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# Pathophysiology in Type 2 Diabetes – Type 2 Diabetes and Sleep-Disordered Breathing/Sleep Apnea – Role of Adipocytokines

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## 1. Introduction

Sleep is a complex behavioral state that occupies one-third of the human life span. Although viewed as a passive condition, sleep is a highly active and dynamic process. Sleep was considered to be primarily important for restoration of brain function. However, to date, there is increasing evidence that sleep also modulates the metabolic, endocrine and cardiovascular systems [Trenell, 2007; Boethel, 2002; Knutson & Van Cauter, 2007; Knutson, 2008]. It is known that if left untreated, sleep disorders can have significant impact on daytime function, including learning, memory, attention, and behavior. The approach to the treatment of these disorders (whether with or without pharmacotherapy) is dependent on a thorough evaluation of the sleep complaint and accurate diagnosis. Previous studies reported a consistent difference between diabetic and non-diabetic subjects in the number of sleep disturbances per hour, indicating possible influence of diabetes on sleep pattern [Resnick, 2003; Kawakami, 2004]. Several studies have shown that patients with T2DM sleep less than the general population [Vgontzas, 2000; Buxton, 2010]. A gradual decrease in self-reported sleep duration seems to have developed over the same period as the dramatic increase in the incidence of obesity and diabetes, including a close relationship between sleep cycle and diabetes [Van Cauter, 1997; Spiegel, 2005; Chasens, 2007; Knutson & Van Cauter, 2008]. Sleeping disorders related to T2DM include insomnia, restless leg syndrome, periodic leg movement disorder, excessive daytime sleepiness, sleepwalking, nightmares, narcolepsy, and SDB, especially SA. T2DM and SDB/SA are both prevalent diseases that share several risk factors, including advanced age and obesity [Tishler, 2003; Young, 1993]. T2DM is associated with higher incidence of cardiovascular, cerebrovascular, and renal diseases. There is also mounting evidence that SDB/SA is an independent risk factor for cardiovascular and cerebrovascular diseases. Interest in a potential independent link between the two diseases continues to grow.

## 2. Sleep loss

Chronic sleep loss is increasingly common in industrialized countries. The sleep impairment may result from various common disturbances, such as insomnia and OSA and may lead to

striking changes in metabolic and endocrine functions [Spiegel, 1999]. Chronic sleep loss is a potential risk factor for obesity, insulin resistance, and T2DM.

Previous studies reported that both short (<6 hours) and long (>8 hours) sleepers as well as those with sleep loss, are at greater risk for glucose intolerance and T2DM [Sridhar & Madhu, 1994; Scheen, 1997; Ayas, 2003; Mallon, 2005; Gottlieb, 2005; Mallon, 2005; Yaggi, 2006; Chaput, 2007; Nakajima, 2008].

### 3. Sleep apnea

SA is a sleep disorder characterized by pauses in breathing during sleep. There are several forms of SA, but the obstructive type is the commonest. In OSA, pauses in breathing are caused by a physical block to airflow, usually in the oropharynx. OSA is usually defined by interruptions of airflow of at least 10-second duration (apneas), or by a decrease in airflow of at least 10 seconds (hypopneas) followed by blood oxygen desaturation and arousal (brief arousal associated with airway opening and resumption of breathing) [Report of American Academy of Sleep Medicine Task Force, 1999; Masood & Phillips, 2000].

#### 3.1 Symptoms

SA is often first noticed by the bed partner who witness episodes of apneas or is suspected based on history of habitual snoring and/or excessive daytime sleepiness, general fatigue or near-miss car accidents. Other symptoms reported by patients with SA include [Bresnitz, 1994; Gupta, 2010; Wickwire & Collop, 2010] 1) irritability, 2) poor memory, 3) morning headache, 4) depression, 5) mood changes, 6) sexual dysfunction, and 7) nocturia.

#### 3.2 Diagnosis

SDB/SA is often diagnosed by an overnight cardiorespiratory test called polysomnography [Jafari & Mohsenin, 2010]; though other simpler methods are currently available, such as type 3 cardiopulmonary monitoring [Collop, 2007]. The recorded signals are analyzed for the numbers of apneas and hypopneas, episodes of oxygen desaturation, as well as lowest oxygen saturation, average oxygen saturation, and time at desaturation <90% in minutes of the total bedtime for the entire night. Apnea is defined as a decrease in the amplitude of the airflow or respiratory effort signal to <10% of the baseline lasting at least 10 seconds. Hypopnea is defined as a decrease in the airflow or respiratory effort to <70% of the baseline for at least 10 seconds accompanied by >4% fall in oxygen saturation. The apnea-hypopnea index (AHI) is defined as the number of apneas/hypopneas per hour of sleep time. The latter is measured from the recorded signals of the electroencephalogram (averaged brain activity), electrooculogram (eye movements) and nuchal muscles electromyogram. An AHI of  $\geq 5$  establishes the diagnosis of SDB/SA. OSA is defined as absence of airflow in the presence of chest wall and/or abdominal excursions. The severity of SA is based on the AHI, and classified as mild (AHI  $\geq 5$  to <15), moderate (AHI  $\geq 15$  to <30), and severe (AHI  $\geq 30$ ), according to the guidelines of the American Academy of Sleep Medicine Task Force [Report of American Academy of Sleep Medicine Task Force, 1999].

#### 3.3 Clinical features

Obese patients with OSA have short and wide neck, large tongue, and excess pharyngeal soft tissues. Significant SA is present in 40% of obese individuals, and 70% of OSA patients

are obese [Vgontzas AN, 1994; Resta O, 2001; Daltro C, 2007]. Not only excess weight but also fat distribution, i.e. intra-abdominal fat accumulation, plays a major role in the development of OSA [Shinohara, 1997; Schäfer, 2002; Vgontzas, 2003]. A recent study of Japanese patients with T2DM found that BMI and waist circumference (WC) were the strongest predictors of the severity of SDB [Kashine, 2011]. OSA is independently associated with insulin resistance, T2DM and hypertension [Idris, 2009]. Several reports found high incidence of SA in both Japanese [Katsumata, 1991] and Caucasian [Einhorn, 2007] diabetic patients.

### **3.4 Treatment**

There are several options for treatment of SA [Rosenberg & Doghramji, 2009]. These include:

#### **3.4.1 Lifestyle changes**

Weight loss, especially visceral fat reduction through caloric diet and exercise, should be recommended for all overweight patients with SA. Avoidance of alcohol and sleeping pills is often beneficial.

#### **3.4.2 Oral devices**

Oral devices such as dental appliances have been used with some success to maintain an open airway during sleep [Ng, 2005].

#### **3.4.3 Nasal Continuous Positive Airway Pressure (nCPAP)**

Nasal continuous positive airway pressure (nCPAP) is the golden standard treatment of SA in which a mask is worn over the nose and/or mouth whilst sleeping. The mask is attached to a machine that delivers a continuous stream of compressed air. The positive pressure pneumatically maintains an open airway during sleep. Treatment of OSA is reported to improve daytime sleepiness and various other clinical features of Sa including insulin responsiveness [Hassaballa, 2005; Harsch, 2004].

#### **3.4.4 Surgery**

Surgery may be considered in some cases, particularly those with tonsillar and adenoidal hypertrophy, narrow nasal airways, or facial deformities such as small jaw, nasal polyp or deviated nasal septum [Sundaram, 2005; Lojander, 1996; Holty, 2010].

## **4. Type 2 diabetes and sleep apnea**

SDB/SA is often observed in patients with T2DM, and known to be potentially associated with atherosclerosis, leading to ACVDs. The International Diabetes Federation (IDF) Taskforce on Epidemiology and Prevention [Shaw, 2008] stated that the pathophysiological consequences of hypoxemia and sleep fragmentation might be involved in the development of insulin resistance and pancreatic  $\beta$ -cell dysfunction through various biological mechanisms, such as direct effects of 1) intermittent hypoxia/desaturation and hypoxemia, 2) sympathetic nervous system activation (catecholamine) [Prabhakar & Kumar, 2010; Esler & Eikelis, 2006], 3) systemic inflammation (tumor necrosis factor-alpha [TNF- $\alpha$ ], interleukin-6 [IL-6], high sensitivity C-reactive protein [hsCRP] and monocyte chemoattractant protein 1 [MCP-1]) [Drager, 2010; Sahlman, 2010; Romero-Corral, 2010], 4) hypothalamic-pituitary-

adrenal dysfunction (cortisol) [Follenius, 1992; Henley, 2009; Vgontzas & Chrousos, 2002], 5) dysregulation of adipocytokines (plasminogen activator inhibitor-1 [PAI-1], adiponectin) [Lam, 2008], 6) sleep architecture [Wang & Teichtahl, 2007] and 7) other factors. Both SDB/SA and T2DM are strongly associated with ACVD [Bradley & Floras, 2009] (Figure 1).

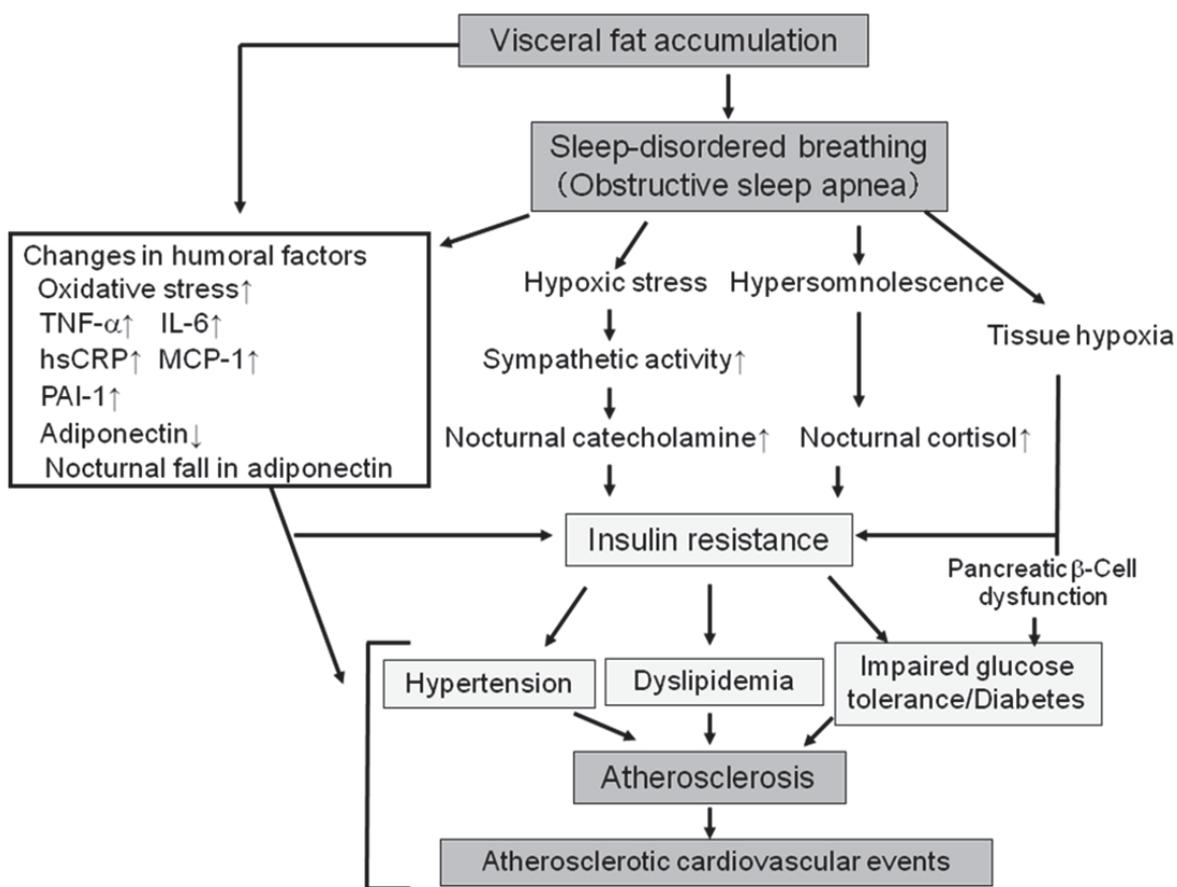


Fig. 1. Relationships among sleep-disordered breathing, visceral fat accumulation and atherosclerosis.

## 5. Type 2 diabetes mellitus and sleep-disordered breathing / sleep apnea: Role of adipocytokines

Both T2DM and SDB/SA have been linked to the metabolic syndrome based on visceral fat accumulation, with clustering of hyperglycemia, intra-abdominal fat accumulation, hypertension, hypertriglyceridemia, and hypo-high-density-lipoprotein-cholesterolemia [Rasche, 2010; Lui & Ip, 2010]. There is a broad overlap between the presumed mechanisms of that link T2DM and SDB/SA and features of the metabolic syndrome (Syndrome X) [Reaven, 1993], which is also known as "Syndrome Z" [Wilcox, 1998].

In addition to the localization and functional properties of visceral fat, experimental evidence links certain molecules in visceral fat to human disorders, especially insulin resistance and ACVD. An important question relates to the profile of molecules or genes expressed in subcutaneous and visceral fat. In order to answer this question, our group in collaboration with the human body map project team investigated the gene expression profile in human adipose tissue. This tissue had been traditionally regarded as a passive

storage of excess energy in the form of triglycerides. Unexpectedly, we found that adipose tissues, especially visceral fat, abundantly express genes that encode secretory proteins including complement factors in the immune system, growth factors, and cytokines, most of which are important bioactive substances [Maeda, 1997; Matsuzawa, 2004]. We found PAI-1 [Shimomura, 1996] and HB-EGF [Matsumoto, 2002] in human visceral and subcutaneous fat cDNA library. Excess visceral fat overproduces and secretes PAI-1, which in turn increases the risk for thrombotic disorders [Shimomura, 1996]. Thus, it seems that visceral fat is directly linked to ACVD. Adipose tissue also produces a variety of the bioactive substances conceptualized as ‘adipocytokines’ [Funahashi, 1999; Matsuzawa, 2010]. Through systematic analysis of adipose tissue-expressed genes, we discovered a novel gene, designated adipose most abundant gene transcript 1 (apM1), for an adipocyte-derived secretory protein [Maeda, 1996], which was later named ‘adiponectin’. At the same time, using different approaches, adiponectin was identified independently by three other groups, as adipocyte complement-related protein of 30 kDa (ACRP30) [Scherer, 1995], adipoQ [Hu, 1996], and gelatin binding protein of 28 kDa (GBP28) [Nakano, 1996]. Adiponectin is specifically expressed in the adipose tissue [Arita, 1999]. The molecule has two domains, namely a collagen-like fibrous domain and a C1q-like globular domain. The single molecules combine and form a high-ordered structure [Arita, 1999]. Adiponectin binds to collagens I, III, and V, which are present in the subendothelial intima [Okamoto, 2000]. In fact, adiponectin adheres to endothelium-injured arterial walls [Okamoto, 2000]. This is the reason why we named this protein ‘adiponectin’ [Arita, 1999]. Numerous experimental studies found that adiponectin has anti-atherosclerotic [Ouchi, 2003] and insulin sensitivity properties [Han, 2009].

The production and secretion of adipocytokines are dynamically regulated by nutritional status. Over-eating and physical inactivity result in visceral fat accumulation, which leads to visceral fat dysfunction and dysregulated production of adipocytokines (overproduction of offensive adipocytokines, such as PAI-1, TNF- $\alpha$ , HB-EGF and angiotensinogen, and underproduction of defensive adipocytokines, such as adiponectin), a state we call adipotoxicity. These changes are probably the major underlying mechanisms of lifestyle-related diseases [Kishida, 2011].

Daytime hypoadiponectinemia and nocturnal falls in circulating adiponectin concentrations in OSA patients with abdominal obesity, are in part, due to hypoxic stress [Nakagawa, 2008 & 2011]. A high frequency of SDB was identified in Japanese patients with poorly controlled T2DM, who also had intra-abdominal obesity with nocturnal dysregulated production of adiponectin [Kashine, 2010]. Obese East and South Asians including Japanese have a mild degree of adiposity, compared with European and American subjects [Wulan, 2010; Fujimoto, 1999; Tong, 2007; Kadowaki, 2006]. Unlike total body fat, body fat distribution, especially excess accumulation of visceral fat, correlates with various diabetogenic, atherogenic, prothrombotic and proinflammatory metabolic abnormalities in Japanese (referred to as the metabolic syndrome), that increase the risk of ACVD [Fujioka, 1987; Matsuzawa, 1994].

## 6. Conclusion

It is necessary to diagnose SDB from the standpoint of prevention of ACVD in diabetic patients. Weight reduction, particularly reduction of visceral fat, intensive glucose-lowering therapy, nCPAP therapy, or the combination of these therapies, have beneficial effects on the outcome of T2DM patients with SDB through improvement of dysregulated production of adipocytokines and SDB-related ACVD.

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## 8. References

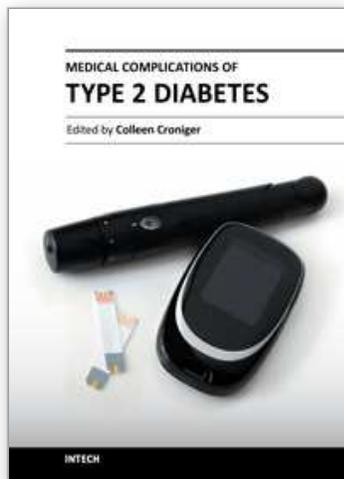
- Trenell MI, et al. (2007) Sleep and metabolic control: waking to a problem? *Clinical and Experimental Pharmacology and Physiology*. Vol.34, No.1-2, (Jan-Feb 2007), pp.1-9
- Boethel CD. (2002) Sleep and the endocrine system: new associations to old diseases. *Curr Opin Pulmonary Medicine*. Vol.8, No.6, (Nov 2002), pp.502-505.
- Knutson KL, Van Cauter E. (2008) Associations between sleep loss and increased risk of obesity and diabetes. *Annals of New York Academy of Sciences*. Vol.1129, pp.287-304.
- Knutson KL, et al. (2007) The metabolic consequences of sleep deprivation. *Sleep Medicine Review*. Vol.11, No.3, (Jun 2007), pp.163-178.
- Resnick HE, et al.; Sleep Heart Health Study. Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. *Diabetes Care*. Vol.26, No.3, (Mar 2003), pp.702-709.
- Kawakami N, et al. (2004) Sleep disturbance and onset of type 2 diabetes. *Diabetes Care*. Vol.27, No.1, (Jan 2004), pp.282-283.
- Vgontzas AN, et al. (2000) Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *Journal of Clinical Endocrinology and Metabolism*. Vol.85, No.3, (Mar 2000), pp.1151-1158.
- Buxton OM, et al. (2010) Sleep restriction for 1 week reduces insulin sensitivity in healthy men. *Diabetes*. Vol.59, No.9, (Sep 2010), pp.2126-2133.
- Van Cauter E, et al. (1997) Roles of circadian rhythmicity and sleep in human glucose regulation. *Endocrine Reviews*. Vol.18, No.5, (Oct 1997), pp.716-738.
- Spiegel K, et al. (2005) Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes. *Journal of Applied Physiology*. Vol.99 No.5, (Nov 2005), pp.2008-2019.
- Chasens ER. (2007) Obstructive sleep apnea, daytime sleepiness, and type 2 diabetes. *The Diabetes Educator*. Vol.33, No.3, (May-Jun 2007), pp.475-82.
- Knutson KL, Van Cauter E. (2008) Associations between sleep loss and increased risk of obesity and diabetes. *Annals of the New York Academy of Sciences*. Vol.1129, (2008), pp.287-304.
- Tishler PV, et al. (2003) Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors in the development of sleep-disordered breathing. *The Journal of American Medical Association*. Vol.289, No.17, (May 2003), pp.2230-2237.
- Young T, et al. (1993) The occurrence of sleep-disordered breathing among middle-aged adults. *The New England Journal of Medicine*. Vol.328, No.17, (Apr 1993), pp.1230-1235.
- Spiegel K, et al. (1999) Impact of sleep debt on metabolic and endocrine function. *Lancet*. Vol.354, No.9188, (Oct 1999), pp.1435-1439.
- Sridhar GR, Madhu K. (1994) Prevalence of sleep disturbances in diabetes mellitus. *Diabetes Research and Clinical Practice*. Vol.23, No.3, (Apr 1994), pp.183-186.
- Scheen AJ, et al. (1996) Relationships between sleep quality and glucose regulation in normal humans. *American of Journal Physiology*. Vol.271, No.2(Pt 1), (Aug 1996), pp.E261-270.
- Ayas NT, et al. (2003) A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care*. Vol.26, No.2, (Feb 2003), pp.380-384.

- Mallon L, et al. (2005) High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. *Diabetes Care*. Vol.28, No.11, (Nov 2005), pp.2762-2767.
- Gottlieb DJ, et al. (2005) Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Archives of Internal Medicine*. Vol.165, No.8, (Apr 2005), pp.863-867.
- Mallon L, et al. (2005) High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. *Diabetes Care*. Vol.28, No.11, (Nov 2005), pp.2762-2767.
- Yaggi HK, et al. (2006) Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care*. Vol.29, No.3, (Mar 2006), pp.657-661.
- Chaput JP, et al. (2007) Association of sleep duration with type 2 diabetes and impaired glucose tolerance. *Diabetologia*. Vol.50, No.11, (Nov 2007), pp.2298-2304.
- Nakajima H, et al. (2008) Association between sleep duration and hemoglobin A1c level. *Sleep Medicine*. Vol.9, No.7, (Oct 2008), pp.745-752.
- Anonymous. (1999) Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep*. Vol.22, No.5, (Aug 1999), pp.667-689.
- Masood A, Phillips B. (2000) Sleep apnea. *Current Opinion in Pulmonary Medicine*. Vol.6, No.6, (Nov 2000), pp.479-484.
- Bresnitz EA, et al. (1994) Epidemiology of obstructive sleep apnea. *Epidemiologic Reviews*. Vol.16, No.2, (1994), pp.210-227.
- Gupta RK, et al. (2010) Obstructive sleep apnoea: a clinical review. *The Journal of Association of Physicians of India*. Vol.58, (Jul 2010), pp.438-441.
- Wickwire EM, Collop NA. (2010) Insomnia and sleep-related breathing disorders. *Chest*. Vol.137, No.6, (Jun 2010), pp.1449-1463.
- Jafari B, Mohsenin V. (2010) Polysomnography. *Clinics in Chest Medicine*. Vol.31, No.2, (Jun 2010), pp.287-297.
- Collop NA, et al.; Portable Monitoring Task Force of the American Academy of Sleep Medicine. (2007) Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. *Journal of Clinical Sleep Medicine*. Vol.3, No.7, (Dec 2007), pp.737-747.
- Vgontzas AN, et al. (1994) Sleep apnea and sleep disruption in obese patients. *Archives of Internal Medicine*. Vol.154, No.15, (Aug 1994), pp.1705-1711.
- Resta O, et al. (2001) Sleep-related breathing disorders, loud snoring and excessive daytime sleepiness in obese subjects. *International Journal of Obesity Related Metabolic Disorders*. Vol.25, No.5, (May 2001), pp.669-675.
- Daltro C, et al. (2007) Prevalence and severity of sleep apnea in a group of morbidly obese patients. *Obesity Surgery*. Vol.17, No.6, (Jul 2007), pp.809-814.
- Shinohara E, et al. (1997) Visceral fat accumulation as an important risk factor for obstructive sleep apnoea syndrome in obese subjects. *Journal of Internal Medicine*. Vol.241, No.1, (Jan 1997), pp.11-18.
- Schäfer H, et al. (2002) Body fat distribution, serum leptin, and cardiovascular risk factors in men with obstructive sleep apnea. *Chest*. Vol.122, No.3, (Sep 2002), pp.829-839.
- Vgontzas AN, et al. (2003) Metabolic disturbances in obesity versus sleep apnoea: the importance of visceral obesity and insulin resistance. *Journal of Internal Medicine*. Vol.254, No.1, (Jul 2003), pp.32-44.

- Kashine S, et al. (2011) Effect of diabetes treatment on changes in sleep-disordered breathing and its related parameters in patients hospitalized with type 2 diabetes mellitus. *Journal of Atherosclerosis and Thrombosis*. in press.
- Idris I, et al. (2009) Obstructive sleep apnoea in patients with type 2 diabetes: aetiology and implications for clinical care. *Diabetes, Obesity & Metabolism*. Vol.11, No.8, (Aug 2009), pp.733-741.
- Katsumata K, et al. (1991) High incidence of sleep apnea syndrome in a male diabetic population. *Diabetes Research and Clinical Practice*. Vol.13, No.1-2, (Aug 1991), pp.45-51.
- Einhorn D, et al. (2007) Prevalence of sleep apnea in a population of adults with type 2 diabetes mellitus. *Endocrine Practice*. Vol.13, No.4, (Jul-Aug 2007), pp.355-362.
- Rosenberg R, Doghramji P. (2009) Optimal treatment of obstructive sleep apnea and excessive sleepiness. *Advances in Therapy*. Vol.26, No.3, (Mar 2009), pp.295-312.
- Ng A, et al. (2005) Oral appliance therapy for obstructive sleep apnea. *Treatment in Respiratory Medicine*. Vol.4, No.6, (2005), pp.409-422.
- Hassaballa HA, et al. (2005) The effect of continuous positive airway pressure on glucose control in diabetic patients with severe obstructive sleep apnea. *Sleep & Breathing*. Vol.9, No.4, (Dec 2005), pp.176-180.
- Harsch IA, et al. (2004) The effect of continuous positive airway pressure treatment on insulin sensitivity in patients with obstructive sleep apnoea syndrome and type 2 diabetes. *Respiration*. Vol.71, No.3, (May-Jun 2004), pp.252-259.
- Sundaram S, et al. (2005) Surgery for obstructive sleep apnoea. *Cochrane Database of Systematic Reviews*. Vol.19, No.4, (Oct 2005), CD001004.
- Lojander J, et al. (1996) Nasal-CPAP, surgery, and conservative management for treatment of obstructive sleep apnea syndrome. A randomized study. *Chest*. Vol.110, No.1, (Jul 1996), pp.114-119.
- Holty JE, Guilleminault C. (2010) Surgical options for the treatment of obstructive sleep apnea. *The Medical Clinics of North America*. Vol.94, No.3, (May 2010), pp.479-515.
- Shaw JE, et al.; International Diabetes Federation Taskforce on Epidemiology and Prevention. (2008) Sleep-disordered breathing and type 2 diabetes: a report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. *Diabetes Res Clin Pract*. Vol.81, No.1, (Jul 2008), pp.2-12.
- Prabhakar NR, Kumar GK. (2010) Mechanisms of sympathetic activation and blood pressure elevation by intermittent hypoxia. *Respiratory Physiology & Neurobiology*. Vol.174, No.1-2, (Nov 2010), pp.156-161.
- Esler M, Eikelis N. (2006) Is obstructive sleep apnea the cause of sympathetic nervous activation in human obesity? *Journal of Applied Physiology*. Vol.100, No.1, (Jan 2006), pp.11-12.
- Drager LF, et al. (2010) The impact of obstructive sleep apnea on metabolic and inflammatory markers in consecutive patients with metabolic syndrome. *PLoS One*. Vol.5, No.8, (Aug 2010), e12065.
- Sahlman J, et al.; Kuopio Sleep Apnoea Group. (2010) The activation of the inflammatory cytokines in overweight patients with mild obstructive sleep apnoea. *J of Sleep Research*. Vol.19, No.2, (Jun 2010), pp.341-348.
- Romero-Corral A, et al. (2010) Interactions between obesity and obstructive sleep apnea: implications for treatment. *Chest*. Vol.137, No.3, (Mar 2010), pp.711-719.
- Follenius M, et al. (1992) Nocturnal cortisol release in relation to sleep structure. *Sleep*. Vol.15, No.1, (Feb 1992), pp.21-27.

- Henley DE, et al. (2009) Hypothalamic-pituitary-adrenal axis activation in obstructive sleep apnea: the effect of continuous positive airway pressure therapy. *Journal of Clinical Endocrinology and Metabolism*. Vol.94, No.11, (Nov 2009), pp.4234-4242.
- Vgontzas AN, Chrousos GP. (2002) Sleep, the hypothalamic-pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. *Endocrinology and Metabolism Clinics of North America*. Vol.31, No.1, (Mar 2002), pp.15-36.
- Lam JC, et al. (2008) Hypoadiponectinemia is related to sympathetic activation and severity of obstructive sleep apnea. *Sleep*. Vol.31, No.12, (Dec 2008), pp.1721-1727.
- Wang D, Teichtahl H. (2007) Opioids, sleep architecture and sleep-disordered breathing. *Sleep Medicine Reviews*. Vol.11, No.1, (Feb 2007), pp.35-46.
- Bradley TD, Floras JS. (2009) Obstructive sleep apnoea and its cardiovascular consequences. *Lancet*. Vol.373, No.9657, (Jan 2009), pp.82-93.
- Rasche K, et al. (2010) Obstructive sleep apnea and type 2 diabetes. *European Journal of Medical Research*. Vol.15, No. Suppl 2, (Nov 2010), pp152-1526.
- Lui MM, Ip MS. (2010) Disorders of glucose metabolism in sleep-disordered breathing. *Clinics in Chest Medicine*. Vol.31, No.2, (Jun 2010), pp.271-285.
- Reaven GM. (1993) Role of insulin resistance in human disease (syndrome X): an expanded definition. *Annual Review of Medicine*. Vol.44, (1993) pp.121-131.
- Wilcox I, et al. (1998) 'Syndrome Z': The Interaction of Sleep Apnoea, Vascular Risk Factors and Heart Disease. *Thorax*. Vol.53, No.Supple3, (Oct 1998), pp.S25-28.
- Maeda K, et al. (1997) Analysis of an expression profile of genes in the human adipose tissue. *Gene*. Vol.190, No.2, (May 1997), pp.227-235.
- Matsuzawa Y, et al. (2004) Adiponectin and metabolic syndrome. *Arteriosclerosis, Thrombosis, and Vascular Biology*. Vol.24, No.1, (Jan 2004), pp.29-33.
- Shimomura I, et al. (1996) Enhanced expression of PAI-1 in visceral fat: possible contributor to vascular disease in obesity. *Nat Med*. Vol.2, No.7, (Jul 1996), pp.800-803.
- Matsumoto S, et al. (2002) Increased plasma HB-EGF associated with obesity and coronary artery disease. *Biochemical and Biophysical Research Communications*. Vol.292, No.3, (Apr 2002), pp.781-786.
- Funahashi T, et al. (1999) Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. *Internal Medicine*. Vol.38, No.2, (Feb 1999), pp.202-206.
- Matsuzawa Y. (2010) Establishment of a concept of visceral fat syndrome and discovery of adiponectin. *Proceedings of the Japan Academy. Series B, Physical and Biological Sciences*. Vol.86, No.2, (2010), pp.131-141.
- Maeda K, et al. (1996) cDNA cloning and expression of a novel adipose specific collagen-like factor, apMa (Adipose Most Abundant gene transcript 1). *Biochemical and Biophysical Research Communications*. Vol.221, No.2, (Apr 1996), pp.286-289.
- Scherer PE, et al. (1995) A novel serum protein similar to C1q, produced exclusively in adipocytes. *The Journal of Biological Chemistry*. Vol.270, No.45, (Nov 1995), pp.26746–26749.
- Hu E, et al. (1996) AdipoQ is a novel adipose-specific gene dysregulated in obesity. *The Journal of Biological Chemistry*. Vol.271, No.18, (May 1996), pp.10697–10703.
- Nakano Y, et al. (1996). Isolation and characterization of GBP28, a novel gelatin- binding protein purified from human plasma. *Journal of Biochemistry*. Vol.120, No.4 (Oct 1996), pp.803–812.
- Arita Y, et al. (1999) Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochemical and Biophysical Research Communications*. Vol.257, No.1, (Apr 1999), pp.79-83.

- Okamoto Y, et al. (2000) An adipocyte-derived plasma protein, adiponectin, adheres to injured vascular walls. *Hormone and Metabolic Research*. Vol.32, No.2, (Feb 2000), pp.47-50.
- Ouchi N, et al. (2003) Obesity, adiponectin and vascular inflammatory disease. *Current Opinion in Lipidology*. Vol.14, No.6, (Dec 2003), pp.561-566.
- Han SH, et al. (2009) Antiatherosclerotic and anti-insulin resistance effects of adiponectin: basic and clinical studies. *Progress in Cardiovascular Diseases*. Vol.52, No.2, (Sep-Oct 2009), pp.126-140.
- Kishida K. et al. (2011) Visceral adiposity as a target for the management of the metabolic syndrome: A Japanese perspective. *Annals of Medicine*. in press.
- Nakagawa Y, et al. (2008) Nocturnal reduction in circulating adiponectin concentrations related to hypoxic stress in severe obstructive sleep apnea-hypopnea syndrome. *American Journal of Physiology. Endocrinology and Metabolism*. Vol.294, No.4, (Apr 2008), pp.E778-784
- Nakagawa Y, et al. (2011) Nocturnal falls of adiponectin levels in sleep apnea with abdominal obesity and impact of hypoxia-induced dysregulated adiponectin production in obese murine mesenteric adipose tissue. *Journal of Atherosclerosis and Thrombosis*. in press.
- Kashine S, et al. (2010) Characteristics of sleep-disordered breathing in Japanese patients with type 2 diabetes mellitus. *Metabolism*. Vol.59, No.5, (May 2010), pp.690-696.
- Wulan SN, et al. (2010) Ethnic differences in body composition and the associated metabolic profile: a comparative study between Asians and Caucasians. *Maturitas*. Vol.65, No.4, (Apr 2010), pp.315-319.
- Fujimoto WY, et al. (1999) Visceral adiposity and incident coronary heart disease in Japanese-American men. The 10-year follow-up results of the Seattle Japanese-American Community Diabetes Study. *Diabetes Care*. Vol.22, No.11, (Nov 1999), pp.1808-1812.
- Tong J, et al. (2007) Intra-abdominal fat accumulation predicts the development of the metabolic syndrome in non-diabetic Japanese-Americans. *Diabetologia*. Vol. 50, No.6, (Jun 2007), pp.1156-1160.
- Kadowaki T, et al. (2006) Japanese men have larger areas of visceral adipose tissue than Caucasian men in the same levels of waist circumference in a population-based study. *International Journal of Obesity (London)*. Vol.30, No.7, (Jul 2006), pp.1163-1165.
- Fujioka S, et al. (1987) Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. *Metabolism*. Vol.36, No.1, (Jan 1987), pp.54-59.
- Matsuzawa Y, et al. (1994) Pathophysiology and pathogenesis of visceral fat obesity. *Diabetes Research and Clinical Practice*. Vol.24, No. Suppl, pp.S111-S116.



## **Medical Complications of Type 2 Diabetes**

Edited by Dr. Colleen Croniger

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Obesity and type 2 diabetes are increasing worldwide problems. In this book we reviewed insulin secretion in both healthy individuals and in patients with type 2 diabetes. Because of the risk associated with progression from insulin resistance to diabetes and cardiovascular complications increases along a continuum, we included several chapters on the damage of endothelial cells in type 2 diabetes and genetic influences on endothelial cell dysfunction. Cardiovascular complications occur at a much lower glucose levels, thus a review on the oral glucose tolerance test compared to other methods was included. The medical conditions associated with type 2 diabetes such as pancreatic cancer, sarcopenia and sleep disordered breathing with diabetes were also discussed. The book concludes with several chapters on the treatments for this disease offering us hope in prevention and successful alleviation of the co-morbidities associated with obesity and type 2 diabetes.

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