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Impact of Aging and Dietary Habits on Pancreatic Islets of Langerhans of Albino Rats: A Histological and Immunohistochemical Study

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Abstract

Background: Ageing refers to a multidimensional process of physical, psychological, and social change. Fructose is widely used in foods and beverages because of its high relative sweetness. Soybean oil is one of the most widely consumed cooking oils; also, coconut is a part of the daily diets of many people.

Aim of Study: The aim of this study was to demonstrate the histological and immunohistochemical changes that may be induced by aging, high-fructose dietsand high-fat dietsin pancreatic Islets of Langerhans in albino rats.

Material and Methods: This study was conducted on 40 albino rats, divided into 4 groups. Group I or Control groupreceived normal diet and were sacrificed by age of 2 months. Group II (aging group) that received a normal diet. Group III: That received normal diet in addition to fructose for one month. Group IV: That received normal diet in addition tococonut and soya bean oil dailyfor 1 month. Animals in group II, III and IV were sacrificed at the age of 12 months. After being sacrificed, their pancreases were extracted and prepared for light microscopic, electron microscopic and immunohistochemical studies.

Results: It was found that aging was associated with degenerative changes in the Islet cells of Langerhans of the pancreas in albino rats and these changes were aggravated by concomitant consumption of high fructose or high fat diets.

Conclusion: Diets rich in fructose and/or fats may exacerbate aging-induced degenerative changes in the pancreatic Islet of Langerhans. Accordingly, it is recommended to keep consumption of fructose and fats at a reasonable level.

Key Words: *Pancreas – Islets of Langerhans – Insulin – Fructose – Fat – Coconut Oil – Soya Bean Oil.*

Introduction

AGING or ageing is the accumulation of physical, psychological, and socialof changes in a person over time [1]. Fructose is a monosaccharide that is naturally present in fruits, vegetables, honey, table sugar and high-fructose corn syrup [2]. It is the sweetest of all naturally occurring sugars, fructose and is widely used in beverages and foods [3]. It was reported that long-term fructose consumption has negative impacts on health [4]. Soybean oil is widely used for cooking and food products [5]. Coconut oil is a part of the daily diets of many people. It is slow to be oxidized and resistant to rancidity [6]. The pancreas has low levels of reactive oxygen species-detoxifying enzymes and istherefore susceptible to the damaging effects of oxidative stress [7]. The aim of this study was to demonstrate the histological as well as the immunohistochemical changes that may be induced by aging, high-fructose diets and high-fat dietsin pancreatic Islets of Langerhans in albino rats.

Material and Methods

Compliance with ethical standards:

The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Tanta University.

Study design:

This study was conducted in the Anatomy department, Faculty of medicine, Tanta University in 2017. Forty albino rats were housed in a normal at mosphere with free access to food and water. They were divided into 4 groups, each included 10 rats. Group I or Control group received normal diet and were sacrificed by age of 2 months. Group II (aging group) that received normal diet and were sacrificed by age of 12 months to study the effect of aging. Group III: (Fructose-fed group) that received specialized diet containing 60% fructose for 6 weeks before being sacrificed [8]. Group IV: (coconut and soya bean oils fed group) that receivedhigh-fat diet containing 42% fat for 4 weeks before being sacrificed. We used a mixture of coconut butter and soya bean oilinstead of coconut

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butter and corn oil used by Lindqvist et al., [9]. Animals in group III and IV were sacrificed at the age of 12 months.

Preparations of the specimens:

By the end of the treatment period, the overnight-fasted rats were anesthetized by diethyl ether then sacrificed and their pancreases were collected. The pancreas was divided into 3 specimens. First specimen was fixed in 10% formol saline, then embedded in hard paraffin and sections (5 microns thick) were prepared for light microscopic studies with Hematoxylin and Eosin [10]. The 2nd specimen was immersed in phosphate-buffered glutaraldehyde solutionand stained with toluidine blue stain for semi-thinsections or uranyl acetate and lead citrate stains for ultra-structural examination using JEOL JEM electron microscope [11]. The 3rd specimen wasincubated with antisera containing primary antibodies for rat insulin and sections were counterstained with Mayer's Hematoxylin for immunohistochemical studies [12].

Results

A- *Light Microscopy:*

- Group I (control group): There were normal islets of Langerhans that appeared as rounded or oval areas with irregularly branching and anastomosing beta cells and blood capillaries. The islet cells appeared polyhedral with prominent basophilic nuclei and abundant acidophilic cytoplasm. The islets were surrounded by normal pancreatic acinar cells that had basal clear nucleus and apical acidophillia (Fig. 1).
- Group II (Aging-group): Islet cells cords were separated by dilated blood capillaries, some of islet cells had small and degenerated nuclei (Fig. 2).
- Group III (fructose-fed group): Findings were nearly similar to those of group II (Fig. 3).
- Group IV: (Coconut and soya bean oils-fed group): The changes were more or less similar to those found in both group II and III (Fig. 4).

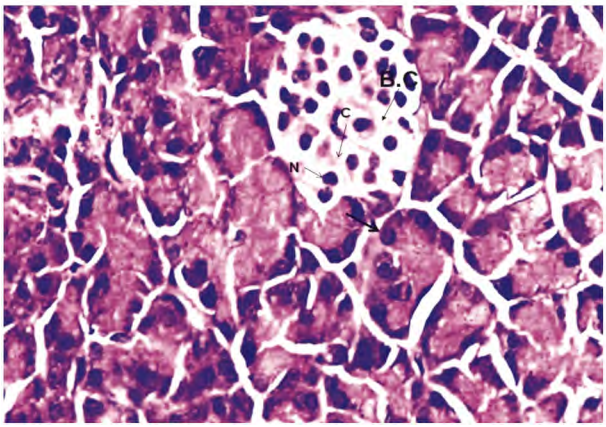

Fig. (1): A Photomicrograph from a group I rat showing islet cells cords with basophilic nuclei (N), acidophilic cytoplasm (C), andcapillaries (B.C). The islets are surrounded by normal acinar cells with basal clear nucleus (arrow). (Hx & E; X 1000).

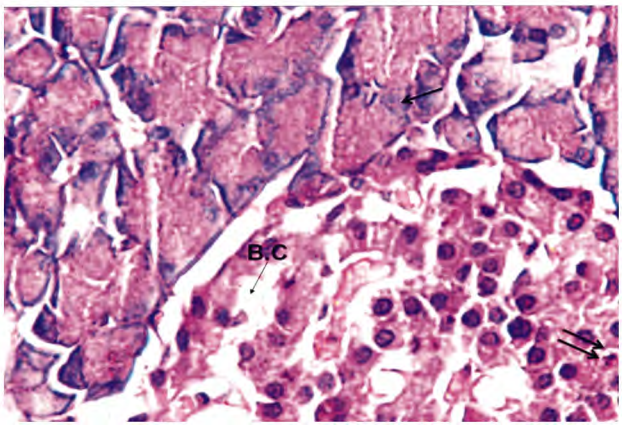

Fig. (2): A Photomicrograph from a group II rat showing normal acinar cells (arrow). Islet of Langerhans with dilated blood capillaries between cells cords (B.C), some of islet cells have small and degenerated nuclei (double arrow). (Hx & E; X 1000).

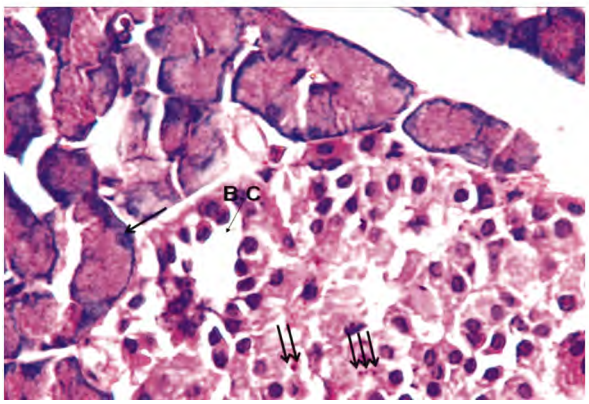

Fig. (3): A Photomicrograph from of a group III rat showing normal acinar cells (arrow). The islet cells are separated with dilated capillaries (B.C), some islet cells have pyknotic nuclei (double arrow), while others have fragmented nucleus (triple arrow). (Hx & E; X 1000).

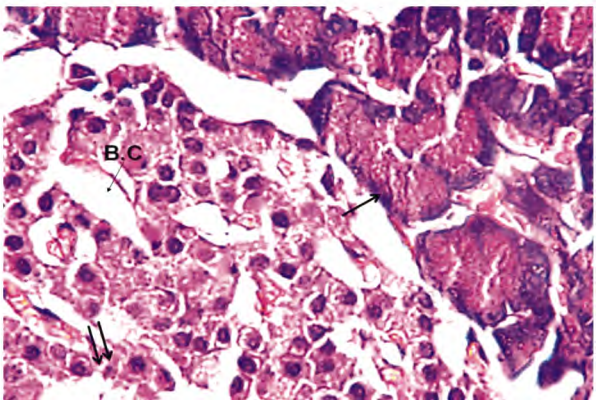

Fig. (4): A Photomicrograph from a group IV rat showingdilated capillaries between islet cells (B.C), some islet cells have small and degenerated nuclei (double arrow), others have vacuolated cytoplasm. Acinar cells are normal (arrow) (Hx & E; X 1000).

B- *Electron microscopy:*

- Group I (control group): Revealed that Beta cell of islet of Langerhans had rounded, euchromatic nucleus, with many membrane-bound secretory granules. The granules appeared with an electron dense core and a wide electron lucent halo. The mitochondria appeared as oval masses around the nucleus, the inner mitochondrial membrane forms the cristae through a series of enfolding while the outer mitochondrial membrane was a smooth continuous envelope that is separate and distinct from the inner membrane. The rough endoplasmic reticulum cisternae appeared clearly in the cytoplasm as membranous cisternae closely packed in parallel arrays. Polyribosomes were present on the cytoplasmic surface of the membrane surrounding the cisternae (Figs. 5,6).

- Group II (aging group): Examination of ultrathin sections revealed that Beta cell had a degenerated nucleus with irregular contour and a peripherally condensed chromatin, dilatedrough endoplasmic reticulum, swollen mitochondria with destructed cristae and depleted secretory granules. (Figs. 7,8).

- Group III (fructose-fed group): It showed Beta cell with oval shrunken nucleus, irregular contour and peripherally condensed chromatin. There was dilated rough endoplasmic reticulum, depleted secretory granules and swollen mitochondria with destructed cristae. (Figs. 9,10).

- Group IV: (Coconut and soya bean oils-fed group): Beta cell nucleus appeared shrunken, with peripherally condensed chromatin. There was dilated rough endoplasmic reticulum, depleted secretory granules and swollen mitochondria with destructed cristae. (Figs. 11,12).

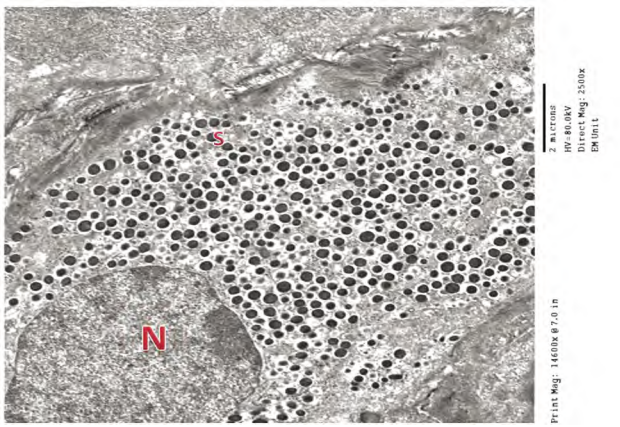

Fig. (5): An electron micrograph fromgroup I l rat showing Beta cell. The nucleus (N) and Secretory granules (S) (EM; X 2500).

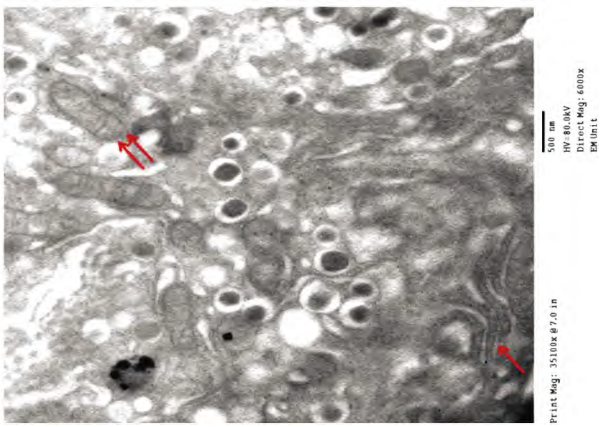

Fig. (6): An electron micrograph from a group I rat showing beta cell mitochondria (double arrow) and rough endoplasmic cisternae (arrow) (EM; X 6000).

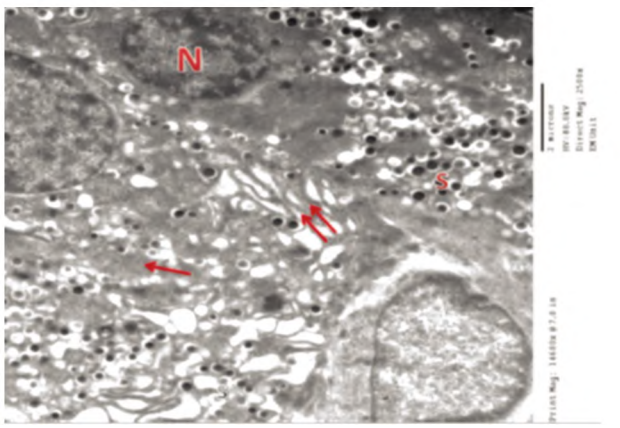

Fig. (7): An electron micrograph from a group II rat showing Beta cell with pyknotic nucleus (N), dilated rough endoplasmic cisternae (arrow), depleted secretory granules (S) and clear mitochondria (double arrow (EM; X 2500).

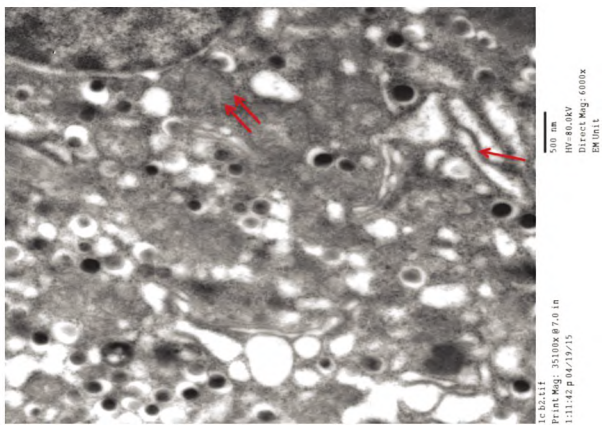

Fig. (8): An electron micrographfrom group II rat showing Beta cell with dilated rough endoplasmic cisternae (arrow). Mitochondria (double arrow) appear swollen with destructed cristae. (EM; X 6000).

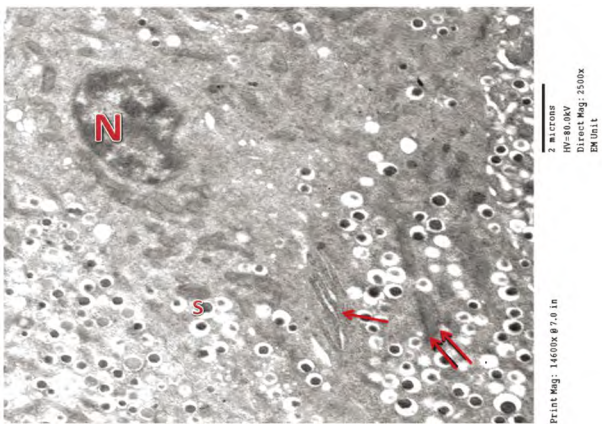

Fig. (9): An electron micrograph from a group III rat showing Beta cell pyknotic nucleus (N), dilated rough endoplasmic (arrow), depleted Secretory granules (S) and mitochondria (double arrow). (EM; X 2500).

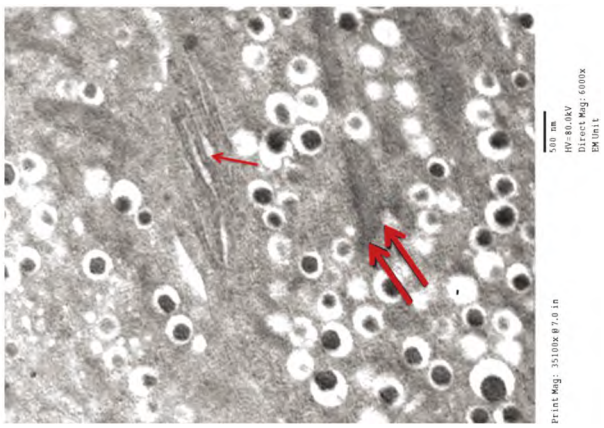

Fig. (10): An electron micrograph from a group III rat showing dilated rough endoplasmic (arrow) and nd swollen mitochondria (double arrow) with destructed cristae. (EM; X 6000).

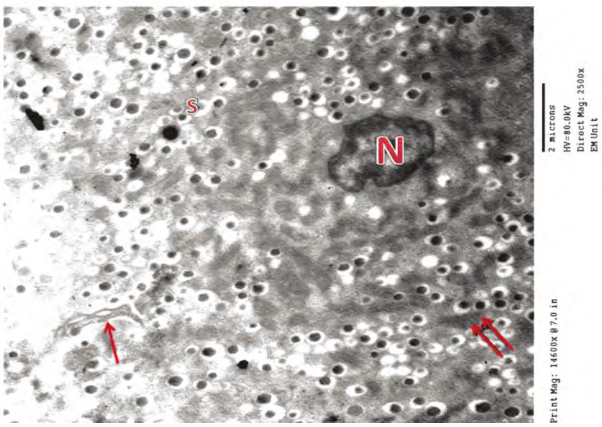

Fig. (11): An electron micrograph from a group IV rat showing Beta cell with pyknotic nucleus (N), dilated rough endoplasmic cisternae (arrow), depleted secretory granules (S) and clear mitochondria (double arrow) (EM; X2500).

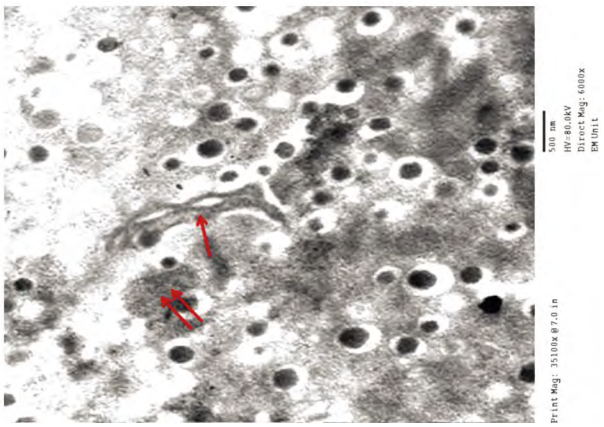

Fig. (12): An electron micrograph from a group IV rat showing Beta cell with dilated rough endoplasmic cisternae (arrow), swollen mitochondria (double arrow) with destructed crista. (EM; X 6000).

C- *Light Microscopy of immunostained sections:*

- Group I (control group): Inspection of immunostained sections from control rats revealed strong immunohistochemical reaction for insulin hormone which appeared as brown granules in cytoplasm of Beta cells, the beta cells were demonstrated as the major population of islet cells. These cells are separated by blood capillaries (Fig. 13).

- Group II (aged group): There were positive immunohistochemical reactions for insulin (Fig. 14).

- Group III (fructose-fed group): Sections from this group showed a moderately positive immunohistochemical reaction for insulin hormone (Fig. 15).

- Group IV: (Coconut and soya bean oils-fed group): A weak positive immunohistochemical reaction for insulin was noticed (Fig. 16).

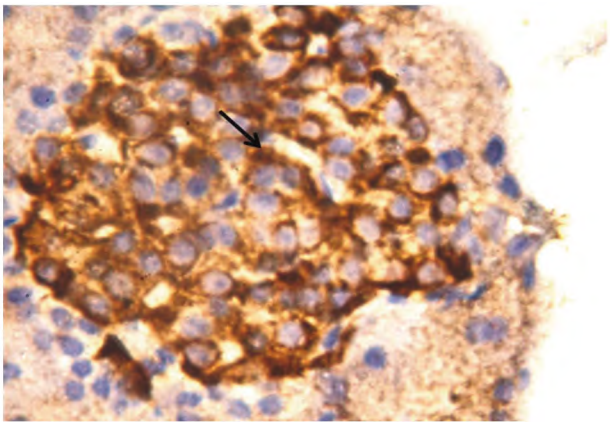

Fig. (13): A Photomicrograph from a group Irat showing positive immunohistochemical reaction for insulin (arrow) (Insulin immunostaining X1000).

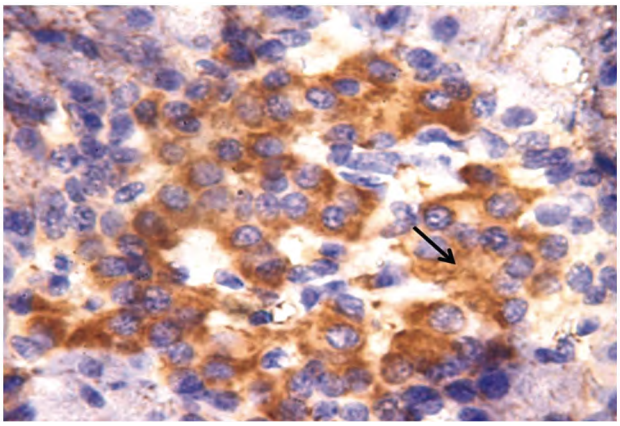

Fig. (14): A Photomicrograph from a group II (aged) rat showing positive immunohistochemical reaction for insulin (arrow) (Insulin immunostaining X 1000).

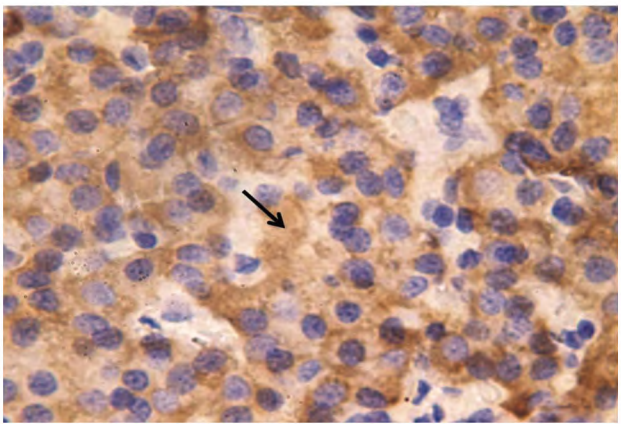

Fig. (15): A Photomicrograph from a group III rat showing a moderately positive immunohistochemical reaction for insulin (arrow) (Insulin immunostaining X 1000).

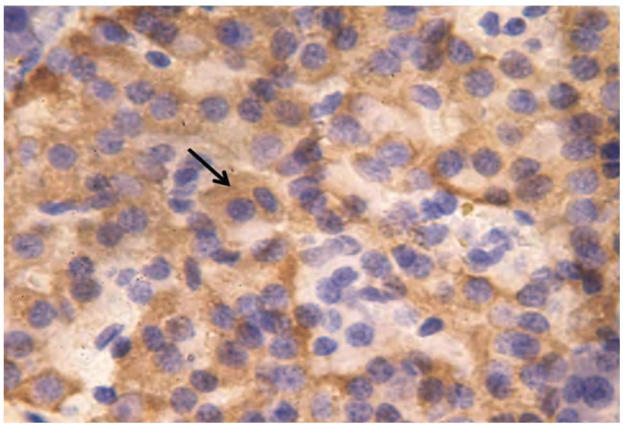

Fig. (16): A Photomicrograph from a group IV rat showing a weak positive immunohistochemical reaction for insulin (arrow) (Insulin immunostaining X 1000).

Discussion

Aging is associated with a decline in both the functional capacity and mor phological integrity of different tissues **[13]**. Fructose is a common component of the human diet. Its widespread use as a sweetener in foods and soft drinks has been accused as a risk factor for obesity and type II diabetes **[14]**. Moreover, consumption of foods rich in is also rising. High-fat diets are risk factors for obesity, diabetes and heart disease **[15]**.

This study was done to assess the effect of these three factors (age, high fructose diet and high fat diet) on the islets of Langerhans of the albino rats' pancreas.

In the current study, Islets of Langerhans from aged rats' pancreas showed pyknotic nuclei, dilated rough endoplasmic cisternae, depletion of secretory granules, swollen mitochondria with destructed cristae and dilatation of islet blood capillaries.

This is inaccordance with previous study by Marantz et al., **[16]**. Svensson et al., reported that augmented islet blood flow may constitute an adaptation mechanism to the increasing demand for insulin secretion in aging rats and hence dilatation of blood capillaries of the endocrinal part **[17]**. Similarly, Herbet and coworkers observed expanded endoblasmic reticulum size in the beta cells from aged rats. They attributed this to the higher demand for insulin biosynthesis **[18]**. Cre et al., also reported an age-associated decrease in pancreatic mitochondrial DNA copy numbers in pancreatic cells from human **[19]**. The oxidative stress theory of aging offers the best explanation of the aging process and related diseases. Terman and associates reported that, aged mitochondria

generate increased amounts of reactive oxygen species that enhance oxidative stress and leads to cell death **[20]**.

In current work, after fructose ingestion, there was augmentation of the changes that were seen in the aged group (pyknotic nuclei, dilated rough endoplasmic cisternae, depletion of secretory granules, swollen mitochondria with destructed cristae). Fructose-induced beta cells apoptosis was reported byother researchers **[21]**. It was mentioned that the increased percentage of apoptosis was not compensated by a similar increase in B-cell replication **[22]**. In agreement with current work, Zaho et al., reported that prolonged use of high-fructose, high fat diets induce oxidative stress, inflammation, reduced islet cells count and size with abnormal secretory functions in the pancreas **[23]**. Mullarkey and coworkers reported that mitochondrial damage appeared due to the fact that reducing sugars are known to produce reactive oxygen species and that mitochondria are the primary target of reactive oxygen species **[24]**.

In current work the rats fed high fat diet showed an exaggeration of the changes previously seen in aged rats (pyknotic nuclei, dilated rough endoplasmic reticulum, depletion of secretory granules, swollen mitochondria with destructed cristae, and dilatation of capillaries of islet of Langerhans). Lupi et al., stated that chronically elevated lipid levels inhibit glucose stimulated insulin secretion and appear to be an important component in obesity-induced β-cell apoptosis and failure **[25]**. Our findings are similar to those reported by Laybutt and colleagueswho found toxic effects of glucose and lipid overexposure on β-cell as indicated by decrease of secretory granules, mitochondrial dysfunction and reactive oxygen species production and endoplasmic reticulum (ER) stress **[26]**. Melo and associates mentioned that consumption of high fat diet and fructose-rich beverages increase body weight, adiposity, lipid droplets in the liver and inflammatory cytokines in the liver, pancreas, skeletal muscle, and adipose tissue **[27]**.

The current work showed decreased islet cells immunoreactivity to insulin with ageing, this result go hand in hand with Watson, (1994), who explained these findings as reduction in glucose oxidation rates with aging would result in reduced insulin secretion **[28]**. In the present study, there was also an additional decrease in insulin immunoreactivity to insulin after fructose ingestion. This finding was in agreement with Basciano et al., who stated that high fructose diet cause increase in body weight which is the result of higher plasma triglycerides which is made from excess fructose in the liver **[29]**. Elevated circulating lipids increase oxidative stress in β-cells and can lead to β-cell dysfunction and damage **[30]**. The high fat-fed group showed decreased insulin immunoreactivity. These findings go hand on hand with Maedler and co-workers who stated that the pancreas has very low levels of reactive oxygen species detoxifying enzymes and is, therefore, susceptible to the damaging effects of oxidative stress induced by hyperlipidemia **[31]**. The mechanisms linking the toxic effects of lipid overexposure to β-cell failure through reactive oxygen species production was proved by other researchers **[32]**.

From the present study it could be concluded that diets rich in fructose and/or fats may exacerbate aging-induced degenerative changes in the pancreatic Islet of Langerhans. Accordingly, it is recommended to keep consumption of fructose and fats at a reasonable level.

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تأثير الشيخوخة والعادات الغذائية على جزر لانجر هانز فى بنكرياس الفئران البيضاء: دراسة نسيجية ومناعية

الخلفية : تشير الشيخوخة إلى عملية متعددة الأبعاد للتغيير البدنى والنفسى والاجتماعى. يستخدم الفركتوز على نطاق واسع فى الأطعمة والمشروبات بسبب حلاوته النسبية العالية. زيت فول الصويا هو واحد من زيوت الطهى الأكثر استهلاكاً على نطاق واسع. أيضاً، جوز الهند هو جزء من الوجبات الغذائية اليومية لكثير من الناس.

الهدف من الدراسة : كان الهدف من هذه الدراسة هو إظهار التغيرات النسيجية والمناعية الكيميائية التى قد تسببها الشيخوخة والوجبات الغذائية عالية الفركتوز والوجبات الغذائية الغنية بالدهون فى جزر لانجر هانز فى لانغرهانس فى الفئران البيضاء

المواد والأساليب :أجريت هذه الدراسة على ٤٠ فأراً أبيض، مقسمة إلى ٤ مجموعات. تلقت المجموعة الأولى أو المجموعة الضابطة نظاماً غذائياً طبيعياً وتم التضحية بها بعمر ٢ أشهر. المجموعة الثانية مجموعة الشيخوخة التى تلقت نظاماً غذائياً طبيعياً. المجموعة الثالثة: التى تلقت بالإضافة إلى الفركتوز لمدة شهر واحد. المجموعة الرابعة التى تلقت نظاماً غذائياً طبيعياً بالإضافة إلى جوز الهند وزيت فول الصويا لمدة شهر. تم التضحية بالحيوانات فى المجموعة الثانية والثالثة والرابعة فى سن ١٢ شهراً. بعد التضحية بها، تم استخراج البنكرياس وإعدادها للدراسات المجهرية.

النتائج :وجد أن الشيخوخة ارتبطت بالتغيرات التنكسية فى أجزاء الغدد الصماء من البنكرياس وتفاقمت هذه التغيرات بسبب الاستهلاك المصاحب للوجبات الغذائية عالية الفركتوز أو عالية الدهون.

الاستنتاج : الوجبات الغذائية الغنية بالفركتوز و/أو الدهون قد تؤدى إلى تفا قم التغيرات التنكسية الناجمة عن الشيخوخة فى جزر لانجر هانز فى البنكرياس. وفقاً لذلك، يوصى بالحفاظ على استهلاك الفركتوز والدهون عند مستوى معقول.