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Original Research Paper

PATHOPHYSIOLOGY OF DIABETES MELLITUS AND ITS RELATIONSHIP WITH OBESITY IN CATS

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Summary: Diabetes mellitus is one of the most common endocrinopathies in cats, and its incidence has increased in recent years associated with a significant increase in the percentage of obese cats. The main factors in the pathophysiology of this disease are the development of insulin resistance, dysfunction and / or loss of β cells, deficient secretion of insulin and islet amyloidosis (IA). Insulin sensitivity is significantly reduced in obese patients, therefore, several authors have tried to find linking factors between obesity and FDM. Among these, alterations in glucose transport, increase in triglycerides and fatty acids, deposits of amyloid in the islets and effect of hormones such as leptin and proinflammatory cytokines have been considered.

Key words: feline obesity; diabetes mellitus, feline adiponectin, feline leptin

Introduction

Diabetes mellitus is a disease of the endocrine pancreas characterized by a relative or absolute deficiency in insulin secretion. In the cat, unlike dogs, antibodies against β cells or insulin have not been detected yet; therefore it has been concluded that the autoimmune destruction, characteristic of diabetes mellitus type 1, does not seem to be a factor in the etiology of Feline Diabetes Mellitus (FDM) (1). Pathophisiology of FDM is similar to that seen in diabetes mellitus type 2 (DMT2) in humans. In both of them it is characterized by insulin resistance, deficient insulin secretion, deposit of amyloid in the islets and dysfunction and loss of β cells.

The incidence of DMT2 in the human population has increased in recent years, primarily associated with an increase in obesity and physical inactivity related to the sedentary lifestyle that man has taken. Metabolic diseases associated with obesity affect over 50% of the adult population (1, 2). This is a phenomenon that also affects felines who share the same environment as humans. Cats have evolved from animals that lived in open environments hunting foods high in protein, to a closed environment where they eat commercial foods high in carbohydrates and spend long periods of time sleeping (3). Approximately 25-40% of domestic cats are considered overweight and it has been found that obesity increases the risk of developing feline diabetes mellitus (FDM) from 3 to 5 times (4).

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Pancreatic Physiology

Pancreatic β cells, which represent approximately 70% of pancreatic endocrine cell population, secrete insulin in response to a influx of glucose through glucose transporters (5).

Insulin binds to its receptors, leading to the phosphorilation of tyrosine residues, thus initiating the signal pathways to perform its action. These receptors are glycoprotein molecules that can be found in various tissues, but in greater proportion in adipose tissue, muscle, heart and liver. Since the lipid bilayer of the cell membrane is impermeable

to glucose,it needs a system of active transport of carbohydrates to get through it. The GLUT4 is the major glucose transporter which responds to insulin. It is mainly located in muscle and adipocytes, and has a great significance in maintaining glucose homeostasis (6). In the absence of insulin or other stimuli, 90% of GLUT4 is retained in intracellular vesicles of deposit; on the contrary, in the presence of stimuli, these vesicles translocate and merge with the cell membrane. This process results in the incorporation of the GLUT4 to the cell membrane and the consequent passive entry of glucose. The cells containing the GLUT4 transporter are also stimulated by physical activity, independently of insulin action (5). In the liver, glucose diffuses freely even in the absence of insulin. The main effects of insulin on the liver are getting glucose trapped inside the liver cells, increasing the enzymatic activity that promotes lypogenesis and glycogenesis, and inhibiting the enzymatic activity that contributes to the processes of gluconeogenesis and glucogenolysis. Other effects of insulin are promoting the entry of amino acids, potassium, magnesium and phosphorus into cells. It also promotes fat storage by stimulating the activity of lipoprotein lipase and the entry of free fatty acids into the adipocyte.

Pathophysiology of Feline Diabetes Mellitus (FDM):

The FDM can be immune mediated (rarely diagnosed) (type 1), or be associated with obesity (type 2), or diseases and drugs that increase insulin resistance such as acromegaly, hyperadrenocorticism, pancreatitis and treatment with corticosteroids or progestagens (type 3). Its development also depends on factors such as age, body weight, sex, genetic predisposition and many others (7, 8). Comparing the clinical behavior and histopathology of the islets, it can be assumed that between 85 and 95% of cats with FDM have DMT2 (9, 10).

Insulin resistance and dysfunction and loss of β cells, is critical for the development of the FDM. Insulin resistance is a pathological condition where the biological response to insulin is diminished, affecting the entry and utilization of glucose by the peripheral tissues, thus leading to compensatory hyperinsulinemia. Insulin resistance also promotes a shift from glycolysis to gluconeogenesis in the liver cells, increasing this way plasmatic glucose levels. Pancreatic β cells eventually fail to compensate the insulin-resistant status, leading to relative insulin deficiency and consequent hyperglycaemia, glucose intolerance and at last, diabetes (7). When glycaemia exceeds the capacity of the renal tubules to reabsorb glucose, the consequent glucosuria determines osmotic diuresis and polyuria. Then compensatory polydipsia prevents dehydration. Hence the presentation of the classic signs: polydipsia and polyuria. The effects of hyperglycaemia can be divided into three phases: insulin resistance, depletion of β cells and glucose toxicity. Initially, exposure to high glucose levels leads to a potentially reversible decrease in insulin production. More prolonged exposure causes depletion of β cells, so that insulin stores are depleted. However, it is a reversible process since there are no alterations in insulin synthesis. Glucose toxicity is an irreversible status, since the cellular defects impair insulin production. The severity of glucose toxicity depends on the degree of hyperglycaemia; insulin secretion can be supressed after two days of persistent hyperglycaemia. The histologic abnormalities associated with glucose toxicity include glycogen deposits and cell death (5,7). A significant number of diabetic cats require insulin therapy to regulate glucose levels. However, it has been shown that between 30 and 85% of diabetic cats do not become insulin-dependent after an initial period of insulin therapy and adequate diet (5). The difference between cats that require or do not require insulin is not clear, although it seems that the degree of loss of β cells and insulin, play an important role.

The presence of islet amyloidosis (IA) and partial loss of β cells are important factors in the pathogenesis of DMT2 and FDM (7, 11). Islet amyloidosis is the result of a deposit of amyloid polypeptide derived from the islets (IAPP), which is co-secreted with insulin by pancreatic β cells. IAPP and insulin are co-regulated, and the production and secretion of both of them are upregulated by insulin resistance (7). IA in the FDM is associated with a loss of approximately 50% of β cells, whereas non-diabetic cats presenting IA show a lower degree of cell loss (7,10,12). It has been proposed that fibrillar forms of IAPP are cytotoxic and can trigger apoptosis, creating a potential link between the IA and the progressive loss of β cells in FDM and DMT2 (7,11).

Obesity and feline Diabetes Mellitus

The regulation of glucose metabolism in specific tissues such as muscle and adipose tissue has been identified as an important factor in insulin sensitiv-

ity. It is also known that the entry of glucose into the tissues is impaired by obesity causing insulin resistance (13,14). Obesity is associated with reversible insulin resistance. It produces changes in insulin secretion and also affects its action, either by alterations in insulin receptor or by post-receptor defects (15,16). The pattern of fat accumulation in obese individuals also affects the severity of insulin resistance. In humans, abdominal obesity is more associated with insulin resistance and risk of developing diabetes than peripheral obesity. Interestingly, the Burmese cat develops an accumulation of abdominal fat, unlike the domestic cat which presents accumulation of fat in the subcutaneous inguinal area (10). Despite these findings, in a study performed by nuclear magnetic resonance imaging it was found that obese cats presented abdominal fat equally distributed subcutaneously and intra-abdominally, suggesting that both may be involved in determining insulin sensitivity (17). In obese cats, the first phase of insulin secretion is significantly reduced or absent, while the second phase is increased compared to animals in their optimal weight (5,11,15).

A study in 34 obese and 14 cats with optimal weight showed that on average all obese cats presented glucose intolerance and abnormal insulin secretion after a high dose of glucose (1g/Kg of body weight). Furthermore, the obese group showed higher basal glucose levels compared to lean animals, although they remained within the normal range of plasmatic glucose (8).

It has been found that cats with diabetes are 6 times less sensitive to insulin than healthy cats (5,7,12). In a study where normal weight cats were allowed to reach obesity, it was observed a 52% decrease in peripheral insulin sensitivity. After losing weight the cats improved glucose tolerance. Other studies showed that cats with normal weight and normal glucose tolerance but with lower insulin sensitivity than the average population, increased 3 times the risk of developing glucose intolerance when gaining weight (3,5,18). This might suggest that there is a genetic predisposition to low insulin sensitivity, as demonstrated in the Burmese breed that in addition to other environmental factors (in this case obesity) leads to glucose intolerance. Other authors found that an increase in 1kg of body weight is associated with approximately a 30% of loss in insulin sensitivity and glucose effectiveness (17), concluding that body weight is an important factor in changes in insulin sensitivity. There are different theories that try to explain why obesity affects insulin secretion and which would be the factors that lead obese cats to reach the diabetic status. One hypothesis is that the hyperstimulation of β cells in the insulin-resistant status caused by obesity, promotes the development of IA, which would replace the functional β cells (19, 20). This way cats would loose the ability to control insulin resistance with compensatory hyperinsulinemia. In human it has been proposed that free fatty acids (FFA) play an important role in the impairment of β cell function (21,22); thus several studies have been performed trying to find the mechanisms by wich lipotoxicity could be involved (23,24). However, it has been concluded that the effects of FFA are influenced by concomitant glucose concentration and therefore, elevated FFA associated with normal glucose concentrations should not harm β cell (25, 26).

Cats that have been obese for a long period of time present dyslipidemia characterized by hypertriglyceridaemia associated with an increase in the very low density lipoprotein fraction (VLDL) and increases in plasmatic non-esterified fatty acids (27,28). Hoening (2002) (8) has proposed that non esterified fatty acids might be involved in defective insulin secretion in cats. Despite this study, it remains uncertain if lipotoxicity can harm β cell function in cats or if this effect is concomitant with hyperglycaemia, like in human. In a recent study the expression of glucose transporters GLUT1 and GLUT4 in muscle and adipose tissue in obese and normal weight cats was evaluated. Each animal was examined at the begining of the study (when they were lean) and after a period of 6 months, being fed ad libitum. The authors found that after weight gain GLUT1 expression was not affected, whereas GLUT4 expression decreased significantly in both muscle and adipose tissue (Figure 1) (6). This confirms that obesity affects insulin action by alterations in GLUT4 and supports the hypothesis that insulin resistance in obese cats is, at least in part, determined by a significant decrease in glucose transporters. The authors also noticed that this defect occurs even before the patients present glucose intolerance. Obesity and insulin resistance also have been related to alterations in adipokines and hormones, including leptin and adiponectin. Leptin is an important regulator of body fat. It decreases food intake, increases energy expenditure, stimulates lipolysis and inhibits lipogenesis (29,30). High leptin levels are most commonly associated with insensitivity of the leptin receptor and peripheral resistance (30). Deficiency and / or

leptin resistance in mice leads to polyphagia and decreased energy expenditure, therefore promoting obesity and insulin resistance (30). It has been postulated that there is an increase of 3 times in plasmatic leptin concentration as result of weight gain in cats (3). Furthermore, it has been found that leptin concentrations are significantly higher in obese cats than in lean ones; and that it decreases with weight loss (17).However, one study showed that in both obese cats and those with normal weight, high leptin levels were related to insulin resistance, independently of the degree of adiposity (3,31).

Adiponectin is synthesized exclusively by adipocytes both in human and cats (32,33). This citokyne enhances insulin sensitivity through different mechanisms, such as activation of AMP-activated protein kinase (AMPK) (34) and inhibition of essential gluconeogenesis enzymes (35). In addition, it increases fatty acid oxidation in skeletal muscle and liver (33, 35). Adiponectin is decreased in obese human and is associated with reduced ability of insulin to induce phosphorylation of tyrosine residues of its receptor, leading to insulin resistance (35,36,37). Recently, it has been found that plasmatic adiponectin concentration is significantly decreased in obese cats compared to normal weight cats (Figure 2) (32). This suggests that hipoadiponectinemia might be related to pathophysiology of insulin resistance and diabetes mellitus in obese cats, just like human. Hiperglucagonemia has been well studied in obesity and DBT2 and it is thought to be secondary to a reduction in insulin action in α cells. Glucagon concentrations are significantly increased in obese cats, and might be important in the progression from obesity to diabetes, since glucagon increases insulin resistance and can exacerbate the depletion of β cells (8). Finally, another factor to consider is the intolerance to carbohydrates in felines. High carbohydrate diets decrease insulin sensitivity and cause hyperinsulinemia compared to high protein diets (8). It has been suggested that cats, being strict carnivores adapted to diets high in protein and low in fat and carbohydrates, are inherently less sensitive to insulin and less able to handle high doses of carbohydrates than omnivorous species. It has been found that cats fed with commercial diets high in carbohydrates develop chronic hyperinsulinemia, increased demand of insulin and progressive destruction of the islets (15). On the other hand, it appears that diets high in protein decrease the required dose of insulin in diabetic cats (5,15). As it can be seen, there are several factors that have proved to be important in the development of diabetes mellitus in obese cats. However it remains to investigate in more depht the pathogenesis of insulin resistance and FDM in order to carry out new treatments and preventive options.

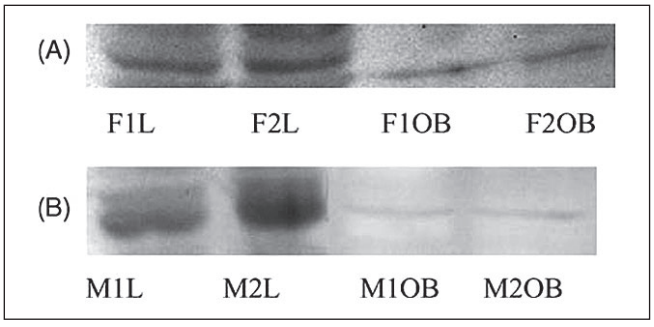

Figure 1: Representative Western blot picture of GLUT4 protein expression in fat (F; part A) and in muscle (M; part B) in a cat before (L) and after (Ob) a 6-month period of ad libitum food intake. (Taken from Brennan et al, 2004. Permission obtained from Dom Anim Endocr, Elsevier)

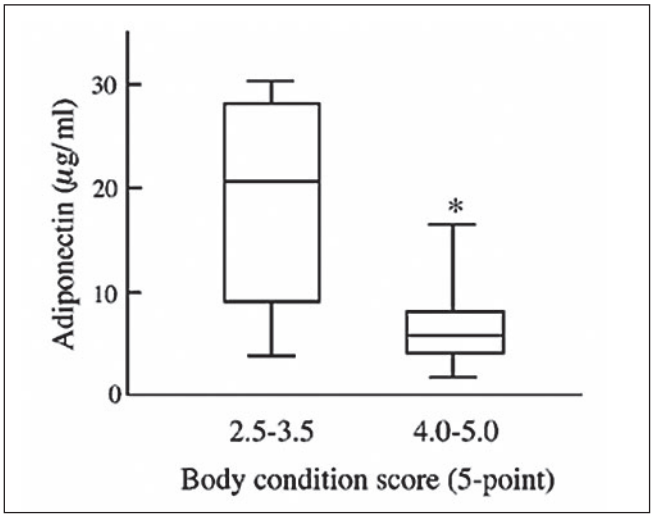

Figure 2: Plasma adiponectin concentrations in cats visiting the veterinary practice. Twenty-two cats were divided to 2 groups depending on their five-point scale body condition scores (BCSs). Normal, BCS=2.5–3.5 (n=11), obese, BCS=4.0–5.0 (n=11). The values are presented as boxplot chart. *, p=0.006 vs normal. (Taken from Ishioka et al, 2009. Permission obtained from Japanese Society of Veterinary Science)

Conclusions

The pathophysiology of FDM is multifactorial, as a consequence of both genetic and environmental factors .The clinical and physiopathological similarities between FDM and DMT2 makes the cat an important animal model to study this disease in hu-

mans; even more considering that obesity is a global problem that affects both the human population and their pets. Studies about insulin resistance and β cell dysfunction associated with obesity and adipokines have opened a great area of investigation. Taking into account this relationship, and until new therapeutic options are carried out, promoting physical activity and giving adequate diets to feline patients are key factors in the preventive treatment of FDM.

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PATOFIZIOLOGIJA DIABETESA MELLITUSA IN NJENA POVEZAVA Z DEBELOSTJO PRI MAČKAH

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Povzetek: Diabetes mellitus je ena izmed najpogostejših endokrinopatij pri mačkah. Njena razširjenost v zadnjem času narašča in je povezana s značilnim povečanjem deleža predebelih mačk. Glavni dejavniki v patofiziologiji te bolezni so razvoj odpornosti proti inzulinu, slabo delovanje ali izguba celic β, nezadostno izločanje inzulina in amiloidoza (AI) otočkov. Občutljivost na inzulin je značilno zmanjšana pri predebelih pacientih, zato veliko avtorjev želi najti pri mačkah povezavo med debelostjo in diabetesem mellitusom (FDM). Proučevali so spremembe v prenosu glukoze, povečanje trigliceridov in maščobnih kislin, odlaganje amiloida v otočke in vpliv hormonov, kot so leptin in predvnetni citokini.

Ključne besede: mačja debelost; diabetes mellitus; mačji adiponectin; mačji leptin