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The Mechanistic and Pathophysiological Role of Adiponectin and Resistin towards Regulation of Food Intake and Appetite in Cardiovascular Associated Risk Factor of Metabolic Syndrome

Mimie Noratqah Jumli and Muhammad Ilyas Nadeem

Abstract

Insulin resistance syndrome or syndrome X is also known as metabolic syndrome (MetS). It is an emerging problem globally with the surge of increasing prevalence among urban population of developing countries. The etiology of pathophysiology of metabolic syndrome includes the inflammatory pathways of insulin resistance, deregulated appetite, diet-induced, inflammation-induced obesity, and cardiovascular diseases (CVD). Adipose tissue is an endocrine organ that secretes adipokines like adiponectin and resistin during physiological and pathological states. Moreover, the adipokines associated with diet-induced and inflammation-induced obesity have secondary deteriorating effects on cardiovascular system. Although, the adiponectin and resistin were potentially found in regulating food intake and appetite but their mediating effect on pathophysiology of CVD still needs future investigations. However, the prior studies reported the association of adiponectin and resistin levels with CVD complications related to food intake but still there is need to understand its multifactorial heterogeneity. Therefore, literature suggests figuring out potential target mechanistic and therapeutic approaches of adiponectin and resistin hormone towards food intake and appetite involvement in metabolic syndrome and CVD.

Keywords: cardiovascular disease, metabolic syndrome, food intake, adiponectin, resistin

1. Introduction: cardiovascular associated with metabolic syndrome

Syndrome X or Insulin resistance syndrome is also known as metabolic syndrome (MetS). It is defined as the concurrence of obesity-associated cardiovascular risk factors inclusive of abdominal obesity, impaired glucose tolerance,

hypertriglyceridemia and hypertension [1]. Meanwhile, CVD is a heart and circulatory system disease that is currently one of the main causes of morbidity and mortality worldwide. They are the series of heterogeneous diseases, like most commonly caused by CVD atherosclerosis and chronic diseases that evolve progressively over a lifetime, and are asymptomatic for a long period of time [2]. It is world leading cause of death worldwide, and 17.9 million people died every year with high record from developed and developing countries. In 2017, World Health Organization (WHO) list out diseases related to CVD such as coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism [3].

In addition, Ford et al. [4] stated that MetS is a syndrome had a link with 3–5 coronary heart disease (CHD) risk factors and increases the incidence of cardiovascular events especially among the elderly population. Some studies have shown that MetS is 1.50–2.00 times more common in individuals with CHD and significantly increases frequency of cardiovascular events, progress and risk of consequences [5, 6]. The risk of CHD is 7 times higher among individuals with MetS and diagnosed diabetes mellitus [7]. On the other hand, obesity plays a major role as an underlying risk factor for cardiovascular disease and changes in cardiac function associated with obesity have been described as “obesity cardiomyopathy”.

Besides that, the relation between obesity and metabolic risk factors is growing rapidly. Across the globe, obesity and related metabolic disorders are becoming significant health care issues. Obesity pathogenesis involves the balance between consumed calories and energy expenditure, followed by body weight maintenance. The complex process of weight loss involves the interaction of diet, physical activity, environmental, behavioral and physiological factors, as there are several hormones and peptides involved in the regulation of appetite, eating behavior and energy expenditure [8]. In addition, chronic increase in body weight and adiposity in the cardiovascular system can lead to significant neuro-hormonal changes and adaptations.

These alterations include renin-angiotensin-aldosterone system activation, altered adipocytokine and pro-inflammatory cytokine levels, and sympathetic nervous system activation. These inflammatory products are produced in abnormal quantities in the event of obesity. Any of these items has been involved in affecting one of the metabolic risk factors or another related to MetS. Activation of the sympathetic nervous system can contribute to the commonly described increase in heart rate, retention of renal sodium, circulating blood volume, end-diastolic ventricular volume, cardiac output, and blood pressure. More generally, vascular and cardiac function abnormalities (vasoconstriction, tachycardia) and metabolic balance abnormalities (excess lipolysis driving the level of fatty acids, peripheral and hepatic insulin resistance induced by catechol) can be simultaneously driven by activation of the sympathetic nervous system [1].

2. Regulation of food intake and appetite

Food intake plays a role as a transportation for food supply which modulated by metabolic drive generated for energy requirement. While appetite is a psychological desire to eat which related to the energy balance model of weight regulation by involving in various aspects of eating pattern such as frequency of eating, serving portion, type of food and palatability of food [9]. The complex interactions between hormones from gastrointestinal tract and the hypothalamus involve particular regions where hormones interact to create feelings of appetite and satiety that can lead to the food intake or a feeling of fullness beyond the metabolic

needs [10]. Meanwhile, homeostatic system plays an important role in balance the energy expenditure and food intake that contribute to the stability of body fat content over time [11].

Generally, ingestion of food started in the oral cavity and taste receptor. The taste of sour, sweet, salty, bitter and savory will be validated by G-protein-coupled receptors by sending the information via blood circulation to the brain. In the stomach, Brain-derived neurotrophic factor (BDNF) and neurotrophin-3 are known as neurotrophic factor helping in innervating of the stomach wall during nutrient storing. Ghrelin is a hormone sending an important signal during empty stomach and rapidly suppressed upon the ingestion of food. Bloodstream is a major route of ghrelin to the brain to control the appetite. In the intestine area, fat, protein and glucose from food intake will enhance enteroendocrine cells and adipocyte to release hormones for the digestion and absorption process with various signaling pathways involved [12]. Enterendocrine cells produced the gut hormones such as glucagon-like peptide 1 (GLU-1), cholecystokinin (CCK) and glucose-dependent insulinotropic polypeptide which rapidly secreted into bloodstream or distributed as local messengers [13].

There are many theories to explain about appetite mechanism such as Glucostat theory, Dual-centre theory, Aminostatic theory and Lipostat theory [14]. In 1950 [15], Mayer proposed the Glucostat theory which states that the drop in blood glucose level below than the threshold regulates the neuronal activity for the food intake. This theory regulates short-term control over appetite. However, this theory had been largely abandoned in 1970 due to the failure of finding any correlation between arteriovenous blood glucose concentration with hunger rate and food intake [16–18].

Next, dual-centre theory involved with two centre of brain known as Vento medial hypothalamus (VMH) and Lateral hypothalamus (LH) which related to blood glucose level (**Figure 1**). Hunger state will be induced by LH in producing ghrelin hormone which trigger by the drop of blood glucose level while after taking meal blood glucose level will be raise and activate VMH to initiate satiety state. In addition, VMH is potentially found to develop over eating which can lead to obesity [14, 19].

In 1956, Mellinkoff [20] proposed the aminostatic theory involving the production of amino acid after protein stores breakdown sends signals to the brain for energy balance. Muscle catabolism activities caused high amino acid production and stimulate eating behavior while satiety will be reached by diminished level of amino acids [14]. However, it should be noted that evidence of such regulation or the existence of “protein-stat” is not extensive; mainly because of the concept has not been a target for investigation [21].

Lipostat theory explains the activity of adipose tissues undergo lipolysis in generate fatty acids and glycerol. Both lipolysis products will be circulated in the blood and brain for energy expenditure maintenance. High rate of lipolysis will lead to increase in food consumption and post prandial will decrease lipolysis as resulted in its termination [14]. Adipocytokines play an important role in orexigenic pathway which enhance the food intake and anorexigenic pathway which inhibit the food intake. In 1994, Zhang et al. [22] had discovered leptin as primary adipose tissue-derived factor secreted from white adipose tissue and acts on hypothalamus to induce satiety in regulating food intake and energy expenditure [23] while adiponectin have opposite functions of leptin. Various experiments have done and accepted that leptin is a signal that conveys information from the periphery to the brain regarding the long-term state of the body's energy stores [21, 24, 25]. Lipostat is not limited to leptin mechanism only but it is involved with all type of adipose tissue hormones.

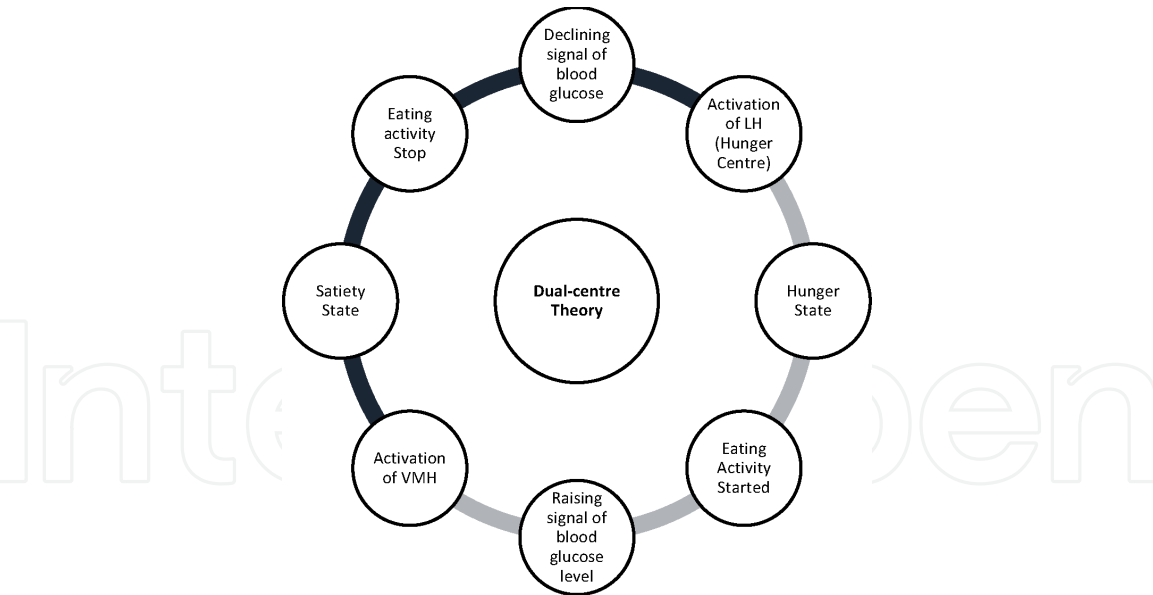


Figure 1.
The circulation of dual-Centre theory related to blood glucose on hunger and satiety.

Energy balance requires an ability of the brain to detect the status of energy stores and match energy intake with expenditure. Dysregulation of appetite and impaired energy expenditure causes excessive food consumption and disrupt the energy balance. In addition, it will cause repeated sense of hunger which contributes to the development of visceral obesity and metabolic syndrome. Frequent intakes of food expose body to store extra calorie which will turn into fat and distribute in different parts of body. There are few hunger hormones known for generating hunger state such as resistin, leptin and ghrelin involve in this process [26]. Previous study mentioned that uncontrolled eating habits like diminishing the frequency of eating, repeated fasting and recurrent over eating were link with obesity-related disorder such as cardiovascular disease, insulin resistance and inflammation [26].

3. Cardiovascular effects on adipocytokines

Over the last two decades adipose tissue had established as a dynamic organ that carries out several important physiological processes. It is considered one of the largest endocrine organs in the body as well as an active tissue for cellular reactions and metabolic homeostasis [27]. It also secretes numerous peptide hormones such as leptin, adiponectin, resistin and many others [28, 29]. Generally, there are three types of adipose tissue in humans which are white adipose tissue (WAT), brown adipose tissue (BAT) and beige/brite/brown-like adipose tissue (bAT). Different types of adipose tissue have distinct morphologies in reflecting their distinct functions [30] (**Figure 2**).

WAT is a major component of body's adipose tissue that provides most of the total body fat and source of fatty acids which are used as energy substrates for the generation of energy through oxidative phosphorylation of adenosine triphosphate (ATP) high-energy bond [31, 32]. Excess accumulation of WAT is potential in developing obesity and obesity-related diseases. There are three types of obesity which are android obesity, central obesity and gynoid obesity. Android or Central obesity is related to the accumulation of WAT at the upper part of body which is potentially related to some inflammatory pathologies. Meanwhile, gynoid obesity is related to the accumulation of WAT at lower part of body which does not affect any metabolic complication (**Figure 2**) [31, 32].

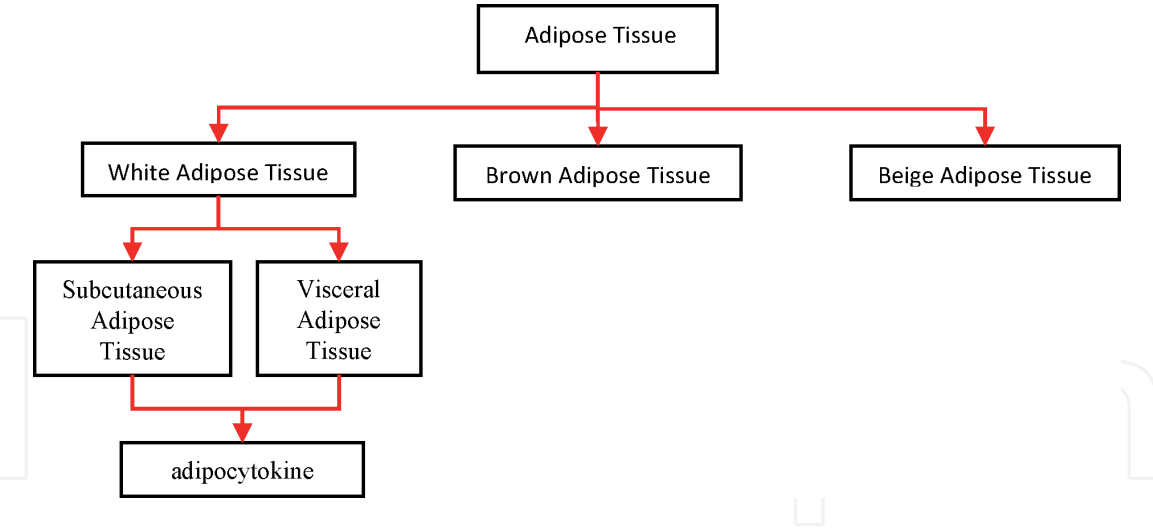


Figure 2.
Types of adipose tissue.

Anatomically, WAT contains two main depots around internal organs which are subcutaneous WAT (SAT) and visceral WAT (VAT). WAT contributes to the whole body insulation and endocrine functions including secretion of leptin, TNF- α , adiponectin, resistin, and other compounds related to the degree of obesity and insulin sensitivity. It is located in the peritoneal cavity, where it forms a compact tissue, or as single adipocytes. Adipocytes contain a single lipid droplet which is known as univacuolar adipocytes. It can be measured between 40 and 120 μm because the size of the lipid droplet may differ significantly [33]. WAT exhibits many essential physiological roles, including the triglyceride accumulation of postprandial glucose and the secretion of signaling factors to control appetite and energy homeostasis. In periods of energy demand by the body, WAT plays role to store excess lipids in the form of triglycerides (TG) and releasing free fatty acids (FFA). It often synthesizes and releases adipokines that control metabolic homeostasis.

The general term for a bioactive substance formed by adipose tissue is known as adipocytokine or adipokine. It is a type of peptide that link the function of adipose tissue to the brain and other target organs [34]. Adipocytokine are hormones formed by fat tissues and play a role in energy homeostasis, the metabolism of sugar and fat, regulation of thermogenesis, reproduction and immunity. They also affect cardiovascular function, either through direct action by paracrine effects on the vascular wall or by influencing endothelial function through altered adipokine plasma and tissue levels relative to the total mass of adipose tissue in the body [34, 35].

3.1 Role of adiponectin

Adiponectin is an abundant circulating hormone present in at least three multimeric forms: trimers, hexamers, and high-molecular-weight (HMW) complexes. Among them, the HMW oligomer is major active form mediating the insulin-sensitizing and cardiovascular protective effects of the adipokine [36–38]. Adiponectin is a protein hormone with 244 amino acids derived from adipose tissue and mainly target adiponectin receptors in regulating energy metabolism and exerts functions such as antiatherogenic, anti-inflammatory, anti-diabetic and cardioprotective effect [39]. It is primarily found in WAT and also could be found in osteoblast, skeletal muscle and cardiomyocytes [40]. Adiponectin's activity is contrary to the function of leptin and resistin. It has two widely expressed receptors (AdipoR1 and AdipoR2) which cross the cerebrospinal fluid in the brain [41].

Plasma protein contains 0.01% of adiponectin and in normal human subjects it is found about 3 to 30 ug/ml [42, 43].

In order to regulate the metabolism of fatty acids, carbohydrates, cholesterol and amino acids, as well as mitochondrial function, autophagy and the growth of cells, both receptors are critical in inducing AMP-activated protein kinase (AMPK) activity. In addition, both receptors are also important in energy balance and energy expenditure as these processes activate CNS and peripheral metabolic system to trigger metabolic processes. The brain suppresses feeding activity in the event of elevated energy consumption or induces the accumulation of surplus energy in other tissues, such as glycogen in liver or triglycerides in adipose tissue [44].

On the other hand, when energy expenditure is greater than energy intake, it increases appetite and reduces energy expenditure through different metabolic pathways, including metabolism of fatty acids and activation of the AMP-activated protein kinase nutrient sensor (AMPK) [44]. Besides that, AdipoR2 contrarily enhances glucose consumption by regulating their gene expression via PPAR- α signaling pathway. Therefore, adiponectin improves hepatic insulin resistance by making balance via reducing glycogenesis and lipogenesis and increase glucose consumption [45]. Besides that, adiponectin receptors also ameliorate vascular dysfunction via activation of endothelial nitric oxide (NO) production and anti-atherogenic effects by inhibiting the inflammation in the various vasculature [46–50].

The administration of adiponectin via intracerebroventricular showed increase in energy consumption and decrease in food intake. It has also been suggested as a mediator of the fasting metabolic response. Previous research has shown that food intake rises, energy expenditure decreases and weight increases occur when adiponectin is administered peripherally to mimic rising levels during fasting. These results were associated with increases in hypothalamus of AMP kinase activity expression [41, 51]. Other than that, an elevation of adiponectin in plasma by either pharmacological or genetic approaches alleviates obesity-induced endothelial dysfunction and also prevents atherosclerosis, myocardial infarction and diabetic cardiomyopathy [36].

At the chromosome 3q27, there is a gene that codes the human adiponectin has been reported by Genom-wide association studies (GWAS), and is linked with susceptibility to diabetes and CVD [36, 52]. Meanwhile, Al Khadli [53] reported that human adiponectin gene exists on chromosome 3q26 which associated with type 2 diabetes mellitus and metabolic syndrome susceptibility [40]. The hypertrophic cardiomyopathy studies show that overexpression of adiponectin had reduced the hypertrophy by activating the AMPK and inhibits the hypertrophic response to α -adrenergic receptor stimulation [21, 54]. The AMPK activation has been shown to inhibit protein synthesis in cardiac myocytes, which is mediated by decrease in phosphorylation of p70S6 kinase and increase in eukaryotic elongation factor-2 phosphorylation [21, 55]. Adiponectin's anti-hypertrophic activities on AMPK are thought to occur via the receptors of AdipoR1 and R2 [21, 56].

Besides a study reported that adiponectin gene mutation causes cellular secretion impairment by preventing trimer assemblage and is clinically associated with hypoadiponectinemia. Hypoadiponectinemia is a condition referred as low concentration of adiponectin as compare to the baseline [40, 57, 58]. In vivo study found that high fat diet causes adiponectin resistance by inhibiting the receptor expression which impacts on the reduction of adiponectin concentration. Adiponectin resistance in skeletal muscle and liver tissue causes development of systemic hyperglycemia and hyperlipidemia consequently causes vascular injury and cardiovascular complications. Cytokine production such as Tumor Necrosis Factor-alpha (TNF α) plays a critical pathogenic role in cardiovascular complication and it is significantly higher in obese or diabetic individuals [59]. There are many in-vivo studies which

supported that decrease level of adiponectin significantly the obesity status, hypertension and type-2 diabetes.

However, diet high in polyunsaturated fatty acids (PUFAs) especially omega-3 potentially increases the gene expression and plasma level of adiponectin [60]. PUFAs are simply fat molecules that have more than one unsaturated carbon bond in the molecule. Omega and omega-6 are the type of PUFAs which cannot be made by the body and should be obtained via dietary sources. Fish oil consumption presented an association to increase the concentration of adiponectin. Generally, omega-3 PUFAs are perceived as a beneficial dietary intervention to enhance the adiponectin levels for the prevention and treatment of CVDs [61].

3.2 Role of resistin

In 2001, resistin was firstly discovered in mice with abundantly found in WAT and has ability to act on insulin resistance actions which link between obesity and diabetes. In mice, studies found that resistin is expressed in several cell types such as intestinal epithelium, skeletal muscle cells, astrocytes and adipocytes. Human resistin is a 12.5 kDa cysteine-rich peptide with a mature sequence consisting of 108 amino acids and located at chromosome 19. It is primarily produced by peripheral blood mononuclear cells (PBMCs), macrophages, bone marrow and adipocytes [62, 63].

Resistin exists in three forms which are trimer, hexamer and a monomer, with lower molecular weight form being the most active [64, 65]. Decorin is a functional receptor for resistin and was identified on the surface of adipose tissue progenitor cells [64, 66]. The normal serum concentration of resistin in human is between 7 to 22 ng/mL⁻¹ [62, 63]. While in obese and diabetic patient, resistin was reported higher than normal reading. A few studies mentioned that, there is a correlation shown between resistin expression with inflammatory markers, coronary artery disease and CVDs in patients with Mets [62, 67, 68]. Jonas [69] mentioned that participant who is suffered from hypertension and diagnosed with metabolic syndrome shows high level of resistin.

Resistin is emerging as an important biomarker and therapeutic target for coronary artery disease and others. It also appears to be involved in angiogenesis, thrombosis and vascular smooth muscle cell (VSMC) migration and proliferation which contribute to atherosclerosis [62]. Toll Like receptor 4 (TLR-4) is the earliest confirmed resistin receptor which is known as a major mediator in innate and adaptive immune responses stimulated by lipopolysaccharide (LPS) [70, 71] while Adenylyl Cyclase-Associated Protein 1 (CAP1) is also a resistin receptor which selected out by immunoglobulin assay [70, 72]. TLR-4 and CAP1 play a role in atherogenesis from endothelial dysfunction to diverse terminal outcome with various pathways.

A study done by Gencer [73] found that there was an association between resistin and increased risk of CVD events independently of clinical variable. Resistin promotes expression of pro-atherogenic molecules such as Intracellular Adhesion molecule -1 (ICAM-1), Vascular cell adhesion molecule-1 (VCAM-1), Monocyte chemo-attractant protein-1 (MCP-1) and Endothelial-1 (ET-1), down regulates anti-atherogenic molecules and implicated in the first stage of the atherosclerosis process via endothelial cell activation.

On the other hand, high fat diet will cause body fat mass increment which can influence the level of resistin and cause insulin resistance and inflammation. Low High Density Lipoprotein (HDL), high triglyceride and high Low Density Lipoprotein (LDL) are characterize as atherogenic dyslipidemia while resistin will induce dyslipidemia to accelerate atherogenesis [70]. A study done by Leon et al. [74]

reported that food rich in saturated fat and triglyceride were found to have positive relationship on the increment of resistin concentration. Atherogenesis is a process of forming plaques in the intima layer of arteries. It developed progressively with inflammation and lipid accumulation varying significantly among individuals [75]. Thus, resistin provide macrophages with overly large lipid fractions inducing dyslipidemia and result in the progress of atherosclerosis plaques.

4. Conclusions and future direction

As a summary, this chapter has explained on the relationship of food intake pathway and adipocytokine hormone effecting CVD in MetS. Adiponectin and resistin were found to have good correlation in the condition of high fat intake. High fat intake such as saturated fat and LDL food sources would potentially induce the level of resistin while polyunsaturated fatty acids and HDL food type potentially increase the level of adiponectin. High level of resistin and low level of adiponectin would contribute to the cardiovascular disease via AMPK and TLR4 pathways, respectively.

There were many studies done in investigating the action of adiponectine and resistin related to MetS and suggested various signaling pathways and mechanisms supporting effect of both protein hormones on CVD. Study believes that food intake would play a huge role in adjusting the level of adiponectin and resistin at various levels such as gene modification. Therefore, there is a scope for future studies to investigate narrowly on the mechanisms affecting adiponectin and resistin single nucleotide polymorphisms (SNPs) towards the development of Mets at cellular level.

Acknowledgements

The authors would like to thank the Faculty of Medicine, Universiti Sultan Zainal Abidin (UniSZA) and Faculty of Health and Life Sciences, Management and Science University (MSU) for providing the facilities and support.

Conflict of interest

The authors declare no conflict of interest.

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