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STRUCTURAL DIFFERENCES IN THE PANCREAS OF RATS OF DIFFERENT AGES AFTER DOSED CALORIC RESTRICTION

It is known that the activity of the pancreas decreases with age. Thus, the volume of the pancreatic juice and its enzymatic activity as well as the activity of the islet apparatus decreases. Therefore, searching for stimulating factors for pancreatic function is a promising research. One of such promising non-drug methods is dosed restriction of the diet. However, the available literature data are often ambiguous. The age of the animals may affect the interpretation of the data obtained. The aim of our work was to investigate and compare structural changes in the pancreas of rats of different ages that were on a caloric restriction, as well as to assess the feasibility of its use as a prophylactic agent in cases of reduced gland function. The experiments were carried out on 48 male Wistar rats. The age of the animals at the beginning of the experiment was 3 and 15 months old. The experimental animals received a calorie restricted by weight (by 30%) diet for 28 days. Tissue samples were taken from the central part (body) of the pancreas for histological studies. Glucose concentration was determined in blood serum. Morphofunctional signs of increased pancreas activity were revealed in 16-month-old rats fed the restricted diet. First of all, the endocrine function of the gland increased. In 4-month-old animals, the effect of caloric restriction slightly reduced the activity of the exocrine pancreas, but did not change the activity of the endocrine function. A decrease in the amount of connective tissue elements in the pancreas in both young and adult experimental rats was shown. The obtained data can be used for further research into the effectiveness of using dosed caloric restriction in cases of age-related decline in pancreas function.

Key words: *dosed caloric restriction, pancreas, age, rats.*

Caloric restriction (CR) is a simple and widespread way to prolong life and prevent age-associated disorders (Di Francesco et al., 2024; Green, Lamming, & Fontana, 2022). There are positive effects of CR on the state of the pancreas, adipose tissue and skeletal muscle, and glucose homeostasis in the course or prevention of age-related diseases, such as type 2 diabetes mellitus, metabolic syndrome, etc. (He et al., 2012; Szczerba et al., 2023). In addition, CR reduces the manifestations of inflammation and accompanying complications in autoimmune or acute pancreatitis (Jaster et al., 2020; Sharma et al., 2022).

Among the possible mechanisms by which CR affects the pancreas, we can include the protein SIRT1, which is one of the seven homologues of Sir2 (silent information regulator 2), which is a nicotinamide adenine dinucleotide-dependent histone or nonhistone diacetylases in mammals. SIRT1 is known to mediate the decrease in blood glucose and insulin concentrations and the increase in insulin sensitivity of peripheral tissues due to the action of CR. In particular, this protein can modulate signaling in pancreatic β-cells, adipocytes and skeletal muscle (Chen et al., 2013; Avilkina, Chauveau & Ghali Mhenni, 2022).

The main attention of researchers is mainly devoted to the endocrine pancreas, and the function of the exocrine pancreas is often ignored, except for some pathological conditions (Jaster et al., 2020; Sharma et al., 2022; Taylor, 2019). In addition, different models of CR, experiments duration, and animals age are used in researches which complicates the interpretation of the results obtained. With age, the pancreas (like most organs) reacts differently to various stress factors. It is known that with aging, the vessels of the pancreas narrow. In the walls of the ducts, connective tissue grows, their elasticity decreases. The number of exocrinocytes decreases, which leads to inhibition of the enzymatic activity of the gland, and as a result, to incomplete digestion of proteins, fats, and carbohydrates (Löhr, Panic, Vujasinovic & Verbeke, 2018). In addition, with age, there is a decrease in the number and activity of β-cells of the pancreatic islets and the number of insulin receptors. This leads to the development of insulin resistance and metabolic disorders (Kehm et al., 2018). In general, a decrease in the mass of the glandular part accompanied by the growth of connective tissue is characteristic age-related features of the pancreas (Matsuda, 2018). Therefore, the search for stimulating factors for pancreatic function is a promising research. One of such promising non-drug methods is the method of dosed restriction of the diet.

The objective of our study was to investigate and compare structural changes in the rats' pancreas of different ages that were on a reduced diet, as well as to assess the feasibility of its use as a preventive measure for correcting age-related declines in gland function.

Materials and methods. The experiment involved 48 male Wistar rats. The age of the animals at the beginning of the experiment was 3 and 15 months. The rats were divided into 4 groups (12 animals each): I, III – control animals aged 3 and 15 months, respectively; II, IV – experimental rats aged 3 and 15 months, which received a weight-reduced- (by 30%) diet. The daily diet of the control rat was 20 g (65 kcal) of specialized compound feed (Recipe K 120-1, Rezon-1, Ukraine), and the caloric restricted rat – 14 g (45 kcal). This level of caloric reduction according to the classification of McKay C. M. is referred to as "mild" CR, which is able to extend life expectancy, increase the efficiency of molecular and cellular systems, and increase the adaptive capabilities of the organism (McCay, Crowell, & Maynakd, 1935). Regular food consumption completeness by all rats was controlled daily. Access to water was free. Animals were housed separately in cages with mesh partitions to minimize stress from social isolation. The duration of the experiment was 28 days. All protocols were approved by the Biomedical Ethics Committee for the Care and Use of Animals of the Bogomoletz Institute of Physiology, NAS of Ukraine. Rats were sacrificed by decapitation under isoflurane anesthesia in accordance with the European Convention (Strasbourg, 1986).

Tissue samples were taken from the central part (body) of the pancreas for microscopic examination. The samples were fixed in Bouin's solution for 2 days. Then the tissue samples were dehydrated in alcohols with increasing concentration and embedded in paraffin. Tissue sections 6 μm thick were made from paraffin blocks using a sledge microtome. The obtained histological preparations of the pancreas were stained by the histochemical method according to Van Gieson (Rehfeld, Nylander, & Karnov, 2017). For histomorphometric studies, the stained samples were photographed with a camera (Levenhuk, USA) on a light-optical microscope (Nicon ECLIPSE E100, Japan). The analysis was performed using the information software "Image J".

Histomorphometric analysis was performed on the obtained micrographs of pancreatic tissue. In the exocrine part of the gland, its relative area, acini size, number of exocrinocytes in them, and epithelial height were determined. The area of exocrinocytes was measured, and the number of nucleoli in them was counted. In the endocrine part of the gland, its relative area was determined, the

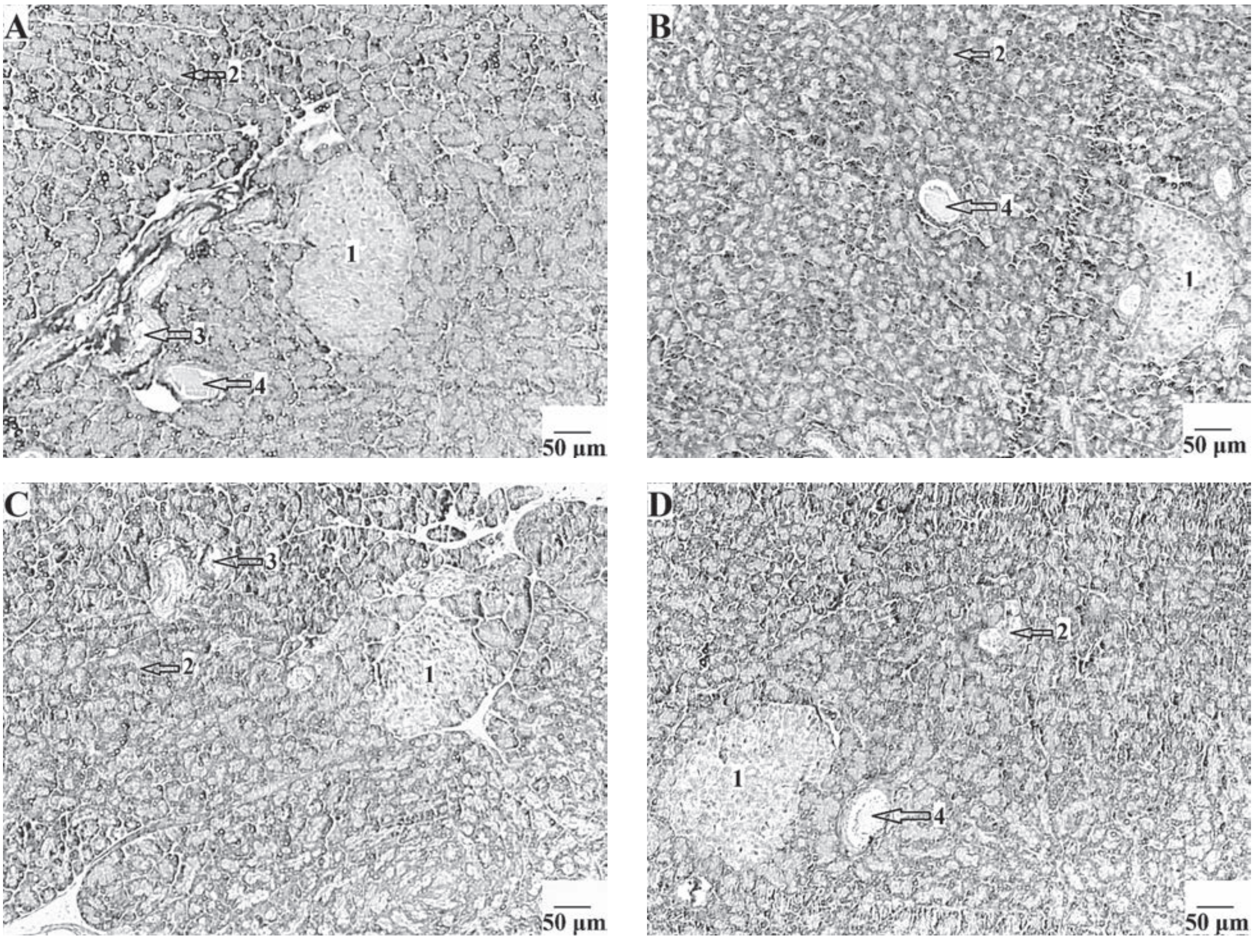

Fig. ***Photomicrograph of the pancreas of the control group's rats (A – 4 months old, C – 16 months old) and rats on caloric restriction (B – 4 months old, D – 16 months old).***

Note*: 1 – Langerhans islet; 2 – acinus; 3 – pancreatic duct; 4 – vessel. Van Gieson's stain. ×200.*

number of pancreatic islets and the number of endocrinocytes in them were counted, and the size of the islets was measured. The width of the interlobular and interacinus connective tissue layers was also measured. Relative areas were determined by the method of superimposing point morphometric grids on micrographs (Hossain et al., 2014; Yanko, Levashov, Chaka, & Safonov, 2020).

Glucose concentration was determined in serum at the end of the experiment (before rats were removed from the experiment). Blood was collected in the morning, and the animals were fasting. For this purpose, reagent kits ("Filisit-Diagnostics", Ukraine) and a biochemical analyzer ("Sinnowa", China) were used.

Statistical analysis was provided by software "Statistica 6.0 for Windows" (StatSoft, USA) and "Excel 2010" (Microsoft, USA) using Student's t-test. The groups were also analyzed using one-way analysis of variance. The data are presented as the mean with standard error of mean (M ± m) with normal distribution. The value $p < 0.05$ was considered significant.

Results and discussion. The parenchyma of the pancreas of rats that were on CR retained its physiological structure and was divided into lobules, between which there are connective tissue partitions with blood vessels, nerves and excretory ducts. The exocrine part is represented by acini, as well as a system of ducts. The acini were predominantly oval in shape and consisted of 7-10 pyramidal exocrinocytes (Fig.).

In the exocrine part of the pancreas of 4-month-old rats on CR, histomorphometric signs of decreased activity were observed. This was evidenced by a moderate decrease in the size of the acini, the area of exocrinocytes (by 13%; $p < 0.05$) and their cytoplasm (by 15%; $p < 0.05$), as well as a lower number of exocrinocytes (by 10%) compared with control. However, the number of nucleoli in these animals' cells was 29% higher ($p < 0.05$, Table 1).

Table 1

Morphometric indicators of the exocrine pancreas (M ± m; n=12)

Indicators	4-month-old rats		16-month-old rats	
	Control	Caloric restriction	Control	Caloric restriction
Relative area of the exocrine part, %	75.2 ± 1.3	79.4 ± 1.7	72.2 ± 1.6	71.5 ± 1.8
Relative area of the connective tissue, %	21.1 ± 0.8**	16.5 ± 0.5*	25.3 ± 1.4	23.2 ± 1.4
Stromal-parenchymal index	0.27 ± 0.03**	0.21 ± 0.02*	0.34 ± 0.02	0.30 ± 0.03
Width of the connective tissue layers, μm:				
interlobular	3.11 ± 0.10**	2.60 ± 0.11*	3.79 ± 0.13	2.74 ± 0.15*
interacinus	0.73 ± 0.01**	0.62 ± 0.02*	0.97 ± 0.02	0.68 ± 0.02*
Diameter of the acinus, μm	30.1 ± 0.7	28.1 ± 0.4	27.4 ± 0.6	30.5 ± 0.5
Cross-sectional area of the acinus, μm^2	948 ± 23**	870 ± 21	688 ± 15	923 ± 19*
Area, μm^2:				
exocrinocyte	137.2 ± 4.7	119.6 ± 3.1*	123.6 ± 2.7	120.5 ± 4.9
nucleus	19.0 ± 1.0	19.1 ± 0.7	17.5 ± 0.5	19.7 ± 0.2*
cytoplasm	118.2 ± 3.8	100.5 ± 2.8*	106.1 ± 2.4	100.8 ± 4.3
Nuclear-cytoplasmic ratio	0.161 ± 0.003	0.190 ± 0.006*	0.165 ± 0.006	0.195 ± 0.006*
Number of nucleoli in an exocrinocyte, pcs	1.53 ± 0.02	1.97 ± 0.04*	1.45 ± 0.06	2.02 ± 0.06*
Height of the epithelium of the acinus, μm	12.6 ± 0.1	12.9 ± 0.3	11.3 ± 0.2	12.5 ± 0.5
Number of exocrinocytes in the acinus, pcs	8.6 ± 0.3	7.8 ± 0.2	7.7 ± 0.2	8.6 ± 0.4

Note: here and in Table 2 * - $p < 0.05$ – compared to the control group; ** - $p < 0.05$ –compared to the control of 16-month-old rats.

In 16-month-old rats that were on CR, the area of the pancreas acinus was 34% larger ($p < 0.05$) than in control animals. The area of the exocrinocyte nuclei was also significantly larger (by 13%), which led to an increase in the nuclear-cytoplasmic ratio by 18% ($p < 0.05$). Hypertrophy of the nucleus and an increase in the nuclear-cytoplasmic ratio indicates, first of all, an increase in the functional activity of the cell. The number of nucleoli in the nuclei of exocrinocytes in these experimental rats was significantly larger by 39% than in the control. Since the main functions of the nucleoli include the synthesis of rRNA, from which ribosomal subunits are formed, it is believed that hyperplasia of the nucleoli indicates an increase in the protein-synthetic activity of exocrinocytes (Dubois, & Boisvert, 2016). The height of the acinar epithelium and the number of exocrinocytes located in them have tended to increase (Table 1). Thus, the nature and degree of severity of changes in the studied morphometric parameters of the pancreas, after exposure to CR, indicate an increase in the activity of its exocrine part in 16-month-old animals, and a slight decrease in 4-month-old rats.

The results of our studies have shown a decrease in the amount of connective tissue (CT) in both 4- and 16-month-old rats that were on CR. Thus, in the pancreatic tissue of 4-month-old experimental rats a significant decrease in the relative area of CT and the stromal-parenchymal index was noted by 22% compared to the control. The width of the interlobular and interacinus CT layers in these animals was significantly smaller by 16% and 15%, respectively. In the pancreas of 16-month-old experimental rats the CT area and the stromal-parenchymal index tended to decrease. And the width of the interlobular and interacinus CT layers in these animals was smaller by 28% and 30%, respectively ($p < 0.05$) (Table 1). Reducing the number of connective tissue elements in the pancreas tissue improves metabolism between acini.

Comparing histomorphometric indicators of the exocrine pancreas of control rats, a decrease in its activity with age was revealed. Thus, in 4-month-old rats a larger acinus area by 38% ($p < 0.05$) and a tendency to a increase in the area of exocrinocytes, their nuclei, epithelial height, the number of nucleoli in cells and the number of exocrinocytes in acinus compared to 16-month-old animals was observed. Also, in the pancreas of young rats, a smaller amount of CT was shown, namely: a significantly smaller relative area of the CT by 17% and a stromal-parenchymal index by 21%, a smaller width of the interlobular and interacinus CT layers by 18% and 25%, respectively, than in adult animals (Table 1). This corresponds to the general pattern of a decrease in pancreas activity with age (Löhr, Panic, Vujasinovic, & Verbeke, 2018).

Differences were also observed in the endocrine pancreas of rats that were on CR. Thus, in the endocrine part of 4-month-old experimental rats a decrease in the area of the Langerhans islets by 16% ($p < 0.05$) was found. However, the density of endocrinocytes per unit area was significantly higher by 37% compared to the control. In 16-month-old experimental animals, the activity of the endocrine function increased. This was indicated by the following morphometric indicators: a significantly larger relative area of the endocrine part (by 112%), the number of pancreatic islets (by 32%), the size of the islets (area by 58%, diameter by 45%), and a larger number of endocrinocytes in them (by 58%) than in the control (Table 2; Fig. 2).

Table 2

Morphometric indicators of the endocrine pancreas (M ± m; n=12)

Indicators	4-month-old rats		16-month-old rats	
	Control	Caloric restriction	Control	Caloric restriction
Relative area, %	3.7 ± 0.6**	4.1 ± 0.3	2.5 ± 0.5	5.3 ± 0.6*
Number of islets (by 0.25 mm^2), pcs	1.14 ± 0.05**	1.13 ± 0.06	0.92 ± 0.06	1.21 ± 0.08*
Area of the islet, μm^2	13800 ± 122**	11567 ± 135*	9525 ± 99	15062 ± 109*
Diameter of the islet, μm	104.0 ± 4.1**	91.7 ± 2.8	82.8 ± 3.9	120.1 ± 7.2*
Number of endocrinocytes in the islet, pcs	142.9 ± 4.3**	164.1 ± 10.6*	117.8 ± 10.8	186.2 ± 7.8*
Density of placement of endocrinocytes in the islet, units/1000 μm^2	10.4 ± 0.7**	14.2 ± 0.5*	12.4 ± 0.2	12.4 ± 0.3

The concentration of glucose in the blood serum of adult rats was significantly reduced by 21% and did not change in young rats. That is, CR activates the endocrine pancreas in adult animals, and does not change its activity in young rats.

The endocrine pancreas in control rats of different ages had even greater differences. In 4-month-old animals, its area was significantly larger (by 48%), the area of pancreatic islets (by 45%), and the number of cells in them (by 21%) were observed to be larger than in 16-month-old rats (Table 2; Fig.).

Thus, we have shown that a 30% reduction in dietary caloric intake during 28 days has a positive effect on the pancreas of 16-month-old rats and generally improves vital indicators related to metabolism. The endocrine function of the gland increased to a much greater extent than the exocrine function. This is consistent with the data of other authors. So, Cheng et al. in experiments on mice with diabetes mellitus, which were on dosed nutritional deprivation, found a decrease in the symptoms of this pathology, activation of β-cell proliferation, normalization of insulin secretion and glucose homeostasis (Cheng et al., 2017). The work of He et al. provides data that rats received a diet reduced in calories by 30% had greater β-cell activity, as evidenced by early insulin secretion during the intraperitoneal glucose tolerance test. At the same time, the size of β-cells and their number in the Langerhans islets increased (He et al., 2012). Gao et al. showed that 40% CR affects β-cell dysfunction and insulin resistance, restores glucose homeostasis, and activates β-cell autophagy in mice (Gao et al., 2015). In addition, oxidative stress in the rats' pancreas was reduced as a result of CR exposure. Also, among the possible mechanisms of the positive effect of CR on the pancreatic endocrine part, there is a decrease in ATP production, which can modulate insulin sensitivity mediated by AMPK, in particular in the liver and skeletal muscles, which causes a decrease in blood glucose and, as a result, a decrease in insulin secretion by the pancreas (Pires et al., 2014).

In contrast, in young animals, CR slightly reduced the activity of the exocrine part of the gland. At the same time, the endocrine function of the pancreas remained unchanged. The literature data on the effect of CR on the morphofunctional state of the pancreas are insufficient for analysis. Similar results were obtained by other scientists when studying short-term fasting and a low-protein diet in young rats. Thus, with short-term fasting, the number of zymogenic granules decreased after just one day. Numerous secretory granules appeared in the apical cytoplasm. Autophagic activity increased. After 3 days of fasting, the level of pancreatic amylase was reduced. Early studies showed a decrease in the size of acinar cells and their nuclei, the number of mitochondria, zymogenic granules, and endoplasmic reticulum cisternae during fasting (Weisblum, Herman, & Fitzgerald, 1962). It is known from the literature that activation of autophagy is not a sign of a pathological process. It is a mechanism that mediates the degradation of "excess" cellular components and mobilizes necessary nutrients. It has been shown that autophagy is impaired after acute pancreatitis, leading to vacuolization of acinar cells and accumulation of trypsin. Fasting is believed to be a potent stimulator of autophagy, which reduces the severity of pancreatitis (Machado et al., 2024; Zhang, Gan, & Zhu, 2023).

Thus, a decrease in the volume of exocrinocyte cytoplasm and their area with an increase in the number of nucleoli can be considered as an adaptive response to CR. The lack of effect of CR on the function of the endocrine pancreas of young animals casts doubt on its positive effect immediately after application. Consequently, the analysis of the literature once again confirms the ambiguity of data regarding the morphofunctional state of the pancreas of animals on CR, which necessitates the continuation of research in this direction and the disclosure of the mechanisms of the influence of fasting on the activity of the gland.

Conclusions. It was found that the age-related difference in the obtained histomorphometric parameters of the pancreas after the influence of dosed food restriction on the functional activity of the pancreas is closely related to its initial state in young and adult rats. A 30% reduction in caloric intake (for 28 days) had a positive effect on the pancreas of 16-month-old rats, in which it was reduced before the start of the experiment. The endocrine function of the gland increased to a much greater extent than the exocrine function. In 4-month-old animals, caloric restriction negatively affected the activity of the exocrine function of the gland. And the lack of effect of caloric restriction on the function of the endocrine pancreas in young animals casts doubt on its positive effect immediately after application.

The results obtained can be used for further studies of the feasibility of using dosed caloric restriction to correct age-related changes in pancreatic function. In the future, we plan to investigate the effect of other caloric restriction regimens, as well as to clarify the mechanisms of its action on the pancreas.

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СТРУКТУРНІ ВІДМІННОСТІ ПІДШЛУНКОВОЇ ЗАЛОЗИ ЩУРІВ РІЗНОГО ВІКУ ПІСЛЯ ВПЛИВУ ДОЗОВАНОГО ОБМЕЖЕННЯ ХАРЧОВОГО РАЦІОНУ

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Відомо, що з віком відбувається зниження активності підшлункової залози. Так, зменшується її ферментативна активність та обсяг панкреатичного соку, а також знижується активність острівцевого апарату. Тому пошук факторів стимуляції функції підшлункової залози є перспективним дослідженням. Одним із таких перспективних немедикаментозних методів є дозоване обмеження раціону. Проте, отримані літературні дані часто неоднозначні. На інтерпретацію отриманих даних може впливати вік тварин. Метою нашої роботи було дослідити і порівняти структурні зміни підшлункової залози у щурів різного віку, які перебували на зниженому раціоні харчування, а також оцінити доцільність його використання в якості профілактичного засобу при зниженні функції залози. Експерименти були проведені на 48 щурах-самцях лінії Вістар. Вік тварин на початку досліду становив 3 і 15 міс. Дослідні тварини протягом 28 діб отримували знижений по масі (на 30%) раціон харчування. З центральної частини (тіла) підшлункової залози брали зразки тканини для гістологічних досліджень. В сироватці крові визначали концентрацію глюкози. Виявлено морфофункціональні ознаки підвищення активності підшлункової залози у 16-міс щурів, які отримували обмежений раціон харчування. Насамперед зростала ендокринна функція залози. У 4-міс тварин вплив обмеженого харчування дещо знижував активність екзокринної частини залози, та не змінював активність ендокринної функції. Відмічено зниження кількості сполучнотканинних елементів в підшлунковій залозі як у молодих, так і в дорослих дослідних щурів. Отримані результати можуть бути використані для подальших досліджень ефективності використання дозованого обмеженого харчування при зниженні функції підшлункової залози, які пов'язані з віком.

Ключові слова: *дозоване обмежене харчування, підшлункова залоза, вік, щури.*