

# LATEST DEVELOPMENTS IN CANINE DIABETES MELLITUS WITH PARTICULAR REFERENCE TO CHEMOTHERAPY

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Diabetes mellitus is a heterogeneous group of disease of varying etiologies in different individuals with a number of characteristic features in common. It is a complex endocrine disorder with disturbance in carbohydrate, lipid and protein metabolism related to either an absolute or relative deficiency of insulin, resulting in hyperglycemia with glycosuria. Diabetes mellitus is of common occurrence with a reported frequency of 1 in 100 to 1 in 500. There is an increased incidence in females with a peak incidence around 6-7 years. Breeds that are predisposed are Poodles, Dachshunds, Cocker spaniels, Collies, Dobermans and Rotweillers. All breeds, and all life styles are susceptible.

## Normal Actions of Insulin

- It is used in the uptake of glucose, amino acids, fatty acids, potassium, and magnesium into peripheral tissue cells.
- It helps in the hepatic glycogen and hepatic lipid synthesis.
- It inhibits glycogenolysis and gluconeogenesis.

## Pathophysiology

### a. Carbohydrate metabolism

Hyperglycemia due to glucose uptake and utilization by the peripheral tissues (skeletal muscle and adipose tissue) and enhanced gluconeogenesis in the liver is its main feature. Glycogen formation remains depressed. Glucosuria results with attendant loss of water, sodium, potassium and chloride ions. Every gram of glucose excreted in urine amounts to a loss of 17 kilojoules of energy leading to more increased food intake, hyperglycaemia and ketonuria.

### b. Lipid metabolism

Increased lipolysis and decreased lipogenesis result from insulin deficiency. Plasma free fatty acid (FFA) is significantly increased, while triglyceride (TG) stores are depressed. Decreased lipoprotein lipase activity reduce TG

## Etiology

### Classification of Diabetes mellitus in man

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Insulin dependant diabetes mellitus/

Juvenile onset diabetes mellitus/

**Type I Diabetes mellitus**

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uptake by peripheral tissue to elevate plasma TG level. The plasma cholesterol level is also enhanced.

Increased plasma FFA will produce more acetyl CoA than required generation of energy through TCA cycle (P oxidation). This will be converted to ketone bodies in excess to be utilized for energy purpose of the body. Accumulating ketone bodies in the blood are excreted in urine, as they have no renal threshold (acetone also exhaled) to produce ketonuria. Ketonemia produces four important effects.

- Metabolic acidosis- due to partial ionization of acid substances there is fall of bicarbonate and excess removal of CO<sub>2</sub>,
- Loss of monovalent cations - Sodium and Potassium are lost as salts of ketone bodies.
- Increased water loss- dehydration and hypovolemic shock occur.
- Loss of electrolytes due to emesis.

### c. Protein Metabolism

Insulin deficiency results in failure of amino acid transport and protein synthesis. Accelerated protein degradation due to excess catabolic hormones leads to muscle wastage and negative nitrogen balance on its elimination in urine. Unchecked gluconeogenesis goes to liver and kidney and the carbon skeleton made available from the above is utilized for glucose formation in spite of persistent hyperglycemia.

## Insulin deficiency

In relative/ absolute insulin deficiency there is impairment of glucose uptake. Gluconeogenesis and glycogenolysis are stimulated to increase glucose uptake to tissues. Triglyceride oxidation is stimulated to release fatty acids and protein catabolism is stimulated to release amino acids.

Non-insulin Dependant

Diabetes mellitus (NIDDM)/

Maturity onset Diabetes mellitus/

**Type II Diabetes Mellitus**

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Normal fasting blood glucose 60-100mg%  
Renal threshold for glucose 160-200mg%

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Under 30 years of age  
Absolute insulin deficiency  
Acute onset  
Anti-receptor antibody  
? virus

#### **Dogs**

#### **1) Juvenile hypoplasia/aplasia of pancreatic islets**

Uncommonly reported

#### **2) 'Maturity onset'**

63% have circulating anti-islet cell antibody.  
Endogenous insulin levels are variable and responsive to exogenous insulin.  
Occasionally post pancreatitis is also documented.

#### **3) Secondary to other disorders**

Hyper adrenocorticism  
Progestagens

#### **Clinical Signs**

- Glycosuria
  - Osmotic diuresis
  - Compensatory polydipsia
  - Nocturia
  - Recurrent cystitis (increased frequency, straining)
  - Chronic obesity followed by rapid weight loss
  - Polyphagia
  - Hepatomegaly adding to abdominal distention
  - Abdominal discomfort or pain, non-specific skin or coat dullness, secondary infections and loss of condition
  - Bilateral cataract development
  - Vague lethargy
  - Panting excessively on exercise
  - Exercise intolerance
- If Diabetes mellitus is left untreated it may lead to Diabetic Ketacidosis (DKA). Classical signs of DKA are:
- Lethargy, listlessness, acute weight loss, and wasting
  - Intermittent and then persistent anorexia
  - Vomiting, loose feces, diarrhoea
  - Tachypnoea, hyperpnoea, panting
  - Rapid dehydration and collapse
  - Coma (death)
  - Ketone bodies demonstrable in urine, blood, tears and on breath by dip-stix/Rothera's test

? environmental pollutants

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Over 40 years of age  
Relative insulin deficiency with peripheral tissue resistance  
Insidious onset and has family tendency

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#### **Diagnosis**

Based on history, clinical signs and laboratory findings (glucosuria and hyperglycemia) and occurrence in middle aged or old females with no breed predilection. Overt diabetes is associated with oestrus and occasionally with pregnancy and lactation.

#### **Laboratory investigations**

Initially investigate blood and urine glucose and ketone body levels.

#### **a) Blood glucose**

Normally fasting blood glucose: 60-100mg% Renal plasma threshold: 160-200mg% Intravenous glucose tolerance test done in doubtful cases.  
Degree of intolerance expressed as T V2 or K values

#### **B) Ketone bodies**

Semiquantitative tests based on Rothera's false negative tests obtained, as hydroxy butyrate does not react positively.

#### **c) Urine glucose and ketone bodies**

Semi quantitative large amounts of ketone bodies inhibit reaction to glucose.

Other serum biochemical abnormalities expected in non-complicated Diabetes mellitus:

- Mild to moderate elevation ALT
- Moderate to high elevation SP
- Elevation of GGT, GFDH
- Elevation of cholesterol and triglycerides
- Haematology: Leucocytosis is common
- Differential diagnosis

Haematology: Leucocytosis is common

#### **Differential diagnosis**

i. Pyometra endometritis complex - abdominal enlargement, vaginal discharge but no fasting hyperglycemia.

ii. Cushing's Syndrome- Increased corticosteroid levels, lymphopenia and eosinopenia.

- iii. Diabetes insipidus- polyuria, polydipsia, low urine specific gravity, absence of glucosuria or hyperglycemia.
- iv. Chronic interstitial nephritis- normoglycemia maintained except in acute pancreatitis or neoplasia.

**Treatment**

**Options**

1. Exogenous insulin replacement therapy
2. Ovariohysterectomy (if performed promptly some bitches regain glycaemic control)
3. Diet (restricted carbohydrate, high fibre diet, little and often), occasionally provides adequate glycaemic control in mildly infected animals.
4. Oral hypoglycemia

Tried in presence of some functioning B cells in pancreas- inadequate if fasting blood glucose cannot be brought below 120mg%. Two types - Sulphonylureas (tolubutamide, Chlorpropamide) increase endogenous insulin secretion. 0.25 - 0.5 mg/Kg twice daily maximum 5mg/ day, Bignemides, increase peripheral uptake of glucose 250-50 mg twice daily (not advisable as hepatotoxic, and rarely work).

5. None / euthanasia

**Insulin Replacement therapy-Considerations**

Owners-motivation

- a. Time/ ability to stick to a routine
- b. Continuing financial burden

**Aim of insulin therapy**

A 24 hour insulin preparation is given S.c. once daily with 1/3 of the total daily food intake. The rest of the food is given at maximal insulin action (usually 7-8 hours after injection)

**Diet** - High quality tins at the rate of 28g Kg b.wt/ day. Add small amount of carbohydrate (e.g. 2 tablespoons whole wheat biscuit/bread)

**Exercise** - Exercise increases insulin 'efficiency' by presenting more to peripheral tissues, so increased exercise reduces requirements. It does not matter how much exercise a diabetic has to do as long as it is constant.

**Urine monitoring:** Monitor 24 hours after previous insulin injection. Aim to maintain at just around renal threshold (1/4, 1/2, 3/4% glycosuria).

**Injections:** Inject with breakfast as dog is eating. Syringes should be able to measure 1 unit accurately i.e. 0.01 ml increments.

0%                    1/4,1/2,3/4%    1%,2% or over  
Reduce            Give same    Increase

previous dose    dose            as yesterday's dose  
by 1 unit            previous day    by 1 unit  
Changes of only 1 unit avoids rapid changes in blood glucose.

**Choice of insulin preparations**

All preparations – 100 iu/ml (i.e. 1unit=0.01ml)

**1.Manufacturing-** Mono component insulins are manufactured by genetic manipulation of bacterial degradation products. It is very pure. Has allowed production of human insulin. Conventional insulins are prepared by purification of bovine or porcine pancreas. Inevitably contaminated with e.g. albumin, pro-insulin.

**2.Species of origin** - porcine, bovine, human. Porcine and bovine insulins are being phased out of manufacture. Canine insulin is identical to porcine insulin so theoretically this should be best.

**3.Length of action** - Soluble insulins are designed for i/v use. Act within 30 min and have short half-life. All the other preparations have been modified (linked to protamine, complexed with zinc, made into suspension) to delay absorption when given s/c and last between 12-36 hours.

**Complications**

- i. Inadequate stabilization and management results in hyperglycemia and ketacidosis.
- ii. Lactic acidotic coma- metabolic acidosis due to lactic acid accumulation.
- iii. Hypoglycemia: In young diabetics due to excess insulin therapy, irregular feeding or over exercise.
- iv. Insulin resistance: When insulin requirements is above 3.0 Lu/Kg/ day.

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