

Syndrome Z and Its Association with Obstructive Sleep Apnea

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To cite this article:

Gulam Hassan, Waseem Qureshi. Syndrome Z and Its Association with Obstructive Sleep Apnea. *International Journal of Diabetes and Endocrinology*. Vol. 3, No. 1, 2018, pp. 15-17. doi: 10.11648/j.ijde.20180301.13

Received: February 26, 2018; **Accepted:** March 16, 2018; **Published:** May 3, 2018

Abstract: It is clear that obstructive sleep apnea (OSA) and metabolism syndrome share a similar pathophysiological milieu that would be expected to increase the risk of cardiovascular disease. In patients with established coronary artery disease, treatment of OSA may confer long term cardiovascular benefits. Prevention of nocturnal hypoxemia, sympathetic activation and pressor surges in addition to reduction of daytime sympathetic activity, blood pressure and insulin resistance by continuous positive airway pressure would improve cardiovascular outcomes in patients with metabolic syndrome.

Keywords: Syndrome Z, Obstructive Sleep Apnea (OSA), Metabolic Syndrome

1. Introduction

Metabolic syndrome is characterized by the occurrence of metabolic risk factors for endothelial dysfunction and atherosclerotic cardiovascular disease that includes abdominal obesity, hyperglycemia, dyslipidemia and hypertension. Other names used for this spectrum of clinical and biochemical findings are syndrome X, insulin resistance syndrome or obesity dyslipidemia syndrome, Reaven's syndrome or Kaplan's deadly quartet [1-3]. This syndrome is a co-occurrence or clustering of metabolic disturbances resulting in a higher risk of type 2 diabetes mellitus and cardiovascular disease, and may contribute to the pathogenesis of other complex diseases like colon and other cancers as well [4].

The metabolic syndrome has been defined by several authorities, including the World Health Organization [5], National Cholesterol Education Program Third Adult Treatment Panel (ATP-III) [6], American Heart Association / National Heart, Lung and Blood Institute [2] and the International Diabetes Federation [7]. Despite some disparity among these definitions, all of these encompass some criteria of the four key elements: insulin resistance/glucose dysregulation, obesity, hypertension and dyslipidemia. The metabolic syndrome is being increasingly more prevalent

worldwide; approximately 25 to 40% of adult Americans are reported to have this disorder [8-9].

As per the (NCEP-ATP) III criteria, metabolic syndrome is 40% greater in patients with obstructive sleep apnea (OSA), an illness characterized by repetitive episodes of partial (hypopnea) or complete (apnea) cessation of breathing during sleep. Though there is circumstantial evidence to implicate OSA in the development of metabolic syndrome, the causal relationship remains unproven. It has been hypothesized that in the setting of OSA and metabolic syndrome, there exists a feed forward relationship between the two which leads to further aggravation of both disorders. It has been proposed that OSA may be one of the manifestations of metabolic syndrome [10, 11]. There is published evidence suggesting independent association of OSA with insulin resistance and other components of metabolic syndrome [12]. The co-occurrence of OSA and metabolic syndrome is defined as Syndrome Z [13].

2. Results

OSA has been associated with all the four of the more established components of the metabolic syndrome, leading to the evolution of syndrome Z [14]. In a recent hierarchical 5-factor model providing empirical evidence for syndrome Z, a

good overall fit was found that obesity was the most important determining factor; followed by sleep disturbance, insulin resistance, hypertension and dyslipidemia [15].

There is a growing experimental and clinical evidence for an independent contribution of OSA toward the development and/or severity of individual metabolic disorders and the syndrome entity. On the other hand, metabolic syndrome and its components – in particular, obesity and insulin resistance / diabetes mellitus may have a conductive influence on the development of sleep apnea, it has also been proposed that OSA itself may be a metabolic disorder and a component of metabolic syndrome [16]. Several well designed studies support the association between OSA and metabolic syndrome in adults [16]. There is now ample evidence of independent association of OSA with systemic hypertension, insulin resistance, ischemic heart disease and stroke [18] as well. The mechanisms of underlying components of the syndrome Z are briefly described here.

3. Discussion

3.1. Hypertension

For hypertension to occur, endothelial dysfunction with decreased nitric oxide (No) production and subsequent predominance of vasoconstrictive mechanisms is considered to be one of the main factors [19]. More recently there has been evidence of synergistic or antagonistic effect of other substances on the arterial system – activation of arginase leading to decreased availability of L-arginine as an accessory factor of No synthase with subsequent fall in its production and decrease in its vasodilating effect [20]. Evidence also indicates that sodium reabsorption is increased in people with metabolic syndrome [21]. The mechanism by which OSA causes hypertension is multifactorial, nocturnal sympathetic nervous system activation being the key factor.

In addition, sodium retention occurs in obesity and probably sleep apnea induced hypertension is associated with activation of the renin angiotensin – aldosterone system, and elevation of leptin levels. Hyperleptinemia may provide a broader link between OSA and hypertension because leptin may increase adrenergic activity per se, that is an important determinant of hypertension in OSA [22].

3.2. Dyslipidemia

In general, with increase in free fatty acid flux to the liver, increased production of apo-B-containing triglyceride-rich very low density lipoprotein (VLDL) takes place. In the setting of insulin resistance, increased flux of free fatty acids to the liver increases the hepatic triglyceride synthesis [23]. The other major lipoprotein disturbance in metabolic syndrome is a reduction in HDL cholesterol. In the presence of hypertriglyceridemia, a decrease in the cholesterol content of HDL results from decreases in the cholesteryl ester content of the lipoprotein core with variable increase in triglyceride, a function in part of cholesteryl ester transfer protein [24].

3.3. Insulin Resistance and Diabetes Mellitus

Insulin resistance is a precursor state of diabetes mellitus, and metabolic syndrome is also highly predictive of diabetes mellitus. OSA may also fuel other derangements attributable to insulin resistance, such as hypertension, hypertriglyceridemia, and visceral obesity, perpetuating the disturbances in metabolic syndrome and to its cardiovascular sequelae. OSA, insulin resistance and metabolic syndrome are closely related to indices of obesity [25]. There is enough published evidence to support the fact that there is increased risk of developing diabetes in individuals with short sleep durations and/or difficulties sleeping at baseline. It is likely that multiple inter-related factors contribute to the complex interaction between OSA, obesity and glucose metabolism (Figure 1).

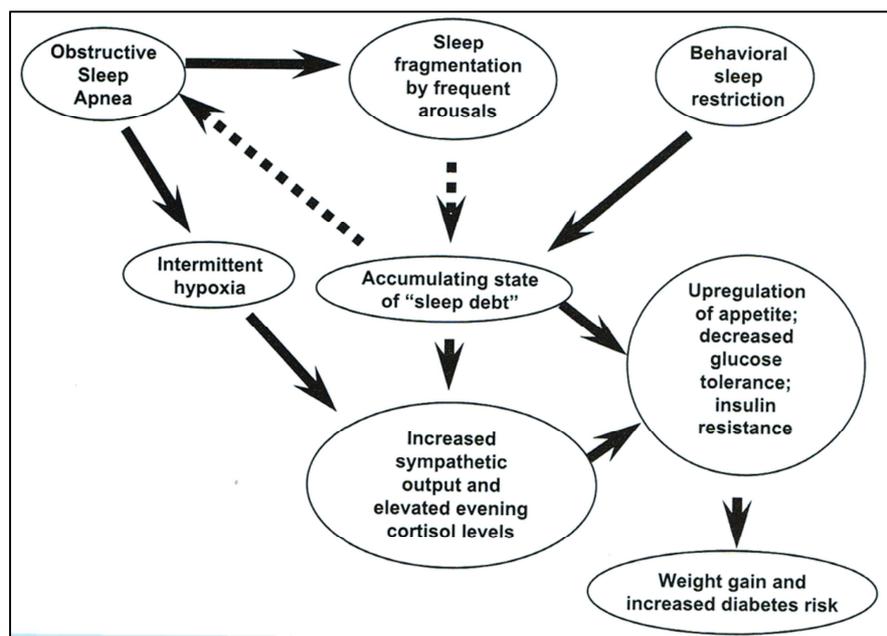


Figure 1. Mechanisms leading to insulin resistance and increased diabetes risk in obstructive sleep apnea.

OSA is associated with chronic intermittent hypoxia and sleep fragmentation, which may adversely affect glucose homeostasis. Increased sympathetic activity, dysregulation of hypothalamus – pituitary axis, generation of reactive oxygen species, and activation of inflammatory pathways have all been proposed as causative stimuli that lead to alteration in glucose metabolism in OSA [17]. Studies have shown a supportive evidence of a dose dependent relationship between the severity of OSA and glucose metabolism [26].

4. Conclusion

It is clear that OSA and metabolism syndrome share a similar pathophysiologic milieu that would be expected to increase the risk of cardiovascular disease. In patients with established coronary artery disease, treatment of OSA may confer long term cardiovascular benefits.

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