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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).

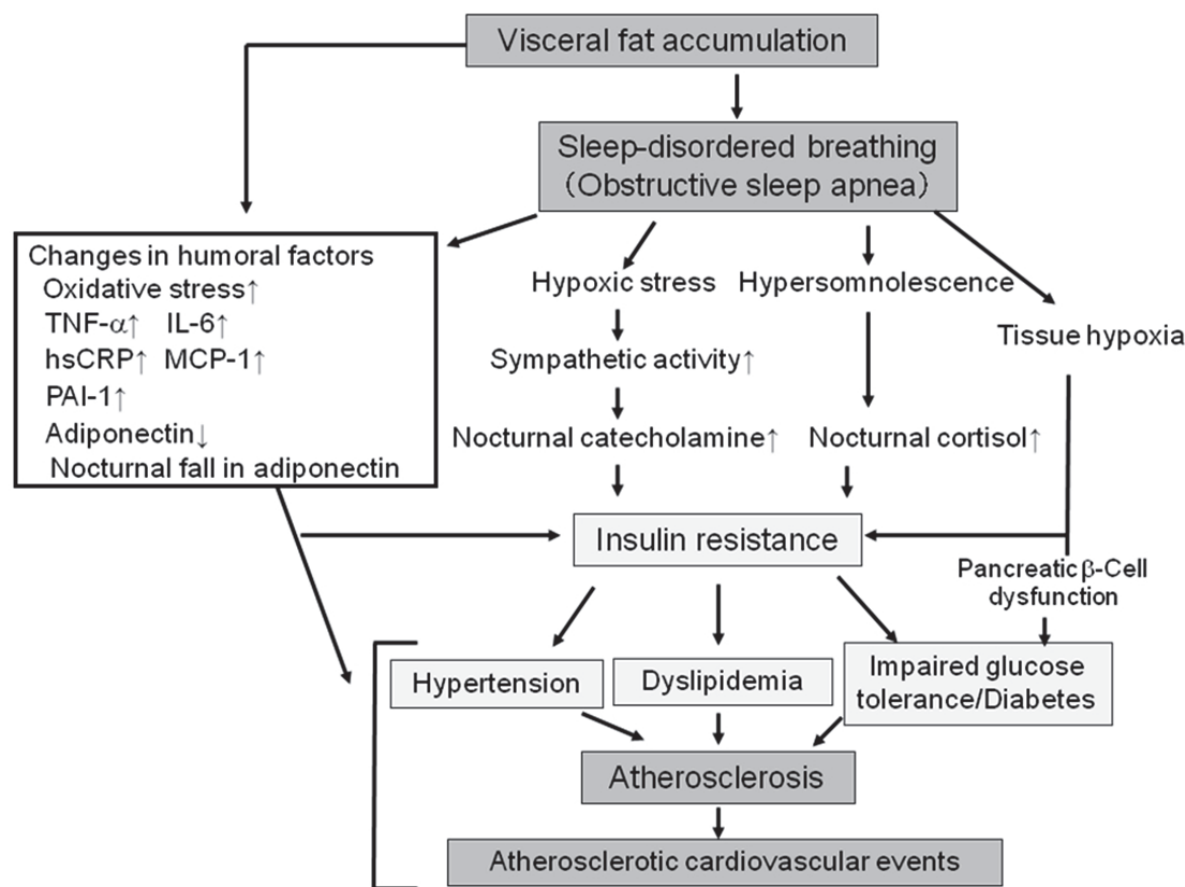


Fig. 1. Relationships among sleep-disordered breathing, visceral fat accumulation and atherosclerosis.

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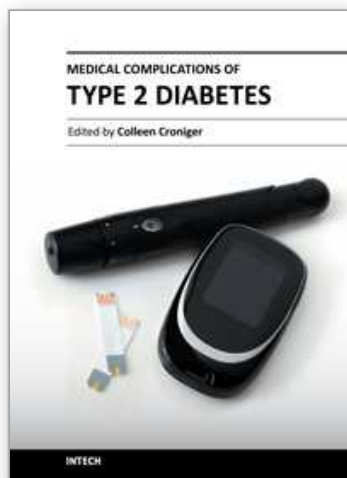
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## **Medical Complications of Type 2 Diabetes**

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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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