CLASSIFICATION, ETIOLOGY, SIMILARITIES AND MANAGEMENT OF DIABETES MELLITUS IN CANINE AND FELINE WITH RESPECT TO HUMANS

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Abstract

Diabetes mellitus relates a metabolic disorder of collective etiology which is characterized by chronic hyperglycaemia caused due to disturbances of carbohydrate, lipid and protein metabolism due to impaired β-cell function of pancreas or insulin resistance or both. Diabetes mellitus is a common disease in canine and feline. The most common form of diabetes in canine resembles type 1 diabetes in humans. Studies suggest that genetics, an immune-mediated component, and environmental factors are involved in the development of diabetes in dogs. A variant of gestational diabetes also occurs in canine. The most common form of diabetes in feline resembles type 2 diabetes in humans. A major risk factor in feline is obesity. Obese cats have altered expression of several insulin signaling genes and glucose transporters and are leptin resistant. Feline also form amyloid deposits within the islets of the pancreas and develop glucotoxicity when exposed to prolonged hyperglycemia. An essential aspect of successful DM management is to ensure that the owner of a diabetic canine or feline is capable of administering insulin, monitoring blood glucose, recognizing the clinical signs of inadequately managed DM, is ideal. Insulin therapy is the mainstay of treatment for clinical DM. This review will briefly summarize our current knowledge about the etiology of diabetes in canine and feline and illustrate the similarities among dogs, cats, and humans.

Keyword: Diabetes, Islet cells, Autoimmune, Obesity, Insulin Resistance, Canine, Feline and Humans

1.INTRODUCTION

Diabetes is a common disorder in dogs and cats, with a prevalence of 0.4-1.2% as has been reported at the hospital level. Typical clinical signs of diabetes include polyuria, polydipsia, perspiration, and weight loss. Clinical signs do not progress until hyperglycemia reaches a concentration that leads to glycosuria, usually at blood glucose concentrations level 180-220 mg / dl in dogs and 220-270 mg / dl in cats. A subclinical or pre-diabetic condition as it originates in humans is documented uncommonly in dogs and cats. The diagnosis of diabetes depends on the presence of appropriate clinical signs and the determination of high blood sugar and diabetes. Hypercholesterol and triglycerides are common and ketoacidosis and ketoacidosis may develop if the owner is unable to identify early signs or is neglected in seeking veterinary care. Treatment possibilities are similar to those for human diabetics and include insulin injections (given twice daily at intervals of 12 hours), dietary adjustments, obesity correction, exercise in dogs, and oral hypoglycemic drugs in cats. The treatment method differs between dogs and cats, in part, due to the main differences in the etiology. Usually, the classification of diabetes in dogs and cats follows in one way or another the guidelines used in human medicine (American Diabetes Association (ADA) 2013). Although the mechanisms of etiology may not be completely similar, the "human model" provides evidence for identifying and distinguishing different types of disease in dogs and cats. Diabetes in dogs is similar to type 1 diabetes in

humans, while diabetes in most cats is similar to type 2 diabetes. The current article explains the causes of diabetes in dogs versus cats and shows the similarity of diabetes in dogs, cats and humans.

2. TYPE 1 DIABETES MELLITUS IN DOGS

The most commonly recognized clinical form of diabetes in dog is similar to type 1 diabetes in humans and is classified by a low level of insulin in the blood, mainly there is no increase in serum insulin or C-peptide concentrations after administration of insulin secretagogue (for example, Glucose, glucagon, and amino acids), specific requirements for exogenous insulin to maintain blood sugar at control level, avoid ketoacidosis, and survive (Montgomery et al. 1996). Almost all dogs rely on insulin at the time when diabetes is identified. Common tissue abnormalities in dogs include a decrease in the number and size of pancreatic islets, a decrease in the number of β-cells within the islets, β-cell emptying and dissolution. An extreme form of the disease may arise in small young dogs, and it is represented by an absolute deficiency of β-cells and a lack of or unpleasant pancreatic islets. Less severe changes that include pancreatic islets and β-cells may predispose an adult dog to diabetes after the dog is exposed to environmental factors, such as insulin antagonistic diseases, anti-infection drugs and pancreatitis.

The etiology of type 1 diabetes in dogs is multifactorial exactly as mentioned in (Table 1). Family associations, genealogy analysis, and genomic studies have recommended genetic sensitivities aimed to determining the complex susceptibility to complex individual models of protection and histological compatibility (Guptill et al. 2003, Kennedy et al. 2006, Val et al. 2007). A number of genes associated with susceptibility to diabetes in humans are associated with an increased risk of diabetes in dogs (Catchpole et al. 2013). Diabetes in dogs has been associated with major histo-compatibility complex class II genes (DLA-dog leukocyte antigen), identifying similar patterns and genotypes in strains or breeds most susceptible to infection. A region was identified that contained a variable number of tandem repeats and multiple polymorphisms were identified in the insulin gene in dogs, with some alleles associated with susceptibility to or resistance to diabetes in a specific way in specific breeds (Catchpole et al. 2013).

Many studies recommend an immuno-mediated component in the development of diabetes in some dogs. Insulin mediated inflammation regarding immunity has been described, characterized by infiltration of lymphocytes into islets, and antibodies directed against islet cells have been identified, insulin, proinsulin, intracellular (glutamic acid decarboxylase65-GAD65), and (insulinoma antigen2-IA2) in dogs with diabetes (Hoenig & Dawe 1992, Davison et al. 2003, 2008, 2011). The presence of autoantibodies circulating against insulin, proinsulin, GAD65 and IA2 usually precedes the development of hyperglycemia or clinical signs in people with type 1 diabetes. A similar series of events may also occur in dogs although the onset of type 1 diabetes usually occurs in dogs that are 8 years or older. Dog diabetes appears to be very similar to the underlying human autoimmune diabetes of adullt category (Andersen et al. 2010). Seemingly, autoimmune mechanisms, in conjunction with genetic and environmental factors, diseases and anti-insulin drugs, and pancreatitis play a potential role in the initiation and development of diabetes in dogs. The end result is loss of β-cell function, insulin deficiency in the blood, poor circulating glucose transport in most cells, rapid hepatic glucose creation and glycogenolysis, and the consequent development of high blood sugar and diabetes. Loss of function of β-cells is irreversible in dogs with type 1 diabetes and lifelong insulin therapy is needed to maintain blood sugar control in case of diabetes.

Table 1 Potential factors involved in the etiopathogenesis of diabetes mellitus in dogs & cats

Dog	Cat
Genetics	Islet amyloidosis
Immune-mediated insulitis	Obesity

Pancreatitis	Pancreatitis
Obesity	Concurrent hormonal disease
Concurrent hormonal disease	Hyperadrenocorticism
Hyperadrenocorticism	Acromegaly
Hyperthyroidism	Hyperthyroidism
Drugs	Drugs
Glucocorticoids	Progestogens
Progestogens	Glucocorticoids
Infection	Infection
Concurrent illness	Concurrent illness
Kidney disease	Kidney disease
Cardiac disease	Cardiac disease
Hyperlipidemia	Hyperlipidemia
Diestrus-induced excess growth hormone	Genetics (Burmese cat)
	Immune-mediated insulitis

3. TYPE 1 DIABETES MELLITUS IN CATS

Unlike to a dog, type 1 diabetes is assumed to be rare in cats. Infiltration of lymphocytes in islets reflux (reflux) was identified as a sign of disease by immunotherapy only in a few cats (Minkus et al. 1991, Hall et al. 1997). In a recent study that examined islets lesions in a larger group of diabetic cats against a control group (identical in age, gender, and body weight), an affinity for lymphocytes was found to be more numerous in diabetic cats (20% of cats with diabetes versus 5% of control cats), but infiltration is usually mild and may redirect an inflammatory condition also known to be present in type 2 diabetes (Zini et al. 2012). Only one of the 27 cats with diabetes had severe lymphatic infiltration, which was similar in severity to that described in various studies, whereas β-cell and insulin antibodies have not been well identified yet in newly diagnosed diabetic cats (Hoenig et al. 2000).

4. TYPE 2 DIABETES MELLITUS IN CATS

Nearly 80% of cats with diabetes have type 2 diabetes, a heterogeneous disease attributable to a combination of poor insulin action in the liver, muscles, fatty tissue (insulin resistance) and β-cell failure. Environmental and genetic factors are assumed to play a role in the development of both defects. Genetic factors began to examine only in the cats (Forcada et al. 2014). Diabetes in a cat is likely a multi-gene disease and many genes are associated with an increased risk of developing the disease. On behalf of the in-breeding lines of the Burmese cat from Australia, New Zealand and the United Kingdom, it turns out that the frequency of diabetes is almost four times higher and the most convincing evidence comes on a genetic basis more than domestic

cats while more than 10% of the offspring of Burmese cat families are affected by diabetes (McCann et al. 2007, Lederer et al. 2009).

Obesity is one of the main risk factors for the development of diabetes in cats. Other types include sex (male risk higher than female), physical inactivity, indoor confinement, increased age, and administration of corticosteroids and progestins (Panciera et al. 1990, McCann et al. 2007, Prahl et al. 2007, Slingerland et al 2009). Fat cats have been shown to be 3.9 times more likely to develop diabetes compared to cats with an ideal body weight (Scarlett & Donoghue 1998). Experimental studies on healthy cats showed that the average weight gain of 1.9 kg during a feeding trial was associated with a decrease in insulin sensitivity by more than 50% (Appleton et al. 2001). Similar results have been reported in another experiment in which each kilogram of weight led to a 30% loss in insulin sensitivity (Hoenig et al. 2007). Insulin sensitivity varies greatly between individuals and it has been suggested that cats with substantially low insulin sensitivity are at increased risk of developing glucose intolerance with weight gain. Male cats tend to have less insulin sensitivity before feeding and gain more weight than female cats, which may partly explain why male cats are at an increased risk of developing diabetes (Appleton et al. 2001).

The mechanisms of insulin resistance at the cellular level and the interrelationships between different outcomes are still very difficult in cats. Most research to date has focused on glucose transporters and insulin signaling genes in insulin sensitive tissues and the secretion of fat cells from adipose tissue. In obese cats, the expression of glucose-sensitive insulin GLUT4 (SLC2A4) in muscle and fat was much less than fat-free cats, while the expression of GLUT1 (SLC2A1), which was not insulin sensitive, remained unchanged (Brennan et al. 2004). The expression of many insulin signaling genes in the liver and skeletal muscles was significantly lower in obese cats than in fat-free cats, and is similar in humans with insulin resistance (Mori et al. 2009). Also similar to humans, it is now known in cats that adipose tissue is an active and complex endocrine organ. Adiponectin, which is produced almost exclusively in adipose tissue, decreases with obesity and diabetes in cats (Hoenig et al. 2007). Adiponectin enhances insulin sensitivity and has anti-inflammatory properties. Thus, the decrease contributes to insulin resistance and inflammation. Leptin, the typical adipokene, is involved in suppressing appetite and energy spending and plays a role in modifying insulin sensitivity (Radin et al. 2009). Fat cats have been found to be resistant to l-lutein, that is, they have significantly higher leptin-concentrations than lean cats without causing an appropriate physiological response (Hoenig 2012). Fatty tissue secretes a number of inflammatory cytokines and obesity is now considered a condition of low grade chronic inflammation. TNFa is the first fat-derived agent to suggest a representation of the relationship between obesity and insulin resistance observed in human type 2 diabetes. This cytokine has a strong negative effect on insulin signals. Now it is also known that many additional cytokines and cytokines (for example, IL6 and MCP1) play an important role in the inflammatory process in humans. Fat tissue in cats may work in a similar manner, as the level of TNFa (in fats) was significantly higher in obese cats than in fat-free cats (Hoenig et al. 2006).

Insulin resistance that develops during weight gain is reversible after weight loss. When healthy cats were fed ad-libitum, weight gain was associated with a significant increase in glucose and insulin concentrations during intravenous glucose tolerance test (IVGTT) compared to baseline and the total amount of insulin secretion was significantly higher. Several weeks after achieving weight loss by eating low-calorie meals, the results of IVGTT were similar to those at baseline (Biourge et al. 1997).

Although obesity leads to insulin resistance, obese cats do not develop diabetes. Diabetes is supposed to develop, there must be a dysfunction of the leading β-cells that leads to poor glucose tolerance and type 2 diabetes eventually. Unfortunately, there is little information about cell function and insulin secretion in cats during the normal development of diabetes.

One hypothesis explaining the loss of cell function in type 2 diabetes includes cell destruction by amyloid deposition. Islet amyloid is derived from a hormone as it is called islet amyloid polypeptide (IAPP) also known as amylin. IAPP is a natural product of β cells, is stored with insulin in the secretory vesicles, and is excreted with insulin in the circulatory system. IAPP levels rise in conditions associated with insulin resistance, for example, in obese cats (Henson et al. 2011). Cats, humans and non-human primates have an amyloidogenic amino acid amino acid structure of IAPP with the ability to form amyloid deposits within the

pancreatic islands/islets (O'Brien 2002, Hull et al. 2004). Islet amyloid cannot deposits have not been identified in hamsters, rats, mice or dogs. Whereas, IAPP and amyloid deposits were identified in the canine with endocrine glands (Jordan et al. 1990, O'Brien et al. 1990). Amyloid deposits are found in many cats with diabetes but also a frequent discovery in cats without diabetes. In a recent study, 56% of cats with diabetes and 42% of control cats matching age, gender, and body weight had amyloid deposits, which could also be compared regarding its amount (Zini et al. 2012). Collapse of disturbed protein folds and / or amylin trafficking within the β-cell leads to the formation of toxic oligomers. These intracellular molecules provoke cell toxicity and may lead to a decrease in β-cell function and to programmed β-cell death. Toxic and represent the end point of an error of mis folding (Costis et al. 2013).

Loss of β-cell function may be present before amyloid deposits appear. Malnutrition may be a reflection of another defect within the β-cell and is not the main cause of dysfunction in the β-cell. When present, however, these anomalies may accelerate further damage.

Hyperglycemia is an additional factor, which has a negative effect on β-cell function and survival in cats, a phenomenon known as glucose toxicity (Link et al. 2013). There is no doubt whether glucose toxicity is a secondary event, as hyperglycemia only appears after to β-cell begin to fail. However, improving blood sugar control with insulin therapy will reflect some of the negative effects of glucose toxicity and reverse glucose toxicity an important mechanism for explaining the remission of diabetes in cats (Nelson et al. 1999). The cellular mechanisms by which chronic hyperglycemia affects insulin secretion and insulin sensitivity are poorly understood. In humans, it has been suggested that oxidative stress and inflammatory cytokines play an important role (Robertson 2009, Donath & Shoelson 2011). In a recent study, glucose-induced lesions in in cells in cats were investigated (Zini et al. 2009). 10 days after the glucose infusion broadcast, healthy cats had a fewer fewer 50% fewer cells per island region than a healthy, non-implanted cat. Island cells showed characteristics of programmed cell death and Caspase 3 (a sign of programmed cell death) was positive. It is interesting that hyperglycemia caused a systemic inflammatory response, characterized by an increased plasma concentration of glucoprotein al-acid. Systemic inflammation has also been described in human type 2 diabetes.

Fat toxicity is the term used for the adverse effect of high-circulating high concentrations of free fatty acids on β-cell function . Fatty toxicity may not be as important as the glucose toxicity in cats (Zini et al. 2009). In contrast to the harmful effect of a 10-day glucose infusion on infusion β-cells, pumping fats over the same time period did not affect the insulin in plasma or glucose concentrations or result in programmed cell death in β-cells . In human medicine, it has been suggested that glucose toxicity occur independently of fat toxicity, while fatty toxicity requires increased blood glucose levels to fully appearly demonstrated.

5. TYPE 2 DIABETES MELLITUS IN DOGS

Insulin resistance caused by obesity has been documented in dogs but there has been no development of type 2 diabetes (Verkest et al. 2012). Studies show that at least some of the pathogenic mechanisms responsible for developing type 2 diabetes associated with obesity in humans and cats, don't occur in dogs. For example, the sensitivity of β-cell cells is lost due to changes in glucose and the first stage of the insulin secretion response by the in β-cell in humans and cats but not in dogs despite years of insulin resistance caused by obesity and compensatory hyperinsulinism (Verkest et al. 2011a). In humans, loss of the first stage of insulin secretion is an important early sign of β-cell failure (Gerich 2002). IAPP constitutes intracellular toxic oligomers in in β-cells in humans and cats but not in dogs and extracellular aspiration does not accumulate as in histologically visible amyloid in pancreatic islets in dogs (Haataja et al. 2008, Scheuner & Kaufman 2008). Concentrations of adiponectin that secrete by adipose cells in obese people are low and low concentrations of adiponectin are expected to advance into type 2 diabetes in humans (Li et al. 2009). By contrast, the circulating adiponectin concentrations were not lower in chronic obese dogs, compared to fat-free dogs, and adiponectin was not associated with insulin sensitivity in obese dogs (Verkest et al. 2011b). Although adiponectin does not appear to play a role in developing insulin resistance associated with obesity in dogs, adiponectin receptors are present in the β-cells of the pancreas and adiponectin has been shown to protect β-cells from the

programmed cell death caused by fatty acids (Kharroubi et al. 2003, Rakatzi et al. 2004).

6. OTHER SPECIFIC TYPES OF DIABETES IN DOGS AND CATS

The category "other specific types" refers to diabetes that develops with diseases or factors other than those described under type 1 or type 2 diabetes. A large number of genetic syndromes are listed in this category for humans but similar syndromes are not described in dogs or cats. Diabetes may occur secondary to exocrine pancreatic disorders, and any process that causes widespread pancreatic injury can cause diabetes, especially pancreatitis. The incidence of acute pancreatitis in dogs with diabetes often can be determined histologically from 30-40% and is believed to be a contributing factor in the development of diabetes and diabetic ketoacidosis in infected dogs (Watson et al. 2010, Bostrom et al. 2013). It is difficult to determine the cause-and-effect relationship between pancreatitis and diabetes in cats. Consistent tissue abnormalities with pancreatitis are found in 22-57% of cats with diabetes and in 60 and 67% of cats without diabetes (Krause et al. 1997, Gossens et al. 1998, De Kok et al. 2007, Zinni et al. 2012). Based on the data available from the authors, pancreatitis is not a frequent cause of diabetes in cats. Although in principle, acute pancreatitis with extensive tissue damage may damage the pancreas islands and β-cell loss but, unlike dogs, this appears to be a rare event in cats. However, pancreatitis appears to be a frequent comorbid disease in cats with diabetes.

Several endocrine diseases, the most prominent of which are hyper cortisolic hyperparathyroidism (adrenal cortex) in the dog and hypersomatotropism (acromegaly) in the cat cause severe insulin resistance and are often diagnosed within a time or within weeks of determining the diagnosis of diabetes (Table 1). Likewise, administration of diabetes-causing drugs, in particular glucocorticosteroids and progestins, may cause glucose intolerance and outright diabetes in dogs and cats that are assumed to have a pre-existing β-cell defect, reflux disease, or both. Diabetes dogs and cats who have been diagnosed with insulin resistance are sub-clinical patients.

7. GESTATIONAL DIABETES: DOGS

The fourth category in the human categorization model is gestational diabetes, which is defined as intolerance to carbohydrates with their first onset or recognition during pregnancy (ADA 2013). Gestational diabetes-like syndrome occurs in humans in older female dogs but not in cats. Female dogs ovulation happen at 7-month intervals and increased progesterone concentration in the blood for two months after ovulation and body formation of corpora lutea. Progesterone stimulates the secretion of growth hormone from the mammary gland of dogs and both hormones cause insulin resistance and carbohydrate intolerance in the dog (Selman et al. 1992). Older female dogs are often diagnosed with diabetes during diestrus or pregnancy when the concentration of progesterone and growth hormone is increased (Fall et al. 2008a, 2010, Mared et al. 2012). Documenting increased insulin concentration in the basal blood supports the presence of functional β-cells. These dogs are assumed to have sufficient functional mass β cells to maintain carbohydrate tolerance when insulin resistance is absent (for example, during periods of ovarian inactivity when progesterone concentrations remain low (0.5 ng / ml), but they are unable to secrete an adequate amount of insulin to maintain blood sugar in the presence of insulin resistance (Fall et al. 2008b). Early recognition and improvement in insulin resistance after ovarian resection, while some β-cell functions are still present, blood sugar may be re-established without long-term treatment needed Insulintreatment. Failure to rapidly correct insulin resistance often leads to progressive loss of β-cells and an increased likelihood of permanent insulin dependence for controlling hyperglycemia (Fall et al. 2010).

Summary: Current knowledge indicates that the causative factors involved in the development of diabetes are similar in dogs, cats, and humans. However, the predominant type of diabetes run by veterinarians varies between dog and cat. Diseases caused by the immune-linked system are very common in dogs, so it is not surprising that type 1 diabetes prevails. In contrast, immune mediated diseases are very uncommon in cats and type 1 diabetes is not recognized in this species. Cats have an amyloidogenic amino acid structure from IAPP with the ability to form amyloid deposits within the pancreatic islets during persistent insulin resistance periods, as happens with obesity. Obese cats also develop other imbalances that promote the development of diabetes. Hence type 2 diabetes

spreads into this species. Dogs do not have the structure of IAPP for amyloidogenic amino acid and do not develop islet amyloidosis during persistent insulin resistance periods.

8. TIPS FOR MANAGING CANINE AND FELINE DIABETES

Even though diabetes is a treatable condition, pet owners have a great role to do a lot to manage their pet's disease, making communication with the veterinary team essential. The No.1 cause of death in diabetic dogs and cats is not the disease itself rather; it's euthanasia resulting from the owner's frustration with the disease. This means communication with the pet owner is perhaps the most important component of managing diabetes mellitus. And the most crucial conversation with the owner is right after you first diagnose the concern condition in owner's pets. With the easy way the clients can easily be prepared to manage the insulin-challenged pets.

8.1. Explain the goals of therapy for diabetic pets.

As the pets don't live as long as the humans live with diabetes for 30-40 years, sequelae such as diabetic retinopathy, nephropathy, painful neuropathies and cardiovascular disease, so there is no need to restore euglycemia in order to avoid the effects of persistent hyperglycemia. There is strongly need of enough glycemic control to eliminate clinical signs, as keeping the blood glucose concentrations below the renal threshold for the majority of the day as the complication are very rare in veterinary patients. In most cases this is going to require twice-daily injections of insulin. Even though the disease is easier to manage in pets than people, owners of diabetic dogs and cats are still being asked to manage their pet's chronic illness. That means its need to make the client's job easier while at the same time taking steps to assure the maximum diabetic control of the pets.

8.2. Go for broke on remission when you first diagnose a cat.

Of course, even better than effective management is complete remission of the disease. Insulin glargine has been shown to produce remission in 90% of newly diagnosed feline diabetics when the cat is also fed on a high-protein, low-carbohydrate diet. The pet owners are needed to know that cats in remission need to continue eating the diet. About 25% of the pets will become diabetic again, often because they've gained weight, so the goal is to maintain ideal body weight. Every time a cat comes out of remission, the chances of re-inducing remission is also much lower if a cat has been on another type of insulin for longer than six months.

8.3. Shake the snot out of your Vetsulin.

The Vetsulin (manufactured by Merck), a porcine-derived intermediate-acting insulin, actually contains two products in the same bottle, resulting in a bimodal onset of action: one to prevent postprandial hyperglycemia and one to provide long-term glycemic control. The bottle is needed to be shaken vigorously, until the product foams before injection in order to provide the appropriate effect in the body. This insulin is only available at a concentration of 40 IU/ml (U-40), so it has needed the availability of appropriate (U-40) syringes to the owner.

8.4. Use home monitoring.

With the AlphaTrak Blood Glucose Monitoring System (Zoetis), pets owner have the ability to measure the very accurately the blood glucose concentrations in both dogs and cats using very small quantities of blood. This allows veterinarians and pet owners to obtain reliable results both in the hospital and at home, which can then be used to make informed decisions about treatment. These decisions might involve the type and dose of insulin, the frequency of insulin administration, assessment of glycemic control, prevention of hypoglycemic episodes and monitoring for remission of diabetes in feline patients.

8.5. Get clients to tell you the truth about what they're feeding.

The best diet for diabetic dogs is a high fiber, low fat, high complex carbohydrate diet. The best diet for diabetic cats is a high protein, low carbohydrate diet. Of course, you can recommend an appropriate food, but clients often won't tell you they're feeding. So when you're discussing diet, do everything you can to get them to tell you the truth about what they're really

feeding, then that's way you'll at least know how to manage the insulin.

8.6. Don't ever talk to clients on the phone.

This rule has increased the quality of life enormously. It is much easier to answer questions this way via cell phone number, text and email address. Plus, with email, you have documentation of the conversation and can include it in the patient record.

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