

## 1. INTRODUCTION

Insulin resistance (IR) is a condition in which a normal amount of insulin produces a lower expected biological response and it is an important component of the pathogenesis of type II diabetes mellitus (DM). The IR can occur secondary to many risk factors in dogs and cats. The clinical manifestation is a persistent hyperglycaemia. To determine the cause of IR is necessary and eliminating it helps to improve the diabetic control.

## 2. OBJECTIVES

- Get further in insulin resistance etiology to define the nature of the uncontrolled diabetic.
- Discuss the administered insulin dose to consider insulin resistance.
- Analyze established diagnosis protocol.

Table 2

## 3. CAUSES

The most common cause of IR in dogs is hyperadrenocorticism, and in cats is acromegaly. Identification of IR requires elimination of problems associated with the insulin itself or owner administration of insulin. It is possible to divide the causes into exogenous and endogenous (table 1).

Endogenous causes are associated with hormone-mediated IR mechanisms and they are summarized in table 2.

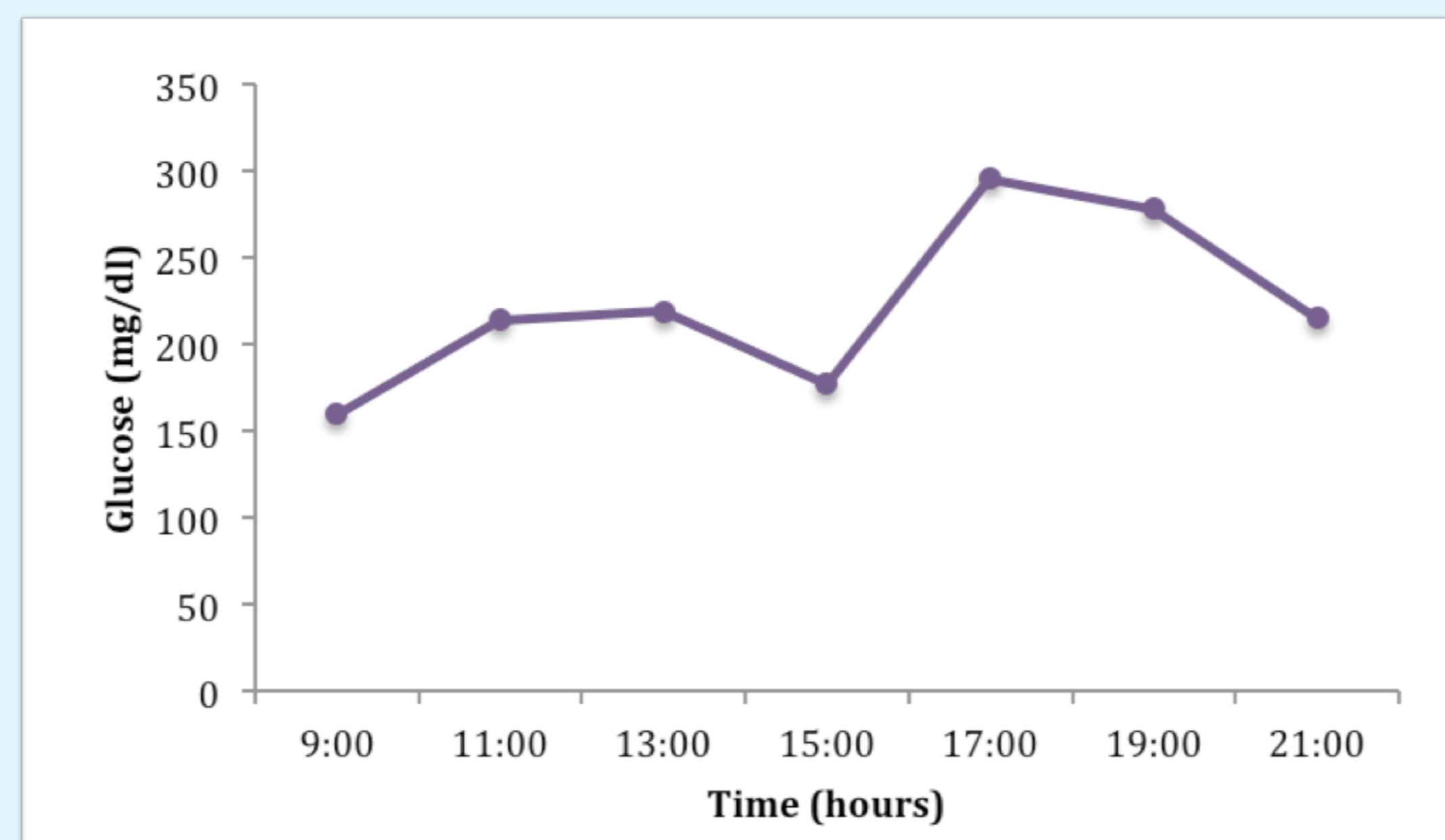
Secondary to insulin	
- Poorly preserved insulin	
- Expired insulin	
- Diluted	
- Inappropriate administration	
- Poor absorption	
- Abnormal activity duration	
- Production of anti-insulin antibodies	
Case management	
- Exercise, diet, inappropriate insulin	
- Incorrect dose and insulin adjustments	
- Incorrect interpretation of laboratorial database	
Concurrent diseases (endogenous)	
- Obesity	
- Diestrus	
- Hyperadrenocorticism	
- Hyperthyroidism	
- Hyperthyroidism	
- Acromegaly	
- Chronic inflammatory conditions (especially pancreatitis)	
- Glucagonoma	
- Pheochromocytoma	
- Hyperlipidaemia	
- Renal insufficiency	
- Heart insufficiency	
- Diabetogenic drugs	

Table 1

## 4. DIAGNOSIS PROTOCOL AND DISCUSSION

IR should be considered in a dog or cat when more than 1.0 - 1.5 UI/Kg per injection of insulin is required to maintain adequate glycemic control<sup>1,2</sup>.

Perform a blood glucose curve is necessary to determine a true insulin resistance. Figure 1 belongs to a 8 years old neutered male of Yorkshire terrier with DM diagnosed 6 months ago. To confirm the cause a laboratorial testing and imaging must be made (illustrated in table 3).



**Figure 1.** Serial blood glucose measurements plotted against time. The concentration of blood glucose stays above 150 mg/dl after insulin administration, indicative of IR.

## 5. CONCLUSIONS

Table 3

- Insulin resistance can occur as a result of any process that alters the availability or action of insulin. Causes can be classified into exogenous and endogenous. The exogenous causes are related to the mismanagement of the case by the veterinarian or the owner and secondary to insulin itself. The endogenous causes are related to concurrent situations or diseases in dogs and cats such as: obesity, hyper and hypothyroidism, diestrus, diabetogenic drugs, bacterial infection, neoplasia, pancreatitis, renal and cardiovascular insufficiency; being hyperadrenocorticism the most common cause of IR in dogs, and acromegaly in cats. All these processes have in common the release of hormones which alter the molecular mechanisms of insulin and glucose acting at pre-receptor, receptor and post-receptor levels.
- Further studies are needed to define a clear dose of insulin to determine resistance. It depends on the underlying cause.
- The diagnosis protocol of insulin resistance requires a detailed anamnesis, clinical history and a physical examination. The blood glucose curve is the most appropriate tool to determine the true insulin resistance. Specific laboratorial tests for each concurrent disease allow to establish a definitive diagnosis. Achieving this diagnosis is important to treat the cause and improve diabetic control.

Hormones	Associated disease	Mechanism of insulin resistance
Progesterone	Exogenous administration Diestrus	Decreased receptor affinity for insulin Reduced glucose transport in tissues
Growth hormone (GH)	Acromegaly	Decreased n° insulin receptors Inhibited glucose transport Increased lipolysis
Glucocorticoids	Exogenous administration Hyperadrenocorticism	Decreased receptor affinity for insulin Decreased n° and affinity glucose transporters Decreased glucose use in tissues Increased hepatic gluconeogenesis
Thyroid hormones	Hyperthyroidism Hypothyroidism	Decreased insulin production Decreased receptor affinity for insulin Increased non-functional pro-insulin Post-receptor defect Impaired glucose transport
Glucagon	Pancreatitis Bacterial infection	Activation hepatic glycogenolysis Increased hepatic gluconeogenesis
Epinephrine	Pheochromocytoma	Increased hepatic and renal gluconeogenesis Mobilization of gluconeogenic precursors Lipolysis to muscular tissue Decreased insulin production

Test	Initial evaluation and monitoring	If insulin resistance is suspected	Diagnosis
Blood glucose curve	Dog, Cat (consider stress)		
Fructosamine	Dog, Cat		
Urianalysis + culture	Dog, Cat		Diabetes Mellitus, UTI, other complications
Biochemical analysis + electrolytes	Dog, Cat		
CBC	Dog, Cat		
FeLV/FIV	Cat (unknown status)		Immunosuppression
T4	Cat		Hyperthyroidism
Thyroid panel (T4, FT4, T3, TSH)		Dog, Cat	Hyper / hypothyroidisms
Progesterone		Dog (intact female)	Diestrus
Adrenal function test		Dog	Hyperadrenocorticism
Catecholamine (blood, urine)		Dog	Pheochromocytoma
Pancreatic panel (TLI, PLI)		Dog, Cat	Pancreatitis
IGF-1 ± TC or MRI		Cat	Acromegaly
Abdominal ultrasound Thoracic radiography		Dog, Cat	Neoplasia, Heart insufficiency, Renal insufficiency
Cobalamin/Folate ± TLI		Dog, Cat	Bacterial overgrowth, Pancreatic exocrine insufficiency

\*CBC = Complete blood count; UTI = Urinary tract infection; FeLV/FIV = Feline Leukemia Virus /Feline Immunodeficiency Virus; T4 = Thyroxine; FT4 = Free Thyroxine; T3 = Triiodothyronine; TSH = Thyroid-stimulating hormone; TLI = Trypsin-like immunoreactivity; PLI = Pancreatic Lipase immunoreactivity; IGF-1 = Insulin like-Growth Factor 1; TC = Computed tomography; MRI = Magnetic resonance imaging