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ORIGINAL ARTICLE

# The Effect of a Heavy Exercise Program on the Distribution of Pancreatic Hormones in the Streptozotocin-Induced Diabetic Rat

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**ABSTRACT**

**Context** Exercise training has long been utilized as an adjunct to pharmacotherapy in the management of diabetes. **Objectives** The effects of a heavy exercise training program on the distribution of insulin, glucagon, somatostatin and pancreatic polypeptide in pancreatic islet cells of diabetic rats was investigated. **Animals** Forty male Wistar rats. **Design** The animals were divided into 4 groups: control sedentary, diabetic sedentary, control heavy exercise, and diabetic heavy exercise. **Intervention** Diabetes was induced with a single injection of streptozotocin (60 mg/kg i.p.). The exercise program included five 60-min sessions per week, speed 18 m/min with a running belt at a 5% incline and began 1 week after the streptozotocin treatment and continued for 12 weeks. **Main outcome measure** Immunohistochemistry was used to label insulin, glucagon, somatostatin and pancreatic polypeptide in islet cells. **Results** The percentage of insulin-positive cells was significantly lower in islets from diabetic rats (24.2±2.3%) as compared to the controls (87.5±2.0%). The percentage of glucagon-positive cells was significantly higher in islets from diabetic rats (44.0±1.7%) as compared to the controls (34.7±2.1%). The percentage of pancreatic polypeptide-positive cells was also significantly higher in islets from diabetic rats (20.8±1.6%) as compared to the controls (12.7±1.8%). The percentage of somatostatin-positive cells was not significantly altered in islets from diabetic rats (28.2±2.0%) as compared to the controls (21.9±2.7%). Heavy exercise did not significantly alter insulin, glucagon, pancreatic peptide or somatostatin labeling in either diabetic or control rats. **Conclusions** Alterations in the distribution of pancreatic hormones in streptozotocin-induced diabetic rats, a model of type 1 diabetes, are not improved with heavy exercise.

## INTRODUCTION

Diabetes mellitus is a serious medical problem. The worldwide prevalence of diabetes is rising dramatically. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 [1]. Cardiovascular complications are the major cause of morbidity and mortality in diabetic patients [2, 3, 4, 5]. Exercise training has long been utilized as an adjunct to pharmacotherapy in the management of diabetes. In terms of pancreatic function, experiments in humans and animals have variously demonstrated that exercise improves insulin resistance, increases insulin sensitivity, increases pancreatic beta-cell mass and generally enhances beta-cell function and insulinotropic action, especially in type 2 diabetes [6, 7, 8, 9, 10, 11, 12].

Reports on the effect of exercise on the glucose-related metabolic parameters in type 1 diabetes remain controversial, especially in animal models of diabetes [10, 13]. Moreover, the cellular basis of the physiological and clinical effects of exercise training in type 1 diabetes is poorly understood. It is well known that insulin, glucagon, somatostatin and pancreatic polypeptide work in tandem to maintain normoglycemia.

This study investigates the effects of a heavy exercise program on the distribution of the pancreatic hormones insulin, glucagon, somatostatin and pancreatic polypeptide in the streptozotocin (STZ)-induced diabetic rat, a model of type 1 diabetes.

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**Key words** Exercise, Glucagon, Insulin, Pancreas, Pancreatic Polypeptide, Somatostatin

**Abbreviations** CHE: control heavy exercise; CS: control sedentary; DHE: diabetic heavy exercise; DS: diabetic sedentary; STZ: streptozotocin; ZDF: Zucker diabetic fatty

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## METHODS

### Animal Model and Exercise Protocol

Diabetes was induced in male Wistar rats (243.3±1.6 g) with a single intraperitoneal injection of STZ (60 mg/kg body weight, Sigma, St. Louis, USA) dissolved

in a citrate buffer. Weight-matched control rats received citrate buffer alone. Animals were divided into 4 groups: 10 control sedentary (CS), 10 diabetic sedentary (DS), 10 control heavy exercise (CHE) and 10 diabetic heavy exercise (DHE) rats. One week after STZ treatment, the CHE and DHE rats started an exercise program which involved 5 60-min sessions per week on a treadmill (Model 800, IITC Life Science, Woodland Hills, CA, U.S.A.) for a period of 12 weeks for the animals in each of the exercise groups. The entire experiment was completed in 12 to 23 weeks. Exercising rats ran at a speed of 18 m/min and on a running belt at a 5% incline. Every exercise session began with a 10 min warm-up when the speed was increased progressively from 0 to 18 m/min. Each lane of the 5 lane treadmill had a shock grid located at one end of the running belt. Mild electrical shocks were used sparingly to motivate the animals to run. Experiments were staggered to ensure equal levels of exercise between different groups of animals. All animals were maintained on the same normal laboratory rodent chow and water *ad libitum*. Body weight and blood glucose (One Touch BasicPlus; Lifescan, Johnson & Johnson, Langhorne, PA, U.S.A.) were measured at the time of sacrifice. The pancreata were removed within 12 hours after exercise training.

### Immunohistochemistry

After sacrificing the rats, the pancreata were rapidly removed from the CS, CHE, DS and DHE rats. Isolated pancreata were trimmed free of adherent fat and connective tissue, and were cut into small pieces (2 $mm^3$) and fixed overnight in freshly prepared Zamboni's fixative. The tissue samples were later dehydrated in graded concentrations of ethanol, cleared in xylene and subsequently embedded in paraffin wax at 55°C. Sections of 6 µm thickness were cut on a microtome (Shandon AS325, Cheshire, UK). The sections were deparaffinized, transferred into absolute ethanol and processed for immunohistochemistry using established Avidin Biotin Complex methods [14, 15]. Briefly, the sections were then incubated for 30 min in 0.3% hydrogen peroxide solution in methanol to block endogenous peroxidase activity and later treated with a blocking reagent for 30 min before incubation in antibodies against insulin, glucagon, somatostatin and pancreatic polypeptide for 24 h at 4°C. The sections were then washed and incubated for 30 min with prediluted biotinylated anti-rabbit IgG (Sigma, Poole, Dorset, UK) for 30 min, before incubation in streptavidin peroxidase conjugate for 45 min. The peroxidase activity was revealed by incubating the specimens for 3 min in 3,3-diaminobenzidine tetrahydrochloride containing 0.03% hydrogen peroxide in PBS. The slides were later washed and counterstained with hematoxylin for 30 s before mounting in Cytoseal 60 (Stephens Scientific, Riverdale, NJ, U.S.A.).

The antisera to insulin, glucagon were supplied diluted (Dako, Copenhagen, Denmark). Somatostatin and pancreatic polypeptide were each used at a dilution of 1:2,000. No specific immunostaining was observed in pancreatic tissue when primary antisera were omitted.

### Morphometric Analysis of Pancreatic Islet Cells

Sections of pancreata were examined with a Carl Zeiss Scientific microscope (Göttingen, Germany) and photographed with a digital camera attached to the microscope. Slides, containing sections of the pancreas, were prepared from all animals. Twenty slides were selected at random from the different animals and 5 sections were labeled for insulin, 5 for glucagon, 5 for somatostatin and 5 for pancreatic polypeptide. Twenty digital photographs were taken of each slide for subsequent offline analysis. The total number of cells in the islets of the CS, DS, CHE and DHE rats were counted using the Axiovision Microimaging System® (Carl Zeiss, Göttingen, Germany). In addition, insulin, glucagon, somatostatin and pancreatic polypeptide-positive cells within a given islet were also counted.

## ETHICS

Approval for this project was obtained from the Faculty of Medicine and Health Sciences Ethics Committee, United Arab Emirates University. All animals received care according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals (1996)" prepared by the National Academy of Sciences.

## STATISTICS

Data were expressed as mean and standard error of the mean (SEM). Statistical comparisons were made using one-way ANOVA with the Bonferroni post hoc adjustment for multiple comparisons. Two-tailed P values less than 0.05 were considered significant. Data were analyzed by means of the SPSS (SPSS Inc., Chicago, IL, U.S.A.; version 15.0 for Windows) statistical package.

## RESULTS

### General Characteristics

Table 1 shows the data observed in the four groups of rats. Body weight, at time of sacrifice, was

**Table 1.** General characteristics of control and exercise-trained rats.

| | Control rats | | | Diabetic rats | | |
|---|---|---|---|---|---|---|
| | **Sedentary (CS)** | **Heavy exercise (CHE)** | **P CHE *vs*. CS** | **Sedentary (DS)** | **Heavy exercise (DHE)** | **P DHE *vs*. DS** |
| Body weight (g) | 426±13 | 412±9 | P=1.000 | 266±10 [a] | 264±14 [a] | P=1.000 |
| Blood glucose level (mg/dL) | 110±4 | 116±6 | P=1.000 | 554±25 [a] | 556±21 [a] | P=1.000 |

Data are presented as mean ± standard error of the mean (SEM). 10 rats in each group.
[a] P<0.001 vs. control rats: DS *vs*. CS or DHE *vs*. CHE.

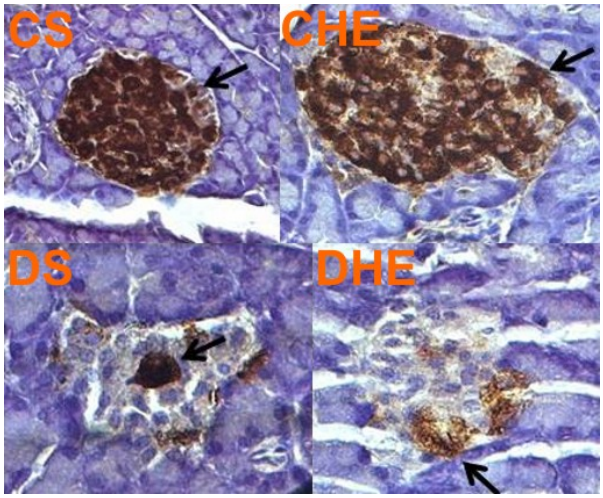


**Figure 1.** Light micrographs showing the pattern of distribution of insulin-immunoreactive cells (arrow) in the pancreatic islets of control sedentary (CS), control heavy exercise (CHE), diabetic sedentary (DS) and diabetic heavy exercise (DHE) rats. (Magnification: x200).

significantly (P<0.001) lower in DS (266±10 g) as compared to CS (426±13 g) rats. Body weight was not significantly (P=1.000) altered by heavy exercise in either the diabetic (264±14 g) or the control (412±9 g) rats.

Blood glucose was significantly (P<0.001) elevated in DS (554±25 mg/dL) as compared to CS (110±4 mg/dL) rats. Blood glucose was not additionally altered (P=1.000) by heavy exercise in either the diabetic (556±21 mg/dL) or the control (116±6 mg/dL) rats.

## Insulin

Typical micrographs showing the distribution of insulin immunolabeling in the islets of the CS, CHE, DS and DHE rats are depicted in Figure 1. The percentage distribution of insulin-positive cells from the CS, CHE, DS and DHE rats is shown in Figure 2. The percentage distribution of insulin-positive cells was significantly (P<0.001) lower in DS (24.2±2.3%, n=83) as compared to CS (87.5±2.0%, n=82) rats

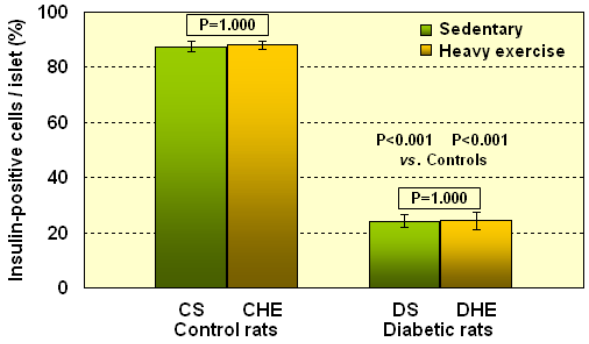


**Figure 2.** Graphs showing the pattern of distribution of insulin-positive islets. Data are mean±SEM; the total number of islets evaluated was 82, 95, 83 and 84 in control sedentary (CS), control heavy exercise (CHE), diabetic sedentary (DS) and diabetic heavy exercise (DHE) groups, respectively.

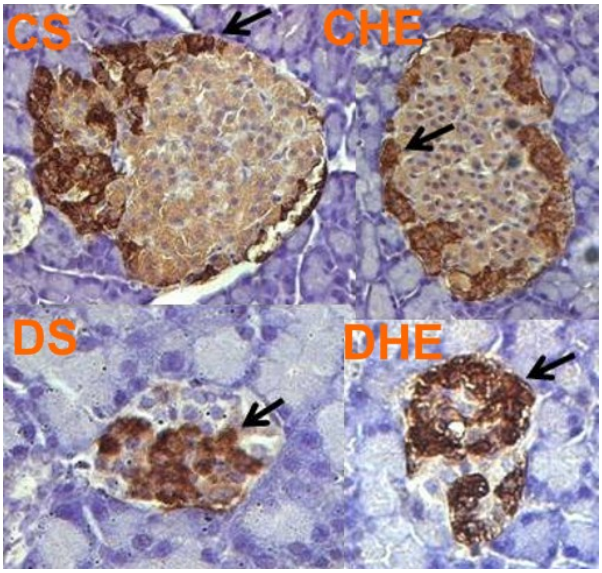


**Figure 3.** Light micrographs showing the pattern of distribution of glucagon-immunoreactive cells (arrow) in the pancreatic islets of control sedentary (CS), control heavy exercise (CHE), diabetic sedentary (DS) and diabetic heavy exercise (DHE) rats. (Magnification: x200).

(Figure 2). Insulin-labeling of the islet cells was not additionally altered (P=1.000) by heavy exercise in either the diabetic (24.3±3.0%, n=84) or the control (88.0±1.4%, n=95) rats.

## Glucagon

Typical micrographs demonstrating the distribution of glucagon in the islets of the CS, CHE, DS and DHE rats are shown in Figure 3. The percentage distribution of glucagon-positive cells from the CS, CHE, DS and DHE rats is shown in Figure 4. The percentage distribution of glucagon-positive cells was significantly (P=0.018) higher in DS (44.0±1.7%, n=84) as compared to CS (34.7±2.1%, n=68) rats. The glucagon labeling of islet cells was not additionally altered by heavy exercise in either the diabetic (50.7±2.1%, n=75; P=0.165) or the control (33.3±2.3%, n=84; P=1.000) rats.

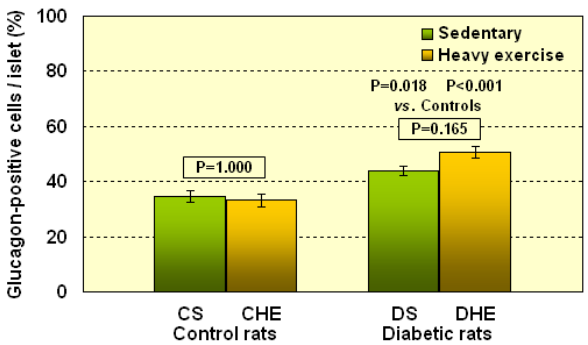


**Figure 4.** Graphs showing the pattern of distribution of glucagon-positive islets. Data are mean±SEM; the total number of islets evaluated was 68, 84, 84 and 75 in control sedentary (CS), control heavy exercise (CHE), diabetic sedentary (DS) and diabetic heavy exercise (DHE) groups, respectively.

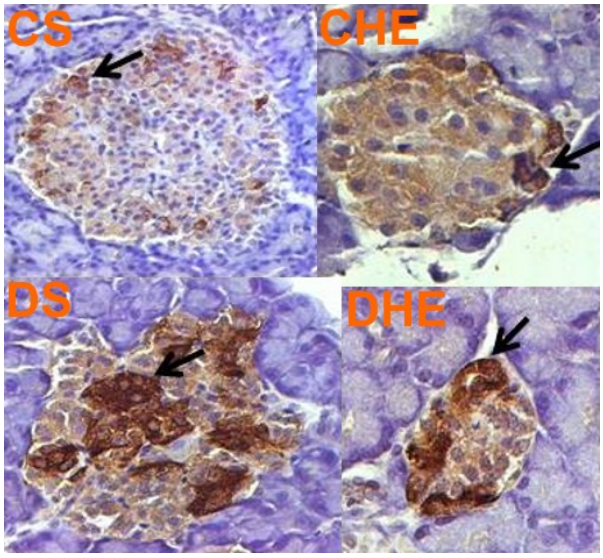


**Figure 5.** Light micrographs showing the pattern of distribution of somatostatin-immunoreactive cells (arrow) in the pancreatic islets of control sedentary (CS), control heavy exercise (CHE), diabetic sedentary (DS) and diabetic heavy exercise (DHE) rats. (Magnification: x200).

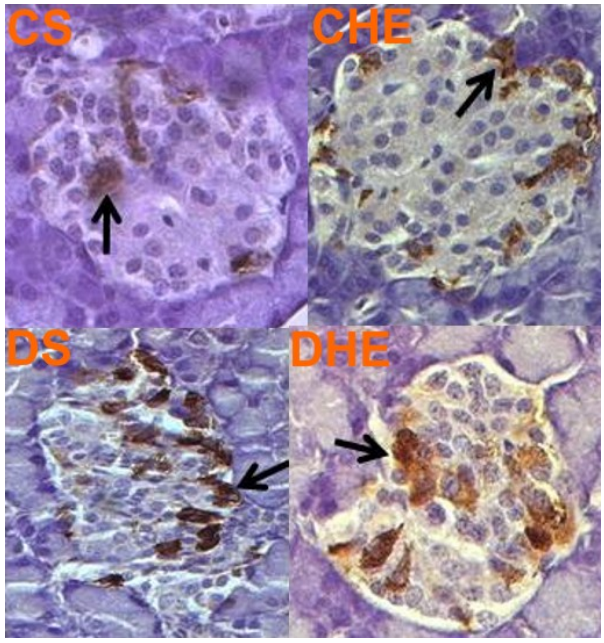


**Figure 7.** Light micrographs showing the pattern of distribution of pancreatic polypeptide-immunoreactive cells (arrow) in the pancreatic islets of control sedentary (CS), control heavy exercise (CHE), diabetic sedentary (DS) and diabetic heavy exercise (DHE) rats. (Magnification: x200).

### Somatostatin

Typical micrographs showing the distribution of somatostatin in the islets of the CS, CHE, DS and DHE rats are shown in Figure 5. The percentage distribution of somatostatin-positive cells from the CS, CHE, DS and DHE rats is shown in Figure 6. The percentage distribution of somatostatin-positive cells was not significantly (P=0.263) altered in DS (28.2±2.0%, n=77) as compared to CS (21.9±2.7%, n=73) rats. Somatostatin labeling of the islet cells was not significantly (P=1.000) altered by heavy exercise in either the diabetic (32.3±2.0%, n=74) or the control (19.4±1.7%, n=97) rats.

### Pancreatic Polypeptide

Typical micrographs showing the distribution of pancreatic polypeptide in the islets of the CS, CHE, DS and DHE rats are shown in Figure 7. The percentage distribution of pancreatic polypeptide-positive cells from the CS, CHE, DS and DHE rats is shown in Figure 8. The percentage distribution of pancreatic polypeptide-positive cells was significantly (P=0.014) increased in DS (20.8±1.6%, n=79) as compared to CS (12.7±1.8%, n=72) rats. Polypeptide labeling of the islet cells was not additionally altered by heavy exercise in either the diabetic (19.9±2.1%, n=62; P=1.000) or the control (16.2±1.4%, n=96; P=0.987) rats.

## DISCUSSION

The effects of heavy exercise on the distribution of pancreatic hormones in the STZ-induced diabetic rat were investigated. The exercise program commenced one week after the administration of STZ and

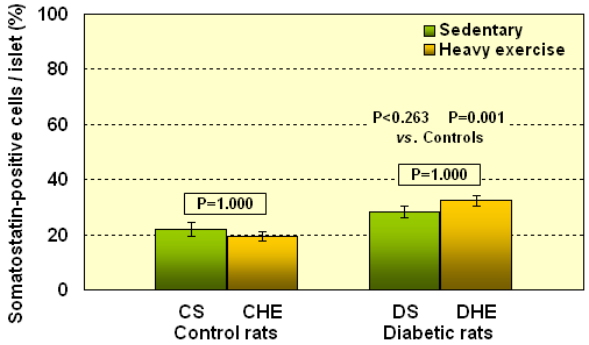


**Figure 6.** Graphs showing the pattern of distribution of somatostatin-positive islets. Data are mean±SEM; the total number of islets evaluated was 73, 97, 77 and 74 in control sedentary (CS), control heavy exercise (CHE), diabetic sedentary (DS) and diabetic heavy exercise (DHE) groups, respectively.

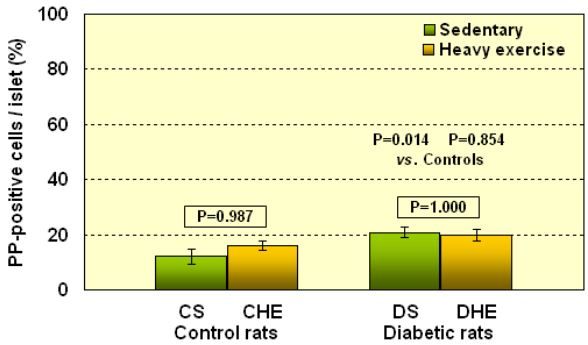


**Figure 8.** Graphs showing the pattern of distribution of pancreatic polypeptide-positive islets. Data are mean±SEM; the total number of islets evaluated was 72, 96, 79 and 62 in control sedentary (CS), control heavy exercise (CHE), diabetic sedentary (DS) and diabetic heavy exercise (DHE) groups, respectively.

continued for 12 weeks. The main findings of the study were that: i) the percentage of insulin-positive cells was lower in the islets of the diabetic rats as compared to the controls; ii) the percentage of glucagon-positive and pancreatic polypeptide-positive cells was higher in islets from the diabetic rats as compared to the controls; iii) the percentage of somatostatin-positive cells was similar in islets from the diabetic rats as compared to controls.

The study utilized a heavy exercise regime consisting of enforced running for one h/day, 5 days/week, for 12 weeks at a speed of 18 m/min at a belt gradient of 5%. Earlier studies in both normal and diabetic rats have demonstrated a close correlation between running speed and oxygen uptake suggesting that running speed can be used to assess training intensity [16]. It has also been shown in STZ-induced diabetic rats that, for treadmill speeds from 3 to 19 m/min, oxygen consumption increases progressively as a function of running speed, thus the relationship between the two can be expressed by a simple linear equation. Based only on running speed, i.e., without taking elevation into account, $O_2$ uptake would be equal to approximately 80% of $VO_2$ max [17]. For comparison, this would translate into approximately hard, strenuous running [18]. Thus, the duration and the intensity of exercise applied in the current study are comparable to previous studies which have demonstrated the effects of exercise on the cardiovascular system [19].

As expected, the body weight of the DS rats was significantly lower (62%) as compared to the CS rats and body weight was not additionally altered by heavy exercise in either the diabetic or the control rats. Our observation that body mass in the control rats and in the diabetic rats was not significantly influenced by exercise is consistent with data from some previous studies carried out on normal Sprague-Dawley rats trained on a treadmill for 14 weeks [20] and in STZ-induced diabetic rats trained on a treadmill using a progressive protocol set at 27 m/min for 1 h/day, 5 days/week for a total of 8 weeks [21]. Clearly, these exercise regimens and the animal models differed from our study. The disparity in exercise regimen and animal model may contribute to the difference in the results obtained. In other studies, where Zucker diabetic fatty (ZDF) rats, a model of type 2 diabetes, were subjected to a swimming regimen of 60 min/day, 3 days/week for a total of 12 weeks, body weight was not significantly different from the control and the exercise-trained ZDF rats [22].

Blood glucose of the DS rats was significantly higher (5-fold higher) as compared to the CS rats and blood glucose was not additionally altered by heavy exercise in either the diabetic or the control rats. Previous studies have demonstrated exercise-induced improvements in glucose metabolism including myocardial glucose oxidation and glycolysis, improved blood glucose levels and reduced ATP levels in diabetic rats [23, 24, 25]. It was somewhat surprising to find that heavy exercise did not appear to have any obvious effects on blood glucose. The disparity between these results and ours may be due to differences in the methodology used by the investigators. For example, Hall *et al*. [24] trained normal and diabetic Sprague-Dawley rats at 20 m/min for 60 min for 5 days/week for a total of 10 weeks. Mokhtar *et al*. [25] observed a slight but not significant decrease in blood glucose level in exercise-trained diabetic rats as compared to controls. In their study, they used 50 mg/kg body weight of STZ to induce diabetes in contrast to 60 mg/kg body weight of STZ in our study. This may contribute to the differences observed between their studies and ours. Another study which showed a beneficial effect on plasma glucose level was that of Tansey *et al*. [26]. They demonstrated that type 1 diabetic patients between 10 and 17 years of age had a significant reduction in blood glucose levels after 75 min of moderate exercise on a treadmill after school physical activity. It is therefore difficult to directly compare the results of Tansey *et al*. with ours due to the long duration of the exercise and different subjects.

However, it should be noted that some previous studies have also failed to demonstrate any significant effect of exercise on glycemic control or insulin levels in diabetic rats [13]. STZ-induced diabetic Sprague-Dawley rats trained on a treadmill using a progressive protocol set at 27 m/min, for 1 h/day, 6 days/week at a 10% inclination for a total of 10 weeks did not show any changes in blood glucose level [27].

Pancreatic islets are neuroendocrine organs which control blood glucose homeostasis. The precise interplay of beta, alpha, delta and pancreatic polypeptide cell populations results in a fine-tuned and balanced release of insulin, glucagon, somatostatin and pancreatic polypeptide hormones [28], and the patterns of distribution of the pancreatic islets within the pancreas vary from species to species [29]. The percentage of insulin-positive cells decreased and glucagon-positive cells increased in islets from diabetic rats as compared to controls. A previous study reported an increase in plasma glucagon in diabetic rats; this would be consistent with an increase in glucagon-positive cells in diabetic rat islets [30]. The decrease in insulin-positive cells can, for the most part, be attributed to the selective diabetogenic action of STZ on beta cells [31] and this, together with an increase in glucagon-positive cells and perhaps an increased release of glucagon, can explain the hyperglycemia observed in the diabetic rats.

Heavy exercise had no significant effect on insulin and glucagon immunolabeling of islet cells. The fact that exercise did not affect insulin cells is consistent with a previous study which showed that pancreatic insulin concentration was unaltered with training in diabetic rats [32]. General intense and/or prolonged exercise is normally associated with a decline in plasma insulin and an increase in glucagon [33]. Another study which employed different intensities of exercise prior to the administration of STZ demonstrated that exercise,

especially moderate exercise, has a protective effect on pancreatic beta-cells. Islet cell degeneration and weak insulin immunohistochemical staining were observed in STZ-induced diabetic rats and there was an increased intensity of staining for insulin and preservation of beta-cell numbers in the exercise-applied diabetic rats [10]. Costun *et al.* [10] subjected normal and STZ (50 mg/kg body weight)-induced diabetic Wistar rats to 15 min of swimming daily for 12 weeks. Again, the major differences between their study and ours do not allow for a direct comparison.

Somatostatin acts as a paracrine agent to inhibit both insulin and glucagon levels and therefore, to modulate their output [34, 35]. The percentage of somatostatin-positive cells was not significantly altered in DS as compared to CS rats and was not additionally altered by heavy exercise in either the diabetic or the control rats.

Pancreatic polypeptide may function as an important feedback inhibitor of pancreatic secretion after a meal [36]. The percentage of pancreatic polypeptide-positive cells was significantly increased in diabetic rats as compared to controls and was not additionally altered by heavy exercise in either the diabetic or the control rats. Previous experiments have demonstrated increases in plasma pancreatic polypeptide with exercise, with aging and in diabetic patients [36, 37]. STZ-induced diabetic rats gain less body weight as compared to controls; this may partly be attributed to the anorexic effects of pancreatic polypeptide which are exacerbated with exercise [38, 39, 40]. The percentage of the pancreatic polypeptide cells counted was slightly more elevated than normal [14]. The majority of the sections used for pancreatic polypeptide-positive cell morphometry were retrieved from the tail end of the pancreas which contains a relatively larger number of pancreatic polypeptide-positive cells.

The reasons for the absence of significant alterations in body weight, blood glucose and distribution of pancreatic hormones are not clear but may be due to several factors including: 1) the intensity of the exercise may not be appropriate for this type of animal model. Several studies have shown that moderate intensity exercise is more beneficial to achieving better glycemic control and regeneration of the pancreatic beta cells [10] as compared to heavy exercise. In fact, it has been shown that heavy exercise induces oxidative stress and may be harmful to an already compromised body [41, 42]; 2) the duration of the exercise regimen used in this study may not have been long enough to induce significant changes in the parameters measured; 3) the loss of insulin-producing pancreatic beta cells in STZ (60 mg/kg body weight)-treated rats may result in few or no beta cells left to stimulate; hence, no reduction in glucose level will be observed.

The role of exercise in controlling body weight is hardly needed in type 1 diabetes since most subjects would have normal or lean weight as compared to those with type 2 diabetes where most patients would be overweight or obese. Moreover, exercise training may induce unwarranted complications in type 1 diabetes, such as hypoglycemia [43]. Since the question of insulin resistance does not arise in type 1 diabetes, exercise training may not be as beneficial in type 1 as it is in type 2 diabetes where enhancement of insulin sensitivity is important in reducing insulin resistance.

In conclusion, alterations in the distribution of pancreatic hormones in STZ-induced diabetic rats are not normalized with heavy exercise.

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**Conflict of interest** The authors have no potential conflicts of interest

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