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MICROMORPHOLOGICAL ALTERATIONS IN THE PANCREAS OF RATS FED DIFFERENT HIGH-CALORIE DIETS AND EFFECTS OF REPLACING SUCROSE WITH STEVIOL GLYCOSIDES

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ABSTRACT

The study aimed to evaluate micromorphological alterations in the pancreas of rats fed different high-calorie diets and the effects of replacing sucrose with steviol glycosides. Six groups of rats were fed different diets for five weeks: standard diet (SD), high-fat diet (HFD), high-carbohydrate diet (HCHD), high-fat high-carbohydrate diet (HFHCHD), standard diet plus E960/RA60 (SDRA) and high-fat diet plus E960/RA60 (HFDRA).

Histological studies demonstrated normal architecture of the pancreas in SD and SDRA groups. In the HFD group, clusters of large adipocytes were visible around blood vessels and in the interlobular connective tissue. In the HCHD group, dilations of sinusoid capillaries were seen in the endocrine islands. In the HFHCHD group, dilated blood vessels and ducts were found in the parenchyma. The acinar cells contained zymogen granules. In the HFDRA group, dilatations of the ducts and sinusoid capillaries in the islets were found. The acinar cells seemed swollen and contained small vacuoles.

Key words: high-calorie diets, pancreas, light micromorphology.

Introduction

The pancreas is located transversely on the back wall of the abdominal cavity. It plays an important metabolic role, having an exocrine function which includes the secretion of digestive enzymes. The endocrine function of the pancreas is carried out through the biological effects of insulin, glucagon, somatostatin and pancreatic polypeptide. Each of the hormones is secreted by specific cells in the islets of Langerhans (Longnecker & Thompson, 2023). Studies on the histo-structure of the pancreas have shown many similarities between rodent and human islets, making the use of rodent models an important tool for the study of various metabolic disorders (Kim *et al.*, 2009). Pancreatic islets make up 1-2% of the parenchyma in most adult mammals. They are made up of alpha (α) cells, beta (β) cells, delta (δ) cells, and PP cells (Lenzen, 2021; Longnecker & Thompson, 2023). The β-cell response, and especially insulin production and secretion, is linked to nutrient intake and blood plasma glucose levels (Newsholme *et al.*, 2014). Metabolic disorders, which are determined by the intake of high-calorie diets, can lead to histological changes in the structure of the pancreas. Biomedical research related to insulin resistance and other associated metabolic disorders often uses experimental high-calorie diets – high-fat diets, high-carbohydrate diets or combined high-fat high-carbohydrate diets, the latter resembling the greatest extent the so-called "Western diet". High-carbohydrate diets are based on increasing the carbohydrate content of

the diet, usually by adding simple carbohydrates to standard pelleted rodent feed or adding carbohydrates to the drinking water. High-carbohydrate diets favour some of the metabolic pathways – glycogen synthesis, lipogenesis (especially hepatic lipogenesis) and gluconeogenesis (Hannou *et al.*, 2018). High-fat diets represent the second option for researchers aiming to induce insulin resistance or metabolic syndrome. According to some researchers, a diet with a fat content of more than 10% is defined as high-fat (Rodríguez-Correa *et al.*, 2020). The most common type of added fat is lard, which contains equal proportions of saturated fatty acids and monounsaturated fatty acids (Buettner *et al.*, 2006). High-fat diets are associated with increased body weight depending on the duration of the diet (Deer *et al.*, 2015). The high-fat, high-carbohydrate diet is essentially the experimental model of the so-called "Western diet". The negative effects of this type of diet are well expressed in both functional and structural terms, including changes in the pancreas, as one of the control organs (Hazarika *et al.*, 2016). Administration of the combined high-fat-high-carbohydrate diet leads to rapidly occurring dyslipidemia, body weight gain, visceral fat accumulation, insulin resistance, and increased blood glucose concentrations, and these changes are accompanied by morphological changes in the pancreas that are largely dependent on the duration of the diet (Rodríguez-Correa *et al.*, 2020). In addition to studying the mechanisms of insulin resistance and related metabolic disorders, experimental models are also widely used in the development of new methods of therapy and prevention. The scientific literature in recent decades abounds with studies on the therapeutic potential of various plant extracts, nutritional supplements and herbs (Raman *et al.*, 2012). One of the extracts most commonly used by patients with insulin resistance, obesity and diabetes is stevia extract, which is obtained from the sweet plant *Stevia Rebaudiana*. World Health Organisation experts on dietary supplements, based on long-term studies, approve a daily intake of steviol glycosides of up to 4 mg/kg body weight (Benford *et al.*, 2006). Research done on the intake of steviol glycosides shows that they have anti-inflammatory and anti-diabetic effects (Mejia & Pearlman, 2019; Ray *et al.*, 2020). Some researchers have found direct stimulation of pancreatic β-cell function (Philippaert *et al.*, 2017).

The aim of the present study was to evaluate micromorphological alterations in the pancreas of rats fed different high-calorie diets and the effects of replacing sucrose with steviol glycosides.

Materials and Methods

Animals

A total of 70 male Wistar rats, aged 8-10 weeks, were used in the study. Rats were housed indoors at a constant ambient temperature of 22 ± 2ºC, controlled humidity – 55 ± 10 %, a 12:12 h light-dark period and had access to water and food ad libitum. All experimental procedures were in accordance with the ethical standards (Permit № 335/25.10.2022 with opinion of the Ethics Committee No. 251 of 19.10.2022 of the Bulgarian Food Safety Agency).

Experimental design

Rats were divided into seven equal groups (n=10) – six of the groups were submitted to different dietary regimens for five weeks, and one pool group was used to measure the initial levels of laboratory parameters before the beginning of the diets.

Groups: 1) group BD (before diet), in which parameters were measured before beginning of the dietary regimens; 2) group SD (standard diet) – rats were fed a standard pellet diet for laboratory rats (Melhran, LTD, Bulgaria); 3) group HFD (high-fat diet) – rats from this group were fed the same standard pellet diet supplemented with lard in such an amount that 40% of the energy intake

was supplied by fat; 4) group HCHD (high-carbohydrate diet) – animals from this group were fed the standard pellet diet supplemented with sucrose in such an amount that 75% of the energy content was supplied by carbohydrates; 5) group HFHCHD (high-fat high-carbohydrate diet) – rats were fed the standard pellet diet supplemented with lard and sucrose (30% of energy coming from fat and 57% from carbohydrates); 6) group SDRA (standard diet with added stevia extract – E960/RA60) – rats from this group were fed the standard pellet diet supplemented with stevia extract equivalent to the amount of sucrose in the HCHD, according to the instructions of the manufacturer (Balgarska Stevia, LTD, Bulgaria); 7) group HFDRA (high-fat diet with added stevia extract – E960/RA60) – rats from this group were fed the standard pellet diet supplemented with lard (same amount as in HFHCHD) and stevia extract (equivalent to the amount of sugar in HFHCHD).

Stevia extract (Balgarska Stevia, LTD, Bulgaria) contents: steviol glycosides (96.8 %) – rebaudioside A (61.06 %), stevioside (30.36 %), rebaudioside C (12.42 %), dulcoside A (2.49 %), steviolbioside (0.2 %), rebaudioside B (0.16 %), rebaudioside (0.12 %).

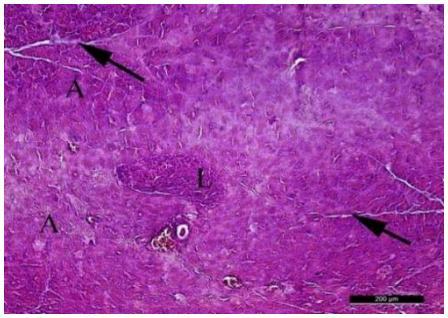
Light microscopic observation of the pancreas

In the last stage of the study, material for histological examination was taken from the pancreas of rats from the studied groups. The collected samples were fixed in a 10% neutral formaldehyde solution for 48 h. After washing and dehydrating the tissue samples in the ascending alcohol series, they were cleared in xylene and embedded in paraffin. Serial histological sections of 3 to 5 µm thickness were obtained with a Leica RM 2235 rotary microtome (Leica Microsystems, Nussloch, Germany) and stained with hematoxylin/eosin. Microscopic observations were performed with a Leica DM1000 -LED light microscope equipped with the Leica Application Suite software platform (LAS, version 4.8.0, Leica Microsystems CMS GmbH, Heerbrugg, Switzerland).

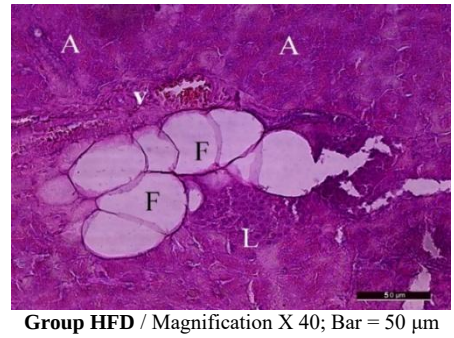
Results

Light microscopic observation of the pancreas of rats from groups BD, SD, and SDRA showed normal architectonics of the parenchyma. Acinar cells were densely packed and arranged in small lobules, separated from each other by intralobular and interlobular connective tissue septa with preserved integrity. Against this background, the endocrine islets (Islets of Langerhans) appear paler in colour. Endocrine cells were densely packed with clearly visible nuclei.

Light microscopic images revealed normal histostructure of the exocrine and endocrine parts of the pancreas of rats fed the HFD. In the pancreas of rats from the HFD group, aggregates of large adipocytes were found around the adventitia of blood vessels along the interlobular connective tissue septa. In the pancreas of rats from the HCHD group, dilations of the sinusoidal capillaries in the endocrine islands were observed. In the HFHCHD group, dilated blood vessels and dilated interlobular and interlobar ducts were found everywhere. When observed with the higher magnifications of the microscope, the cytoplasm of the exocrine acinar cells showed zymogen granules. In the HFDRA group, dilatations of the ducts and sinusoid capillaries in the islets were found. The acinar cells seemed swollen and contained small vacuoles (Fig. 1).



Group HFD / Magnification X 10; Bar = 200 µm



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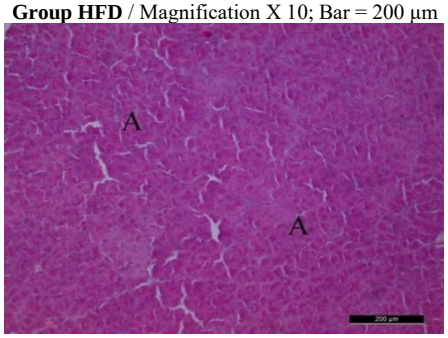
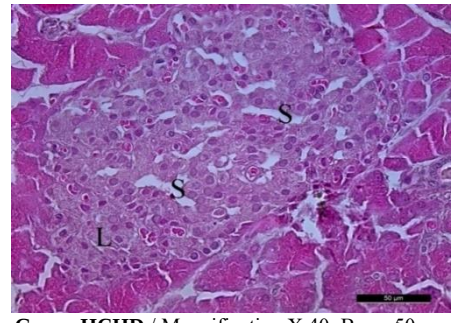
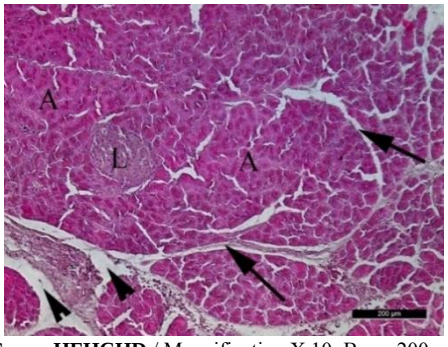


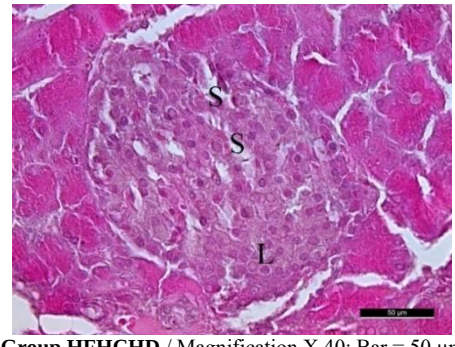
Group HCHD / Magnification X 10; Bar = 200 µm



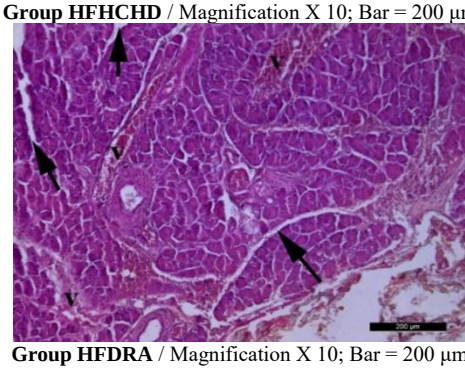
Group HCHD / Magnification X 40; Bar = 50 µm



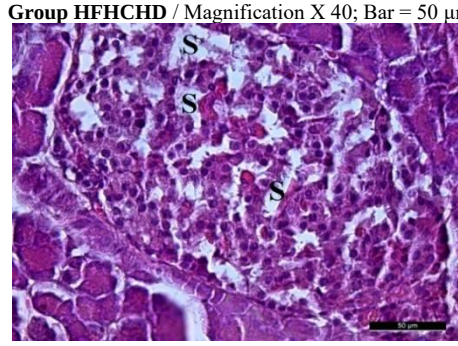
Group HFHCHD / Magnification X 10; Bar = 200 µm



Group HFHCHD / Magnification X 40; Bar = 50 µm



Group HFDRA / Magnification X 10; Bar = 200 µm



Group HFDRA / Magnification X 40; Bar = 50 µm

Figure 1: Light microscopic images of the structure of the pancreas of rats from the HFD group, HCHD group, HFHCHD group and HFDRA group.
A – pancreatic acini; L – endocrine part of the pancreas (Islets of Langerhans); F – a group of adipocytes in an interlobular connective tissue septum, near the islet of Langerhans; v – interlobular blood vessels; black arrows – interlobular ducts; black arrowheads – interlobar ducts; S – dilated sinusoidal capillaries in the islets of Langerhans. Staining with Hematoxylin–Eosin.

Discussion

Results from our study demonstrate a normal histostructure of the pancreas of rats from groups BD, SD and SDRA, while in groups HFD, HCHD, HFHCHD and HFDRA, micromorphological changes were found in both exocrine and endocrine parts of the pancreas. In general, there is a limited number of studies that have focused on the histopathological changes occurring in the pancreas of rodent animal models fed high-calorie diets, which makes the interpretation of results complicated. Several theories for the onset of diet-induced insulin resistance link this metabolic disorder to specific histological changes in the pancreatic tissue.

Histological changes in the pancreatic tissue, affecting both endocrine and exocrine activity, determine the metabolic disorders that are observed during the onset of insulin resistance (Röder *et al.*, 2016). The decrease in β-cell mass during type-2 diabetes is a consequence of the increased need for insulin as a compensatory response during insulin resistance, which eventually leads to β-cell depletion (Wang *et al.*, 2021). Histological changes in cell mass may differ between humans and animals due to anatomical and physiological interspecies variations. However, animal models are widely used in the study of antidiabetic mechanisms of new drugs due to the limited availability of human samples (Noordin *et al.*, 2021). Diet-induced obesity is one of the leading causes for the development of insulin resistance in humans. Under such conditions, excessive production of amylin (IAPP), which is co-secreted with insulin and contributes to glycemic control, may eventually lead to extracellular islet amyloid formation. Amyloid is known to trigger β-cell apoptosis (Paulsson & Westermark, 2005; Zhang *et al.*, 2016; Kanatsuka *et al.*, 2018). Some studies state that amyloid forms only in the pancreas of humans, non-human primates and cats, while some animal species, such as rodents (rats and mice), express IAPP, but without the specific amyloidogenic properties that would damage pancreatic β-cells (Westermark *et al.*, 2011). Nevertheless, the use of transgenic mouse models has demonstrated that high-fat diets stimulate islet amyloid formation (Hull *et al.*, 2003). Although amyloid can be identified or suspected on hematoxylin and eosin samples, our study did not find any evidence for the presence of amyloid in the pancreatic islets. A high-fat diet applied for a period of five weeks does not lead to any histological abnormalities related to amyloid formation.

Other theories explaining the development of diet-induced insulin resistance claim that ectopic deposition of lipids has a negative effect on tissue cells. Excess free fatty acids enter the cells of organs such as the liver, muscles, pancreas, and pericardium, and lipotoxicity occurs, thus disrupting the function of mitochondria, endoplasmic reticulum, and lysosomes (Yan *et al.*, 2006; Ahmed *et al.*, 2021). Our study has found lipid accumulation in the pancreatic tissue of rats fed a high-fat diet. This finding could represent the initial stage of a more serious disorder. Increased fatty acids alone or in combination with high glucose can inhibit insulin secretion and initiate apoptosis of β-cells (Mir *et al.*, 2015). Other studies have also found that high-fat diets lead to the accumulation of interlobular adipocytes and vacuolization in pancreatic tissue as observed by light microscopy (Ickin Gulen *et al.*, 2015). Further, the excess of nutrients in cells generates more reactive oxygen species, leading to mitochondrial dysfunction (Tirichen *et al.*, 2021). As a result of impaired mitochondrial function and the presence of excess lipids, an increase in the concentration of some intermediate lipid metabolites, such as ceramide and diacylglycerols, has been found. The latter may exert toxic effects on pancreatic beta cells, hepatocytes, skeletal muscle cells and cardiomyocytes (Lair *et al.*, 2020). It has been shown that the destructive effects of these lipid substances are

associated with insulin resistance (Sokolowska & Blachnio-Zabielska, 2019). In addition to the deposition of lipids, high-calorie diets also provoke cancer formations (Hori *et al.*, 2011).

Although our study has found lipid accumulation in pancreatic tissue, there are no indications of cellular damage, which may be attributed to the short duration of the diet. The described dilatations of interlobular and interlobar ducts, and the increased volume of the acinar cells, as well as the expanded sinusoid capillaries in the endocrine islands of the pancreas of rats fed high-calorie diets, could be considered to be a morphological expression of increased secretory activity.

Replacing the sucrose in the high-fat, high-carbohydrate diet with an equivalent amount of steviol glycosides has no effect at the micromorphological level of pancreatic tissue, as the changes in HFHCHD and HFDRA are identical. Although steviol glycosides reduce the overall energy content of the diet, the HFDRA, due to its high fat content, is still considered to be a high-calorie diet. Moreover, the sweet taste of the diet, which is due to the presence of steviol glycosides, could potentially increase food intake when rats have free access to food.

Conclusion

High-calorie diets increase the secretory activity of the pancreas and could potentially lead to the accumulation of lipids in pancreatic tissue. Further studies are needed to precisely evaluate the effects of long-term high-calorie feeding and the reversibility of the potential changes.

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