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EXPERIMENTAL INDUCTION OF TYPE 2 DIABETES MELLITUS AND THE EFFICIENCY OF BARIATRIC SURGERY IN ITS REVERSAL IN RATS

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Abstract

Background. Following recent years, there is an increased body of literature on the connections that might exist between type 2 diabetes mellitus and the efficiency of bariatric surgery in its reversal compared to other medical approaches such as dieting.

Aim. To induce experimentally type 2 diabetes mellitus in rats in order to observe the effects of bariatric surgery in the recovery as well as the reestablishment of normal insulin levels in order to extend the findings in house animals.

Materials and methods. This study was conducted in three stages: the first consisted in inducing type 2 diabetes mellitus (T2DM) in 40 young Wistar male rats, by initially feeding them human food high in vegetal fats, oleaginous seeds, simple and complex carbohydrates, sugars, lipids, fats, proteins and fructose for a period of 8 weeks followed by a single low dose of streptozotocin (STZ), administered through intraperitoneal injection. The second stage of the study started when the rats became obese and therefore qualified for the bariatric procedure and the third stage consisted of post-operation supervision and care. The surgical procedure, performed on 10 obese rats, consisted in reducing the size of the stomach by partial gastrectomy of a 1.5 – 2.0 cm wide and 6.5 – 7.5 cm long area on the large curvature.

Results. Showed rapid improvements in body weight and blood sugar control after 9 days.

Conclusion. After putting the rats on a diet high in carbohydrates, sugars, lipids and fats and administering them STZ, the induction of type 2 diabetes was successful and the partial gastrectomy led to a better blood sugar control. The bariatric procedure provides a faster therapeutic response than conventional diets.

Keywords: Diabetes mellitus, streptozotocin, rats, bariatric surgery.

INTRODUCTION

For a long time, there has been an increasing interest in studying diabetes mellitus (DM), both in inducing and treating it, therefore experiments have been conducted on animal models and human subjects. From animal models, rats are often used because they are small, easy-to-maintain animals, have an acceptable life expectancy for experiments, respond well to the experimental factors to which they are subject, have a good recovery capacity and a high similarity to human anatomy and physiology thus they representing viable models for a plethora of disorders (1,2).

In the current literature, DM is described as a chronic metabolic disease characterized by an impairment of the body's ability to produce or respond to insulin. This impairment results in abnormal metabolism of ingested carbohydrates and therefore in increased levels of blood glucose. Besides its widespread in humans, DM is also one of the most common metabolic disorders that have been diagnosed in canines and felines (3). The molecular mechanisms of DM in humans and animals are described in the literature as almost similar. Hence, small laboratory animals, such as rats, are often used in research studies (4). The most important clinical feature of DM is considered to be the incapacity of β-cells to generate enough insulin for the organism's metabolic pathway (5).

Also, lately there has been an increased interest in the connections that might exist between DM and the bariatric surgery (6,7). The treatment and reversing of diabetes have become a topic of high interest at the worldwide level with an increasing number of institutions dedicating resources and time into elucidating the best approach for this disease.

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More and more studies are being published on the advantages and disadvantages between bariatric surgery and low-calorie intake as a means of treatment (8). Bariatric surgery stands by advantages such as glycemia improvement shortly post-op compared to low calorie intake (9), high rates of T2DM remission compared to non-surgical groups (10) and 3-year remission rates over 60% (11). As any other invasive procedure (surgery), bariatric surgery is subject to risks of complications, mortality, morbidity as well as the cost of the surgery itself, whereas the low calory intake imposes a substantial caloric restriction with severe energy restriction eventually leading to maintenance difficulties and possible negative long-term effects (8). An interesting study conducted by Patkar *et al.* (12) on mice fed with a high-fat diet and then subject to either bariatric surgery or caloric restriction, has illustrated that Roux-en-Y gastric bypass surgery prevents the biologically adaptive hunger response (through hypothalamic AgRP responsible for feeding behavior and NYP – stimulates food intake with a preference for carbohydrates) triggered by undernutrition and weight loss and suppresses weight-loss induced hypothalamic inflammation markers highlighting some of the molecular effects of bariatric surgery (12).

Several studies have reported that postsurgical patients with T2DM showed more immediate improvements of insulin secretion, raising the possibility that bariatric procedures might induce specific responses to rectify abnormalities in β-cell function (13,14). It has been observed that prior to the actual weight loss, bariatric surgery lowers the glucose blood level in diabetic patients and studies on mice subject to vertical sleeve gastrectomy surgery displayed improved glucose tolerance and insulin secretion *in vivo* within 2 weeks of surgery (15,16).

As regards the inducing of DM in rats, the most often used mechanism is the chemical one because it is considered the fastest and most cost-effective option. The most common chemical substance used for inducing DM is streptozotocin (17,18). For our experiment involving the bariatric surgery, we decided to use a low dose of STZ after a prolonged high fat diet (56 days), to induce T2DM in healthy, young, Wistar rats in order to avoid surgical complications and postoperative complications(19). Thus, the main goal of the present animal model of induced T2DM was to assess the pathological consequences of diabetes and to screen potential therapies for the treatment of this condition as an alternative to current therapies used in house pets. Specifically, in our experiment we wanted to assess the potential benefits of a bariatric procedure using T2DM in rats as, despite its numerous advantages and rapid and definite improvements, it is not always the treatment of choice especially in house animals. Despite the increasing prevalence of this disease, it still has a broad area of unknown mechanisms regarding how the treatments work. For pharmaceutical and molecular findings, the easier and significantly less risky way is by using animal models, in our case Wistar rats, as they are a potential model for diet-induced obesity. The general literature on the subject seems to point towards improvement of insulin resistance through bariatric surgery. The protocol we used for inducing T2DM was previously validated in the literature (20–22).

METHODS

Our experimental study group consisted of 40 young Wistar rats (3 months old). The experimental design of our study was structured in three well-built stages leading to the final results. The designed stages were the following: the pre-experimental phase, the experimental phase and the post-experimental phase. The study was approved by the Ethical Committee with the registration number 882/12.09.2018 and the animals were housed, cared for and handled according to Council Directive 86/609/EEC. The experimental protocol of the study is depicted in Figure 1.

In the first phase of our study, we created the experimental groups, the diets and weighted each individual weekly.

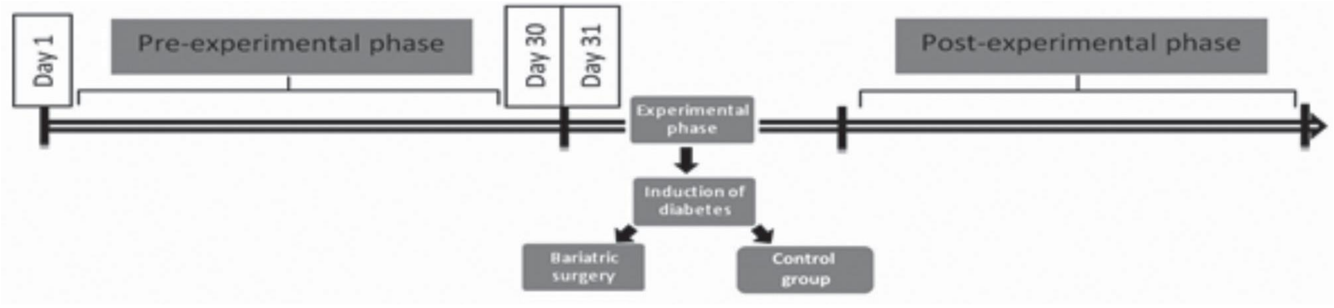

Figure 1. The experimental protocol of the study.

The second phase, involved the induction of T2DM and the bariatric surgery.

The last stage was carried out immediately after the surgery and included observation and monitoring of the operated rats and the possible underlying mechanisms of the visible changes.

Regarding the physical and biological materials, for the accommodation of subjects, we had specific cages with a grille for food and water. For the weighting of the animals we used an electronic weighing scale. Blood tests were performed at the Physiology Laboratory whereas the bariatric surgery was performed in collaboration with the surgical department. The measurement of glycaemia was performed using the GlucoMeter OneTouch Select Plus.

The pre-experimental protocol

The first stage of this protocol consisted of the allocation of the study groups: 40 Wistar male rats were randomly distributed in: the high fat diet group and the control group.

The next step was the establishment of the rats' diets. Food was chosen to cover all three macronutrients (proteins/lipids/carbohydrates). The difference between the two groups was the addition of excess saturated and unsaturated fat, with a ratio of 17.4%protein, 42.9% carbohydrates and 39.7% fat in the high fat diet group. The composition of the hypercaloric diet as well as the macronutrients can be observed in Table 1. The control group was given smaller weights of mixed seeds and sunflower seeds.

Food was given at two different intervals during the day, in the morning and in the evening whereas the water was changed once every two days. The light cycle was the natural light (12h day/12h night) without artificial lighting.

After we created the groups and established the hypercaloric diet, the animals were weighted weekly in order to monitor their progress regarding the weight gain. The purpose of these procedures was to induce obesity and to create a proper environment for the development of type 2 diabetes.

The glycemic control was conducted in the mornings before food was given. At baseline, the fasting glucose of all animals was in the normal range.

It is important to be mentioned that side veins, dorsal vein and ventral artery were used for the peripheral blood sampling.

After the blood sampling was finished, the experiment continued with either hypercaloric diet or normal diet, depending on the experimental group, for another period of 30 days. The purpose of this part of

Table 1. The foods utilized for the normal diet and the hypercaloric diet with their corresponding macronutrients and weights used, cells with thick borders illustrate the main macronutrient and the source it represents. The second part of the table describes the calorie breakdown of each food as well as the percentages of each macronutrient per 100g of product.

Food		Fats				Carbohydrates			Protein	Cal. breakdown(100g)		
		Total	Sat.	Polyunsat	Monounsat	Total	D. fiber	Sugar		Fats	Carbs.	Prot
Mixed Seeds	ND (50g)	23.85g	3.467g	13.41g	5.93g	9.14g	3.6g	0.905g	11.83g		12%	
	HD (100g)	47.71g	6.935g	26.82g	11.86g	18.28g	7.2g	1.81g	23.66g			
Puffed wheat with sugar	ND (40g)	0.648g	0.1g	0.29g	0.22g	35.98g	0.64g	21.98g	2.38g	4%		6%
	HD (20g)	0.324g	0.05g	0.1454g	0.11g	17.99g	0.36g	10.99g	1.19g			
Sunflower seeds	ND (50g)	25g	2.5g	16.665g	5g	10g	5g	1.665g	6.83g		13%	
	HD (100g)	50g	5g	33.33g	10g	20g	10g	3.33g	13.66g			
Fruit yoghurt (Activia)	ND (50g)	1g	0.5g	0g	0g	11g	0g	9.5g	2.05g	15%		13%
	HD (50g)	1g	0.5g	0g	0g	11g	0g	9.5g	2.05g			
Plain biscuits	ND (20g)	1g	0g	0g	0g	13.5g	0g	1.5g	1.5g	13%		9%
	HD (20g)	1g	0g	0g	0g	13.5g	0g	1.5g	1.5g			
Cornflakes	ND (40g)	0.184g	0.054g	0.096g	0.034g	35.98g	1.24g	3.74g	2.652g	1%		9%
	HD (20g)	0.092g	0.027g	0.048g	0.017g	17.99g	0.62g	1.87g	1.326g			
Green lettuce	ND (100g)	0.15g	0.02g	0.082g	0.006g	2.79g	1.3g	0.78g	1.36g	8%		30%
	HD (100g)	0.15g	0.02g	0.082g	0.006g	2.79g	1.3g	0.78g	1.36g			
Carrots	ND (25g)	0.06g	0.008g	0.028g	0. 002g	2.395g	0.7g	1.135g	0.232g	5%		8%
	HD (25g)	0.06g	0.008g	0.028g	0.002g	2.395g	0.7g	1.135g	0.232g			
Apples	ND (40g)	0.068g	0.01g	0.02g	0.002g	5.524g	0.96g	0.104g	4.156g	3%		2%
	HD (20g)	0.034g	0.005g	0.01g	0.001g	2.762g	0.48g	0.052g	2.078g			
Total daily food intake (cal)	ND					787.68 kcal						
	HD					1471.96 kcal						

*ND-Normal Diet, *HD-Hypercaloric diet, *Sat.-Saturated, *Polyunsat.-Polyunsaturated, *Monounsat.-Monounsaturated, *D. fiber-Dietary fiber, *Carbs.-Carbohydrates, *Prot.-Proteins.

our study was to try to induce a pronounced increase in insulin resistance in the high fat diet group.

Induction of diabetes

The first experimental stage of this study consisted of streptozotocin administration as a diabetogenic substance with a dose specifically chosen to induce an adequate insulin deficiency in the setting of the obesity-related insulin resistance to emulate the physiologic state of type 2 diabetes. The animals from the high fat diet group received their respective diets for a period of 30 days, and on the day 31, a single dose of STZ was administered intraperitoneally (35 mg/ kg body weight) to animals fasted for 12 h. We used this dose of STZ because it is low enough to guarantee the development of type 2 diabetes in rats which received a high fat diet without causing absolute insulin absence for testing the bariatric procedure.

To induce diabetes to our animals a specified protocol was followed. Blood glucose, temperature and vital functions were monitored the day before the substance was used. The dose of streptozotocin used was calculated for the current weight of each individual. After the injection of the substance at the intraperitoneal level, an individual daily observation file was kept with all the data observed during the development and manifestation of diabetes. For the next stage of our experiment, we randomly assigned the rats from the high fat diet group in two groups: 10 rats received the bariatric surgery intervention, the other 10 were used as controls.

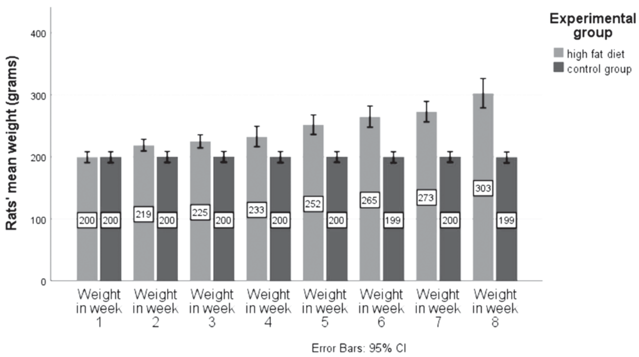

Figure 2. The evolution of the rats' mean weight from week 1 to week 8 of normal diet, as well as hypercaloric diet. Both groups started at a weight of 200g and significant differences were observed from week 2 as follows week 2- p=0.004, week 3- p<0.001, week 4- p=0.001, week 5- p<0.001, week 6- p<0.001, week 7- p<0.001, week 8- p<0.001. The high fat diet group exhibited a significant and constant increase in weight over the 8 weeks period going from a mean weight of 200g to a mean weight of 303g, while the control group maintained a constant 200g mean weight.

Bariatric surgery

A sleeve gastrectomy was conducted, resecting about 70% of the stomach, including most of the fundic portion (which in the rat is the bottom of the stomach). A vascular forceps was used to outline the area to be resected. The gastrorrhaphy was conducted with an invaginating continuous polypropylene hand-sewn suture (Schimieden pattern). Hemostasis and suture-line integrity were checked, and an additional stitch was applied when necessary. Subcutaneous fluids were administered, and body warming was performed

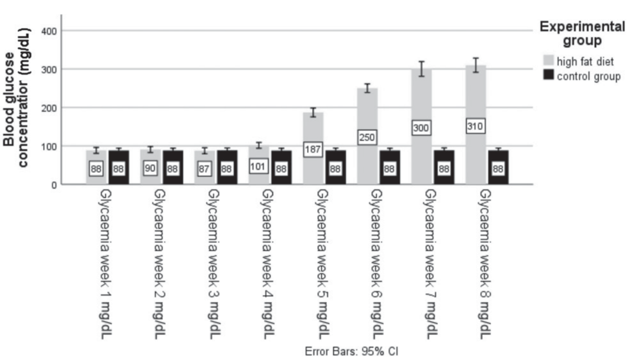

Figure 3. The evolution of the rats' glycaemia from week 1 to week 8 pre-surgery on normal diet(control group) and hypercaloric diet(high fat diet). Both groups started at the same glycaemia level (88 mg/dL) and no significant differences were observed for the first 3 weeks between the 2 groups (week 1- p=0.623, week 2- p=0.111, week 3- p=0.238) with this aspect changing from week 4 (week 4- p<0.001, week 5- p<0.001, week 6- p<0.001, week 7- p<0.001, week 8- p<0.001.Throught the 8 week period, the control group maintained a constant glycaemia level (88 mg/dL) while for the fat-diet group it kept increasing and reached 310 mg/dL.

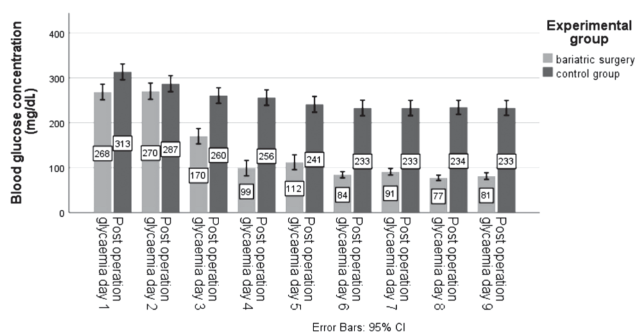

Figure 4. The evolution of the fasted glycaemia after the bariatric procedure over a 9 days time frame in control and bariatric surgery group, both fed with a hypocaloric diet. The control group started with a glycaemia of 313 mg/dL, while the bariatric group started at 268 mg/dL. All post-operation glycaemia values were significantly different between groups for all supervised days (p<0.001)(day 1- p<0.001, day 2- p<0.001, day 3- p<0.001, day 4- p<0.001, day 5- p<0.001, day 6- p<0.001, day 7- p<0.001, day 8- p<0.001, day 9- p<0.001). After a 9 days observation period, the glycaemia of the bariatric group reached normal values (81 mg/dL) while for the control group it still remained high (233 mg/dL).

Table 2. The foods utilized for the hypocaloric diet fed to both groups (control and bariatric surgery) post-op with their corresponding macronutrients and weights used. The second part of the table describes the calorie breakdown of each food as well as the percentages of each macronutrient per 100g of product.

Food	Fats				Carbohydrates			Protein	Cal. breakdown(100g)		
	Total	Sat.	Polyunsat.	Monounsat.	Total	D. fiber	Sugar		Fats.	Carbs.	Prot.
Green lettuce(100g)	0.15g	0.02g	0.082g	0.006g	2.79g	1.3g	0.78g	1.36g	0%	67%	33%
Arugula (50g)	0.33g	0.043g	0.159g	0.024g	1.825g	0.8g	1.025g	1.29g	19%	47%	33%
Carrots(25g)	0.06g	0.008g	0.028g	0.002g	2.395g	0.7g	1.135g	0.232g	5%	87%	8%
Apples (20g)	0.034g	0.005g	0.01g	0.001g	2.762g	0.48g	2.078g	0.052g	3%	96%	2%
Organic Cereal Pap Multicereal(100g)	3.9g	0.6g	-	-	69.7g	7.9g	1g	12.1g	3%	83%	14%

Table 3. The glycaemia of the rats (mean) after the bariatric surgery compared to controls

	Control group	Bariatric group
Day 1	313 mg/dL	268 mg/dL
Day 2	286 mg/dL	270 mg/dL
Day 3	260 mg/dL	170 mg/dL
Day 4	256 mg/dL	99 mg/dL
Day 5	241 mg/dL	112 mg/dL
Day 6	232 mg/dL	84 mg/dL
Day 7	232 mg/dL	91 mg/dL
Day 8	234 mg/dL	77 mg/dL
Day 9	233 mg/dL	81 mg/dL

with warm blankets. No food was given for 48h, and starting with day 3 post-operated rats were given low-caloric foods illustrated in Table 2.

Data analysis

Data was statistically analysed and all results are expressed as mean± standard error of the mean (SEM) and ANOVA for repeated measurements was applied using SPSS v. 17.0 software.

RESULTS

The pre-experimental results

The animals from the high fat diet group gained constant weight during the 8-week period, while the weight of the control group remained constant.

When we analyzed the weight gain only in the high fat diet group, the results showed statistically significant increases from week to week (week 1 to week 2 $p= 0.001$, week 2 to week 3 $p= 0.022$, week 3 to week 4 $p= 0.028$, week 4 to week 5 $p=0.023$, week 5 to week 6 $p=0.003$, week 6 to week 7 $p=0.003$, week 7 to week 8 $p=0.022$) (Fig. 2).

In addition, as expected, the differences regarding the weight between the high fat diet group and the control group were statistically significant from week 2 to week 8 ($p<0.05$).

Regarding the glycaemia (measured in mg/dL) our statistical analysis revealed that it took some time until the differences between groups became significant. For the first three weeks p was non-significant ($p>0.05$), but the differences became significant starting from week 4 ($p<0.05$) (Fig. 3).

After this statistical analysis, it was possible to conclude this first stage. In the next part of our experiment we divided the 20 rats from the high fat diet group which already met the obesity criteria, in two distinct groups: one group received the bariatric procedure, the other group of rats was used as a control.

Post-operative evolution and results

After the bariatric surgery, the 10 subjects were observed. The operation was shown to be well performed without the occurrence of post-operative complications. Due to the lack of food administration for the first two days post-operation but only the use of infusion food (saline, glucose 33%), the rats lost about 20g of body weight. Blood glucose was checked only in the mornings before food was given.

The post operation glycaemia values were significantly different between the bariatric surgery group and the control group starting from day one($p<0.005$) as observed in Figure 4.

Based on the presented figures and data, we can see that from the second post-operative period, the fasted blood glucose level begins to return to normal physiological values. Starting from days 4 and 5, normal values were observed in the bariatric surgery group. In Table 3, it can also be observed a decrease in the glycaemia of diabetic control groups that is most likely due to the low-calorie diet they have been fed with, that started at the same time as the bariatric group. As expected, the surgical procedure showed the benefit of stimulating a rapid decrease of blood glucose concentration. Therefore, when the pancreas and liver lose some of the lipid tissue, they can perform their functions under normal conditions.

DISCUSSION

The symptoms of diabetes are relatively similar between humans and animals. The similarities continue as it is known that sedentary and inadequate nutrition rich in simple carbohydrates and lipids leads to obesity in both humans and animals.

Knowing the evolution and symptoms of diabetes mellitus, we decided to study through an animal experimental model a therapeutic process applicable by a bariatric surgery technique in obese rats. We induced diabetes mellitus through a prolonged high fat diet followed by the administration of a beta-cytotoxic drug, streptozotocin (STZ). Regarding the molecular mechanism, "streptozotocin diabetes" is caused by the necrosis of the pancreatic beta-cells, and this agent is the first choice for diabetes induction in animal models (22,23).

The results of our study suggest that the bariatric procedure in obese, type-2 diabetes suffering animals may lead to rapid and visible improvement by counteracting on the metabolic effects due to diet-induced body weight gain and streptozotocin injection. The rats from the bariatric procedure group presented a lower glycaemia just after a few days post operation. Furthermore, this positive trend of the observed improvement continued throughout the whole observation period of our study. These results are not surprising, and they are in concordance with those found in the literature(2,24). The improvements brought by the various bariatric procedures are well documented (25).

Regarding the underlying mechanism of action of vertical sleeve gastrectomy (VSG), currently there are several possible hypotheses on how and why it affects the impaired glucose homeostasis specific to T2DM by normalizing it, but subsequent studies on the matter are required. An impaired glucose homeostasis is determined by a combination between insulin resistance and pancreatic β-cells's incapacity to release sufficient insulin with elevated blood glucose levels as a consequence. One possible explanation of how VSG can repair the imbalance is through the weight loss, rapidly observed post-op, determined by a reduced energy intake as a consequence of little to no malabsorption of nutrients; VSG determines the rate increase at which nutrients enter the small intestine. Through procedures like bypass and VSG, the delivery of ingested glucose into the systemic circulation is improved causing a spike in plasma glucose concentrations (26). Also, it is known that VSG determines an accelerated gastric emptying of liquid and solid nutrients therefore it affects the nutrients absorption leading to faster and higher peaks of blood glucose levels following the rapid delivery of carbohydrates to the absorptive surface of the intestine, but also a rapid clearance from the circulation. These changes have been linked to increased glucagon-like peptide 1 levels and insulin responses. Gut peptides like gastrin or peptide YY and cholecystokinin have been observed to be increased after VSG (13). Another interesting hypothesis involves the gut microbiome changes as it was observed that post surgery the bacterial profile becomes leaner and several studies have illustrated that by the use of fecal transplants from surgery treated mice to recipient/germ-free mice has led to weight-loss and reduced adiposity. Altogether, changes in weight, nutrient absorption, gut microbiota, circulation bile acids, GLP-1 are likely to contribute to the antidiabetes effects (16).

Although it is established as a well proven method to combat obesity in humans, bariatric procedures are rarely used as a therapeutic method to combat obesity and/or diabetes in house animals (27,28). In the present study, this therapeutic approach was based on the desire to treat the cause of diabetes and not the symptoms by influencing the level of glucose present in the blood. All pharmaceutical drugs with biological or hormonal synthesis are strictly aimed at regulating glycemic levels.

The objectives of this study were to observe the efficiency of such a therapeutic protocol on the recovery from T2DM through bariatric surgery as a potential therapy for house pets by using animal models - Wistar rats. In addition, this experimental design was intended as a scientific model for obesity research and type 2 diabetes using animal protocols.

Knowing the methodology of bariatric intervention in human medicine, we understood that this procedure plays a role in the treatment of obese patients who often have complications with secondary diabetes. Of course, a multitude of factors must be taken into consideration before undertaking such intervention in order to not further deteriorate the general health.

Based on this study, it was possible to demonstrate that the non-specific diet based on a hypercaloric consume of lipids (saturated and unsaturated) and carbohydrates (simple and complex) causes a debilitating state of health which is mainly characterized by obesity. It is also important to note that, according to the diet composition, the amount of saturated fatty acids is very limited, but considering our results, the obesity induction was successful and allowed us to continue with STZ injection and bariatric surgery as it also determined elevated glycaemia levels. Maintaining such a chaotic eating pattern that causes obesity in subjects may lead to complications characterized by increased insulin resistance and secondary to type-2 diabetes, but such parameters were not measured in our present study in the absence of streptozotocin injection.

Therefore, treating obesity problems in pet animals may include a variety of therapeutic protocols consisting of a combination of medications, specific diets and surgical bariatric techniques. In order to perform the bariatric surgery, the patient must be monitored and examined in such way not to affect its health more by this intervention. By applying the bariatric method of reducing the stomach by surgical removal along the greater curvature, visible improvements were seen on both weight loss and plasma glucose adjustment without the use of insulin in less than 4 days after the operation.

In conclusion, the positive effect of bariatric surgery on glycemic control of type-2 diabetes is already well known as the bariatric procedure provides a therapeutic response faster than conventional diets that pet-owners often do not administer or do not follow in a well-established program although our study is limited by not measuring a set of parameters (glycaemia before streptozotocin administration, circulation insulin, peptide C) important to such an experimental design. Thus, alternative diets to the ones provided by literature have been illustrated and we strongly encourage further studies to add on our results and go even further, by trying to better characterize the mechanism by which VSG actions. Further studies should focus on assessing them in order to obtain a more complete picture as to why and how such a therapeutic approach is indeed a great alternative even in house animals. However, it is important that after the bariatric procedure, the animals maintain a hypocaloric diet, specific for their species and their physiological needs in order to avoid a possible relapse.

Conflict of interest

The authors declare that they have no conflict of interest.

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