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Review Article

Diabetes as the risk of cancer: a literature review

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ABSTRACT

Cancer is a non-communicable disease with high mortality and morbidity rates. Data recorded by GLOBOCAN in 2018 shows the number of cancer patients is reached 18 million people with a death rate of 9 million people and predicted to increase every year. Diabetes is known to affect morbidity and mortality in cancer patients through increasing cancer cell proliferation and the risk of metastasis. This literature study not only explains the epidemiology, but also the mechanisms underlying the association of diabetes to cancer in general. Literature search was done using four search engines from PubMed, ProQuest, Science Direct and Google Scholar in the last 5 year, but relevant older articles were included. Cancer occurs due to the carcinogenesis process. This process is complex, where normal cells do not immediately mutate and become cancer cells but through several stages. The possible mechanisms underlying carcinogenesis in diabetic patients are hyperglycaemia, hyperinsulinemia, chronic inflammation, genetic variation, obesity, and hyperlactatemia. Examination of sugar levels in cancer patients, as well as cancer screening in patients with diabetes need to be done to detect early events and reduce morbidity and mortality.

Keywords: Insulin resistance, Hyperglycaemia, Carcinogenesis, Malignancy

INTRODUCTION

Cancer is one of the leading causes of death in the world. The number of cancer patients recorded in 2018 by GLOBOCAN was 18.1 million with the number of deaths was 9.6 million.[1,2] The causes of cancer are divided into non modifiable risk factors such as due to genetic mutations, age, gender, race/ethnicity or modifiable risk factors such as smoking, alcohol, physical activity, diet, and obesity. The high incidence of cancer is also associated with several factors such as socioeconomic and lifestyle.[2] In addition to these factors, several studies have linked diabetes and cancer incidence. Diabetes is associated with high morbidity and mortality in cancer patients, especially type 2 diabetes.[3]

Diabetes is still a big challenge for decades with 460 million cases or it can be said that 1 in 11 people aged 20-70 years diagnosed with diabetes and it is predicted to reach 640 million cases by 2040.[4] Diabetes categorized as type 1, type 2, gestational diabetes mellitus and specific types of diabetes due to other causes.[5] While cancer is classified based on its anatomical location (e.g. lung, breast, liver, lymphoma, leukemia, and others) and there may be several subtypes (e.g. leukemia, breast).[6] Diabetes shares some similar risk factors as cancer such as age, gender, race/ethnicity, diet, physical activity, smoking and alcohol.[7,8]

Correlation of diabetes and cancer was reported in a meta-analytic study from Vigneri et al with a result of patients with diabetes (especially type 2) showed a tendency to develop cancer.[9] Patients with diabetes are said to be 2 times more likely to develop pancreatic, liver and endometrial cancer, while in breast, colon and bladder cancer are 1.2-1.5 times.[6] Similar results was shown by Iliana et al that diabetes is 3 times more likely to develop into pancreatic cancer.[10] Research by Katri et

al shows that type 2 diabetes has a 70% risk of increasing the incidence of pancreatic cancer, 3 times more likely to develop liver cancer in men and 2 times in women.[11] Study by Ballotari et al also shows that patients with diabetes have an increased risk of liver, bladder, pancreatic.

METHODS

Diabetes can be a risk factor for cancer through several mechanisms. This literature study not only describes the epidemiology of diabetes in cancer patients but biological factor related to cancer in general. Literature search was done using four search engines from PubMed, ProQuest, Science Direct and Google Scholar in the last 5 years, but relevant older articles were included. The search was conducted with keywords: malignancy or cancer or tumor and diabetes or diabetes mellitus or diabetes type 1 or diabetes type 2 and hyperglycemia or hyperinsulinemia or insulin resistance.

DISCUSSION

Diabetes and Cancer

Cancer is a non-communicable disease with the highest mortality rate in patients under the age of 70 in 2015 in more than half of the countries in the world. The cause of this high mortality rate is related to age and complications. (Freddie, 2020) The cause of cancer depends on each type, but basically occurs due to the carcinogenesis process. Carcinogenesis is a complex process which cells do not easily mutate and become cancer cells but undergo through several stages. Carcinogenesis occurs due to a combination of factors such as physical, biological, chemical and genetic.[13] One of the factors that can cause carcinogenesis is diabetes.[14]

Diabetes type 1, also known as insulin dependent diabetes, occurs due to autoimmune or idiopathic damage to pancreatic beta cells. Diabetes type 2 or non-insulin dependent diabetes is the most common type with 90-95% of all types of diabetes. Diabetes type 2 occurs due to insulin resistance; therefore, insulin level can be normal or increased. Gestational diabetes mellitus (GDM) is diagnosed at 24-28 weeks of gestation in patients with no prior history of diabetes. Diabetes can be diagnosed based on plasma glucose criteria, either a fasting plasma glucose value or a 2 hours plasma glucose value during an oral glucose tolerance test or an A1C levels.[5]

Several studies showed that patients with diabetes have a tendency to develop cancer later. Ballotari et al reporterd that the risk of cancer can appear in patients with a history of diabetes for at least 2 years and is highest at 6-10 years and then decreases thereafter.[12] In contrast, research by Cuiping et al showed that the highest risk to developed cancer is history of diabetes more than 20 years with 70.4% followed by 10-19 years with 19.9% and under 10 years with 9.6%.[1]

Research by Katri et al on 74.000 cancer patients with a history of diabetes type 2 shows that cancer can occur not only in the pancreas or liver, which are organs associated with diabetes but in all organs.[11] A cohort study on 407.000 cancer patients in Italy by Ballotari et al showed 23.300 (5.7%) samples had a history of diabetes which was dominated by type 2 diabetes with 96%.[12] Study by Wang et al explains the epidemiological and biological relationship between diabetes in several types of cancer, which suggests it may be caused by several factors including the similarity in risk factors for both diseases, or conditions related to diabetes such as insulin resistance, hyperglycemia, pro-inflammatory cytokines, and sex hormones.[15]

Association between diabetes and cancer

Diabetes increases the risk of cancer with the highest risk recorded is pancreatic cancer (82%)(16), cholangiocarcinoma (60%), colorectal (35%) and breast (25%).[17-19]

Table1: Association between diabetes and types of cancer.

Types of cancer	Possible association with diabetes
Gliom	Genetic variants
Thyroid	Hyperinsulinemia, chronic Inflammation
Pancreas	Inflammation
Liver	Hyperinsulinemia, chronic inflammation, genetic variants
Lung	Hyperinsulinemia, chronic inflammation, genetic variants
Breast	Hyperinsulinemia, chronic inflammation, genetic variants obesity
Bladder	Hyperinsulinemia, chronic inflammation
Ovarium	Hyperinsulinemia, chronic inflammation
Endometrium	Hyperinsulinemia
Cervix	Hyperinsulinemia
Prostat	Genetic, genetic variants, obesity
Colorectal	Hyperglycemia, hyperinsulinemia, chronic inflammation, genetic variants

Pancreatic cancer and diabetes have a bidirectional relationship, pancreatic cancer can cause new onset diabetes, whereas diabetes can lead to pancreatic cancer.

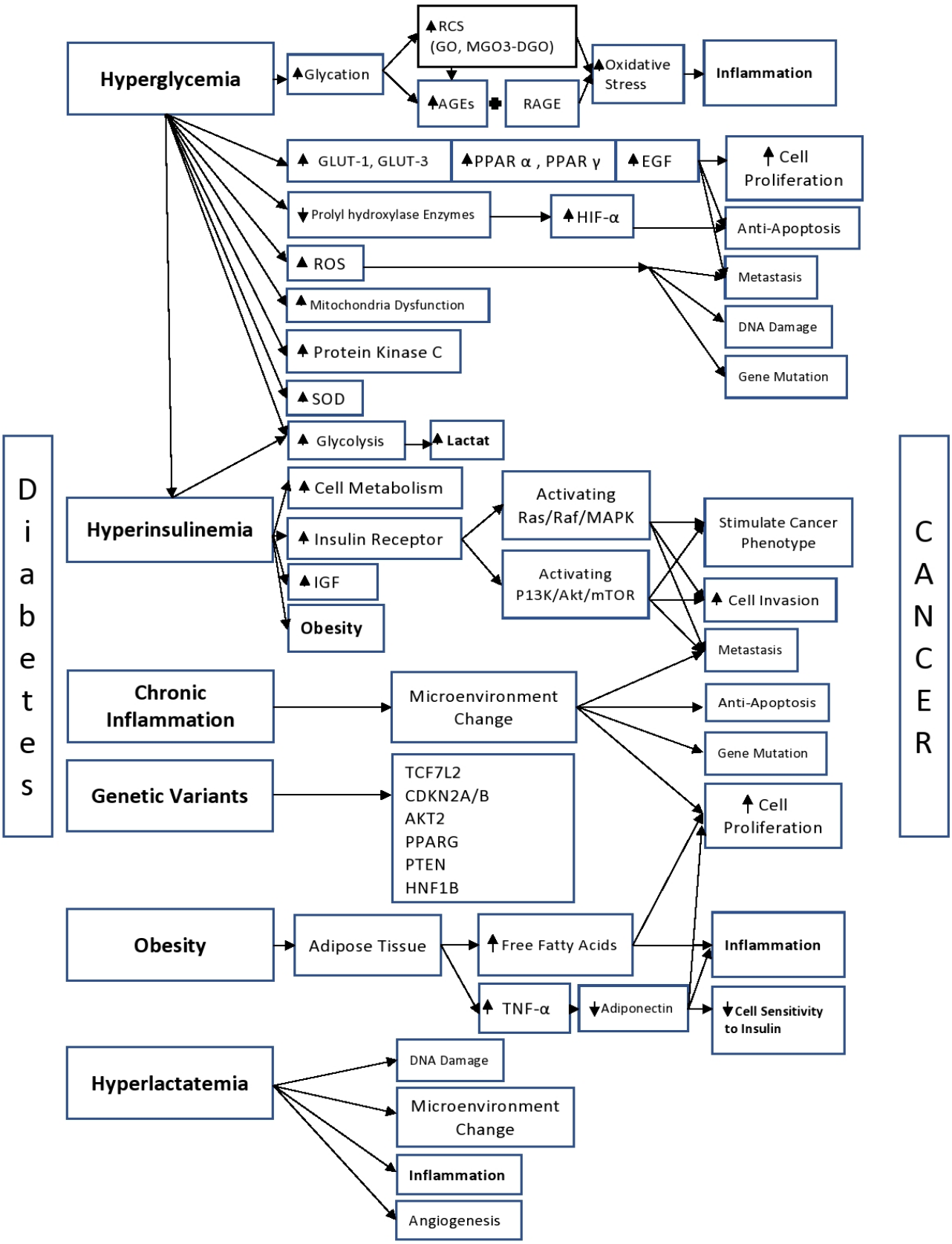

Figure 1: Mechanism of diabetes induced carcinogenesis.

As explained that cancer is diagnosed based on its anatomical location, in type 2 diabetes there will be damage to the beta cells of the pancreas, inflammation in these cells will cause changes in the micro environment leading to cell mutation. Meanwhile, new onset diabetes in pancreatic cancer occurs due to paraneoplastic phenomena due to adrenomedullin secretion which inhibits insulin secretion.[3] The possible association between diabetes and types of cancer and diagram of the correlation between diabetes and cancer can be seen in (Table 1) and (Figure 1).

Hyperglycemia

Diabetes is a metabolic disorder characterized by hyperglycemia, which is one of the factors that play a role in developing cancer. Generally, cells obtain energy through the tricarboxylic acid cycle, but in cancer cells, Warburg effect is known, which explains that cells will increase glucose uptake and rely on aerobic glycolysis to produce energy.[20] Hyperglycemia will accelerate the glycation reaction leads to the formation of reactive carbonyl species (RCS) and advanced glycation endproducts (AGEs). RCS consists of glyoxal (GO), methylglyoxal (MGO) and 3-deoxyglucosone (3-DGO) which are known to affect oxidative stress in cells. The RCS itself is also said to contribute to the formation of AGEs. AGEs are found to be elevated in both type 1 and 2 diabetes. AGEs will bind to the receptor for advanced glycation end prodcuts (RAGE). The AGE-RAGE bond is said to be involved in inflammatory-related diseases including diabetes, atherosclerosis and cancer.[21]

Hyperglycemia express other factors such as are glucose receptors (GLUT-1, GLUT-3), Peroxisome Proliferator-activated receptor (PPAR) α and γ, and eptithelial growth factor (EGF) which can increase proliferative activity, anti-apoptosis. and metastasis.[22] Hyperglycemia will reduce the production of the enzyme prolyl hydroxylase, where the function of this enzyme is to eliminate hypoxia inducible factor α (HIF-α). HIF-α plays a role in anti-apoptosis of cancer cells.[23]

Hyperglycemia will also induce the formation of insulin, growth factors and the secretion of proinflammatory cytokines which support cancer cell proliferation, metastasis and the ability to avoid apoptosis.[24] This is supported by a meta-analysis by Xu et al on 35 studies which showed that glucose metabolism, including hyperglycemia and hyperinsulinemia will increase the risk of colon cancer.[25] Hyperglycemia condition can accelerates mitochondrial dysfunction and forms free radicals and other reactive molecules such as protein kinase C, suporxide dismutase (SOD), and reactive oxygen species (ROS).[23,26] Apart from damaging DNA, ROS also causes genetic mutations and triggers the activation of protein kinase and p21 activated kinase leading to metastasis. ROS is also able to bind to protein kinase C and protein tyrosine phosphatase, which are key molecules involved in cancer cell invasion and help cancer cells to adapt to the environment.[27]

Hyperinsulinemia

Insulin is a hormone that plays a major role in regulating carbohydrate and fat metabolism by increasing glucose absorption. In diabetes, insulin loses its function to increase glucose uptake and utilization. In response to this condition, pancreatic beta cells release more insulin as compensation and hyperinsulinemia will occur.[28] Hyperinsulinemia can also lead to the development of cancer cells directly, especially in type 2 diabetes by affecting cell metabolism and indirectly through pro-tumoral effects through abnormal stimulation of the oncogenic signalling pathway and increasing growth factor-dependent cell proliferation.[21] Some cancer cells are said to express insulin receptors including Isoform A and Insulin Growth Factor (IGF). Isoform A receptors are capable of stimulating insulin-mediated mitogenesis, even in cells deficient in IGF receptors.[29]

Insulin receptors are also able to stimulate proliferation and metastasis in cancer cells. After the insulin receptor or IGF interacts with its ligands it will activate several signalling pathways including Ras/Raf/MAPK and P13K/Akt/mTOR (30-33) and will stimulate several cancer phenotypes including proliferation, protection from apoptotic stimuli, invasion and metastasis. The activation of insulin receptors on neoplastic cells is more related to cell survival and mitogenesis rather than glucose uptake.[6] Several previous studies found an increase in IGF receptors in breast, colorectal, lung, ovarian, and thyroid cancers, where insulin is said to cause oxidative stress which will cause chronic inflammation, resulting in susceptible cells and DNA damage. leading to cell mutase.[11,34]

Hyperglycemia conditions will induce IGF stimulating the proliferation of vascular smooth muscle cells.[35] Although this process is a pathophysiology of atherosclerosis, abnormal blood vessel growth can also cause cancer. Hyperinsulinemia in premenopause will increase the synthesis of androgens in the ovaries and adrenals which is associated with an increased risk of postmenopausal breast cancer, endometrium, and possibly other cancers.[6] In liver cancer, the thing that might underlie this incident is exposure of liver cells to high concentrations of insulin related to portal circulation.[9]

Apart from the condition of diabetes tyoe 2, hyperinsulinemia also thought to play an important role in the development of cancer in GDM. A study by Fuchs et al on 100.000 patients followed for 12 years showed that patients with GDM increased their risk of developing endometrial, ovarian, breast and cervical cancer by 70%.[36] A similar result was found by Park et al that GDM was said to increase the risk of breast cancer by 68%.[37] In contrast, research by Bejaimal et al shows that although

GDM increases the risk of developing thyroid cancer, it reduces the risk of developing breast cancer.[38] Research reported GDM reduce the risk of developing breast cancer was also reported by Powe et al, Brandt et al, and Xie et al.[39,41] Recent research related to the history of GDM as a risk factor for cancer needs to be done.

Chronic inflammation

Diabetes and inflammation can be a bidirectional relationship, where diabetes is said to be a chronic inflammatory disease. It also said to generate inflammation which is marked by an increase in IL-1, TNF-α, or other pro-inflammatory cytokines such as chemokines, growth factors, free radicals, prostaglandins, and proteolytic enzymes.[42] This condition will cause a micro environment that supports the growth of tumor cells such as macrophages, neutrophils, lymphocytes, dendritic cells, natural killer cells, fibroblasts, adipocytes and endothelial cells.[42,43] Some of these factors work directly on cancer cells, by increasing proliferation, avoiding apoptosis and causing cell mutations.[42] Although TNF-α is an important mediator of the anti-tumor immune response, chronic exposure to TNF-α will activate a series of signalling pathways, such as NF-κB, mitogen protein kinase activation, and Jun kinase, which will prevent cell apoptosis and accelerate the growth and metastasis of cancer cells.[44] Studies show that at least 20% of cancers are caused by chronic inflammation, inflammation by tumor cells is also thought to be involved in most solid tumors including colorectal cancer.[45,46]

Genetic variants

Genetic variants are believed as factor related to cancer in diabetic patients.[47] The Transcription factor 7 like 2 (TCF7L2) gene is found in both diabetes and cancers such as colorectal (48-50), breast, liver, prostate, lung, and glioma.[39,45,46,51-53] Likewise with other genes such as CDKN2A/B, AKT2, PPARG, PTEN and HNF1B.[46] Research related to the role of certain genes in diabetes as a risk factor for cancer needs to be done. This can later be used as an initial examination, predictor factors, or developed into therapy.

Obesity

Hyperinsulinemia is associated with obesity, where it is also dependently a risk factor for cancer.(34) Research by Iliana et al shows that obesity was present in 5.7% of cancer patients and estimated to increase related to latest lifestyle.[10] Insulin resistance and inflammation will induce lipolysis by white adipose tissue which is causes a high release of free fatty acids into the plasma and associates with the growth of cancer cells.[54] Research by Emma et al shows that adiposity is a most likely contributing factor to developing cancer in patients with diabetes.[47]

Adipose tissue is capable of producing free fatty acids, interleukin-6 (IL-6), where IL-6 is can activating signal transducer and activator of transcription protein, monocyte chemoattractant protein, plasminogen activator inhibitor-1 (PAI-1) which is associated with poor prognosis in breast cancer patients.[6] Adipose will also increase the production of TNF-α which functions to reduce adiponectin levels. Adiponectin has a role to suppress inflammation and increase insulin sensitivity in cells, induce apoptosis through AMPK activation leading to activation of p53, p21, inhibiting proliferation.[55,56] TNF-α also stimulates leptin production via HIF-1α. Leptin has a mitogenic effect which is believed to be the cause of the proliferation of breast, prostate and esophageal cancer cells.[57] This allows a role in mutation of normal cells and regulates the development of cancer cells.

Hyperlactatemia

Hyperlactatemia is one of several factors that bridge diabetes and cancer.[58] Lactate is produced in the cytoplasm via glycolysis, through the reduction of intermediate metabolite pyruvate.[59] Diabetes will increases glycolysis activity through the enzymes phosphofrukkinase and pyruvate dehydrogenase due to insulin resistance, hyperglycemia and hyperinsulinemia.[60-62] In addition, insulin resistance will cause a decrease in glycogen synthesis and glucose oxidative metabolism leading to lactate accumulation. Lactate is able to facilitate the intrinsic effect of cancer cells on metabolism and induce tumorigenesis in normal cells. In addition, lactate also acts as a signalling molecule that can stimulate inflammation and tumor angiogenesis.[63]

Hyperlactatemia can also change the micro environment, causes acidosis, and is associated with immunosuppression. LDH examination has long been used to assess prognosis in cancer patients.[58] Although this condition is a bidirectional relationship, which cancer will also cause hyperlactatemia, its role as a risk factor for cancer in diabetes patients is a hypothesis that might be accepted regarding the pathophysiology described. Further research on LDH examination in cancer patients with diabetes needs to be done as epidemiological data which can later become the basis for examinations and therapy to reduce patient morbidity and mortality.

Morbidity and mortality in cancer related to diabetes

The systematic review and meta-analysis study by Bethany et al showed that diabetes can increase mortality in patients with cancer.[64] It was also shown by the study of Lorraine et al that breast cancer patients with comorbidities diabetes had a higher mortality rate of 1.39 times.[65] Research by Ballotari et al shows that the mortality rate in cancer patients with diabetes is 4 times higher than without diabetes.[12] Regarding the relationship between diabetes and obesity, a study by Gallagher et al

shows that an increase in BMI is said to be in line with an increased risk of death in almost all types of cancer.[66]

Diabetes is responsible to patients mortality and morbidity through the hyperinsulinemia and hyperglycemia as it increase proliferation of cancer cells and also risk of metastasis.[64] Diabetes also increases the mortality of cancer patients related to other conditions such as cardiovascular disease, chronic kidney disease, secondary infection, and when undergo surgery.[67-69] Study from Xiao et al in liver cancer patients with diabetes shows that the high mortality rate is also caused by other factors such as hepatitis and alcohol consumption.[70]

CONCLUSION

Although diabetes type 2 is more associated with a possible association with cancer, other types of diabetes such as diabetes type 1 and GDM also have a risk of developing cancer through mechanisms such as gene factors, hyperglycaemia, and chronic inflammation. Research related to diabetes and cancer in particular needs to be done. Blood glucose examination in cancer patients as well as cancer screening in diabetes patients need to be done to detect early incidence and reduce morbidity and mortality.

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