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Effect of Social Overcrowding and Isolation Stress on Alloxan-Induced Diabetic Male Albino Rats

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ABSTRACT

Background: Crowding, social isolation, and a lack of social support negatively impact health and are significant contributors to human illnesses.

Aim of the work: The study aimed to assess the potential impacts of social crowding or isolation on male albino rats with diabetes caused by alloxan.

Patients and methods: Ninety-six adult male albino rats of the local strain were selected. They were split into six groups: the control normal group, isolated group, overcrowded group, diabetic group, isolated diabetic group, and overcrowded diabetic group. At the end, serum fasting blood glucose, insulin level, AST, ALT, albumin, GH, ACTH, and cortisol were estimated. Animal body weight and food intake were also measured. Slices of the liver and pancreas were acquired for histopathological analysis.

Results: In rats with alloxan-induced diabetes, crowding or isolation caused the disease to worsen. This included changes in body weight and food intake, significant cellular alterations on histopathological analysis, and more disrupted glucose metabolism, serum insulin, liver functions, serum growth hormone, serum cortisol, and ACTH.

Conclusion: Crowding and Social Isolation had harmful effects on diabetes. Thus, stress relieve must be a standard item in the treatment or prevention of diabetes mellitus.

Keywords: Diabetes; Stress; Alloxan; Social Isolation; Social Overcrowding.

INTRODUCTION

The development, severity, and chronicity of diabetes are significantly influenced by stress, which is one of the primary issues among diabetic patients. It had been suggested that, there is a significant link between the stress and the development or severity of diabetes [1].

Loneliness is a painful feeling. It reflects a stress state due to difficulties in the social relationships already the subject had. Lack of social support and social isolation are detrimental to one's health. They are considered to be among the most significant causes of human illnesses [2]. Social support is beneficial for people with chronic illnesses [3]

The mechanism between loneliness [isolation] and the development of diabetes is not fully understood. However, it is suggested that, the activation of a stress response [due to social isolation or overcrowding] over time may be responsible for the development of diabetes. This includes the adrenergic system and hypothalamic pituitary adrenal axis [HPA]. Specifically, activation of HPA axis leads to over secretion of cortisol, which in turn increases glycogenolysis and insulin resistance [IR]. The eating behavior is also deregulated leading to increased consumption of carbohydrates, that shares in elevated levels of blood sugar [1-3, 4-13].

Alloxan and streptozotocin are the most popular diabetes-induced [i.e., diabetogenic] substances used to induce diabetes to assess the effects of the antidiabetic, hypoglycemic or other effects. However, alloxan is far less expensive and readily available than streptozotocin. This experimental work was designed to assess the potential impacts of social crowding or isolation on male albino rats with diabetes induced by alloxan.

PATIENTS AND METHODS

This was a prospective cohort, which included 35 patients with septic shock The study was conducted for 6 weeks from January 2024 at the animal house of the physiology department, at Al-Azhar University.

Animals: 96 adult male albino rats of a local strain were selected; weighing between 130 and 150 grams. The animals were acquired from Egyptian Company for production of vaccines [EGYVAC] Pharmaceuticals Company and housed in appropriate cages [31 cm by 25 cm by 20 cm /4 rats], at room temperature with the natural light-dark cycle, fed standard food, and allowed unrestricted access to water and kept for 14 days before the experiment to allow acclimatization.

Chemicals: Alloxan and Nicotinamide were purchased from EL-Gomhouria Pharmaceuticals Company, Egypt.

Study design. Rats were divided into 6 equal groups for the study. Group I: The typical control group was kept in 4 cages, each with 4 rats. Group II: Isolated rats: housed in 16 cages [one rat per cage]. Group III: Overcrowded rats and housed in 2 cages with 8 rats each. Group IV: Diabetic rats and kept in 4 cages, each containing 4 rats. Group V: Isolated diabetic rats and kept in 16 cages, each with a rat. Group VI: Overcrowded diabetic rats and kept in 2 cages with 8 rats each.

Induction of type II-diabetes: was induced by alloxan according to **Madkor et al.** [4]

Crowding Model: was induced by multiplying the normal rat density [8 rats per cage] [5]

Isolation Model: The rats in the experimental cage were left alone [6].

Biochemical parameters in blood: Following the 6-week experiment blood sample was withdrawn from the tail after 8 hours of fasting and serum was extracted, and maintained frozen at -20°C until determination of: fasting blood sugar [FBS] [7], Aspartate transaminase [AST] and alanine transaminase [ALT] [8], Albumin [9]. Insulin [10], growth hormone [GH] [11], adrenocorticotrophic hormone [ACTH] [12] and Cortisol [13]. Histopathological examination of liver and pancreas specimens were done using [H & E] stains. Animals were sacrificed after anesthesia by diethyl ethers. Both liver and pancreas were obtained. Paraffin blocks were prepared and sectioned for hematoxylin and eosin histological examinations.

Ethical aspects: The study protocol was reviewed and approval by The Institutional Animal Care and Use Committee [IACUC] [a branch of institutional review board, DFM, Egypt].

Statistical analysis: The collected data were fed to SPSS software version 26 [IBM Co., USA]. Mean and standard deviation were used to summarize the continuous data and groups were compared by ANOVA followed by a post-hoc least significant differences [LSD] for comparison between two means. with $P \leq 0.05$ indicating a statistically significant.

RESULTS

Comparing stressed [isolated and crowded] rats to normal control rats, the former showed significantly higher blood glucose and lower insulin levels [p<0.001]. Additionally, compared to the diabetic rats, the stressed diabetic rats showed significantly lower insulin levels and increased blood glucose [p<0.001]. However, the serum glucose or insulin levels of the overcrowded diabetic rats and the isolated diabetic rats did not differ significantly **[Table 1].**

When compared to normal control rats, stressed rats showed significantly higher serum levels of ALT and AST as well as lower levels of albumin. Additionally, compared to the diabetic rats, the stressed diabetic rats showed significantly greater ALT, AST, and reduced albumin levels [p<0.001]. Lastly, compared to the overcrowded diabetic group, the isolated diabetic group had considerably lower albumin levels and higher ALT and AST values **[Table 1].**

In contrast to the normal control group, the stressed control groups had significantly higher serum cortisol and ACTH levels and significantly lower serum GH levels. In addition, the stressed [isolated and crowded] diabetic group also had significantly higher mean serum cortisol and ACTH levels and lower GH than the diabetes control group. The isolated diabetic group had considerably higher serum cortisol and ACTH levels than the overcrowded diabetic group without an apparent significant change in GH **[Table 2].** The ultimate body weights of all groups were much higher than their initial weights. Compared to the normal control group, the body weight and food intake of the stressed control groups was noticeably lower while food intake was higher in control diabetic rats. Likewise, in diabetic rats, the stress [overcrowding and isolation] led to a higher drop in body weight and food intake than in the diabetic control group. Additionally, compared to the overcrowded diabetes group, the isolated diabetic group's final body weights and food intake were much lower **[Table 3]**.

Table [1]: Changes in serum blood glucose, insulin, AST, ALT, and albumin levels in tested groups [Mean ± SD]

	FBS [mg/dl]	Insulin [µIU/mL]	AST [U/L]	ALT [U/L]	Albumin [g/dl]
Group [1]: Control	88.1 ± 4.7	3.6 ± 0.61	47.6 ± 0.9	26.6 ± 1.58	4.5 ± 0.01
Group [II]: stressed isolated control	102 ± 4 .6[a]	2.1 ± .26[a]	59.6 ± 5.4[a]	32 ± 2.83[a]	4.2 ± 0.03[a]
Group [III]: stressed overcrowded control	101 ± 3.9[a]	2.2 ± .3[a]	59.3 ± 6.6[a]	31.9 ± 2.91[a]	4.1 ± 0.01[a]
Group[IV]:diabetic control	391.4 ± 6.5[a]	1.5 ± 0. 23[a]	127.2 ± 14.5[a]	72.3 ± 2.85[a]	4 ± 0.31[a]
Group [V]: stressed isolated diabetic	400.3± 4.1[b,c]	0.9 ± 0.13[b,c]	157.2 ±15.5[b,c]	81.9 ± 2[b,c]	2.3 ± 0.5[b,c]
Group [VI] stressed overcrowded diabetic	403.4 ± 9.6[b,d]	0.9 ± 0.14[b,d]	141.8 ±13.8[b,d,e]	77.1 ± 2.8[b,d,e]	3 ± 0.34[b,d,e]

[a] Significance vs Group 1 [b] Significance vs Group IV [c] Significance vs Group II [d] Significance vs Group III [e] Significance vs Group V

Table [2]: Changes in GH, cortisol, and ACTH in tested groups [Mean ± SD]

	GH [pmol/l]	Cortisol [ng/mL]	ACTH [pg/ml]
Group [1]: Control	20.5 ± 0.35	36.2 ± 4.7	40.7 ± 4.33
Group [II]: stressed isolated control	16.5 ± 0.08[a]	49 ± 1.56[a]	56.9 ± 2.69[a]
Group [III]: stressed overcrowded control	17 ± 0.23[a]	45 ± 0.98[a]	55.9 ± 2.31[a]
Group[IV]:diabetic control	13.2 ± 1.57[a]	40.4 ± 5.69[a]	47.2 ± 3.45[a]
Group [V]: stressed isolated diabetic	10.1 ± 1.81[b,c]	53.3 ± 4.35[b,c]	67.5 ± 4.4[b,c]
Group [VI] stressed overcrowded diabetic	11 ± 1.50[b,d]	48.9 ± 0.39[b,d,e]	62.2 ± 5.44[b,d,e]

[a] Significance vs Group 1 [b] Significance vs Group IV [c] Significance vs Group II [d] Significance vs Group III [e] Significance vs Group V

Table [3]: Changes in body weight [g] and food intake [g/d/rat] in tested groups [Mean ± SD]

	Body weight [g]		Food intake [g/d/ rat]
	Initial	**Final**	
Group [1]: Control	145.1 ± 5.16	286.8 ± 3.77*	18 ± 1.89
Group [II]: stressed isolated control	144.3 ± 3.84	257 ± 5.8[*,a]	15.1 ± 1.46[a]
Group [III]: stressed overcrowded control	145.1 ± 3.26	263.8 ± 5.72[*,a]	16 ± 2.25[a]
Group[IV]:diabetic	145.4 ± 4.57	238.6 ± 5.19[*,a]	38.3 ± 3.39[a]
Group [V]: stressed isolated diabetic	143.7 ± 4.9	160.8 ± 6.53[*,b,c]	28 ± 2.07[b,c]
Group [VI] stressed overcrowded diabetic	143 ± 4.99	179 ± 7.18[*,b,d,e]	32.3 ± 2.03[b,d,e]

[*] Significance vs initial body weight of the same group [a] Significance vs group 1
[b] Significance vs Group IV [c] Significance vs Group II [d] Significance vs Group III [e] Significance vs Group V

Light microscopic results using Hematoxylin and Eosin-stain

The rat liver from the control group showed normal hepatic lobules. There were vacuolated hepatocytes, apoptotic cells, vacuolated cytoplasm, and a pyknotic nucleus in isolated rats, as well as vacuolated hepatocytes and big cell dysplasia in overcrowded stressed rats. Diabetic control rats showed dilated sinusoids and a disorganized hepatic cord. In both isolated and overcrowded diabetic rats, hepatocytes showed apoptotic cells, pyknotic nucleus, vacuolated cytoplasm, lymphocytic infiltration, dilated sinusoids, and hepatic cord disarray.

The pancreatic acini and islets were both normal, according to histological analysis of the control pancreas. Inflammatory cells and cellular degradation were seen in isolated stressed rats. In addition, most Langerhans cells have dark nuclei. However, the majority of Langerhans cells had dark nuclei and vacuolated cytoplasm, and overcrowding-stressed rats showed a decrease in cells with a lack of typical cell cord architecture. Although the acini were similar to those of the control group, the diabetic control rat, diabetic isolated group, and diabetic overcrowded group all showed vacuolated cytoplasm, karyolytic nuclei, loss of some cells, dilated congested blood vessels, and apoptotic cells in their islet cells.

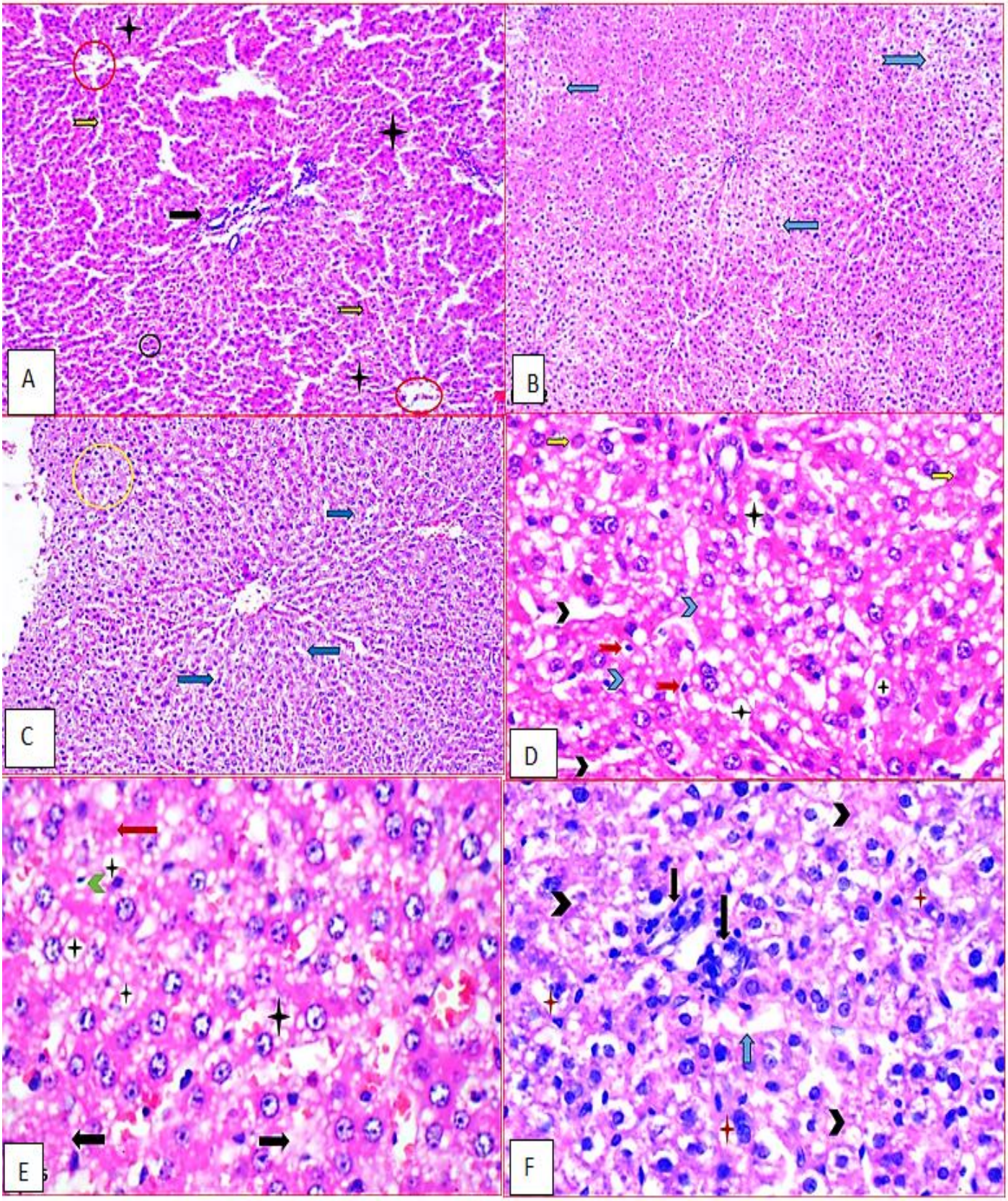

Figure [1]: Hepatocellular histological analysis using H&E in several groups; **A:** Rat liver from group I, showing a normal histological appearance. **B:** Group II displayed vacuolated hepatocytes, apoptotic cells, vacuolated cytoplasm, and a pyknotic nucleus. **C:** group III displayed vacuolated hepatocytes with large cell dysplasia **D:** group IV disordered hepatic cord and dilated sinusoids were also seen in diabetic control rats. **E & F:** Degenerative hepatocytes, apoptotic cells, pyknotic nucleus, vacuolated cytoplasm, lymphocytic infiltration, dilated sinusoids, and hepatic cord disarray in both groups V and VI.

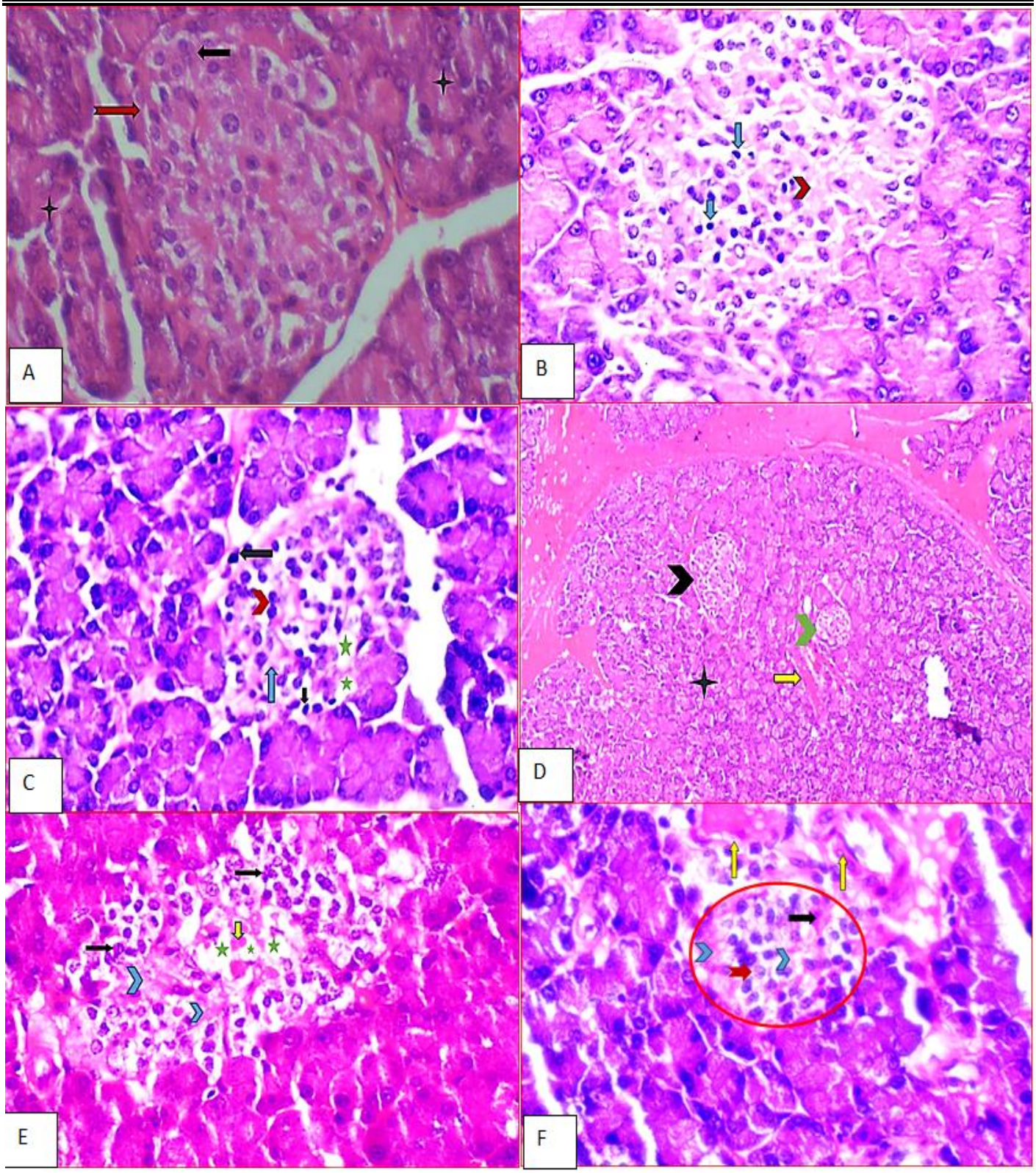

Figure [2]: histological analysis of pancreas using H&E in several groups; **A: group [1**] showed normal acini and islets. **B: Group [1I]** displayed cellular deterioration and inflammatory cells. The majority of Langerhans cells have dark nucleic**: C: group [1II]** overcrowded rats exhibited a decrease in cells with a lack of normal cell cord organization, and the majority of Langerhans cells had dark nuclei and vacuolated cytoplasm. **D, E, and F**: The islet cells displayed numerous indications of degeneration and necrosis, including vacuolated cytoplasm, karyolytic nuclei, loss of some cells, dilated congested blood vessels, and apoptotic cells in groups **[1V, V and VI].**

DISCUSSION

Isolation and overcrowding stress significantly raise fasting blood glucose and decrease insulin levels; and a more significant in diabetic rats. These findings concurred with previous result**s,** which found that social isolation and other forms of psychosocial stress cause rats to have higher glucose levels and glucose dysmetabolism [14]. Additionally, overcrowded rats had higher fasting glucose levels than normal control rats [15]**.**

Additionally, isolation was found to be substantially linked to increased blood glucose, poor diabetic management, and more consequences from diabetes [16]**.** Housing instability and congestion lead to uncontrolled diabetes, a decline in the ability to follow self-management routines, purchase diabetic supplies and prescriptions, and eat healthily [17].

These findings corroborated with previous research that demonstrated that the diabetes model stress group's insulin levels were noticeably lower

than those of the diabetic model group [18]. Furthermore, compared to the control group, others found that the insulin level significantly decreased in the overcrowded, stressed group [19]. The rats in this study who were subjected to stressors may have hypoinsulinemia as a result of hyperglycemia, which can wear down the Langerhans β cells and cause insulin insufficiency and diabetes mellitus [20].

Inflammatory cells and cellular degradation were observed in the pancreas of control rats that were either isolated or overloaded. The majority of Langerhans cells have dark nuclei and exhibit cell loss along with a diminution in their typical cell cord configuration. These findings were consistent with previous studies [21]. According to their findings, oxidative stress may be the cause of the pancreatic damage caused by chronic stress in the islet and acinar cells. Elevated glucose levels caused endothelial cells to secrete more fibronectin and collagen I and III, which increased fibrosis and caused the islets to lose their shape [22].

Isolation and overcrowding significantly raise AST and ALT and lower albumin levels; in diabetic rats, these effects are more pronounced. These findings concurred with a recent study, which discovered that the diabetic rats' serum AST and ALT activity were much higher than those of the control rats [23]. Additionally, other researchers demonstrated that chronic unpredicted moderate stress mice exhibited a considerable increase in ALT and AST activity [24]. Rats subjected to a variety of long-term environmental stressors had elevated levels of AST and ALT, which were closely linked to necrosis, cell damage, and enhanced cell membrane permeability [15].

These findings were corroborated by an additional investigation that found alloxan decreased albumin levels [25]. Others discovered that the diabetic group's serum albumin level was noticeably lower than that of the control group [26]. Furthermore, a prior study discovered that the crowding and isolating groups had considerably lower serum albumin levels [27].

Rats' liver tissue underwent some pathological alterations as a result of stress exposure. Vasospasm and centrilobular hypoxia are two ways that social stress, particularly isolation, affects hepatic blood flow [28]. Hypoxia in hepatic tissue results in the generation of reactive oxygen species, primarily in the mitochondria, which causes endoplasmic reticulum stress, cell necrosis, and liver damage [29].

This investigation demonstrated that stress from overcrowding and isolation significantly raised cortisol and ACTH levels while significantly lowering GH levels. More pronounced changes were seen in diabetic rats. Compared to the overcrowded diabetes group, the isolated diabetic group's serum ACTH and cortisol levels dramatically increased, reflected the harmful stress effect of isolation other than overcrowding.

A study in 2018 found that diabetic rats had considerably lower levels of GH secretion [30]. Isolation stress results in a decrease in plasma growth hormone [31]. Furthermore, hypercortisolism and chronic stress system activation have detrimental effects on growth hormone [32]. Type 2 diabetes patients had significantly higher cortisol levels than the control group [33]. Stress exposure resulted in a considerably greater level of serum cortisol [34]. Similarly, others found that rats under stress had significantly higher levels of stress hormones [cortisol and ACTH] than the control group [19, 31].

The current study found that stress from overcrowding and isolation significantly reduced both food intake and final body weights, with diabetic rats experiencing a greater loss in final body weights with higher food intake. Additionally, compared to the overcrowded diabetes group, the isolated diabetic group's food intake and final body weights were much lower. These findings concurred with a recent study, which found that the rats in the diabetic group had considerably lower body weights than those in the control group [35]. Both crowded and isolated rats had significantly lower body weights, with isolated rats showing this effect more clearly [27].

A different study discovered that type II diabetic rats significantly increased their food intake [36]. Additionally, compared to non-diabetic control rats, diabetic rats significantly increased their food and water intake [37]. However, in rodents, stress decreases body weight and food intake in a way that is directly proportional to the level of stress [38]. When there is a lack of insulin or insufficient insulin utilization by the target organs, cells in diabetes are unable to use glucose efficiently. When the body senses that it is starving, hunger and subsequent food consumption increase [36].

Conclusion and recommendation:

Both isolation and overcrowding had harmful effects on the diabetic rats. Thus, it is recommended to routinely monitor those under these stressors, especially their liver function and diabetic profile to keep their diabetes under control and avoid potential complications.

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