Sympathetic Neural Mechanisms in Obstructive Sleep Apnea. J. Clin. Invest. 96: 1897-1904

Soriano-Co M, Vanhecke TE, Franklin BA, Sangal RB, Hakmeh B, McCullough PH (2010). Increased Central Adiposity in Morbidly Obese Patients with Obstructive Sleep Apnea Internal Medicine Journal (Epud ahead of print).

Sundaram S, Lim J, Lasserson TJ (2009). Surgery for obstructive sleep apnoea in adults (Review). Cochrane Database Syst Rev. 19; CD001004.

Taheri S, Lin L, Austin D, Young T and Mignot E (2004) Short Sleep Duration Is Associated with Reduced Leptin, Elevated Ghrelin, and Increased Body Mass Index. PLoS Medicine 1: 210-217

Terris DJ (1999). Cosmetic Enhancement Associated With Surgery for Obstructive Sleep Apnea. The Laryngoscope 109: 1045-1050.

Tschop M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E and Heiman ML (2001). Circulating ghrelin levels are decreased in human obesity. Diabetes 50: 707–709.

Turgut Celen Y and Peker Y. Cardiovascular consequences of sleep apnea: Ill-impact of continuous positive airway pressure treatment. Anadolu Kardiyol Derg 3:274-80.

Ulukavak Ciftci T, Kokturk O, Bukan N and Bilgihan A (2005). Leptin and ghrelin levels in patients with obstructive sleep apnea syndrome. Respiration 72: 395-401.

Unger RH and Orci L (2002). Lipoapoptosis: its mechanism and its diseases. Biochim Biophys Acta 1585: 202–12.

Vasquez MM, Goodwin JL, Drescher AA, Smith TW and Quan SF (2008). Associations of Dietary Intake and Physical Activity with Sleep Disordered Breathing in the Apnea Positive Pressure Long-term Efficacy Study (APPLES). Journal of Clinical Sleep Medicine, 4 :385-390.

Vcontzas AN (2008). Does obesity play a major role int he pathogenesis of sleep apnoea and its associated manifestations via inflammation, visceral adiposity, and insulin resistance? Archives of Physiology and Biochemistry 114: 221-223.

Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP (2000).Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistancen and hyperxytokinemia. J Clin Endocrinol Metab 85(3):1151-8.

www.obesitasvereniging.nl Prevelentie en cijfers. (27 juli 2010).

Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA and Chen H (2003). Chronic inflammation in fat plays a crucial rol in the development of obesity-relatied insulin resistance. J Clin Invest 112: 1821-30.

Yang L, Samarasinghe YP, Kane P, Amiel SA and Aylwin SJ (2010). Visceral adiposity is closely correlated with neck circumference and represents a significant indicator of insulin resistance in WHO grade III obesity. Clin Endocrinol (Oxf). 73(2):197-200.

Yee BJ, Phillips CL, Banerjee D, Caterson I, Hedner JA, Grunstein RR (2007). The effect of sibutramine-assisted weight loss in men with obstructive sleep apnoea. Int J Obes 31: 161-168.

Young T, Palta M, Dempsey J, Skatrud J, Weber S and Badr S (1993). The occurrence of sleep-disordered breathing among middle-aged adults. New England Journal of Medicine. 328:1230–1235.