Chapter 19

Obstructive Sleep Apnea and the Metabolic Syndrome: Pathophysiological and Clinical Evidence

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Chapter Outline

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a common nocturnal disorder characterized by the presence of repetitive apnea and hypopnea during sleep, daytime sleepiness, and cardiopulmonary dysfunction. Patients with OSAS experience recurrent episodes of cessation of breathing that expose the cardiovascular system to cycles of hypoxia, exaggerated negative intrathoracic pressure, and arousals. The number of apneas and hypopneas per hour of sleep is termed the apnea-hypopnea index (AHI) and has been used as a marker of OSA severity. An OSA disorder is generally defined as five or more apneas or hypopneas per hour of sleep. Moderate and severe OSA are defined as AHI ≥ 15 and ≥30, respectively.

EPIDEMIOLOGY OF OSAS

OSAS is a common condition affecting at least 1–5% of middle-aged individuals in various ethnic populations. OSA has an increasing prevalence worldwide.

Approximately 13% of men and 6% of women between 30 and 70 years of age have moderate to severe forms of OSA. Present data show an impressive increase in the prevalence of OSA in the last decades (Peppard et al., 2013). Prevalence of OSA may reach up to 50% in obese people. Moreover, 60% of patients with metabolic syndrome (MetS) have OSA and this prevalence is even higher in obese patients with diabetes (Angelico et al., 2010). Notably, many studies demonstrated that successful treatment of OSA helps better control many of the associated diseases and chronic conditions.

Most patients with OSA syndrome remain undiagnosed, and the recognition of this condition is poor even in people with obesity or hypertension.

OSAS AND CARDIOVASCULAR DISEASES

Sleep-related breathing disorders are highly prevalent in patients with established cardiovascular disease (CVD). In particular, the prevalence of OSA is higher in populations with hypertension, heart failure, ischemic heart disease, and stroke.

Multiple comorbidities, such as obesity, hypertension, CVD, and MetS, are present in the majority of patients with sleep apnea (Angelico et al., 2010). Hence, it is difficult to understand whether abnormalities evident in the OSA

Modulation of Sleep by Obesity, Diabetes, Age, and Diet. http://dx.doi.org/10.1016/B978-0-12-420168-2.00019-3

patient with CVD are secondary to the sleep apnea, the cardiovascular condition, or both.

Observational studies suggest OSA as an important cardiovascular risk factor for incident ischemic heart disease, stroke, and CVD-caused mortality. In fact, several clinic-based longitudinal studies have found an association between OSA and the development of coronary artery disease (CAD), after adjusting for other risk factors, mainly in untreated individuals referred to continuous positive airway pressure (CPAP) treatment.

Currently, OSAS is also considered an independent risk factor for stroke. In particular, in an observational cohort study, an independent association between OSA and a combination of stroke and death was reported (Yaggy et al., 2005). Furthermore, the risk was found to increase with higher severity of OSA.

OSA interrupts the cardiovascular quiescence typical of sleep by triggering a cascade of acute hemodynamic, autonomic, chemical, inflammatory, and metabolic effects, these alterations cause chronic aftereffects capable of initiating or exacerbating CVD.

Thus, OSA can exacerbate CVD by many different mechanisms. Ineffectual inspiratory efforts typical of OSAS cause negative intrathoracic pressure that, by hemodynamic mechanisms, may impede left ventricular filling and decrease stroke volume. Moreover, hypoxia during OSA might also directly impair cardiac contractility and diastolic relaxation. Besides, intermittent hypoxia can even induce the production of oxygen free radicals and activate inflammatory pathways that impair vascular endothelial function and increase blood pressure. It has been demonstrated that OSA can also promote oxidation of lipoproteins, increase the expression of adhesion molecules, promote monocyte adherence to endothelial cells, and induce vascular smooth-muscle cells proliferation. Notably, platelet activation and aggregability, markers of increased susceptibility to thrombosis, are increased during sleep in patients with OSA, and morning fibrinogen concentration is increased and plasminogen activator inhibitor type-1 activity is decreased (Steiner et al., 2005).

These adverse events, combined with increased sympathetic vasoconstrictor activity and inflammation, could predispose to hypertension and atherosclerosis. Finally, cerebral blood flow declines significantly during the episodes of obstructive apnea due to a decrease in cardiac output; so in patients with flow-limiting lesions of the cerebral arteries, this can further predispose to ischemic events (Balfors & Franklin, 1994).

DEFINITION AND CLINICAL PRESENTATION OF METS

Clustering of cardiovascular risk factors (termed "the metabolic syndrome" in 1981) was recognized as early as the 1920s and is currently thought to be related to the underlying pathophysiology of insulin resistance and hyperinsulinemia. MetS represents a constellation of metabolic derangements, including central obesity, hypertension, glucose intolerance, and dyslipidemia. It is a well-recognized risk factor for CVD and type 2 diabetes. Obesity increases the likelihood that this cluster of abnormalities will occur.

In 2001, the National Cholesterol Education Program Adult Treatment Panel III report (ATP III) recommended the use of five variables, with established diagnostic cutoffs, to define MetS: abdominal obesity, hypertension, insulin resistance or glucose intolerance, low serum high-density lipoprotein (HDL) cholesterol, and elevated serum triglycerides. Any individuals satisfying three of these five criteria would be classified as having MetS. The International Diabetes Federation (IDF) criteria included the same five components as the ATP III version, but indicated that one abnormality had to be present to diagnose MetS; namely, abdominal obesity, as assessed by measuring waist circumference. An enlarged waist circumference, and any two of the remaining four components were sufficient to diagnose MetS. More recently, ATP III and the IDF, joined by several other prestigious organizations, have proposed a "harmonized" definition of MetS, including different ethnic threshold criteria for waist circumference definition of abdominal obesity (Eckel, 2010). In this "working" definition, all criteria are clinically identifiable, thus making it easy to recognize MetS in practice. However, since different clinical and biochemical criteria may be proposed for the definition of MetS, using the broad clinical criteria, the diagnosis of MetS is very common and patients may have a different clustering of risk factors and present various degrees of insulin resistance and secretion. Moreover, MetS may have multiple clinical and pathophysiological presentations and among them, most important, its presentation with or without diabetes. The goal of diagnosing MetS is to identify persons at increased risk of CVD and type 2 diabetes.

OSAS AND METS

Current data suggest that there is an increased prevalence of MetS in subjects with OSA. Many epidemiological and clinical studies have demonstrated independent associations of OSA with MetS (Coughlin, Mawdsley, Mugarza, Calverley, & Wilding, 2004; Sasanabe et al., 2006). In fact, the majority of OSAS patients show the cluster of metabolic and non-metabolic cardiovascular risk factors of MetS, including also proinflammatory and prothrombotic states and increased systemic oxidative stress. It appears that more than two-thirds of severe OSA (AHI≥30) patients have MetS in both Eastern and Western countries. Moreover, the prevalence of MetS is increasing with the epidemic of obesity across different ethnic origins. For these reasons, it has been suggested that OSA may be a further manifestation of MetS. Syndrome Z (Wilcox, McNamara,

Collins, Grunstein, & Sullivan, 1998) is defined as the co-occurrence of OSA and MetS.

There are a number of possible reasons why OSA may be independently associated with an increase in the clinical and biochemical features typical of MetS. It is possible that OSA either directly increases these factors, or that OSA and MetS share common risk factors. In particular, it has been suggested that this association may be due to the relation of OSAS and MetS with obesity. However, although MetS and OSA may simply be coincident syndromes, there is growing, albeit inconclusive, evidence that the pathophysiology of OSA and MetS may overlap considerably. Moreover, an independent association of OSAS with the individual risk factors of MetS seems to be present. In fact, it is also possible that OSAS might directly contribute to the development of insulin resistance and the other cardiovascular risk factors found in patients with MetS. Therefore, based on these considerations, a model of bidirectional association between OSA and MetS may be proposed.

In a previous study performed by our group in a large series of heavy snorers, a strong association between OSAS, MetS, and its clinical and metabolic components was found in subjects of both sexes examined in an internal medicine setting (Angelico et al., 2010). Patients with severe OSA were more obese, more hypertensive, and more insulin resistant than those with a less severe OSA and control snorers. Polysomnographic indices – AHI, ODI, and average SaO2 – were independent predictors of central obesity, serum insulin, and the metabolic score, i.e., the number of components of MetS. In particular, an independent association was found between ODI and insulin resistance (HOMA-IR), which is generally believed to play a central role in the clustering phenomenon of CVD risk factors that defines MetS. The concurrent presence of MetS and OSA may have an additive effect on atherosclerosis.

OSAS AND CENTRAL OBESITY

Most patients with newly diagnosed OSA have a history of excessive weight gain in the period preceding the diagnosis. Obesity is an important risk factor for the development of OSA. Prevalence of OSA is probably rising as a consequence of increasing obesity. The mechanisms of this association are probably multifactorial. In fact, obese people have extrinsic narrowing of the area surrounding the collapsible region of the pharynx and regional soft tissue enlargement; moreover, they have also increased neck circumference and fat deposits posterolateral to oropharyngeal airspace at the level of soft palate, in the soft palate, and in submental area.

Sleep apnea patients have a greater amount of visceral fat compared with obese controls matched for BMI, suggesting that central or abdominal obesity are more closely associated with OSA than general obesity. Moreover, central adiposity and visceral fat deposition also appear to be the hallmark of increased risk for OSA. Obesity also plays a vital role in the pathogenesis of the core feature of MetS, insulin resistance, which in turn may induce OSA.

OSAS AND ARTERIAL HYPERTENSION

Epidemiological studies have shown that approximately 40% of patients with sleep apnea have hypertension, and that about 40% of patients with hypertension have sleep apnea (Nieto et al., 2000; Young et al., 1993). Sleep-related breathing disorders are common contributing factors to the production of essential hypertension but are neglected, underdiagnosed, and undertreated. Evidence that OSA can cause elevated blood pressure levels during sleep and during the day is very strong. In fact, several reports have shown that the prevalence of hypertension is greater in patients with OSA and vice versa (Wolk, Shamsuzzaman, & Somers, 2003). Actual figures vary, depending on the definitions and thresholds for sleep apnea and hypertension. Moreover, severity of OSA is correlated with the presence of hypertension (Steinhorst et al., 2013).

Recent guidelines for the management of arterial hypertension recognized OSA as an identifiable and not uncommon cause of resistant hypertension (Mancia et al., 2007). OSAS is an independent risk factor for hypertension, and hypertension is a frequent comorbid condition with sleep apnea. Compared with controls, OSA patients have higher blood pressure and heart rate, and a reduction of the sleep-related nocturnal blood pressure drop. In fact, repetitive episodes of airway occlusion and hypoxemia induce paradoxical rises in blood pressure during sleep. Moreover, patients with OSA do not manifest the usual fall in mean arterial blood pressures during sleep and have a non-dipper 24 h blood pressure profile.

OSA may have a causal role in the development of hypertension. In the Wisconsin Sleep Cohort Study, an independent dose–response relation between sleep-disordered breathing at baseline and the development of new hypertension 4 years later was demonstrated. The odds ratios for the presence of incident hypertension at follow-up were 1.42, 2.03, and 2.89 with an AHI of <5, 5 to 15, and >15 events per hour at baseline, respectively.

Furthermore, there is a growing experimental evidence that OSA can cause blood pressure rise, by increasing the activation of the renin-angiotensin system (Peppard et al., 2013). This hypothesis has been strengthened by evidence from intervention trials showing that treatment with CPAP may lower both systolic and diastolic blood pressures. OSA may also cause acute nocturnal surges in blood pressure in response to chemoreflex-mediated hypoxic stimulation of sympathetic activity and in part, may contribute to the nocturnal "non-dipping" pattern of hypertension. Therefore, sleep deprivation is itself now being understood as

an important cause of neural, vascular, and endocrine disruption, leading to increases in blood pressure. All these findings suggest that OSA is likely to be a risk factor for hypertension and consequent cardiovascular morbidity in the general population.

OSAS, INSULIN RESISTANCE AND DIABETES

Insulin resistance is the hallmark and key feature of MetS, which may predispose to type 2 diabetes, atherogenic dyslipidemia fatty liver infiltration, and increased global cardiovascular risk. It is estimated that 34% of adult Americans have insulin resistance as a result of the increased prevalence of obesity and sedentary lifestyles. It is unknown whether OSA contributes to insulin resistance, although it has been suggested that the intermittent hypoxia associated with sleep apnea may cause a drop in insulin sensitivity.

Patients with severe OSA are more insulin resistant than those with a less severe OSA and control snorers (Angelico et al., 2010).

Rates of OSA are much higher among people with type 2 diabetes. In people who have diabetes, the prevalence of OSA may be up to 23%. At the same time, rates of diabetes are higher among people with OSA. The two diseases also share risk factors, including obesity and advancing age. However, it has been proposed that OSA and type 2 diabetes mellitus may be associated independently of the degree of adiposity and that OSA may be a risk factor for diabetes mellitus. By contrast, a longitudinal study of 1300 subjects in the Wisconsin Sleep Cohort did not find any independent relationship between OSA and incident diabetes at 4-year follow-up, despite a higher prevalence of diabetes in OSA subjects independent of other risk factors at baseline (Reichmuth, Austin, Skatrud, & Young, 2005).

Several pathophysiologic mechanisms have been proposed to explain the alterations in glucose metabolism in OSA patients. Intermittent hypoxia, endothelial dysfunction, inflammatory state, sleep fragmentation, and high sympathetic nervous system activity all can play a pivotal role in the dysregulation of glucose control. Poor sleep quality and intermittent hypoxemia from OSA may serve as the catalyst for glucose dysregulation. Over time, these abnormalities may accelerate weight gain, which may increase the severity of OSA. Moreover, it should be taken in to account that many patients with type 2 diabetes have undiagnosed OSA. Finally, it should be considered that most diabetic OSA patients satisfy the criteria for MetS and are affected by hypertension and central obesity. In fact, in our study of heavy snorers, more than 90% of diabetic OSA patients satisfied the criteria for MetS and were affected by hypertension and central obesity, while the corresponding figures in non-diabetic OSA were 54.0%, 67.8%, and 80.9% respectively (Angelico et al., 2010).

OSAS AND ATHEROGENIC DYSLIPIDEMIA

Few cross-sectional studies suggested that OSA is independently associated with hyperlipidemia. In subjects with OSA, a higher prevalence of dyslipidemia was found after adjustment for BMI (McArdle, Hillman, Beilin, & Watts, 2007) and AHI was independently associated with low HDL levels (Borgel et al., 2006). Elevations in total cholesterol, triglycerides, and corresponding reduction in HDL have been coupled to oxidative processes commonly found in OSA (Li et al., 2007). Moreover, it has been suggested that hypersympathetic tone and oxidative stress induced by OSA may have adverse impact on cholesterol metabolism via generation of stearoyl-coenzyme A desaturase-1, reactive oxygen species (ROS), peroxidation of lipids, as well as systemic inflammation (Adedayo et al., 2012).

OSAS AND INFLAMMATION

A number of markers of systemic inflammation are elevated in patients with OSA; they include tumor necrosis factor alpha (TNF-a), IL-6, and C-reactive protein (CRP) (Punjabi & Beamer, 2007). Patients with OSA have also decreased levels of anti-inflammatory substances, including IL-10 and adiponectin. OSA itself further exacerbates systemic inflammation especially in obese patients. In fact, OSA may initiate a cascade of events that may promote the activation of macrophages and subsequent release of proinflammatory cytokines.

Several studies demonstrated higher serum levels of TNF-a in subjects with OSA than in subjects without OSA (Ciftci, Kokturk, Bukan, & Bilgihan, 2004; Kanbay, Kokturk, Ciftci, Tavil, & Bukan, 2008), whereas other studies did not find significant differences between OSAS patients and their matched control group (Vgontzas et al., 2000).

Many other cytokines/adipokines involved in the development of atherogenesis were also investigated in patients with OSAS, including IL-6, IL-8, IL-12, IL-18, and γ-interferon.

IL-6 is a major initiator of the acute-phase response and the main regulator of hepatic CRP production. Moreover, IL-6 is produced by a variety of cells, is predictive of future cardiovascular events, and is expressed in human atherosclerotic lesions (Luc et al., 2003). However, there are conflicting reports in the literature regarding both IL-6 levels and CRP levels in the circulation of patients with OSAS. In fact, while some studies report increased levels of CRP or IL-6 in OSAS, others have shown that obesity rather than OSAS severity was associated with systemic inflammation.

OSAS AND OXIDATIVE STRESS

Several studies have provided evidence supporting an increase of systemic oxidative stress in OSAS (Barcelò et al., 2000; Carpagnano et al., 2003; Del Ben et al., 2012;

Katsoulis, Kontakiotis, & Spanogiannis, 2011). Oxidative stress is characterized by an imbalance between oxidant and antioxidant mechanisms, in which many different enzymatic and non-enzymatic antioxidants take place. It has been postulated that intermittent hypoxia and reoxygenation can induce ROS generation, which may lead to chronic inflammation, endothelial dysfunction, and increased cardiovascular risk. In fact, in hypoxic reoxygenation conditions, mitochondria becomes dysfunctional to produce even higher amounts of ROS.

Increased oxidative stress in OSA has been primarily shown by using various markers of lipid peroxidation in plasma and urines. Urinary isoprostanes, a reliable marker of lipoperoxidation, correlate best to the average desaturation index in OSA, which suggests that they are reliable biomarkers for chronic intermittent hypoxia and oxidative stress (Del Ben et al., 2012). An open question is whether OSA itself results in oxidative stress or it is simply a consequence of metabolic comorbidities frequently associated to OSAS. In a study performed in otherwise healthy OSA patients, without any other comorbidities, no evidence for higher oxidative stress and lipid peroxidation was observed (Svatikova et al., 2005). By contrast, we provided evidence that patients with MetS have endothelial dysfunction and increased systemic oxidative stress (Del Ben et al., 2012). In fact, in our series of consecutive patients with heavy snoring, those with severe OSAS had higher levels of urinary 8-iso-PGF2α and serum NOX2, a ROS generating enzyme and lower NOx, stable NO derivatives, reflecting overall NO production.

OSAS AND ENDOTHELIAL DYSFUNCTION

Oxidative stress is a major component in the initiation and development of endothelial dysfunction, which depends on the reduction in NO bioavailability and is widely accepted as an early marker of atherosclerosis.

Recent studies suggest that the repetitive episodes of hypoxia and reoxygenation could promote the activation of proinflammatory pathways and disrupt normal endothelial function by mechanisms similar to those of the ischemia/reperfusion injury model. Moreover, previous studies have demonstrated that total nitrate and nitrite (NOx) production is lower in OSAS patients than in controls (Del Ben et al., 2012).

Flow-mediated, brachial artery vasodilation (FMD) is a well-established marker of endothelial function, as the result of endothelial release of NO. Endothelial dysfunction is markedly reduced in patients with moderate/severe OSAS and in those with MetS (Angelico et al., 2011; Del Ben et al., 2012; Del Ben, Loffredo, Violi, & Angelico, 2013).

FMD is impaired in subjects with OSA independently of obesity and conventional risk factors (Namtvedt et al., 2013) and in the absence of known CVD (Jones et al., 2013).

Subjects with major overnight oxygen desaturation show significant impairment in both endothelium-dependent and -independent vasodilatation in response to intra-arterial infusion of acetylcholine and sodium nitroprusside, respectively (Cross et al., 2008).

However, even in those OSA subjects with minimal symptoms, endothelial function has been shown to be impaired (Kohler et al., 2008).

A recent study found that when regression analysis was limited to the subgroup of subjects less than 50 years old, OSA was the only independent predictor of FMD, replacing age. Thus, the authors concluded that OSA may exert a "premature aging effect" on endothelial function (Yim-Yeh et al., 2010).

CPAP AND MetS

Cardiovascular complications in OSAS are multifactorial, and involve alterations of endothelial dysfunction, inflammation, oxidative stress, and insulin resistance as a consequence of intermittent episodes of hypoxia and reoxygenation. Therefore, CPAP therapy may play an important role in reversing the above alterations and reducing high cardiovascular risk, particularly in patients with MetS. In fact, it has been reported that treatment with CPAP ameliorates oxygen desaturation and decreases CV morbidity and mortality (Doherty, Kiely, Swan, & McNicholas, 2005; Marin, Carrizo, Vicente, & Agusti, 2005). However, although nasal CPAP is highly effective in controlling OSAS, compliance data show only moderately satisfactory results. Moreover, obesity and visceral fat distribution may represent important confounding variables in this context.

Whether CPAP might be a novel method to reverse MetS in patients with OSA is a matter of debate. A recent paper in the New England Journal of Medicine (Sharma et al., 2011), claimed to show that CPAP can reverse MetS. In fact, in a double-blind, placebo-controlled trial, 3 months of CPAP therapy was able to lower blood pressure and partially reverse metabolic abnormalities, leading to a dramatic reversal of MetS among 11 of 86 treated patients. However, after a request to see the primary data, which had mysteriously gone missing, the authors retracted the article (Sharma et al., 2013).

Treatment with CPAP improves some components of MetS. Notably, it lowers blood pressure in patients with OSA. This effect is modest but consistent, and is more evident in patient with more severe hypertension. Two recent randomized studies comparing therapeutic and sub-therapeutic CPAP showed that blood pressure in those individuals receiving therapeutic CPAP was significantly lower, both at night and during the daytime. A meta-analysis of placebo-controlled, randomized trials confirmed greater reductions in ambulatory mean blood

pressure among patients with more severe OSA and better effective nocturnal use of CPAP device (Haentijens et al., 2007).

Whether CPAP treatment of OSA can reverse insulin resistance and prevent body weight gain is controversial. Some studies showed decreases of blood pressure and oxidative stress without relevant changes in insulin resistance in patients treated with CPAP (Murri et al., 2011). Conversely, a recent meta-analysis of randomized control trials showed a favorable effect of CPAP on insulin resistance as measured by HOMA-IR in patients with OSA without diabetes (Iftikhar, Khan, Das, & Magalang, 2013).

Interventional data regarding glucose metabolism in OSA have also shown conflicting results. In a small study using the hyperinsulinemic euglycemic clamp, CPAP was found to improve insulin sensitivity (Harsch et al., 2004), and in a further study, CPAP treatment reduced HOMA-IR in sleepy but not in non-sleepy OSA subjects with similar AHI levels (Barcelò et al., 2000). By contrast, a study of diabetic men with OSA showed no change in insulin sensitivity during 3 months of CPAP treatment compared with sham CPAP (West, Nicoll, Wallace, Matthews, & Stradling, 2007), and similarly, a crossover study of non-diabetic OSA men found no change in HOMA-IR during 6 weeks of CPAP treatment.

A few observational studies reported that nasal CPAP treatment improved serum lipid parameters. However, to date, there are no consistent data from randomized, controlled studies to support that treatment of OSA can modify dyslipidemia.

CPAP treatment is able to reduce oxidative stress in patients with OSA (Carpagnano et al., 2003). CPAP treatment significantly inhibited lipid peroxidation levels in hypertensives with severe OSA (Alzoghaibi & Bahammam, 2012), and plasma 8-isoprostanes decreased and NOx increased after effective CPAP (Del Ben et al., 2012).

Few data on the effects of CPAP on inflammation have been reported. One-month CPAP significantly decreased levels of both CRP and IL-6 and spontaneous IL-6 production by monocytes in patients with mild to moderate OSAS (Yokoe et al., 2003). CPAP treatment was also reported to increase serum adiponectin (Carneiro 2009) and to decrease serum leptin levels significantly (Chin et al., 1999).

Recently, CPAP therapy improved endothelial dysfunction and decreased the levels of oxidative stress and inflammatory cytokines in patients with MetS (Del Ben et al., 2012).

Long-term compliance to nasal CPAP (NCPAP) therapy was found to be effective in reducing the levels of systemic oxidative stress and improving endothelial dysfunction (Cross et al., 2008). In fact, NCPAP therapy normalized urinary 8-iso-PGF2α and serum sNOX2-dp values and increased flow-mediated brachial artery dilation even though there was no significant change in body weight or cardiovascular risk factors during the 6 months of treatment (Del Ben et al., 2012).

CONCLUSIONS

Based on current evidence, clinicians need to address the risk of OSA in patients with MetS and, conversely, evaluate the presence of MetS in patients with OSA. In fact, it is possible that the relationship goes in both directions. The concurrent presence of MetS and OSAS may have an additive effect on atherosclerosis. Early detection and treatment of OSAS in asymptomatic hypertensive patients is essentially important to prevent hypertensive target organ damage and cardiovascular events. Finally, weight loss should be recommended for all overweight or obese patients with sleep apnea, as it has also many beneficial effects on the metabolic profile in OSA subjects.

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