Diagnosis of some diseases through biomarkers

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Diagnosis of PIF, and other diseases in cats under biomarkers

Problem

Many cats, like dogs, suffer from different diseases. which at the time do not allow to show symptoms or signs that allow to identify that the pet is suffering a serious and severe disease, since the characteristics of the cats are different from those of the dogs, since these are predators, therefore the Diagnosis of diseases in this species is difficult, and in most cases the diagnosis is made during the advanced stages, thus causing difficult treatment and poor prognosis. These diseases include: feline hypertrophic cardiomyopathy, feline hepatic lipidosis, feline immunodeficiency virus, chronic renal failure and feline infectious peritonitis. It requires knowledge about biomarkers to be able to give the result. Biomarkers are a tool that is not yet widely known and this is necessary. Since it allows to improve the quality of life of cats and their owners, since cats have become increasingly important as pets. It is estimated that a high percentage of the world population has chosen to have cats as pets because of their physiological and behavioral characteristics.

Justification

Cats, other mammals and pets have different disease viral, bacterial, parasitic and congenital among others, since the diagnosis of the same is done in the traditional way, through clinical examinations and additional tests, you need to seek alternatives to a diagnosis early and effective. Within these options are biomarkers, which are molecules present in blood and other fluids, represent a specific disease so the diagnosis and early prognosis may be of great help and thus it allows improve the quality of life of patients. The importance of biomarkers in the early diagnosis of FIP, as well as demonstrating that its use may also help in diseases such as acute renal insufficiency and hypertrophic cardiomyopathy, the idea is to provides well-being to the pet because the early diagnosis allows the realization of treatment soon and in the same way an early management of the disease, the idea is to Provides information to the professionals collected and updated, information that allows them to make decisions regarding the diagnosis and prognosis of the diseases, in this way to inform in a timely manner the owners of affected pets. Since animal welfare is the most important for veterinarians and owners, provides knowledge about the use of biomarkers that allow the diagnosis and early prognosis of different diseases,the knowledge about the use of biomarkers in the diagnosis and prognosis of these diseases allows the work of veterinarians to be a little easier and thus improves the quality of life of patients who require the use of them. Some biomarkers that are useful in humans have not been counted useful in felines, however, recent studies have shown that there are some quite promising new candidates.

Framework

¿which is a biomarker?

A biomarker is a physiological, biochemical or morphological characteristic that is measurable and evaluable at the molecular, biochemical or cellular level that acts as an indicator of a normal or pathological biological process, or as a response to a therapeutic intervention. The Biomarkers are increasingly being investigated in the treatment of different disease. There has been a growing focus on the use of biomarkers as an alternative or adjunct to invasive procedures.

A biomarker is a substance that is:
- ✓ Specific for the organ or tissue under study
- ✓ Released in proportion to an injury or illness

What biomarkers are for?

Biomarkers are used to confirm exposure to a harmful agent, and they also allow provide a system to monitor the individual susceptibility to a toxic, also to quantitatively assess the harmful effects that a toxic agent may be generating within the body of the affected individual or organism.
The biological markers are also they use to recognize, characterize and monitor the state, and also to follow up on a disease(1).

What is the discovery of a biomarker?

The discovery of biomarkers is a complex and challenging process. The main rating corresponds to mass spectrometry (MS) technology combined with the associated disease differential(2). An analysis should be performed, a widely used approach to statistically significant differences in protein expression or production of metabolites between disease and control. Cohorts identify potential biomarkers(2).

Biomarker Discovery workflow(2):
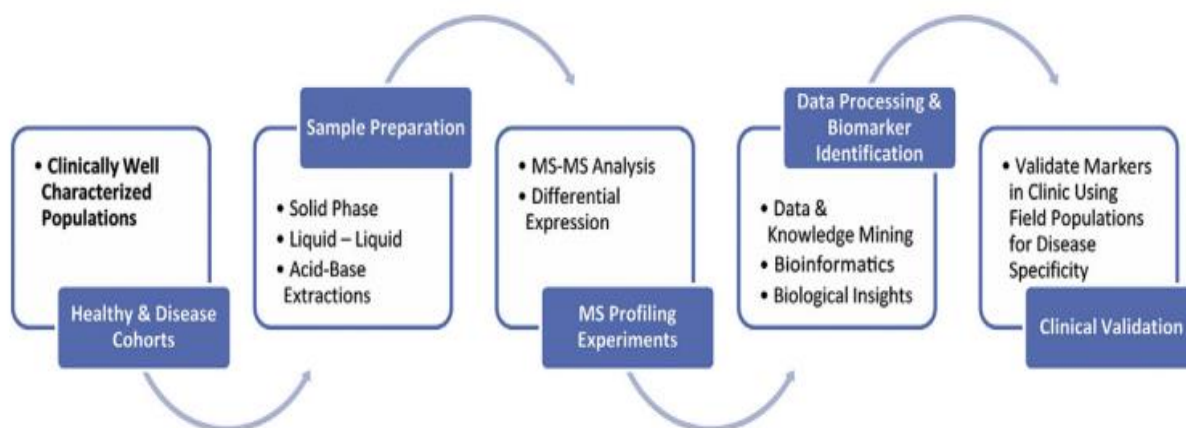
Are biomarkers specific for diseases?

Biomarkers are not always specific for the organ of interest because some proteins that act as biomarkers are secreted by various tissues(2).

For example clusterin messenger RNA is found, which is ubiquitous in all tissues of animals and is abundant in the liver, stomach, brain and testicles. Similarly, NGAL is expressed and secreted by immune cells, hepatocytes, adipocytes, epithelial cells, liver, lung, colon and renal tubular cells in various pathological states, as well there is alkaline phosphatase that serves as an example and is secreted by multiple tissues, and is used to evaluate liver function, however, current diagnostic methods measure Levels of alkaline phosphatase, both hepatic and bone(2).

the use of this marker to control bone metabolism or liver dysfunction can be compromised if an immunosorbent assay linked to a simple enzyme is performed The approach (ELISA) that measures all the isoforms is adopted.

Therefore, it is important to measure the proteins specifically of the target organ or disorder to avoid false diagnoses. This specificity could be achieved through orientation subtle differences, such as post-translational modifications (PTM) that are specific to the disease process to develop accurate diagnoses(2).

Which is the biomarker of preference?

The serum is preferred because it is considered the most complete circulating representative the bodily processes and the physiological and pathological processes(2).

What are the parameters that biomarkers detect?

- ✓ Heart disease in early stages (asymptomatic patients)
- ✓ differentiate if dyspnea has a cardiac or respiratory origin
- ✓ And finally follow up on medical treatment and as a guide for early and timely diagnosis.

There are different types of biomarkers that allow measurements of the stages of different diseases in cats, therefore they are the ones that are responsible for showing in which state the patient is in, in the same way it allows everything to be perform more safely and quickly to achieve a quick recovery.

¿How a biomarker is defined?

A biomarker is defined as a physical, functional or biochemical indicator of a physiological or disease process that has a diagnostic and / or prognostic utility with the ability to be measured accurately and reproducibly(2).

The current role of biomarkers is rapidly going into
Expansion beyond the diagnosis of progression and regression of diseases(2).

Why are biomarkers becoming essential?

They are becoming indispensable since they allow to accelerate the discovery and development of drugs, they allow to understand the effectiveness and the toxicity of the therapies and to determine the duration of the therapies(2).

What is the role of a biomarker?

Meet the ability to measure accurately and reproducibly, the current role of biomarkers is to allow rapid expansion beyond the diagnosis of progression and regression of diseases(2).

How is the journey of a biomarker?
From the bank to the clinic is long and difficult, there is a variety of biomarkers discovered and reported regularly, but some of them reach the clinics. There are several requirements and strict criteria that a the biomarker must comply to be an ideal marker and be adopted in clinical practice(2).

Journey of biomarkers from research laboratory to clinic(2).
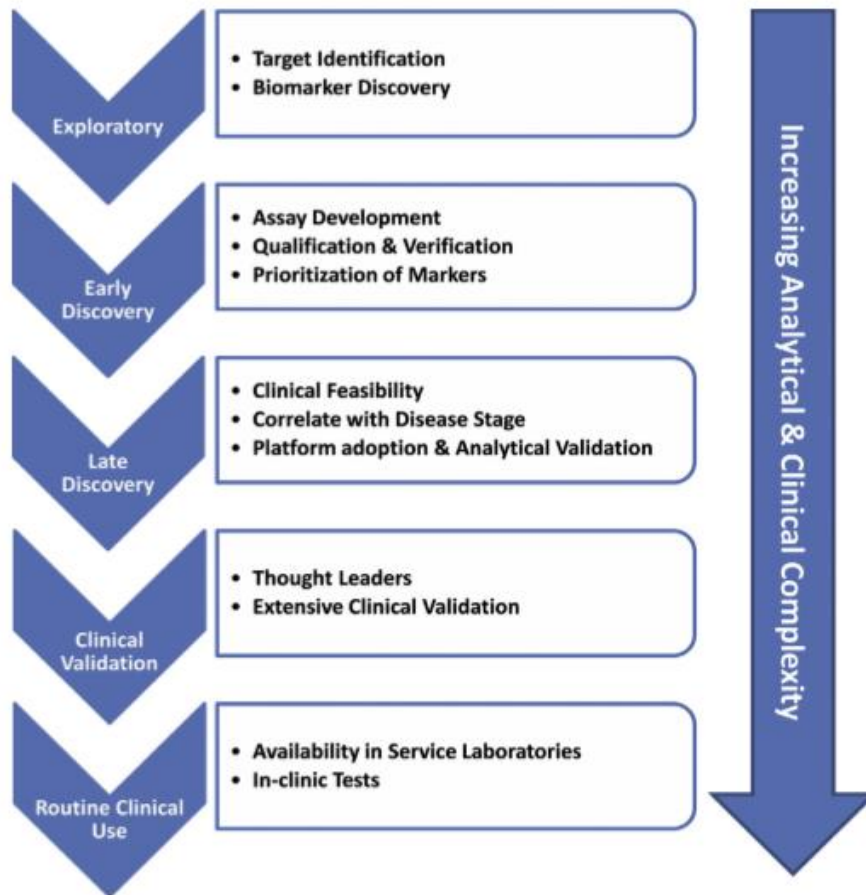
CRITERIA FOR DETECTING A GOOD BIOMARKER IN A CLINICAL PRACTICE(3)

- ✓ Should provide information that is not available through a clinical evaluation
- ✓ allow the average level at which it should assist doctors in decision making
- ✓ the measurements on the disease level must be precise and repeated must be offered at a reasonable cost and with short response times

THE FOLLOWING CAN BE USED AS BIOMARKERS

The blood-based biomarkers can able to report that so advanced or the state of the disease are a subject of considerable interest. A biomarker is a substance that have many features :(4)

Cardiac biomarkers allow veterinary physicians to assess the presence of cardiac conditions in both dogs and cats, through quantitative assessment using the following analytical parameters:

- ✓ Myocardial function
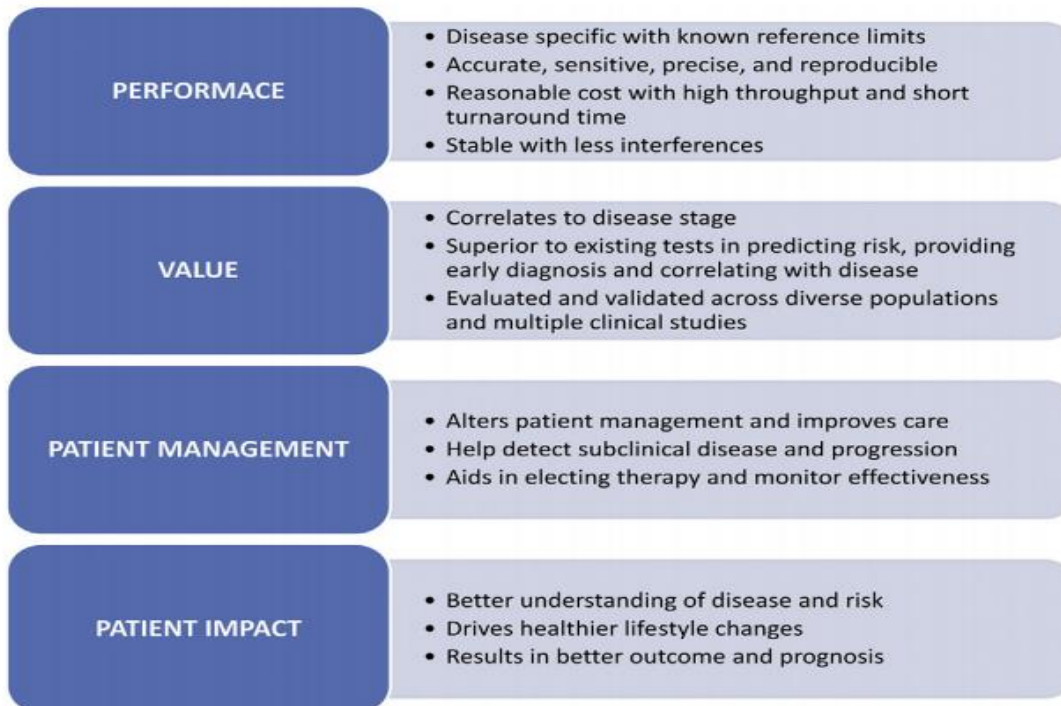- ✓ Myocardial injury (with loss of the integrity of cardiac myocytes)

Another biomarker can be the thymidine kinase (TK) is a cytoplasmic enzyme involved in the phosphorylation of deoxythymidine in deoxythymidine monophosphate as part of the important one-step recovery pathway of pyrimidine synthesis. TK exists in both cytosolic (TK1) and mitochondrial (TK2) forms, TK1 is closely associated with cell proliferation, and its activity markedly increases after the G1-S transition in the cell cycle and then decreases. The experience of measurement of sTK activity in cats is limited to a small pilot study that indicated the potential of this marker in feline lymphoma and justified further study, the clinical response to treatment, feline leukemia virus status (FELV), location and clinical stage remain the only factors that remain the only predictions so far consistent in cats, this due to the scarcity of information on the

prognosis, a marker that can help the diagnosis and prognosis of this disease may be thymidine kinase(5).

What are the properties of an ideal biomarker?

From a physiological point of view, an ideal biomarker produces a constant rate and maintains a constant plasma concentration; it is characterized by low intraindividual variation, and there is no plasma protein binding, tubular secretion, tubular reabsorption without catabolism or extrarenal authorization (Ghys et al., 2014a).

Medically, an ideal biomarker for CKD must be strongly correlated with GFR, more sensitive and specific than creatinine, and is not affected by comorbidities, age, sex or race If the biomarker is correlated with a specific pathological process such as the child (damage or renal tubular fibrosis or phosphorus metabolism), this would shed additional light on the pathophysiology of the disease as it progresses. In addition, the ideal biomarker should be shown to alter this in response to the therapy performed.

Characteristics of an ideal biomarker(2).

PERFORMACE
- Disease specific with known reference limits
- Accurate, sensitive, precise, and reproducible
- Reasonable cost with high throughput and short turnaround time
- Stable with less interferences

VALUE
- Correlates to disease stage
- Superior to existing tests in predicting risk, providing early diagnosis and correlating with disease
- Evaluated and validated across diverse populations and multiple clinical studies

PATIENT MANAGEMENT
- Alters patient management and improves care
- Help detect subclinical disease and progression
- Aids in electing therapy and monitor effectiveness

PATIENT IMPACT
- Better understanding of disease and risk
- Drives healthier lifestyle changes
- Results in better outcome and prognosis

✓ Natriuretic peptides: they are released when there is cellular stress, which is why they are indicators of cardiac functionality. Its action would be to promote natriuresis and vasodilation, they have an inhibitory action of renin, are antiarrhythmogenic and have lusitropic effects (relaxation) in the heart (6).

✓ Atrial natriuretic peptide: (ANP) it is secreted in the atrial tissue in response to the atrial stretch that occurs when cardiac dysfunction is generated, by increasing the left atrial pressure and when a heart failure situation is going to occur(2).

✓ Natriuretic type B peptide: (BNP) It is synthesized mainly in the ventricle when there is heart disease, due to an increase in ventricular stress (volume or pressure overload, ventricular hypertrophy). It is the one that is being used more on a practical level. For identification, a fragment (aminotermin form) of its pro-hormone (proBNP) is used, which is called NT-proBNP (with greater size, stability and half-life than BNP, making it easier to measure) (6).

CARDIAC TROPONINS: are specific indicators of myocardial cell damage, since they are released when cardiac, acute or chronic injuries occur. Blood levels will be proportional to the severity of the existing myocardial injury. There are three protein subunits of the Troponin complex found in skeletal and cardiac muscle:

✓ TnI- TnT- TnC Its function in the cell corresponds to the coordination of the excitation contraction of sarcoplasmic proteins. Cardiac troponin I (cTnI) is the most specific for the cardiac muscle(7).

ENDOTHELINES: as the main effect vasoconstriction, corresponds to fibrogenic and are responsible for promoting contractility. They are a powerful stimulus for the Renin-Angiotensia-Aldosterone system, and also for the sympathetic nervous

system. Its plasmatic levels increase significantly in congestive heart failure (with good correlation to the functional type of CHF) and with pulmonary circulatory alterations, which is why it can be very useful for the assessment of pulmonary hypertension and pulmonary vessel anomalies(6). For over a decade have been using the biomarkers for the diagnosis of heart disease in cats, and this has created intrigue in veterinary medicine professionals, willing to implement the use of biomarkers for the diagnosis of other diseases such as hypertrophic cardiomyopathy and liver lipidosis. The role of cardiac biomarkers in clinical decision-making(5). Although echocardiography is useful for identifying cats with cardiogenic respiratory distress, it may not always be available. Measurement of a cardiac biomarker may be helpful if a blood sample can be obtained with minimal restraint, and this might be safer than thoracic radiography. Eight studies were identified that compared cardiac biomarker concentrations in cats with cardiac and non-cardiac causes of respiratory distress: four studies investigated cTnI1e4 and four investigated natriuretic peptides (of which, all four featured NTproBNP and one also featured NTproANP). Only a cutoff value to identify cardiogenic dyspnea in cats is unlikely to be clinically useful(5), the hepatopathy induced by metabolic changes that lead to an excessive accumulation of triglycerides in the liver tissue, with resulting cholestasis and hepatic dysfunction(7). The general disease signs in cats are various but consistent with hepatic failure, enlargement, or insufficiency. The course of the disease is generally chronic, but clinical illness may appear acute. Concurrent conditions associated with poor nutrition may also be present. The laying hen may die acutely of fatty liver hemorrhagic syndrome resulting from rupture of hepatic blood vessels during egg lying. It should be stressed that other forms of lipid deposition (e.g., atherosclerosis; fat deposition in kidneys, skin, abdomen, lungs, and spleen) that lead to other physical findings can be found concurrently with hepatic lipidosis(7).

IN DISEASES THAT ALLOW TO BE DIAGNOSED AND TREATED WITH BIOMARKERS ARE FOUND

Feline hypertrophic cardiomyopathy

This disease is characterized by diastolic dysfunction that occurs as a consequence of thickening of the myocardium of a non-dilated left ventricle due to disorders related to the cardiac muscle itself, instead of secondary processes that present with ventricular hypertrophy such as aortic stenosis. hyperthyroidism, acromegaly or other diseases of non-cardiac origin (Kittleson, 2005). Males are more predisposed than females and the condition is more frequent in young cats (from 5 months to 6 years of age).

CMH can be mild, moderate or severe. The severe form increases the stiffness of the left ventricle by itself. In addition, the blood flow that supplies a very thickened myocardium can be compromised, inducing ischemia, cell death and fibrosis. In turn, the formation of fibrous tissue in the heart muscle further intensifies the rigidity of the chamber and is probably the main cause of the marked diastolic dysfunction seen in this disease (Kittleson, 2005).

Feline hepatic lipidosis

Feline hepatic lipidosis (FHL), the most common hepatobiliary disease in cats, is characterized by the accumulation of excessive triglycerides (TGs) in more than 80% of the hepatocytes, resulting in a greater than 50% increase in liver weight, secondary impairment of liver function, and intrahepatic cholestasis(7).

This disease have A specific geographic distribution has been suggested based on the available reports of FHL from different areas, including North America, Great Britain, Japan, and Western Europe. The higher prevalence of FHL in these areas might be secondary to feeding habits of cat owners and a high incidence of obesity

in the feline population, the main metabolic abnormalities that lead The accumulation of TG in hepatocytes is not yet completely known, but could consist of alterations in the pathways of uptake, synthesis, degradation and fatty acid secretion (FA)(7).

Chronic kidney disease:

Chronic kidney disease commonly affects dogs and cats and generally with poor or erroneous results during its advanced stages, the general prevalence of the disease in dogs is 5 to 7% and in cats it ranges from 6 to 20%, but the prevalence is increasing according to the age of the pets, that is, in dogs it has an increase of 15% when they are older than ten years, and in felines it has an increase of 31% when they are over fifteen years of age(8). The chronic kidney disease (CKD) is a progressive disease in elderly cats; it has no known etiology and there is no specific cure other than renal transplantation, this disease is characterized by its continuous advance, which generates the irreversible loss of renal function, which is caused by the loss of renal architecture. And the individual nephrons characterized by progressive scars that ultimately result in structural damage to the kidney, CKD is a silent disease that can remain asymptomatic until an advanced stage, cats become more vulnerable to acute kidney injury (ARF) after being exposed to risk factors such as nephrotoxic drugs or major surgeries. AKI is characterized by an abrupt deterioration of renal function and important causes include nephrotoxic medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and chemotherapy, infections, vasculitis, surgery, neoplasia and obstruction of the urinary tract by kidney stones. acute renal injury (AKI) has a poor prognosis and is associated with mortality rates that range between 50% and 60% in companion animals (8). After AKI, renal function could recover completely in surviving patients; there could be an incomplete recovery that results in CKD; I could have exacerbation of the pre-existing CKD, accelerating its progression; or there may also be no full recovery that requires permanent kidney replacement therapy.

Biomarkers allow developing an attempt to improve diagnostic capacity, which allows precision for the detection of acute and chronic kidney diseases including the potential for early detection of the disease(8).

¿why the use of biomarkers should be promoted?

Because biomarkers allow to identify the different processes that cause various diseases such as kidney disease, glomerular damage, tubular stress or dysfunction(8).

What are the characteristics of a specific biomarker for kidney disease(8)?

- ✓ Able to detect AKI and CKD
- ✓ Sensible to detect the disease early
- ✓ Able to document the disease, and allow monitoring of disease progression
- ✓ Predictive of clinical outcome
- ✓ Should not be invasive
- ✓ Must be low cost
- ✓ Must be available in a laboratory or reference point

Feline infectious peritonitis:

feline infectious peritonitis (FIP), is a viral disease resulting from feline coronavirus (FCoV) in which inflammation plays an important role in FIP infection, since the inflammatory response occurs during the course of FIP that participates in pathogenesis, producing fibrinous serositis, with accumulations of highly proteinic fluid within the body cavities, disseminated pyogranulomatous formation, hypergammaglobulinemia, and the development of immune complexes. Increases in acute phase proteins (APP), which are markers of inflammation, such as alpha-1 The serum glycoprotein or amyloid A can be used as a diagnostic aid in this disease. Knowing the relationship between inflammation and oxidation stress, it could be postulated that oxidative stress may be present in cats affected by FIP(4)

Table 1. The clinical indications, advantages, disadvantages, and common assay methodology of selected serum and urinary biomarkers of renal disease reported in veterinary medicine

Biomarker	Sample(s) needed	Condition(s) leading to marker elevation	Advantages	Disadvantages	Common method(s) of measurement
Surrogate markers of GFR					
Creatinine	Serum	Declining GFR Various non-renal causes	Widely available Inexpensive Familiar assay Most accurate in steady state GFR	Minor assay interference from non-creatinine chromogens (e.g. proteins, glucose, ketoacids) Non-linear relationship with GFR Proportional to patient muscle mass Influenced by pre and post-renal azotaemia and hydration status Higher creatinine levels in breeds with increased muscle mass (e.g. Boxers, Greyhounds, sled dogs, Birmans)	Jaffe (alkaline picrate) reaction Enzymatic reactions
Cystatin C	Serum Urine	Proximal tubular damage causing decreased reabsorption	Good marker of GFR in early stages of renal disease	Questionable effects of age and weight in dogs Not consistently shown to be superior to creatinine as a marker of GFR	Particle-enhanced turbidimetric immunoassay (PETIA)
Markers of tubular dysfunction					
RBP	Urine	Proximal tubular damage causing decreased reabsorption	Stable in acidic urine and frozen samples Useful for monitoring chronic disease due to progressively increases in later disease stages	Wide intra-individual variation in feline CKD and hyperthyroidism	ELISA Western blot
α1-microglobulin	Urine	Proximal tubular damage causing decreased reabsorption	Stable in acidic urine	Decreased by hepatic disease	Western blot
β2-microglobulin	Plasma Urine	Proximal tubular damage causing decreased reabsorption	Good predictor of GFR in dogs	Unstable in acidic urine Decreased sensitivity for monitoring disease progression	ELISA Western blot
NAG	Urine	Proximal tubular damage causing increased release	Can measure activity from spot urine sample Marker of AKI secondary to pyometra, leishmaniasis and nephrotoxins	Affected by proteinuria, hyperthyroidism, diabetes mellitus, alkaline urine pyuria, long-term storage, ±sex Lack specificity as NAG B isoenzyme associated with protein processing and lysosomal activity	Enzymatic colorimetric assay
GGT	Urine	Proximal tubular damage causing increased release	Can measure activity from spot urine sample Used to identify nephrotoxicity secondary to gentamicin	Unstable in acidic urine. Hematuria and pyuria cause assay interference Less sensitive to detect CKD	Spectrophotometric assay
NGAL	Urine, plasma or serum	Tubular damage causing increased release	Samples stable with freeze-thaw cycles	Hematuria and pyuria may cause assay interference Malignancy, inflammation and infection may decrease specificity	ELISA (several species-specific assays, including dogs)

GFR glomerular filtration rate, CKD chronic kidney disease, AKI acute kidney injury, ELISA enzyme-linked immunoabsorbant assay, RBP retinol-binding protein, NAG N-acetyl- β-D-glucosaminidase, GGT γ-glutamyl transpeptidase, NGAL neutrophil gelatinase-associated lipocalin

(8).

What is the creatinine?

Creatinine is a by-product of endogenous muscle metabolism, creatinine is distributed in the body water, is almost entirely freely filtered at the glomerulus, is not absorbed by the renal tubules and undergoes minimal tubular secretion. As such, it inversely correlates(8).

What are the limitations of creatinine?

- ✓ Creatinine measurement is insensitive for early stage renal failure(8).

- ✓ The relationship between glomerular filtration rate and serum creatinine is nonlinear when kidney disease is early(8).

- ✓ factors such as age, sex, bodyweight and breed can all affect measured GFR values(8).

What is cysteine C?

Cystatin C is a cysteine proteinase inhibitor produced constitutively by all nucleated cells, which is filtered freely in the glomerulus and is absorbed and catabolized in the cells of the proximal tubule, with minimal tubular secretion(8).

Which are the biomarkers for the tubular dysfunction?
- ✓ Low molecular weight proteins: Retinol-binding protein(8).
- ✓ Low molecular weight proteins (LMW): `1 and a2-microglobulins(8).
- ✓ Enzymuria: N-acetyl-a-D-glucosaminidase and f-glutamyl transpeptidase(8).
- ✓ Neutrophil gelatinase-associated lipocalin(8).

Retinol-binding protein in cats

Retinol-binding protein (RBP) is a 21-kDa low molecular weight protein (LMW) protein synthesised in the liver. Unbound RBP is filtered at the glomerulus and is almost completely reabsorbed and catabolised in the proximal tubular cells(8).

Assessment of tubular function using RBP in hyperthyroid cats is problematic secondary to large inter-individual variation, and may indicate that this is not a suitable marker of feline renal tubular injury(8)

Enzymuria: N-acetyl-a-D-glucosaminidase and f-glutamyl transpeptidase
N-acetyl-β-D-glucosaminidase (NAG) and γ-glutamyl transpeptidase (GGT)

Are proximal tubular enzymes involved in protein processing.
Studies have shown poor correlation between creatinine concentration and the NAG index in healthy cats and cats with urinary tract disease, and NAG index was not predictive of development of azotemia in geriatric cats or those with treated hyperthyroidism. Therefore, it is suggested that NAG is not a good biomarker for CKD in cats(8). But NAG and GGT may be well suited for detection of early tubular injury. In ongoing kidney injury, depletion of tubules decreases enzyme excretion(8).

Nexus between CKD and acute kidney injury(2).

CREATININE AS A BIOMARKER OF KIDNEY FUNCTIONS AND FALSE ANSWERS(2).

✓ Serum creatinine has been characterized as the standard care test for renal function and disease for about 100 years.

✓ Ceric creatinine is a product of muscle metabolism degradation and correlates with muscle mass. As a result, renal function is overestimated in cachectic.

✓ Animals of low musculature, can give rise to false diagnoses of renal dysfunction.

✓ In heavily muscled animals, the metabolism of creatinine must reach and remain stable.

Arginine as a biomarker

Arginine is a conditional essential amino acid and most animals produce theirs.

The post-translational transformation of the arginine protein groups occurs in the mitochondria. The methylation of arginine occurs mainly in histones for the purpose of transcriptional regulation. In general, the asymmetric methylation of arginine. (ADMA) activates transcription, while symmetric methylation (SDMA) is a repressive signal. The proteolysis of these methylated proteins results in the release of SDMA and ADMA in the cytoplasm and then from the cell to the circulation through cationic transporters, although ADMA has been shown to be an endogenous inhibitor of nitric oxide synthase (NOS) and a marker for cardiovascular disease, SDMA does not interfere with NOS36 activity or arginine transport at physiological concentrations. Approximately 80% of circulating ADMA is eliminated through enzymatic pathways, which makes it a poor marker for kidney function. However, SDMA is strictly eliminated through the kidneys by filtration and renal excretion, therefore circulating concentrations are affected mainly by changes in GFR and correlate with renal function(2).

THE GLOMERULAR FILTRATION RATE AND CORRELATION

GFR is the gold standard for determining renal function in people and animals. However, the GFR can not be measured directly, this is measured through the urinary or plasma clearance of several small molecules, including inulin and iohexol(2).

The first evidence of the use of SDMA to assess kidney disease in dogs that use a remnant the kidney model was published in 2007 and resulted in strong correlation of SDMA with mGFR by inulin elimination, but the most recent study showed a linear relationship between GFR levels and SDMA in a population of cats and female carriers, affected and males from a colony of dogs with hereditary nephropathy

linked to X54 compared to mGFR using iohexol clearance. In another study on CKD, SDMA concentrations showed an increase and correlated with serum creatinine. the evaluation of hyperthyroid cats showed that the level of SDMA correlated better than serum the creatinine level with mGFR estimated by elimination of iohexol before starting the diet therapy and at 6 months of follow-up(2).

Feline infectious peritonitis (FIP)

The diagnosis of feline infectious peritonitis is usually made when the disease is at a very advanced stage, making it more difficult to diagnose and convert the treatment. As we know, this is a virus, for example, feline infectious peritonitis can be detected early, this is a virus. What can be done quickly with leukocytes, macrophages and monocytes? The production of plasma levels of VEGF, was also more important in cats by PIF (feline infectious peritonitis), this virus is an RNA virus(9), this virus can be attacked in several ways, such as wet or dry and more aggressive It is the dry form(9). It has also been shown that the virus has several factors that can act as inhibitors in the first phase or in vitro(9), but that they do not have the capacity to behave as such. The virus can kill cats in just a few days and is highly lethal because medical treatment is too strong, it is like treating cancer in humans, medicines that are used for the body, decreasing the resistance of the body and there when bacteria Opportunists enter the body to attack in different ways. This virus has been validated with the theory of mutation in several studies that have resulted in the FIP gaining tropism due to the alteration of macrophages, which causes the virus to deviate from the service and become a systemic pathogen of the virus of macrophages(9). This virus does not have an effective vaccine at this time, it is available only to prevent, but this is not enough, it must be a vaccine that does not allow the virus to enter the body. We have found 16 compounds that function as antiviral compounds against a local strain of FIP(9).

The state of the health of cats is related and associated with the functions of the proteins of the acute phase. These results were obtained using multivariate regression models(6).

Still no studies have been conducted in which there is shown that the presence of oxidative stress during FIP , but this is present in various diseases in this species, such as, diabetes mellitus, feline immunodeficiency virus (FIV) infection, chronic renal failure The inflammation plays an important role during the infection FIP as a major inflammatory response occur during the course of FIP, which is involved in the pathogenesis producing fibrous serositis with accumulations of high protein fluid into body cavities(4). During the acute phase proteins increased (APPs), which are markers of inflammation such as alpha - 1 glycoprotein or serum amyloid A can be used as an aid in the diagnosis of FIP. A way of knowing if there is the presence of oxidative stress in FIP, is given from knowledge of the relationship between inflammation and oxidative stress(4). Also this corona-virus is associated with mild or subclinical enteric infections, only between 5% and 12 % of cats test positive develop FIP(10). Among serotypes they have been identified the type I and type II that everyone has the capacity to develop FIP. Corona-viruses have been discovered in a variety of species such as; birds, humans, farm animals and other mammals(10).

A reverse transcriptase polymerase chain reaction (RT-PCR) for the detection of feline corona virus (FCoV) messenger RNA in peripheral blood mononuclear cells (PBMCs) is described(11) The corona viruses are abundant in populations of cats with particularly high prevalence in farms and households with multiple cats, the virus reproduces sporadically (not cause epidemics) disease is mostly fatal, its biology is still little known, its prevention is difficult, occurs worldwide and affects domestic and wild cats(11), persistently infected cats may harbor in their intestines, blood FCoV or tonsils, and remove the virus in feces or spittle, these cats can act as a continuous source of infection, be able to detect these cats it is essential; not only for our understanding of their role in the spread of corona virus infection, but also in

determining what is the chronic potential role in the induction of clinical FIP(12). Now known to FCoV can be detected using RT-PCR techniques, blood up to 95 % of healthy cats FCoV endemic households(12).

The infection with feline infectious peritonitis as a result of clinical signs is an invariably fatal virus despite clinical intervention. As FIP is an immune disease, treatment is directed primarily to control the immune response triggered by infection with feline corona virus (FCoV)(13).The infection is controlled by immunosuppressants such as prednisolone or cyclophosphamide which can slow the progression of the disease but can't produce the cure is known that in almost every case reports of attempted therapy for FIP clinic, glucocorticoids have been used(13).

Many studies evaluated the effect of glucocorticoid therapy for uncontrolled FIP(13). the chronic renal disease is more frequent in geriatric cats reaches a prevalence from 30% to 60%, frequently present in cats older than 10 years, taking into account that chronic renal cat disease is irreversible and progressive, for this reason it becomes necessary that this disease is detected and prevented in time since this allows the improvement of the quality of life of the cat as well as allows it to live for a longer time. The glomerular filtration rate is considered gold and is the standard method for the evaluation of renal function, but it is not used frequently since it spends too much time, but there are indirect GFR markers such as serum creatinine and urea which are frequently measured and allow to estimate GFR, these markers are insensitive, the urinary cystatin is a biomarker for tubular damage in humans and canines, a study made it possible to find that cystatin is a promising biomarker for estimating TGF in feline medicine(14).

an imbalance between oxidative and antioxidant system or oxidative stress, as well as the accumulation of reactive oxygen in the organism, produce a detrimental effect on the functional and structural integrity of biological tissues, in this way then cats

are more susceptible to stress and damage oxidative, with great influence by the form of the spleen of this species(4).

The relationship between stress and oxidative damage has been demonstrated in diseases such as diabetes mellitus, chronic renal failure and feline immunodeficiency virus. Studies on the influence of oxidative stress on feline infectious peritonitis are not yet known(4). FIP disease in some populations can attack between 50% and 80% of pure-bred cats and in creole cats reaches a 15% affectation. This disease also has different forms of presentation, by effusion rich in proteins within the body cavities(11).

And the dry PIF that has characteristics like:(11)

•   The presence of piogranulomas in different organs.

•   At the cutaneous level, PIF produces granulomatous nodules and ulcers present by vasculitis around the head and neck.

The most frequent clinical signs in cats with any FIP variance are:(11)
•   Fever
•   increase in weight loss
•   lethargy

The type of FIP that is present depends on the cat's immune system, and other clinical signs also depend on the affected organ, the serological test, with a high titre of antibodies can reveals FcoV infection, but it is impossible determine whether the cat will develop PIF, to detect the presence of this disease, some combinations have been made as is the concentration of SAA with a high title of antibodies against the coronavirus to diagnose the presence of FIP. This study yielded significant results that allowed the conclusion to be obtained by comparing levels of SAA of cats with

FIP and of healthy cats with a high titer of antibodies. The SAA concentration was increased 10-fold in cats with FIP, compared to healthy cats exposed to FCoV(11). As it is already known during FIP disease inflammation occupies a very important place because in its different phases attacks in various ways, within its pathogenesis is the production of fibrinous serositas, which has accumulations of liquid with high protein content inside the cavities as well as the formation of disseminated piogranulomatous, hypergammaglobulinemia, and the development of immune complexes. During the acute phase of this disease increases of the proteins (APP), which are markers of the inflammation such as:(4)

- alpha-a
- the glycoprotein or amyloid A contained in the serum

Which are used and are help to diagnose, it could be said that oxidative stress is present in cats with FIP(4). Quantitative analysis of acute phase proteins, especially type A serum amyloid (SAA) and the alpha-1 acid glycoprotein (AGP) provides excellent guidance for diagnosis, prognosis, and monitoring as well as the prognosis of many other diseases and conditions affecting the world's feline population, the acute phase protein (AGP) plays an important role during the diagnosis of FIP, it can also be used in studies of pathogenesis of this disease. The quantification of feline PGA in the diagnosis of FIP has allowed an improvement in the specificity and clinical sensitivity of this disease. Since the forecast of cats with this infection is very poor(11). It is important to differentiate it from conditions with signs such as myopathies. Plasma AGP values or feline exudate infected with FIP reach levels greater than 1.5 g / L. The Hp concentration is higher in cats with FIP than in healthy cats, but this protein has no any value in the diagnosis of FIP. The total concentration of acid serum can allow the support of a diagnosis of FIP with extremely high serum concentrations (greater than 800 mg / L), suggesting that the saturation of AGP with sialic acid (hypersialization) may be involved with interactions between this virus and its host(11).

The results were the following:

- ✓ The concentration of amyloid A serum log -transformed was higher in older cats, in sick cats and in females.
- ✓ The concentrations of logarithmically transformed α1 glycoprotein acid and haptoglobin were higher in old cats and were associated with interactions of health status (sick / healthy) and sex (male / female).

How to determine protein concentrations in the acute phase feline(7)*.*

- ✓ **Amyloid serum A**

The concentration of serum amyloid A was determined using a solid phase sandwich Elisa kit.

- ✓ **Alpha 1-acid glycoprotein**

A radial immunodiffusion kit (Tridelta Development Limited) was used to measure acid-1 glycoprotein.

- ✓ **Haptoglobin**

Haptoglobin was measured using a kit (Tridelta Development). This kit is based on the detection of a color change as a result of the interactions between haptoglobin, hemoglobin, a chromogen and hydrogen peroxide.

- ✓ **Albumin**

Serum albumin concentrations were determined at the University at the Veterinary Clinical Pathology Laboratory of Queensland using an Olympus analyzer using a photometric color test for the quantitative determination of albumin concentration.

Measurements of acute phase protein concentrations work as biomarkers and allow veterinarians to have a more detailed and real result of the disease phase of the patient, as well as provide a diagnosis, prognosis and timely treatment to the patients. Cats affected by the various diseases to which they are exposed every day.

Feline acute pancreatitis

Feline acute pancreatitis is the most common disorder this disease characterized by acute inflammation of the exocrine pancreas, and which results in clinic-pathological findings compatible with extra-hepatic cholestasis, the incidence of acute pancreatitis, the causes are unknown, this disease has association occasionally with pancreatic neoplasia and fortuitous infestation. Because hepatic lipidosis and acute pancreatitis can have very similar clinical presentations in felines. but necropsy studies suggest that it is not uncommon. A small number of cases in which this disease has been related to trauma, infection with feline infectious peritonitis virus or Toxoplasma gondii, or inflammation of the biliary tract have been presented(15).

Feline pancreatic disease can be detected under direct and indirect serum markers of hepatic fibrosis, such as hyaluronic acid; new markers of hepatocellular injury, such as circulating microRNAs; and quantitative tests of hepatic microsomal function(16).

General Aim

Collect information about the different biomarkers used for the diagnosis, prognosis and treatment in the various diseases in cats such as feline hypertrophic cardiomyopathy, feline hepatic lipidosis, feline immunodeficiency virus, chronic renal failure and feline infectious peritonitis. Information on biomarkers for the analysis of feline viruses and their ability to perform an examination that allows to have more detailed information about these diseases, although most of these are fatal, may contain some factors that act as inhibitors, some of them they are: chloroquine, mefloquine, amiloride and hexamethylene which are present during the initial stage of the virus, the infection can also change the stages of the vascular endothelial increase factor (VEGF) making these changes to extend the amount of plasma, since which is related to the abundance of the disease, the vascular components of the absorption as amounts of the spills and the cats with increased FIP.

Materials and methods

Perform a search of information in the different databases, such as Science direct, scopus, pub med, clinical key, web of science, articles in English and Spanish of the last ten years.

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