DIABETE MELLITO CANINO

Unità 3.0

CI Semeiotica e Patologia Medica Veterinaria, modulo di Patologia Medica AA 2017/18

INTRO

- Il Diabete Mellito canino è una malattia endocrina COMUNE nel cane
- Prevalenza del 1% nei centri di referenza (0,3%)
- Caratterizzata da IPERGLICEMIA PERSISTENTE (CRONICA)
- Risultanto di un deficit nella PRODUZIONE di insulina
- nella AZIONE dell'insulina

CLASSIFICAZIONE ED EZIOLOGIA

- Uomo: «Diabete giovanile» e «diabete senile»
- INSULINO-dipendente / NON insulino dipendente
- Tipo 1/ Tipo 2

- Cane: la forma più frequente è quella simile al Tipo 1 (uomo) (**ipo-insulinemia persistente**), necessità di insulina esogena

Untargeted metabolomic analysis in naturally occurring canine diabetes mellitus identifies similarities to human Type 1 Diabetes

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- **Istologia** Riduzione del numero e delle dimensioni delle isole di Langherans pancreatiche, del numero della beta-cellule, vacuolalizzazione, degenerazione delle stesse
- **Cause**: non ancora chiarite. Genetiche ed «ambientali» Uomo/cane/razze specifiche
- In Cani diabetici → associazione con MHC tipo 2, aplotipi/genotipi simili in molte razze «predisposte» → regioni VNTR (*variable number of tandem repeats*) e **polimorfismo** identificato nel gene-insulina canino : predisposizione o resistenza a DM

Deficit della produzione di insulina

- Perdita delle Beta-cellule (**idiopatica**)
- **Congenita** ipoplasia/atrofia delle beta cellule
- Perdita delle Beta cellule associate a **pancreatite/infiammazione**
- Esaurimento funzionale delle Beta cellule/ **glucosio tossicità-insulina resistenza**

Insulino - Resistenza

- Antagonismo all'azione insulinica da pare di altri ormone e spesso esarcerbato dalla presenza di infezione o infiammazione
- Diestro/gravidanza
- Malattie endocrine concomitanti (sindrome di Cushing, ipotiroidismo, acromegalia)
- Iatrogenica (glucocorticoidi, progestinici)
- Intolleranza ai carboidrati associata ad obesità
- Infezioni/Infiammazione
- Malattie concomitanti, CKD, malattie cardiache
- Iperlipidemia
- Deficit di recettori insulinici

- **Tipo I A** (immuno mediato) → infiltrazione linfocitica «insulite», presenza di autoanticorpi sierici diretti a componenti panceatici (insulina, **GAD 65** – decarbossilasi 65 acido glutamico intracellulare- IA2 – insulinoma antigen 2)
- Tipo I B (defincenza idiopatica)
- Cane?
- Autoanticorpi diretti alle isole pancreatiche, insulina, proinsulina, GAD65, IA2 …
- CANI di età adulta – anziana (?) → Latent Autoimmuny Diabetes in Adults (LADA)

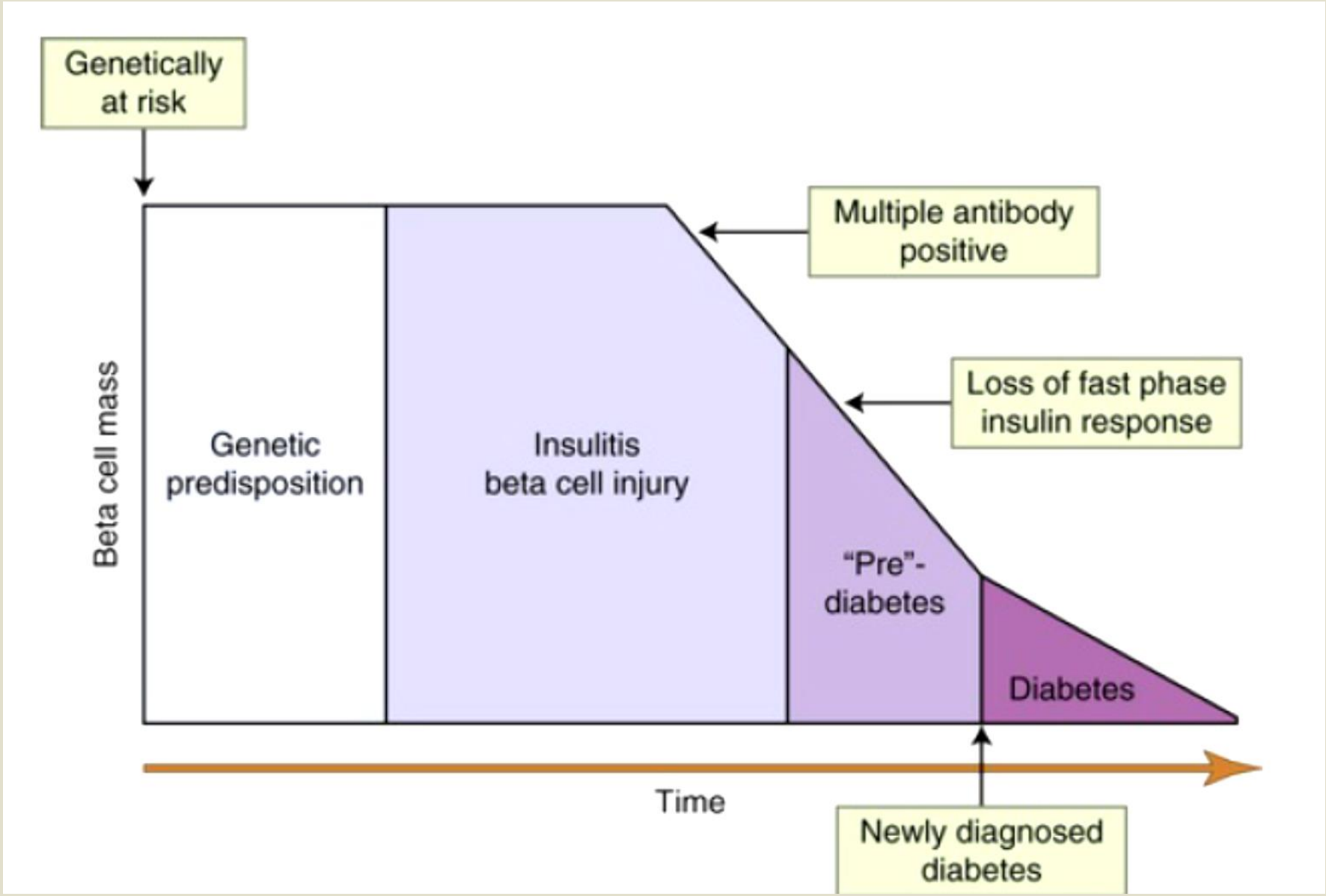
MODY Maturity Onset Diabetes of the Young (legato ad un gene autosomico dominante)

TIPI DI DIABETE

Caratteristiche chiave dei diversi tipi di diabete

	TIPO 1	TIPO 1.5 (LADA)	TIPO 2
Età di insorgenza	INFANZIA Età adulta	ETÀ ADULTA	ETÀ ADULTA
Progressione all'insulino-dipendenza	RAPIDA (gg/sett)	LATENTE (mesi/anni)	LENTA (anni)
Presenza di auto-anticorpi*	SI	SI	NO
Insulino-dipendenza	ALLA DIAGNOSI	ENTRO 6 ANNI	PROGRESSIVA (ANNI)
Insulino-resistenza	NO	ALCUNI CASI	SI

* Proteine che indicano che il corpo ha lanciato un attacco auto-immunitario alle cellule beta pancreatiche, responsabili della produzione dell'ormone insulina.


Genetically at risk
Multiple antibody positive
Loss of fast phase insulin response
Beta cell mass
Genetic predisposition
Insulitis beta cell injury
"Pre"-diabetes
Diabetes
Time
Newly diagnosed diabetes

Cause Secondarie di DM

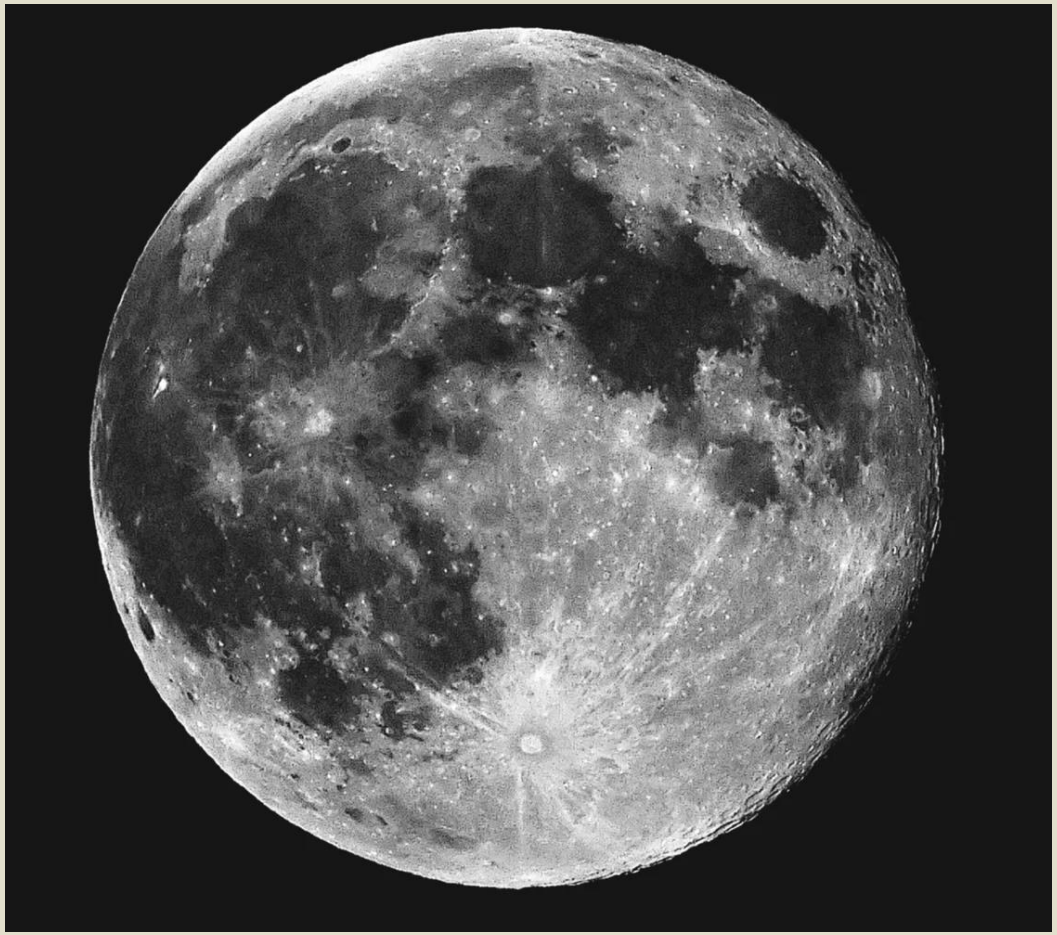
- Malattie pancreatiche → PANCREATITE (nei cani DM prevalenza AP 30% - 40% ! Ketoacidosi !)
- DM TRANSITORIO
- Sub-clinico…
- condizioni di **insulino-resistenza** (diestro, gravidanza), farmaci ad effetto anti-insulinico (glucocorticoidi), … malattie endocrine (iperadenocorticismo, ipotiroidismo canino, ipertiroidismo felino)

→ INFIAMMAZIONE- INFEZIONE SISTEMICA

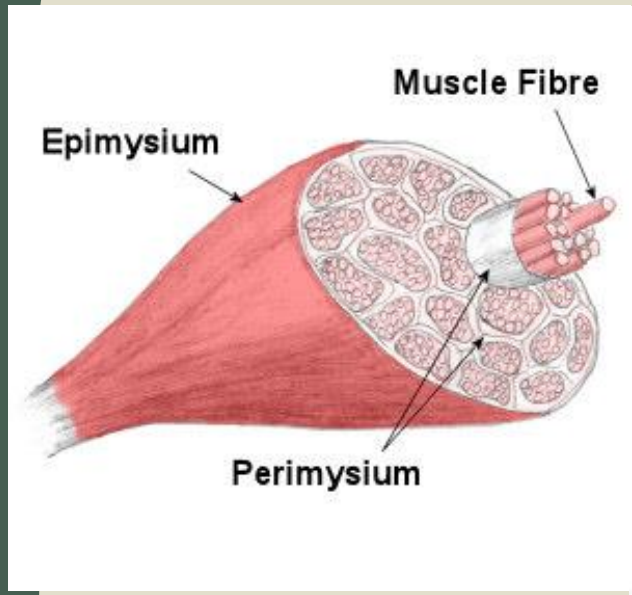
- Progesterone (GH simile)→ stimola la secrezione di GH dalle gh. Mammarie→ Diabete Diestrale,…fattori predisponenti, complicazioni

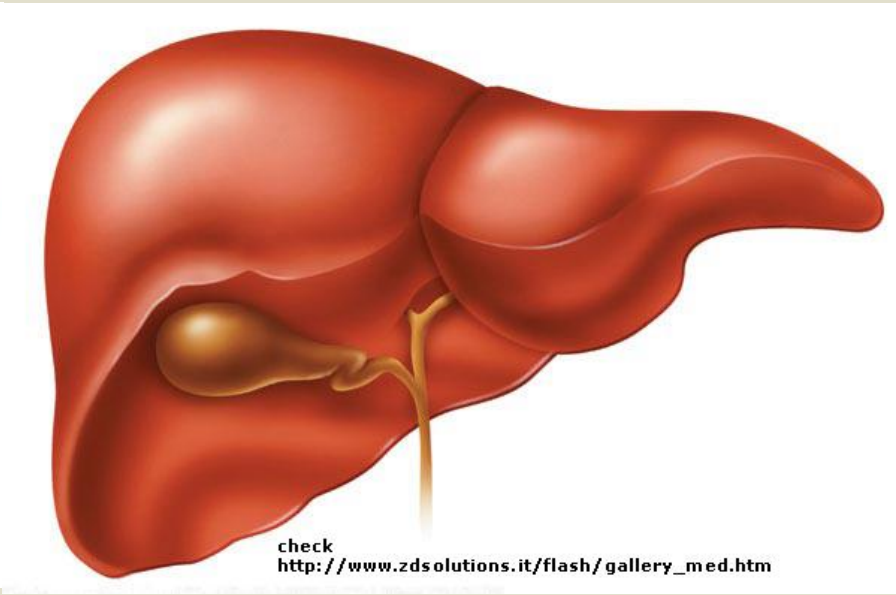
HONEY MOON

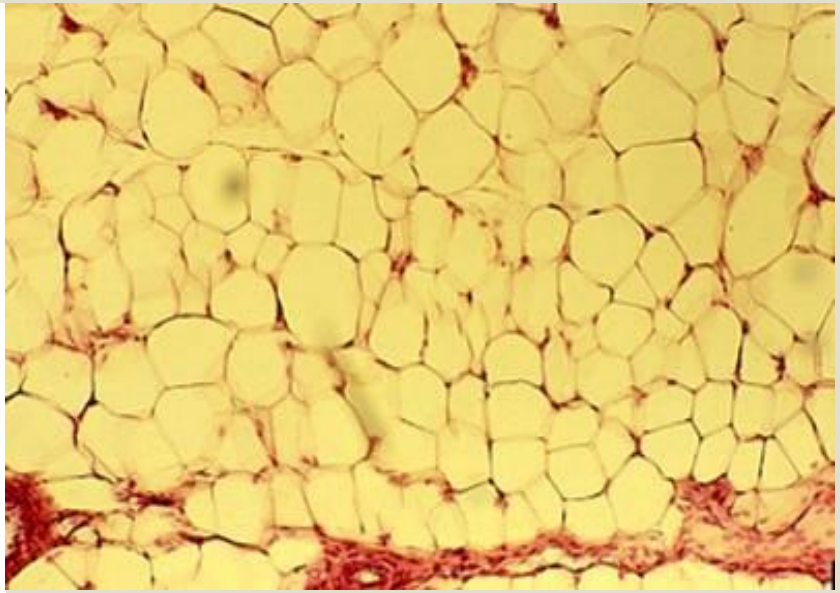
- Eccellente controllo glicemico a dosi di insulina esogena basse **(< 0,2 UI/Kg**, ad iniezione)
- Funzionalità residua delle Beta cellule
- ***Tipo 1***
- **Obesità/insulino resistenza** → *tipo 2*, nel cane la progressione in DM non è MAI stata dimostrata (al momento)



AZIONI DELL'INSULINA







+	Sintesi proteine Captazione glucosio Captazione potassio	Sintesi lipidi Sintesi proteine Sintesi glicogeno	Sintesi lipidi Captazione glucosio Captazione potassio
-	Degradazione proteine	Gluconeogenesi Chetogenesi	Degradazione lipidi

PATOGENESI

- Deficit di insulina

→Diminuito utilizzo di glucosio, aminoacidi, acidi grassi

→ aumento glicogenolisi, gluconeogenesi

→ IPERGLICEMIA

NON → assorbimento intestinale di glucosio, membrana – metabolismo degli eritrociti, reni e cervello

- Soglia renale di assorbimento (!) >180 mg/dL fino a 220mg/dL → GLICOSURIA
- POLIURIA … POLIDIPSIA
- bilancio energetico negativo → POLIFAGIA

- Metabolismo energetico NEGATIVO
- Metabolismo proteico: diminuzione della sintesi, aumento della proteolisi → aumento degli aminoacidi → aumento della gluconeogenesi (iperglicemia) → perdita di massa magra
- DIMAGRIMENTO
- **CATABOLISMO LIPIDICO**, mobilizzazione di trigliceridi e aumento di acidi grassi liberi nel plasma → fegato → beta ox. (ciclo di Krebs, ATP) → **Acetil CoA**: corpi chetonici
- **Chetoacidosi**
- **Iperlipidemia**
- **Lipidosi Epatica**

SEGNALAMENTO

- Età tra 5 e 12 anni
- Predisposizione genetica tra razze e diverse linee di sangue

BREEDS AT HIGH RISK	ODDS RATIO	BREEDS AT LOW RISK	ODDS RATIO
Australian Terrier	9.39	German Shepherd Dog	0.18
Standard Schnauzer	5.85	Collie	0.21
Miniature Schnauzer	5.10	Shetland Sheepdog	0.21
Bichon Frise	3.03	Golden Retriever	0.28
Spitz	2.90	Cocker Spaniel	0.35
Fox Terrier	2.68	Australian Shepherd	0.44
Miniature Poodle	2.49	Labrador Retriever	0.45
Samoyed	2.42	Doberman Pinscher	0.49
Cairn Terrier	2.26	Boston Terrier	0.51
Keeshond	2.23	Rottweiler	0.51
Maltese	1.79	Basset Hound	0.56
Toy Poodle	1.76	English Setter	0.60
Lhasa Apso	1.54	Beagle	0.64
Yorkshire Terrier	1.44	Irish Setter	0.67

ANAMNESI

- PU/PD/PoliFagia /Perdita di peso (insorgenza)
- Pancreatite, chetosi, lipidosi epatica (…) → diminuiscono l'appetito
- Cecità improvvisa
- Vomito, letargia, anoressia, debolezza (DKA)

ESAME CLINICO

- Segni clinici → dipendono dalla durata DM, presenza di patologie concomitanti
- Peso normale o sovrappeso → perdita di peso
- Buone condizioni cliniche → scadenti
- Cataratta, uveite, cherato-congiuntivite secca
- Segni neurologici (debolezza del arti posteriori, atassia, atteggiamento plantigrado)

DIAGNOSI

- IPERGLICEMIA (> 200mg/dL) persistente
- Glicosuria
- Segni corrispondenti (PU/PD)

- Iperglicemie >100 ng/dL - < 180mg/dL asintomatiche, senza glicosuria
- Stress inducente iperglicemia: non comune nel cane, (GATTO)
- Ketonuria/Ketonemia
- > 3.8 mmol/L → DKA (pH !)
- FRUTTOSAMINE
- Hb -glicata

CAUSE DI IPERGLICEMIA

Diabetes mellitus
Stress, aggression, excitement, nervousness, fright (quite uncommon)
Pancreatitis
Postprandial (diets containing monosaccharides, disaccharides, and propylene glycol)
Hormonal antagonism:

- Cushing's syndrome
- Diestrus
- Pheochromocytoma
- Acromegaly

Iatrogenic:

- Glucocorticoids
- Progestagens
- Thiazide diuretics
- Alpha 2-agonist sedatives
- Dextrose-containing fluids
- Parenteral nutrition solution

Head trauma

CAUSE DI GLICOSURIA

Diabetes mellitus

Renal tubular dysfunction:

- Fanconi syndrome
- Primary renal glycosuria
- Acute kidney injury (e.g., leptospirosis)
- Nephrotoxins

Iatrogenic:

- Dextrose-containing fluids

Causes of false positive glycosuria:

- Glucose in the owner's collecting jar for urine (e.g., jam jar)
- Vitamin C or pigment in urine can affect dipstick results

Gestione DM canino

- Diagnosi
- Valutazione ematobiochimico ed esame delle urine
- Esame ultrasonografico, Cpli
- Sospensione di farmaci «diabetogeni»
- Terapia insulinica
- Gestione terapeutica dei problemi concomitanti (iinfezioni)
- Dieta (!!!) e educazione alimentare (!!!)

Pasti regolari (correlati con insulina…) contenuto in fibra/calorie → BCS e peso ideale ! Dieta / malattie concomitanti (CKD, allergia alimentare !)

- Istruzioni per i proprietari (scritte)
- Sterilizzazione

ESAMI COLLATERALI

Complete Blood Count

1. Typically normal
2. Neutrophilic leukocytosis or toxic neutrophils may be observed if pancreatitis or infection is present

Biochemistry Panel

1. Hyperglycemia
2. Hypercholesterolemia
3. Hypertriglyceridemia (lipemia)
4. Increased alanine aminotransferase activity (typically <500 IU/L)
5. Increased alkaline phosphatase activity (typically <500 IU/L)

Urinalysis

1. Urine specific gravity typically >1.025
2. Glycosuria
3. Variable ketonuria
4. Proteinuria
5. Bacteriuria

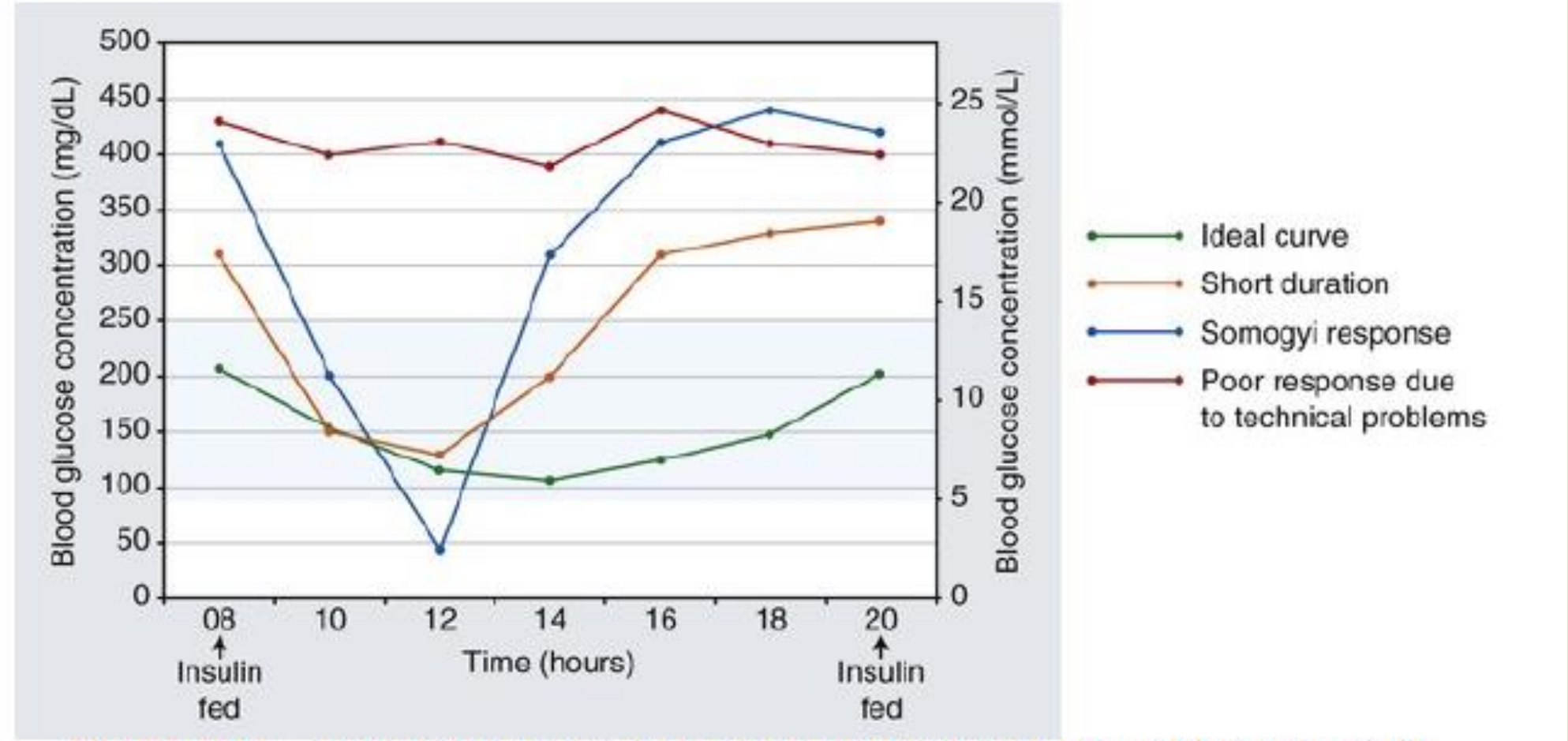
PIANO TERAPEUTICO

Successo terapeutico → completa fiducia da parte del proprietario !!!

- Risoluzione dei sintomi clinici, normalizzazione del peso corporeo
- Buon controllo glicemico: 120 mg/dL – 250 mg/dL
- Fruttosamine: 350 (320) – 450 micromol/L (meno importante nella valutazione del controllo metabolico)
- Emoglobina glicosilata
- Educazione del proprietario (!)

Controlli

- 1- 3 gg – controllo glicemia pre-post prandiale
- 1 settimana
- Curva glicemica: pre-post prandiale, ogni 2 -3 ore → variazioni individuali (comportamento del paziente, compliance del proprietario)
- Fruttosamine – aggiustamento dose insulina)
- Settima 2-3
- Controllo clinico, anamnestico, BGC, fruttosammine
- HM (home monitoring)
- Settimana 6-8 ; 10-12
- Dogni 2 – 4 mesi …



Sensibilità insulinica – glicemia - carboidrati
Insulino-resistenza

INSULINA

insulina	prodotti	origine	concentrazione	durata	Freq – dose iniziale
lenta	Caninsulin	porcina	40	8-14	12 q – 0,25
NPH	Humulin N Novolin N	Ricombinante umana	100	4-10	12q - 0,25
PZI	Prozinc	Ricombinante umana	40	10-16	12q -0,25-0,5
Glargina	Lantus	Ricombinante umana	100	8-16	12q – 0,3
Detemir	Levemir	Ricombinante umana	100	8-16	12q – 0,1

Traditionally available human insulin preparations

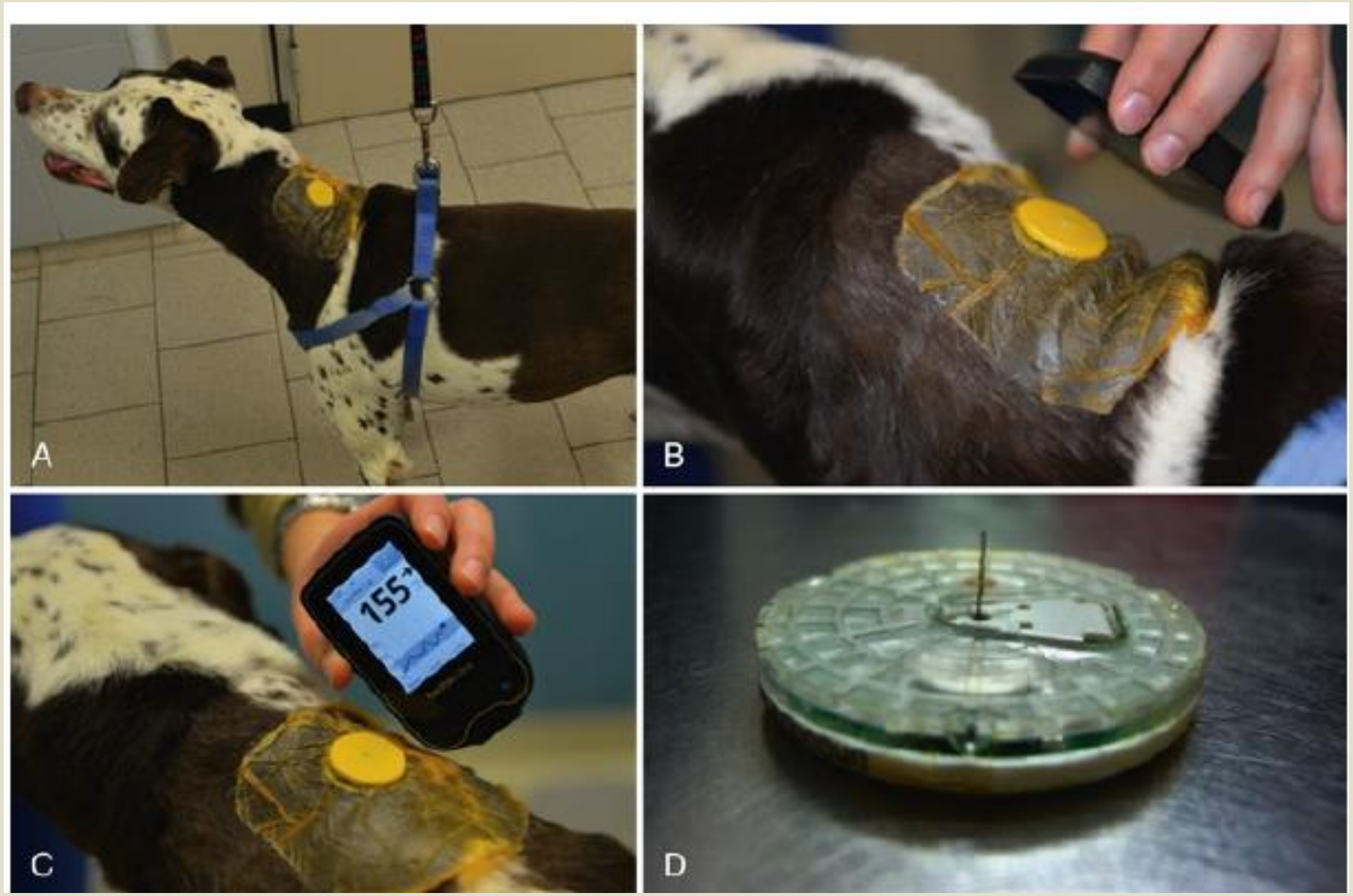
Regular insulin	100 (and 500**)	Humulin R	Eli Lilly	3 and 10	None
Regular insulin	100	ActRapid	Novo Nordisk	10	NovoPens including Junior/Demi[a]
Isophane (NPH) insulin	100	Humulin N	Eli Lilly	10	HumaPen Luxura incl. HD;[a] Humulin N Pen[b]
Isophane (NPH) insulin	100	Protaphane	Novo Nordisk	10	NovoPens incl. Junior/ Demi;[a] InnoLet;[a] NovoLet[b]
50% regular and 50% isophane (NPH)	100	Mixtard 50/50	Novo Nordisk	None	NovoPens including Junior/Demi;[a] InnoLet[a]
30% regular and 70% isophane (NPH)	100	Mixtard 30/70	Novo Nordisk	None	NovoPens including Junior/Demi;[a] InnoLet[a]
30% regular and 70% isophane (NPH)	100	Humulin 70/30	Eli Lilly	10	HumaPen Luxura incl. HD;[a] Humulin 70/30 Pen[b]

New human insulin preparations					
Insulin lispro	100	Humalog	Eli Lilly	3 and 10	Humapen Luxura including HD;[a] Autopen;[a] KwikPen[b]
Insulin aspart	100	NovoLog; NovoRapid	Novo Nordisk	10	NovoPens including Junior/Demi;[a] FlexPen[b]
Insulin glulisine	100	Apidra	Sanofi Aventis	10	OptiClik;[a] SolarStar[b]
50% lispro and 50% lispro protamine	100	Humalog Mix 50/50	Eli Lilly	10	HumaPen Luxura including HD;[a] KwikPen[b]
30% aspart and 70% aspart protamine	100	NovoLog Mix 70/30; NovoMix 30	Novo Nordisk	10	NovoPens including Junior/Demi;[a] FlexPen[b]
25% lispro and 75% lispro protamine	100	Humalog Mix 75/25	Eli Lilly	10	HumaPen Luxura including HD;[a] KwikPen[b]
Insulin glargine	100	Lantus	Sanofi Aventis	10	Autopen;[a] SolarStar[b]
Insulin detemir	100	Levemir	Novo Nordisk	10	NovoPens including Junior/Demi;[a] FlexPen[b]

INEFFICACIA DELLA TERAPIA INSULINICA

CAUSED BY INSULIN THERAPY	DISORDERS TYPICALLY CAUSING SEVERE INSULIN RESISTANCE	DISORDERS TYPICALLY CAUSING MILD OR FLUCTUATING INSULIN RESISTANCE
Inactive insulin Diluted insulin Improper administration technique Inadequate dose Somogyi response Inadequate frequency of insulin administration Impaired insulin absorption Insulin-binding antibodies	Cushing's syndrome Diestrus in intact female Progesterone secreting adrenocortical tumor Diabetogenic drugs GlucocorticoidsProgestagens	Obesity Infection Hypothyroidism Chronic inflammation Chronic pancreatitis Inflammatory bowel disease Disease of the oral cavity Chronic kidney disease Hepatobiliary disease Cardiac disease Hyperthyroidism Pancreatic exocrine insufficiency Hyperlipidemia Neoplasia Glucagonoma Pheochromocytoma

From Feldman EC, Nelson RW, Reusch C: *Canine and feline endocrinology*, ed 4, St Louis, 2015, Saunders.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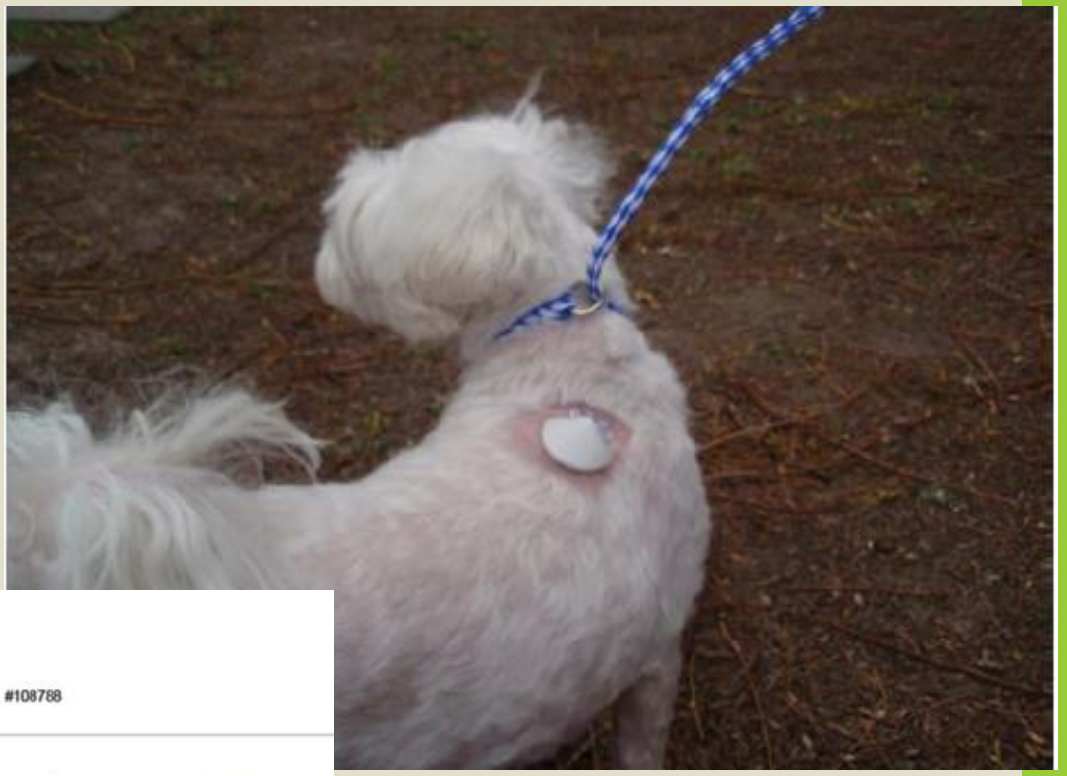


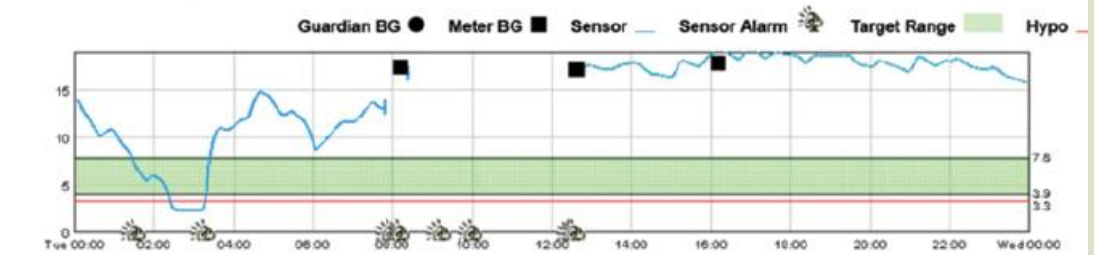
Medtronic

Daily Summary for Linda Fleeman
12/08/2008

HbA1c: No Data

Monitor: Guardian REAL-Time #108788
Sensor: In use

Glucose (mmol/L)



Insulin Injection Log

DIETA

- Appetibilità → garantire un consumo regolare
- Completa nei valori nutrizionali e costante nella composizione dei principi nutritivi / calorie → migliora la coerenza tra tipo di insulina, la richiesta insulinica, la risposta alla terapia.
- Ideale→ la condizione corporea ottimale, ed il suo mantenimento.
- Il Peso ideale.
- Insulina è un ormone anabolico. Diabetici trattati aumentano facilmente di peso.
- → In un soggetto diabetico e sotto terapia insulinica la perdita di peso è difficoltosa
- → Obesità/insulino-resistenza, diminuzione di peso- miglior controllo glicemico
- → Perdita di peso: aumento della fibra insolubile, low-fat e diminuzione della densità calorica

- Diverse tipologie dietetiche commerciali
- → iperglicemia post-prandiale: no zuccheri semplici
- Calorie derivate essenzialmente da carboidrati complessi (< 55% ss 39 r/d 48 HF Diabetic) e proteine (15 – 35% ss)
- Minime concentrazione in grassi (< 25% 9-12) → evitare l'aumento in circolo di colesterolo, trigliceridi, acidi grassi e glicerolo liberi (specie se iperlipidemia/pancreatite).
- Fibra solubile / insolubile (7 – 18% 3- 17) : regola glicemia post-prandiale e assorbimento intestinale- complicazioni legate al transito intestinale (aumento frequenza defecazione/costipazione o diminuzione della consistenza – flatulenza fibra solubile)
- Palatabilità/perdita di interesse (!!): aggiunta di carne macinata …
- Due pasti al giorno… 3 … ad libitum ?

ESERCIZIO

DIABETE MELLITO FELINO

Unità 3.1

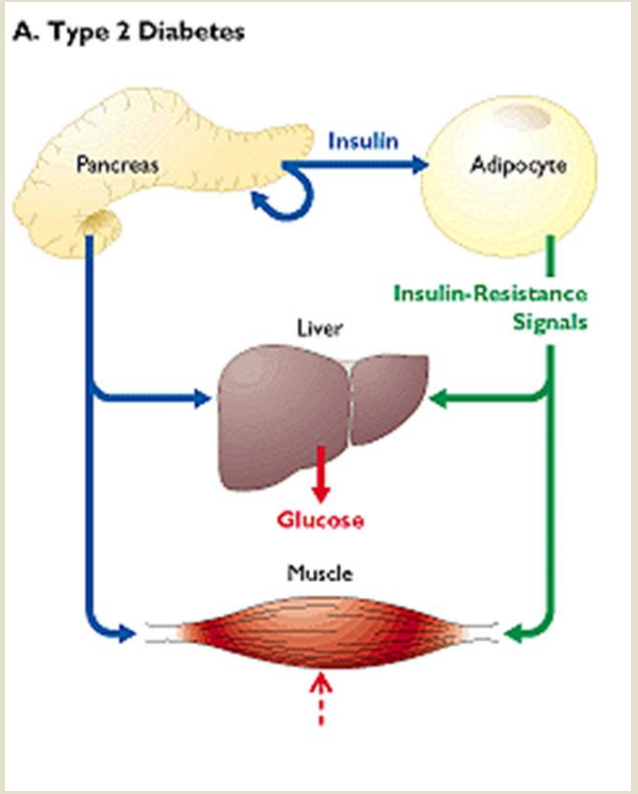
CI Semeiotica e Patologia Medica Veterinaria, modulo di Patologia Medica AA 2017/18

TIPO 2

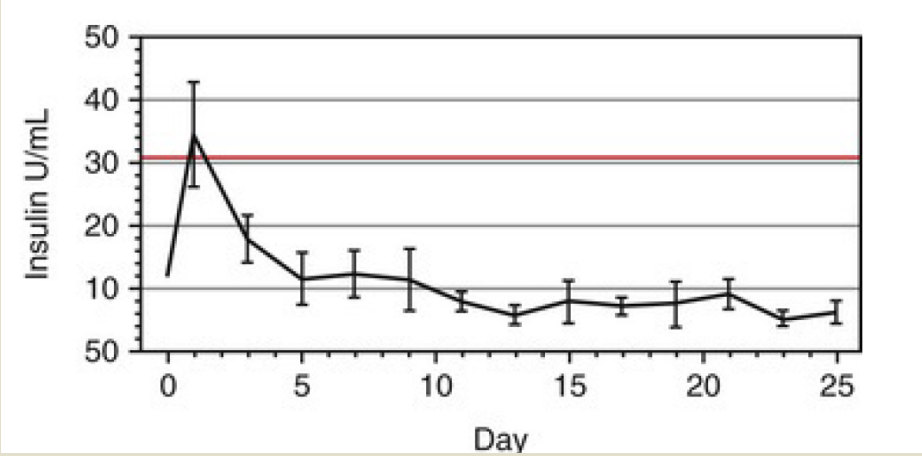
- Prevalenza del 0,25% - 1%
- 80 % «tipo 2»
- Distruzione per neoplasia, pancreatite (20%)
- acromegalia, iperadenocorticismo
- *Burmese, Russian Blu, Maincoon, Siamese…Europeo*
- *Età, genere (maschio:femmina =1,5)*
- Fattori genetici (polimorfismo *gene recettore melanocortino* 4 – Mc4r- legato al sovrappeso/**obesità**)-
- Fattori ambientali: età, genere, **obesità,** attività fisica-abitudini domestiche, trattamenti prolungati con farmaci diabetogeni

- Insulino resistenza: diminuzione della sensibilità insulinica
- **Sensibilità insulinica** = capacità di 1UI di insulina a diminuire la concentrazione di glucosio:
- obesità/inattività fisica
- glucocorticoidi/progestinici
- Gatto DM ha una riduzione in media di 6 x della sensibilità insulinica (produzione glucosio epatico/diminuzione dell'utilizzo periferico)

Soggetti magri che diventano obesi: aumento di ogni Kg p.c. / 30% diminuzione della sensibilità a insulina, aumento del 44% del peso → 50% dell'efficacia dell'insulina.



- Riduzione della secrezione insulinica→ processi associati a obesità e danno beta cellule (metabolismo glucosio, acidi grassi e amino acidi)
- Obesità/ DM tipo 2 → infiammazione cronica, aumento di citochine e infiltrazione di cellule immunitarie coinvolge il metabolismo energetico
- Beta cell-failure: diminuzione del gene espressione di insulina, incapacità di una risposta metabolica all'aumentare della richiesta.
- Glucosio tossicità: dose dipendente (540mg/dl in 3- 7 giorni, chetonemia in 10 – 30 giorni)

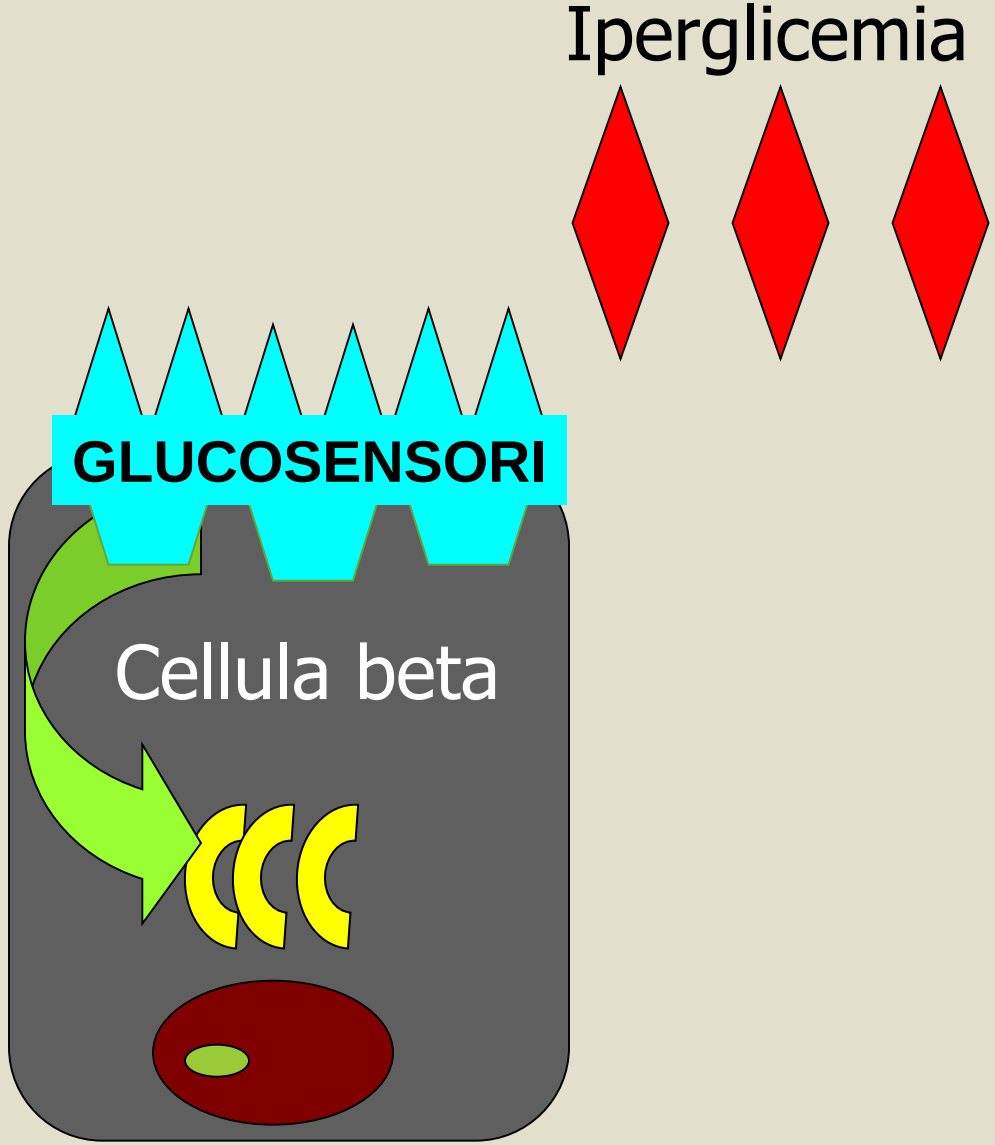


REGOLAZIONE SECREZIONE INSULINA

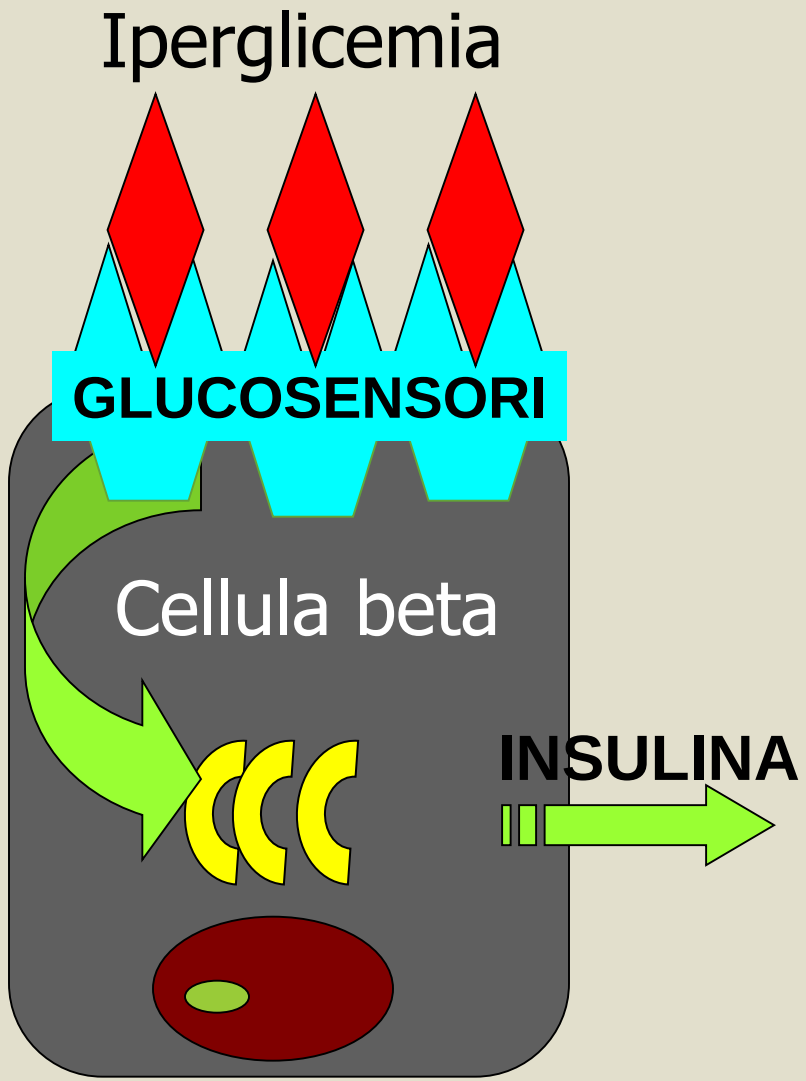
Valori normali
di glucosio ematico

NESSUNA SECREZIONE INSULINA

REGOLAZIONE SECREZIONE INSULINA



REGOLAZIONE SECREZIONE INSULINA



TOSSICITA' DEL GLUCOSIO

Accumulation of misfolded IAPP oligomers as aggregates and fibrils in beta-cells, and as amyloid within islets, leads to beta-cell death. Intracellular aggregation is particularly toxic and triggers apoptosis. It also contributes to islet inflammation by recruiting and activating macrophages and beta-cell production of chemokines and cytokines.

Generation of reactive oxygen species (ROS) secondary to nutrient overload. Chronic hyperglycemia increases glucose metabolism through oxidative phosphorylation, which induces mitochondrial dysfunction and production of ROS. ROS are also increased in chronic hyperlipidemia. Oxidative stress results in down-regulation of insulin and amylin production, and up-regulation of pro-inflammatory and apoptotic pathways.

Beta-cell endoplasmic reticulum (ER) stress occurs secondary to conditions that require prolonged high insulin production such as insulin resistance and high glucose concentrations, and with lipotoxicity and inflammatory conditions. ER stress results in reduced protein folding capacity of the ER, and accumulation and aggregation of unfolded proteins, including insulin. If the accumulation of unfolded protein is in excess of what can be managed by the unfolded protein response (UPR), it reduces insulin secretion and triggers apoptosis.

Increased glucose flux through the hexosamine biosynthetic pathway results in alteration in protein function, changes in gene expression, and decreased insulin secretion.

Exposure of beta-cells to overabundant supply of nutrients—glucose, free fatty acids and branched chain amino acids—associated with insulin resistance and obesity leads to beta-cell dysfunction and

Chronically increased glucose leads to **glucotoxicity**, which has a central role in beta-cell failure by decreasing both beta-cell function and mass.

Increased long chain free fatty acids (FFAs) and lipid intermediates associated with obesity lead to **lipotoxicity.**

Enhanced toxicity occurs when both glucose and free fatty acids are increased (glucolipotoxicity).

Increased branched-chain amino acids may have a role in beta-cell failure—for example, increased leucine results in decreased beta-cell function and insulin resistance.

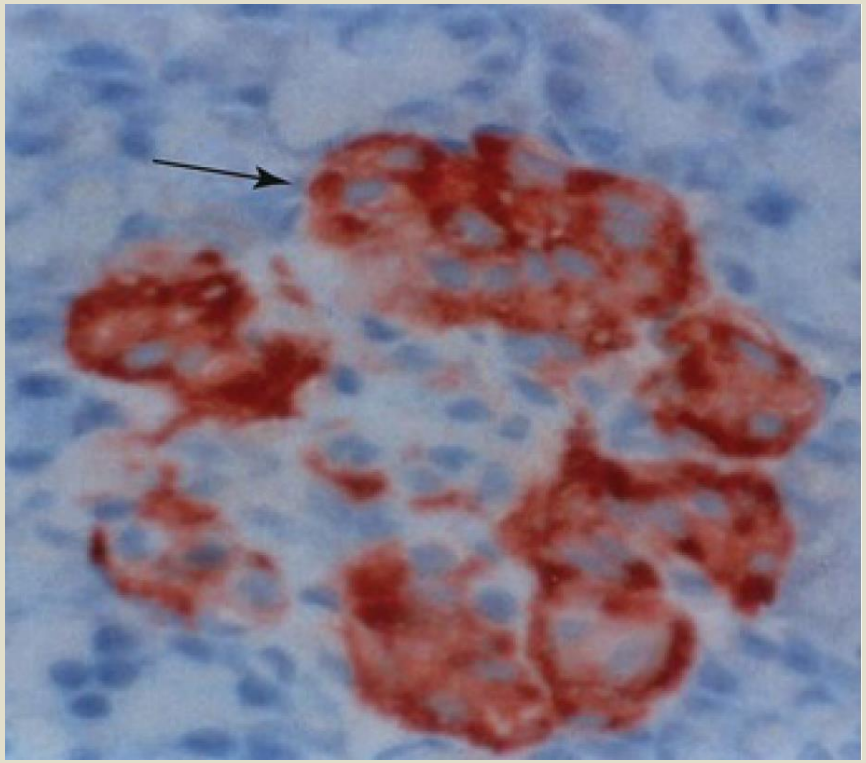
Advanced glycation end products (AGEs) form secondary to increased glucose concentrations and result in damage to tissues including beta-cells.

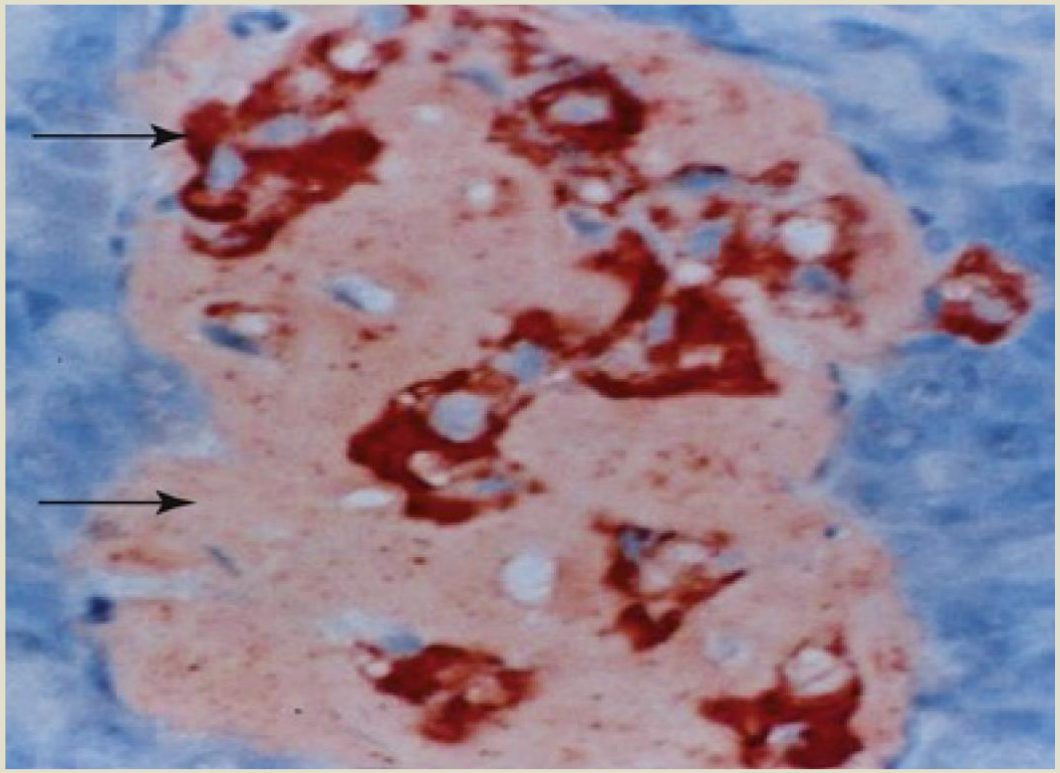
Inflammation is initiated when there is over-nutrition and obesity resulting in high concentrations of glucose, free fatty acid and branched chain amino acids, but the mechanism is not fully characterized. Beta-cell induction of proinflammatory cytokines and chemokines results in immune cell infiltration into islets, including macrophages. Islets respond to glucolipotoxicity by generating inflammatory factors such as IL-1 and IL-6. IL-1 release is stimulated by hyperglycemia and IL-1 blockade improves beta-cell function.

Beta-cell dedifferentiation: Beta-cells progressively lose beta-cell characteristics, which to a certain degree is reversible. Dedifferentiation is triggered by glucolipotoxic conditions, ER and oxidative stress, and inflammation, but the relative contribution to beta-cell dysfunction and loss in type 2 diabetes is unknown.

Beta-cell death through apoptosis, necrosis and autophagy (programmed cell death) is triggered by many of the mechanisms above.

AMILINA





Original article

MOLECULAR METABOLISM

Causality of small and large intestinal microbiota in weight regulation and insulin resistance

Torsten P.M. Scheithauer [1,2,3], Geesje M. Dallinga-Thie [1], Willem M. de Vos [4], Max Nieuwdorp [1,2,3,*,5], Daniël H. van Raalte [2,3]

Objective: The twin pandemics of obesity and Type 2 diabetes (T2D) are a global challenge for health care systems. Changes in the environment, behavior, diet, and lifestyle during the last decades are considered the major causes. A Western diet, which is rich in saturated fat and simple sugars, may lead to changes in gut microbial composition and physiology, which have recently been linked to the development of metabolic diseases.

Methods: We will discuss evidence that demonstrates the influence of the small and large intestinal microbiota on weight regulation and the development of insulin resistance, based on literature search.

Results: Altered large intestinal microbial composition may promote obesity by increasing energy harvest through specialized gut microbes. In both large and small intestine, microbial alterations may increase gut permeability that facilitates the translocation of whole bacteria or endotoxic bacterial components into metabolic active tissues. Moreover, changed microbial communities may affect the production of satiety-inducing signals. Finally, bacterial metabolic products, such as short chain fatty acids (SCFAs) and their relative ratios, may be causal in disturbed immune and metabolic signaling, notably in the small intestine where the surface is large. The function of these organs (adipose tissue, brain, liver, muscle, pancreas) may be disturbed by the induction of low-grade inflammation, contributing to insulin resistance.

Conclusions: Interventions aimed to restoring gut microbial homeostasis, such as ingestion of specific fibers or therapeutic microbes, are promising strategies to reduce insulin resistance and the related metabolic abnormalities in obesity, metabolic syndrome, and type 2 diabetes. This article is part of a special issue on microbiota.

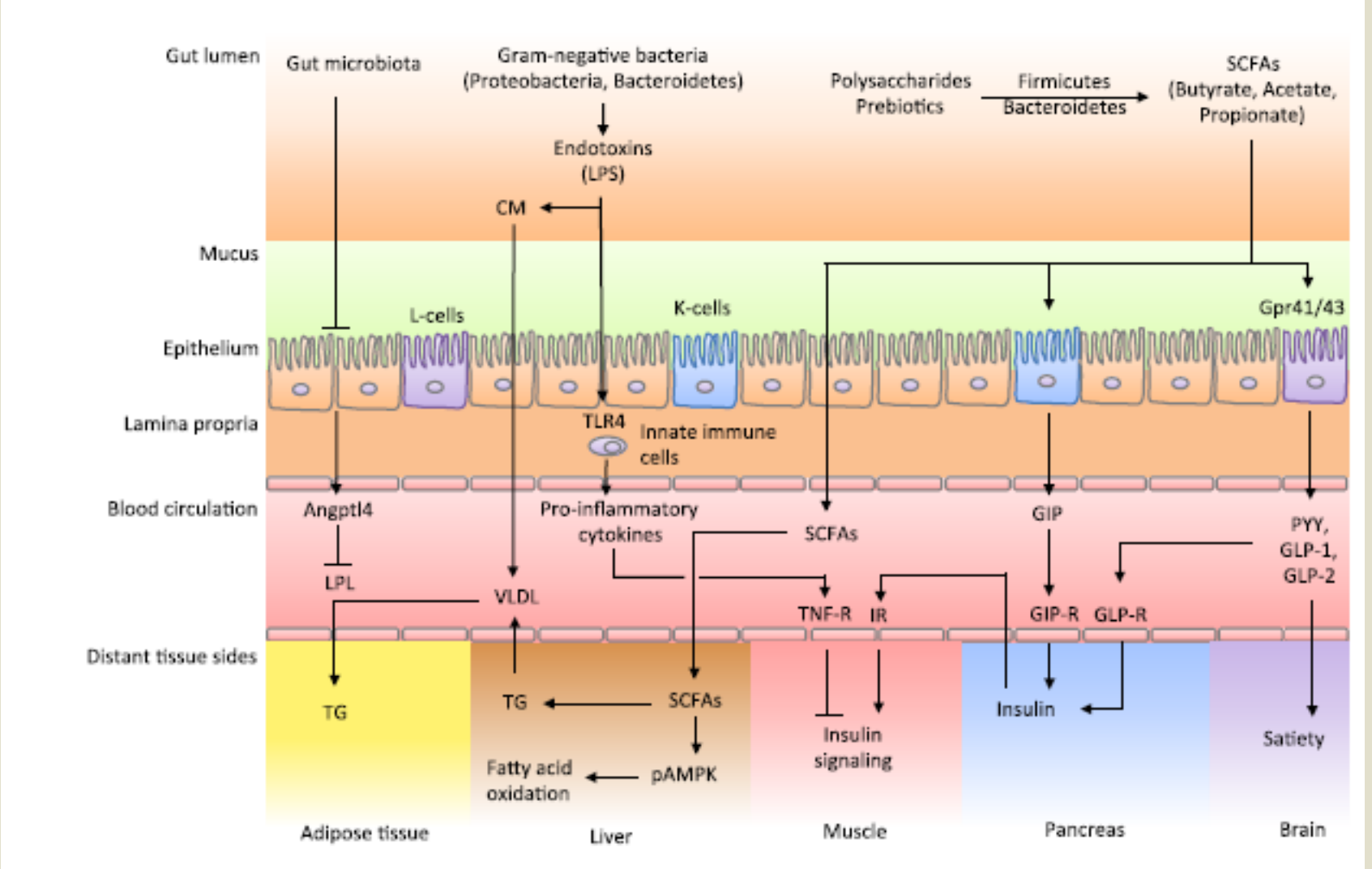


Figure 2: Involvement of the gut microbiota in weight regulation and insulin resistance. The gut microbiota is able to ferment polysaccharides into monosaccharides and short-chain-fatty-acids (SCFAs). These products are taken up by the epithelium and transported to the liver. An obese type of microbiota shows higher levels of Firmicutes than Bacteroidetes, which is associated with a higher SCFA production leading to more energy extraction from the diet. Further, the altered microbiota leads to a lower expression of Angiopoietin-like 4 (Angptl4), which inhibits Lipoprotein lipase (LPL) activity. This enzyme facilitates the hydrolysis of triglycerides (TG) in very low-density lipoprotein (VLDL) and chylomicrons resulting in the uptake of fatty acids in skeletal muscle, heart, and adipose tissue. An obese-type microbiota shows higher TG storage in adipocytes. Similarly, obese subjects show lower activities of phosphorylated adenosine monophosphate protein kinase (pAMPK), which is necessary for the activation of fatty acid oxidation. Lastly, an altered microbiota is associated with lower expression of satiety inducing gut hormones such as peptide YY (PYY), glucagon-like peptide (GLP) 1 and 2.

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Faecal Microbiota of Cats with Insulin-Treated Diabetes Mellitus

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- 30 gatti, 10 diabetici, 20 non-diabetici (10 gr. Controllo, 10 effetti della dieta)

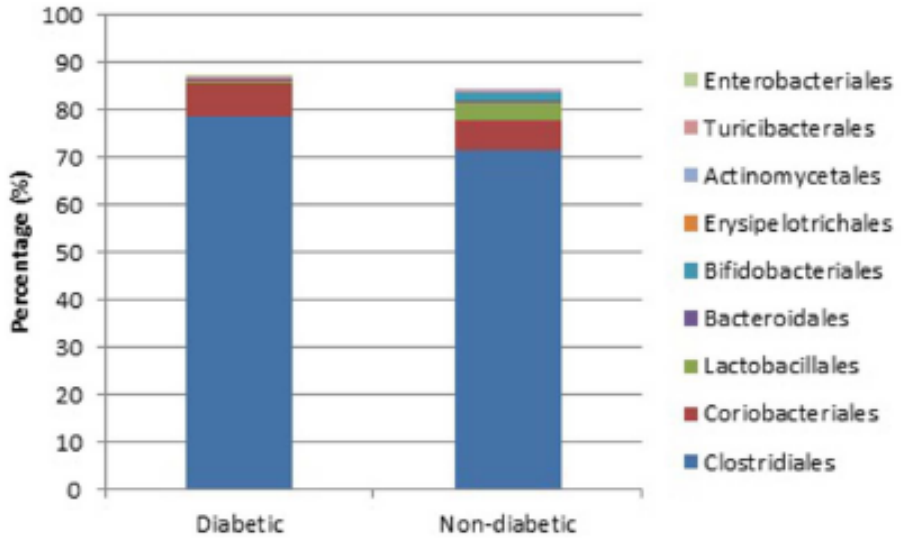
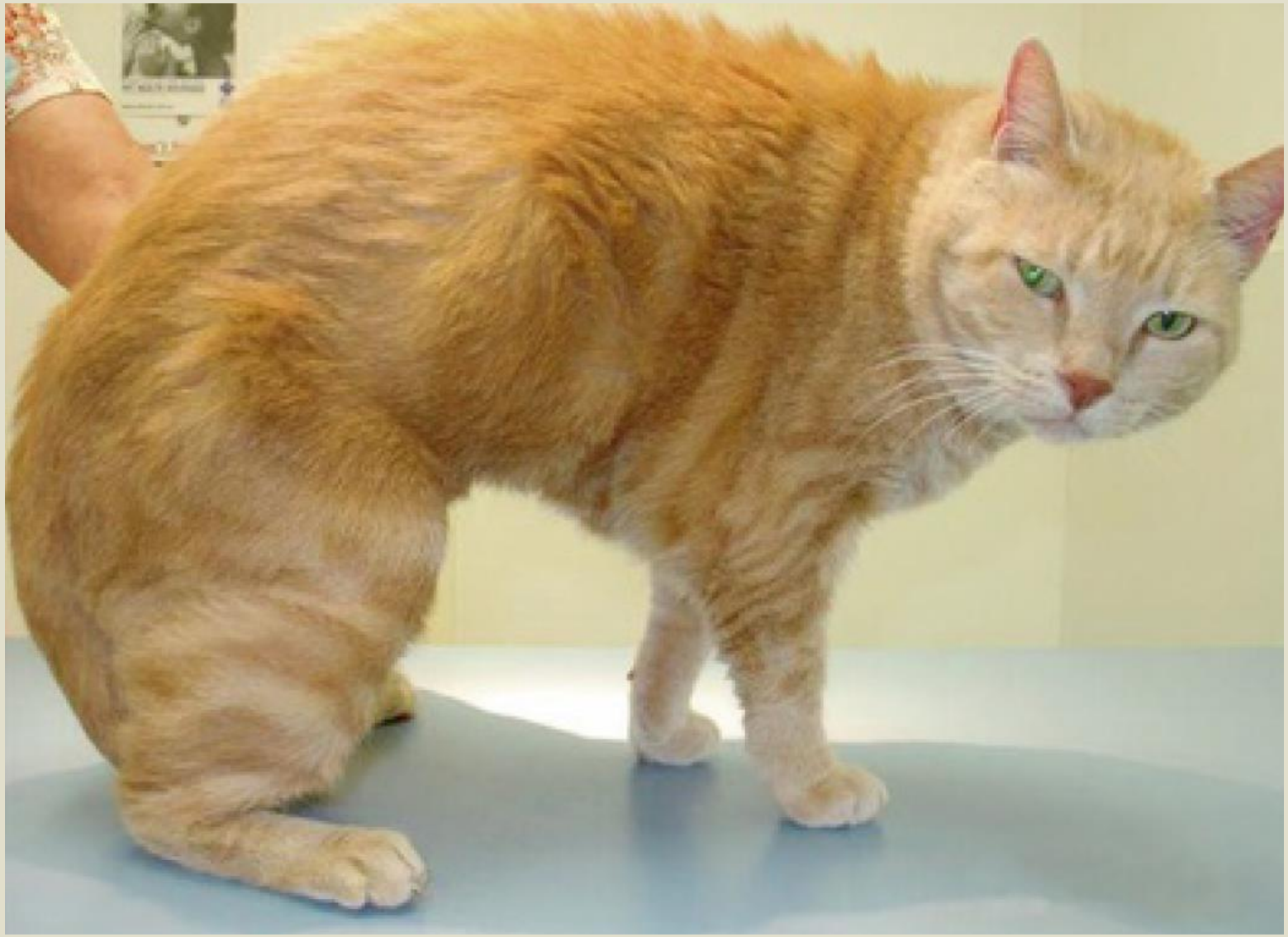


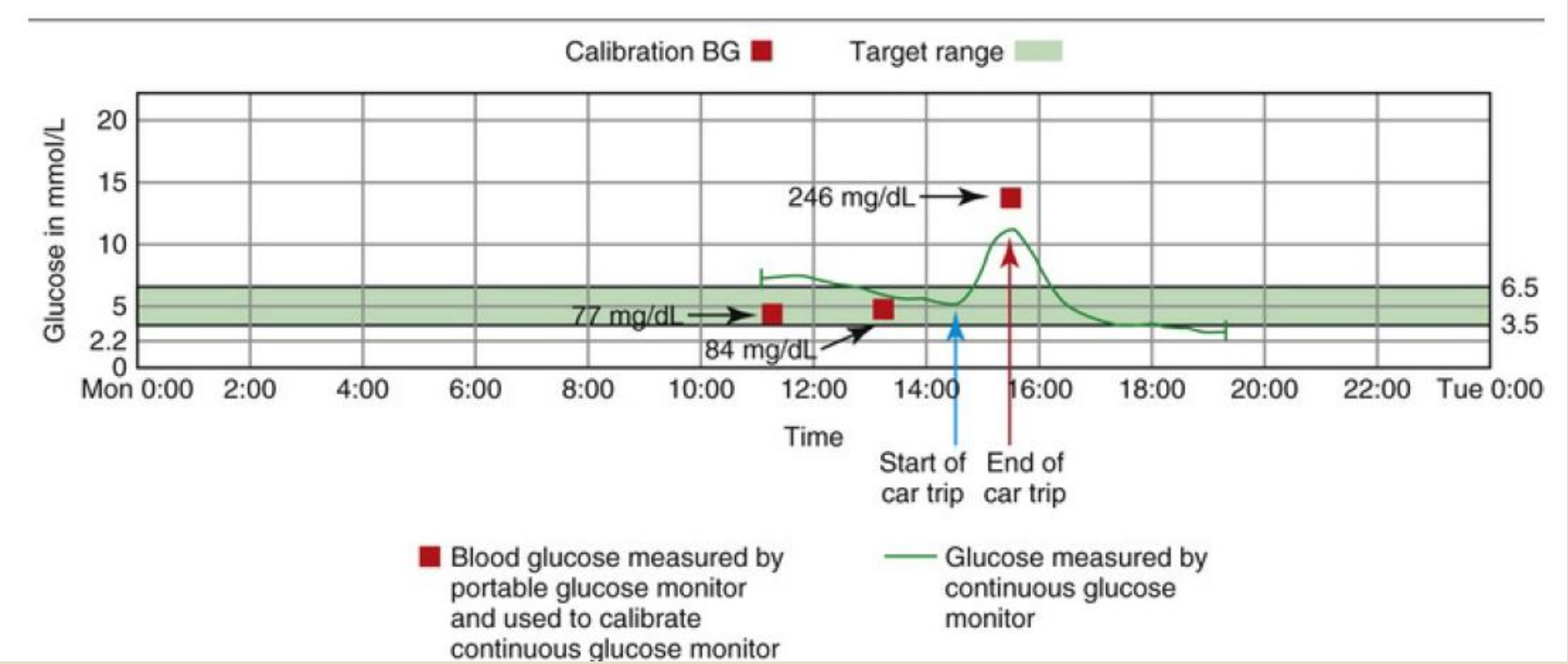
Figure 1. Median percentage of bacterial orders identified in diabetic and non-diabetic cats.
doi:10.1371/journal.pone.0108729.g001

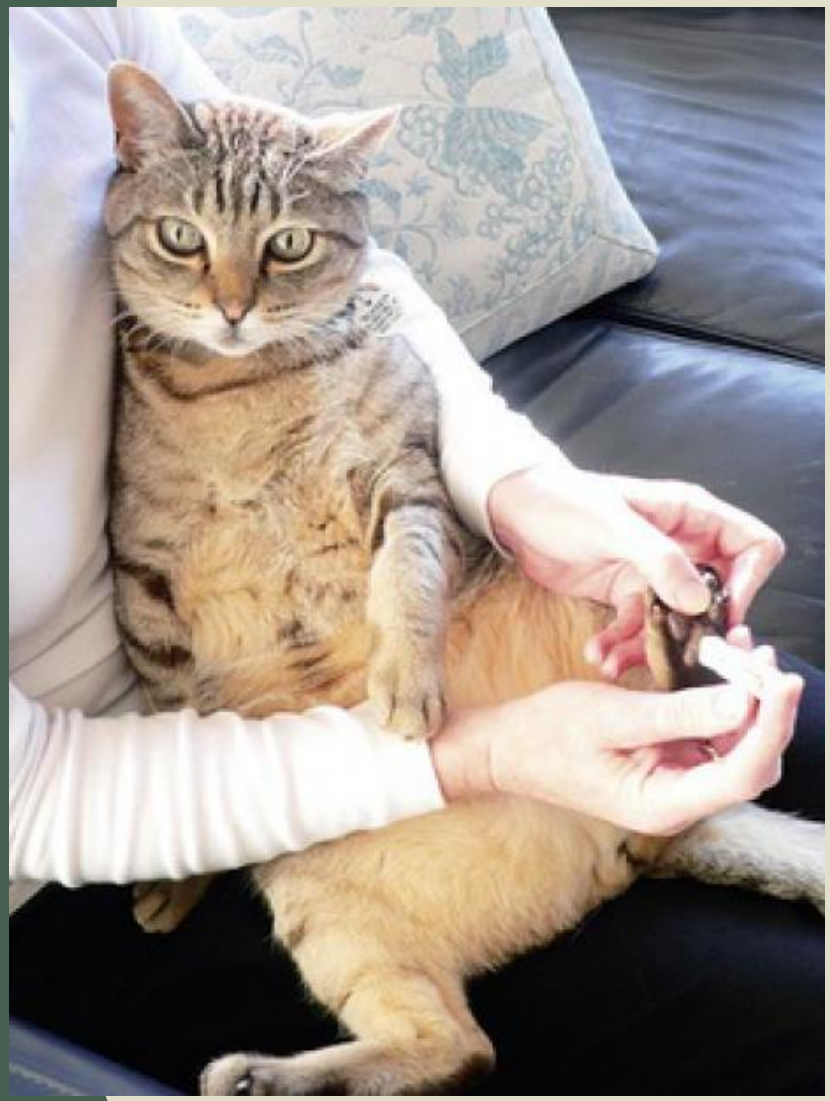
Table 5. Quantitative PCR evaluation of the faecal microbiota in diabetic versus non-diabetic cats.

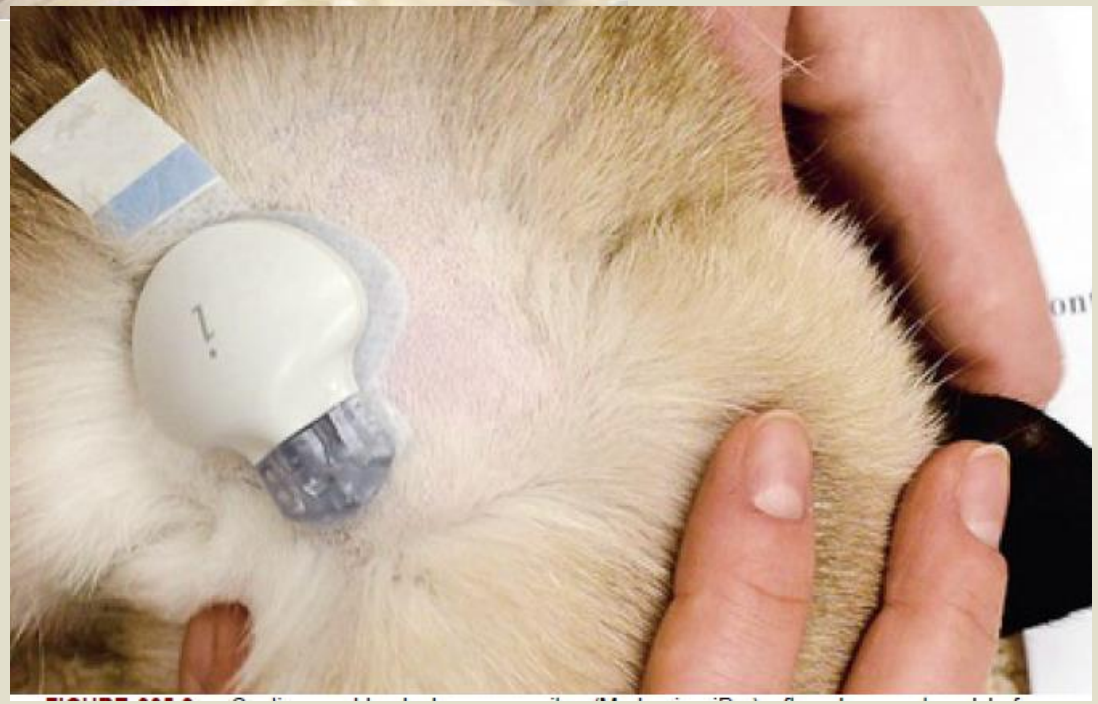
	Mean amount of bacteria		
	Diabetic cats	**Non-diabetic cats**	***P*-value**
All bacteria	11.86±0.10	11.79±0.23	0.443
Bifidobacterium	4.06±1.28	5.38±1.75	0.072
Faecalibacterium	5.33±1.17	6.04±0.69	0.118
Lactobacillus	4.14±0.55	4.33±0.73	0.517



STRESS/IPERGLICEMIA







OBIETTIVI TERAPEUTICI

- Controllo glicemico, più vicino possibile al range di normalità (70 mg/dL – 180 mg/dl)
- Remissione
- Dieta low carbohydrate (12% vs 26% di energia), stretto controllo glicemico, insulina long-acting «stabile» (0,4 UI/Kg – 0,7 UI Kg), glicemia media < 288 mg/dl. Lenta progressione della malattia (basso colesterolo, no neuropatia periferica, no complicazioni, età ?)
- Recidiva (6 - 9 mesi)

Glargine, Detemir or PZI Dosing Protocol, Monitoring Glucose Every 1-2 Weeks Using a Glucometer Calibrated for Cats (e.g., AlphaTRAK, Abbott Animal Health)

PARAMETER USED FOR DOSAGE ADJUSTMENT	CHANGE IN DOSAGE
Begin with 0.5 U/kg SC q 12 h if blood glucose >360 mg/dL (>20 mmol/L) or 0.25/kg SC q 12 h of ideal weight if blood glucose is lower Do not increase in first week unless minimal response to insulin occurs, but decrease if necessary. Monitor response to therapy for first 3 days. If no monitoring is occurring in first week, begin with 1 U/cat SC q 12 h	
If pre-insulin blood glucose concentration >216 mg/dL (>12 mmol/L) provided nadir is not in hypoglycemic range OR If nadir blood glucose concentration >180 mg/dL (>10 mmol/L)	Increase by 0.25-1 U depending on total insulin dose (greater or less than 3 U/cat) and degree of hyperglycemia (how close blood glucose is to 180 mg/dL [10 mmol/L])
If pre-insulin blood glucose concentration ≥180-≤216 mg/dL (≥10-≤12 mmol/L) OR Nadir blood glucose concentration is 90-160 mg/dL (5-9 mmol/L)	Same dosage
If nadir glucose concentration is 63-<72 mg/dL (3.5-<5 mmol/L)	Use nadir glucose, water drunk, urine glucose and next preinsulin glucose concentration to determine if insulin dosage is decreased or maintained
If pre-insulin blood glucose concentration <180 mg/dL (<10 mmol/L) OR If nadir blood glucose concentration <63 mg/dL (<3.5 mmol/L)	Reduce by 0.25-1 U depending on total insulin dose (greater or less than 3 U/cat) and degree of hyperglycemia (how close blood glucose is to 180 mg/dL [10 mmol/L]) If total dose is 0.5-1 U q 12 h, change to q 24 h If total dose is 0.5-1 U q 24 h, stop insulin and check for diabetic remission
If clinical signs of hypoglycemia are observed	Reduce by 50%

Glargine or Detemir Dosing Protocol and Intensive Home Blood Glucose Monitoring (Minimum 3 Measurements Per Day with Average of 5) during Stabilization Period (6-12 Weeks) Using a Plasma-Equivalent Meter Calibrated for Cats (e.g., AlphaTRAK from Abbott Animal Health)[94]

PARAMETER USED FOR DOSAGE ADJUSTMENT	CHANGE IN DOSAGE
Phase 1: Initial dosage and first 3 days on glargine.	
Begin with 0.25 U/kg of ideal weight SC q 12 h OR If the cat received another insulin previously, increase or reduce the starting dose, taking this information into account. Glargine has a lower potency than lente insulin or PZI in most cats.	
Cats with a history of developing ketones and blood glucose remains >300 mg/dL (>17 mmol/L) after 24-48 hours of beginning insulin	Increase by 0.5 U
If nadir blood glucose is <72 mg/dL (<4 mmol/L) and no clinical signs of hypoglycemia.	Reduce dose by 0.25-0.5 U depending on whether cat is on low or high dose of insulin (greater or less than 3 U/cat) and severity of hypoglycemia

Phase 2: Increasing the dosage.	
If nadir blood glucose concentration >300 mg/dL (>16.6 mmol/L)	Increase every 3 days by 0.5 U
If nadir blood glucose concentration 200-300 mg/dL (11.1-16.6 mmol/L)	Increase every 3 days by 0.25-0.5 U depending on whether cat is on low or high dose of insulin and severity of hyperglycemia
If nadir blood glucose concentration 117-<200 mg/dL (6.5-<11 mmol/L) and peak is >200 mg/dL (>11 mmol/L)	Increase every 5-7 days by 0.25-0.5 U depending on whether cat is on low or high dose of insulin, and severity of hyperglycemia
If nadir blood glucose is <63 or <72 mg/dL (<3.5 or <4 mmol/L)	Actual concentration used to decrease dose depends on frequency of monitoring and previous response to insulin dose changes when blood glucose is around the lower limit of the normal range. Reduce dose by 0.25-0.5 U depending on whether cat is on low or high dose of insulin. If clinical signs of hypoglycemia occur, reduce dose by 0.5 to >1 U depending on severity
If blood glucose at the time of the next insulin injection 72-117 mg/dL (4-6.5 mmol/L)	Initially test which of the alternate methods is best suited to the individual cat: a. Feed cat and reduce the dose by 0.25-0.5 U depending on whether cat is on low or high dose of insulin b. Feed the cat, wait 1-2 hours and when the glucose concentration increases to >117 mg/dL (>6.5 mmol/L) give the normal dose. If the glucose concentration does not increase within 1-2 hours, reduce the dose by 0.25 U or 0.5 U (as above). c. Split the dose: feed cat, and give most of dose immediately and then give the remainder 1 to 2 hours later, when the glucose concentration has increased to >117 mg/dL (>6.5 mmol/L) If all these methods lead to increased blood glucose concentrations, give the full dose if pre-insulin blood glucose concentration is 72-117 mg/dL (4-6.5 mmol/L) and observe closely for signs of hypoglycemia. In general for most cats, the best results in phase 2 occur when insulin is dosed as consistently as possible, giving the full normal dose at the regular injection time.
Phase 3: Holding the dosage. Aim to keep blood glucose concentration within 72-200 mg/dL (4-11 mmol/L) throughout the day.	
If nadir blood glucose is <63 or 70 mg/dL (<3.5 or 4 mmol/L)	Reduce dose by 0.25-0.5 U depending on whether the cat is on low or high dose of insulin
If nadir or peak blood glucose	Increase dose by 0.25-0.5 U depending on whether the cat is on low or high dose of

- Dieta e prevenzione
- Gatti sovrappeso → 4,6 volteil rischio DM
- Carboidrati / sensibilità e aumento della glicemia post prandiale/ insulina
- Picco glicemico 151 mg/dL (dieta 47% C ME 12,9 g/100 Kcal g), 115 mg/dL (dieta 46% proteine, 27% carboidrati 7,1 g/100Kcal)… trend simile per insulinemia
- Simile per diete high protein / high fat (27% ME dai carboidrati)
- Educazione alimentare. Ad libitum

- Riduzione della magnitudo e durata del picco post-prandiale, esacerbata dallo stato sovrappeso
- Gatti obesi con dieta mantenimento; picco medio/24 ore 119 ± 18 mg/dl (51% C, 14,5 ME/100Kcal), picco post prandiale 214 mg/dl
- High fat diet, sopra le richieste di mantenimento → obesità
- Vet wet (elevati grassi, bassi carboidrati) / dry food (elevati C, bassi fat) hanno rispettivamente 3 contro 2 volte il rischio di Dm rispeto una dieta low Carboidrate.