Exenatide-Induced Chronic Damage of Pancreatic Tissue in Rats

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Objective: The study aimed to explore exenatide-induced damage of pancreatic tissue in rats.

Methods: At first stage, 30 male rats were randomly divided into exenatide and control groups. At second stage, 10 male and 10 female rats were treated according to sex, exenatide dose and time, and with or without inhibitor. Exenatide was injected subcutaneously twice a day, and body weights were measured once a week. At approximately 10 weeks, blood and pancreatic tissue samples were harvested. Amylase, lipase, interleukin 1, interleukin 6, and tumor necrosis factor α in serums were determined. Pancreatic tissues were divided for dry-wet ratio, myeloperoxidase, hematoxylin-eosin staining, and electric microscope imaging.

Results: Compared with the control group, myeloperoxidase in pancreatic tissue of rats administered with exenatide exhibited a significantly high level; dry-wet ratio of pancreatic tissue in rats administered with exenatide exhibited a significantly low level. Chronic pancreatic damage was observed in 30% of rats from exenatide group for both sexes and showed pycnosis of acinar cells, increased cytoplasmic vacuoles, widened cellular gap, and inflammatory cell infiltration in pancreatic tissue. No pancreatic damage was observed in the control and the inhibitor groups. Histopathological evaluation scores in exenatide group were significantly higher than those of the control group.

Conclusion: Long-term administration of exenatide in rats can result in chronic pancreatic damage.

Key Words: exenatide, pancreatitis, amylase, cytokines, histopathology

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Exenatide, a human glucagon-like peptide 1 (GLP-1) analogue, is the first new incretin analogue on the market, which has the function to mimic the natural secretion of hormone in human body and can regulate blood glucose level. Since 2008, increasing incidence of pancreatitis has been reported.[1–5] Currently, clinical studies demonstrate that exenatide can induce acute pancreatitis; however, the definitive evidences and mechanism of exenatide-induced pancreatitis are still unknown. The correlation between exenatide and pancreatitis has been rarely reported. Recently, although Nachnani et al[6] reported that the extended use of exendin-4 in rats leads to pancreatic acinar inflammation and pycnosis, they did not further describe the edema situation, infiltration of inflammatory cells, and changes of intercellular substance and inflammatory cytokines. Therefore, exploring the relationship between exenatide and pancreatic tissue damage has important clinical significance. In this study, the effect of exenatide on pancreatic tissue of rats was further investigated from inflammatory cytokines and histopathological aspects, which will benefit exploration of possible causes of pancreatitis.

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MATERIALS AND METHODS

Animals

Animal experimental protocols were approved by the University Animal Care and Use Committee in the Association for Assessment and Accreditation of Laboratory Animal Care. At first stage, 30 Sprague-Dawley male rats weighing 250 to 320 g were randomly divided into 2 groups, which were designated as the exenatide group and control group. The rats were free to access food and water. After 1-hour feeding, the rats were administered with exenatide or normal saline. Animals were housed in individual cages in a room with constant temperature and humidity on a 12-hour light-dark cycle throughout the experiment period. At second stage, 10 male and 10 female rats were divided randomly into 5 groups; each group included 2 male and 2 female rats, for treatment of different time and dose, as well as with or without drug inhibitor.

Exenatide Administration and Specimen Collection

Highly purified exenatide (Capgemini Biomedical, Chengdu, China) was stored at −70°C and prepared as per needed dosages. According to previous publications,[7] at first stage, the rats in the exenatide group were administered with exenatide at a dose of 5 μg/kg through subcutaneous injection twice a day at 8:00 A.M. and 6:00 P.M., 1 hour before feeding. The whole experiment period was 10 weeks. At second stage, 1 group was treated with 2.5 μg/kg exenatide for 10 weeks, 2 groups were treated with 5 μg/kg exenatide for 8 and 10 weeks, 1 group was treated with 5 μg/kg exenatide for 10 weeks and for another 2 weeks without exenatide, and 1 group was treated with 5 μg/kg exenatide and 5 μg/kg GLP-1 receptor inhibitor (exendin 9-39) simultaneously for 10 weeks. Body weights of the rats were measured once a week for adjusting the dosage of exenatide. The rats in the control group were administered with saline at an identical volume. At the end of the experiment period, all rats were anesthetized with 2% pentobarbital at a dose of 40 mg/kg according to body weights through intraperitoneal injection. After the sequential procedure including laparotomy, venous chamber removal, heart exposure, and infusion to the left ventricle with 150 to 200 mL of 0.9% saline until the light color of the pancreas is achieved, pancreas tissue was harvested.

Histology

After killing the rats, pancreases were harvested and immediately placed in 10% buffered formalin (4% [vol/vol] formaldehyde). Specimens from each animal were paraffin embedded, and the 4-μm-thick sections were stained by hematoxylin and eosin. The degree of injury visible by light microscopy was

scored by 2 researchers, who were not aware of the slide identification, according to a technique previously described and applied by one of the researchers on the pancreas of experimental animals.[8–10] Organ damage was evaluated by the changes of pancreatic acini, ducts, small arteries, and interstitial matrix. A subjective rating for each slide ranging from 5 (minimal) to 40 (severe and extensive damage) was assigned to each component of the organ. In the previous publications, the components of the histopathological scoring system were strongly correlated.[8] Acinar damage was evaluated according to cellular morphology, pyramidal structure, regular patency of acinar lumens, the presence of inflammatory cells, the number of pycnotic nuclei, and the amount of intraluminal secretion of zymogenic granules. The severity of vasculitis was evaluated according to the thickness of the medial wall, reduction of the lumen, intima hypertrophy and the number of inflammatory cells in the adventitia, and the presence of intraluminal hemorrhages. The ductal changes reflected a more irregular disposition of the epithelial cells and the presence both of edema in the wall and of inflammation.

Determination of Amylase, Lipase, Interleukin 1, Interleukin 6, and Tumor Necrosis Factor α in Serums and Myeloperoxidase in Pancreatic Tissues

The collected blood was centrifuged at 3000*g* immediately for 10 minutes, and the supernatant was stored at −80°C for the analysis of amylase, lipase, interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α) by enzyme-linked immunosorbent assay (ELISA) kits (New Inspiration Biotechnology Company, Wuhan, Hubei, China) according to the manufacture's instructions. Pancreatic tissue was homogenized to obtain the supernatant and then subjected to myeloperoxidase (MPO) determination through its ELISA kit (New Inspiration Biotechnology Company) according to the manufacture's instructions.

Dry-Wet Ratio of Pancreatic Tissue

The fresh pancreatic tissue was weighed and then subjected to drying at 65°C for 48 hours. The dried pancreatic tissue was weighed again, and then, the dry-wet ratio of pancreatic tissue was calculated.

Electron Microscopic Examination of Pancreatic Tissue

The collected pancreatic tissue was subjected to fixing, gradient dehydration, soaking in acetone, embedding in the blocks, and semithin sectioning and double staining with uranyl acetate and lead nitrate. The imaging of pancreatic tissue was taken by using Nissan/H-7500 transmission electron microscope (Nissan, Japan).

Statistical Analysis

The data were expressed as mean (SD). The grade data were expressed as the mean rank. SPSS 13.0 software was used for data analysis. The effect of exenatide on body weight was evaluated by one-way analysis of variance. Results of ELISA and dry-wet ratio of pancreatic tissue samples were analyzed by *t* test. Pancreatic pathological scores were tested by rank method at the level of $\alpha = 0.05$.

RESULTS

Effect of Exenatide on Body Weight of Rats

There was no significant difference in body weights between the rats from exenatide group and those from the control group ($F = 0.021$, $P = 0.885$) at the beginning. In the first-stage experiment, after 10 weeks, compared with the control group, a significant reduction in the body weights of the exenatide-treated rats was observed ($F = 21.812$, $P < 0.001$), which revealed a 16% reduction in the body weights of the rats treated with exenatide, as shown in Figure 1A. In the second-stage experiment, there was a difference in the growth between male and female rats in the 5 groups. As shown in Figure 1B, for both males and females, compared with the exenatide + inhibitor rats, exenatide-treated rats in other groups had less body weight (male, $P = 0.0006$; female, $P = 0.01$). Between the first-stage and second-stage experiments, 10-week male rats showed similar body weights ($P = 0.14958$).

Serum Amylase and Lipase in Control and Exenatide-Treated Rats

Direct assays of amylase and lipase activities in serum were performed in 96-well plates (BioAssay Systems). α-Amylase and lipase are important exocrine pancreatic enzymes. The mean (SD) serum amylase value in the rats from exenatide group was 1001.40 (142.79) U/L, whereas the mean (SD) serum amylase value in the rats from the control group was 986.13 (146.17) U/L, which did not exhibit a significant difference ($P = 0.77$). Similarly, serum lipase did not reveal a significant difference between the exenatide group and the control group either (mean [SD], 5.30 [0.58] U/L and 5.11 [0.47] U/L, $P = 0.92$) (Fig. 2).

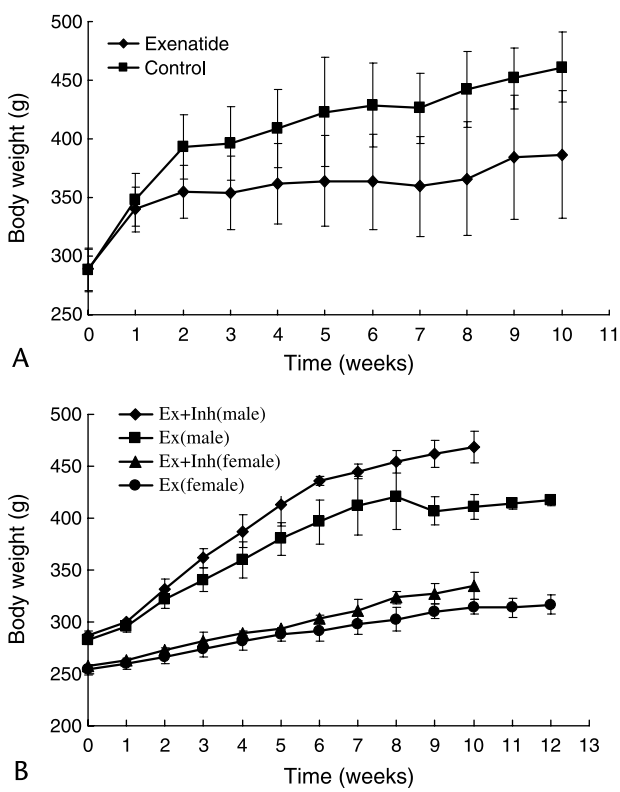

FIGURE 1. Correlation of exenatide application with body weight during the period of the study. Rats were weighed at weekly intervals. A, In the first-stage experiment, there was a significant difference in the body weight of the rats from 2 groups during the period of the study (10 weeks; n = 15 per group). B, In the second-stage experiment, for both male and female rats, compared with the exenatide + inhibitor rats, exenatide rats in other groups had less body weight (male, $P = 0.0006$; female, $P = 0.01$), respectively. Symbols indicate the mean body weight; vertical lines indicate SD.

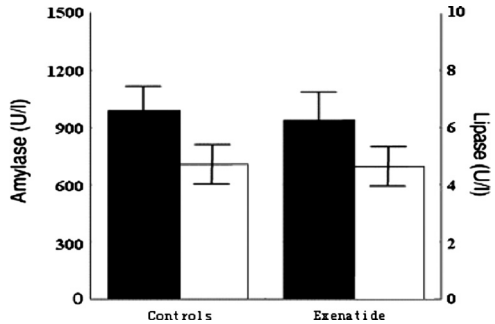

FIGURE 2. Serum amylase (black bars) and lipase (white bars) levels in the control and exenatide-treated rats were determined. Serum from both groups was assayed by quantitative colorimetric enzyme tests. The serum amylase in the rats from the exenatide group was 1001.40 (142.79) U/L, whereas the serum amylase in the rats from the control group was 986.13 (146.17) U/L, which revealed a nonsignificant difference ($P = 0.774$). Serum lipase exhibited 120-fold magnification with nonsignificant difference in the exenatide group when compared with the control group (5.30 [0.58] and 5.11 [0.47] U/L, $P = 0.924$). All data were expressed as mean (SD).

Effect of Exenatide on the Contents of Cytokines and MPO

The contents of cytokines and MPO in the serum of the rats from the control and exenatide groups were performed in 96-well plates (BioAssay Systems). Compared with the control group, the contents of IL-1, IL-6, and TNF-α in the serum of the rats administered with exenatide did not exhibit a significant difference (mean [SD], 2.26 [0.8] vs 2.14 [0.79], $P = 0.694$; 22.43 [13.53] vs 19.79 [12.7], $P = 0.587$; 26.26 [5.68] vs 27.76 [9.09], $P = 0.594$), whereas a significant increase of MPO in the rats from the exenatide group was observed when compared with the control group (mean [SD], 0.24 [0.07] vs 0.18 [0.05], $P = 0.043$) (Table 1).

Effect of Exenatide on Dry-Wet Ratio of Pancreatic Tissue

The dry-wet ratio is an important index indicating the degree of tissue edema. The dry-wet ratio of pancreatic tissue in the rats administered with exenatide was significantly lower than that of the rats from the control group (mean [SD], 0.183 [0.049] vs 0.256 [0.064], $P = 0.02$), as shown in Figure 3.

TABLE 1. Indices of Exenatide-Induced Rat Serums and Pancreatic Tissues Damage

Detection Index	Exenatide Group, n = 15	Control Group, n = 15	*P*
IL-1, pg/mL	2.14 (0.79)	2.26 (0.89)	0.694
IL-6, U/L	19.79 (12.76)	22.43 (13.53)	0.587
TNF-α, pg/mL	27.76 (9.09)	26.26 (5.68)	0.594
MPO, U/L	0.24 (0.07)	0.18 (0.05)	0.043

Values are expressed as mean (SD).

The contents of IL-1, IL-6, and TNF-α in the serum and MPO in pancreatic tissues were determined. Compared with the control group, the contents of IL-1, IL-6, and TNF-α in serums of the rats administered with exenatide did not exhibit a significant difference ($P > 0.05$), whereas MPO was significantly increased in the exenatide group when compared with the control group ($P = 0.043$).

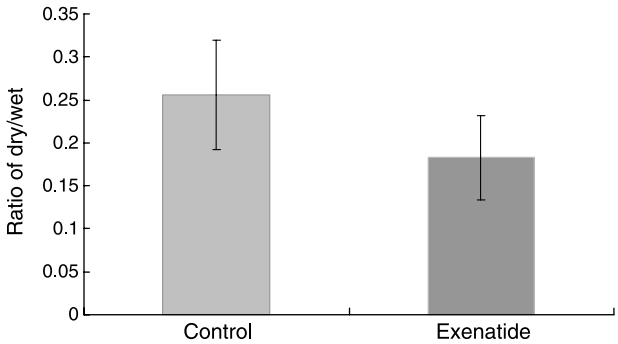

FIGURE 3. Effect of exenatide on dry-wet ratio of pancreatic tissue. The dry-wet ratio is an important index to express the degree of tissue edema. The dry-wet ratio of pancreatic tissue in the rats administered with exenatide was significantly lower than that of the rats from the control group (mean [SD], 0.183 [0.049] vs 0.256 [0.064], $P = 0.02$).

Hematoxylin-Eosin Staining of Pancreatic Tissue

The pancreatic tissue samples from 11 rats (5 from the exenatide group in first-stage experiment and 6 from the exenatide groups in second-stage experiment) exhibited typically chronic inflammatory change such as fibrosis, atrophy, inflammatory cell infiltration, and edema. Pancreatic tissue samples from the rats in the control group of the first-stage experiment and the exenatide + inhibitor group of the second-stage experiment did not exhibit inflammatory change, as shown in Figure 4.

Scanning Electron Microscope Examination

Under the scanning electron microscope examination, pycnosis change in acinar cells, increased cytoplasmic vacuoles, widened cellular gap, and inflammatory cell infiltration were observed in 5 pancreatic tissue samples from the rats administered with exenatide. On the other hand, normal nucleus shape, a small amount of cytoplasmic vacuoles, and no inflammatory cell infiltration were observed in the pancreatic tissue of the rats from the control group, as shown in Figure 5.

Pancreatic Pathological Evaluation Scores

According to the pathological evaluation score standard established by previous studies[11] and the pancreatic tissue lesion scores by the improved method of Schmidt et al,[12] the degree of damage of pancreatic tissue was evaluated. Compared with the control group, lesion area, fibrosis, inflammation, and edema of pancreatic tissue from the rats administered with exenatide revealed a significant difference. Pathological scores for 5 cellular variables analyzed in sections of the pancreas from the 2 groups are shown in Figure 6. Compared with the control rats, the rats treated with exenatide had more significant inflammation change in the aspects of lesion area, gland atrophy, edema, fibrosis, and inflammatory cell infiltration ($P = 0.016$).

In the second-stage experiment, using 2.5 μg/kg exenatide for 10 weeks for 1 group, the 2 male rats showed inflammatory pancreas. In the group treated with 5 μg/kg exenatide for 8 weeks, 1 male and 1 female rat had inflammatory pancreas. One male in the group treated with 5 μg/kg exenatide for 10 weeks and 1 female in the group treated for another 2 weeks without exenatide were found with inflammatory pancreas. In total, the damage rate in exenatide group is 6 of 16 rats in our second-stage experiment, ratio being similar as that of the first-stage experiment.

DISCUSSION

The study of Nachnani et al[6] has shown that exenatide can induce inflammatory change in pancreatic tissues, pycnosis change in acinar cells, and significant increase of serum lipase. In this study, no significant difference of serum amylase and lipase levels between the exenatide group and the control group was observed. In addition, to further explore the effect of exenatide-induced pancreatic inflammatory change on the

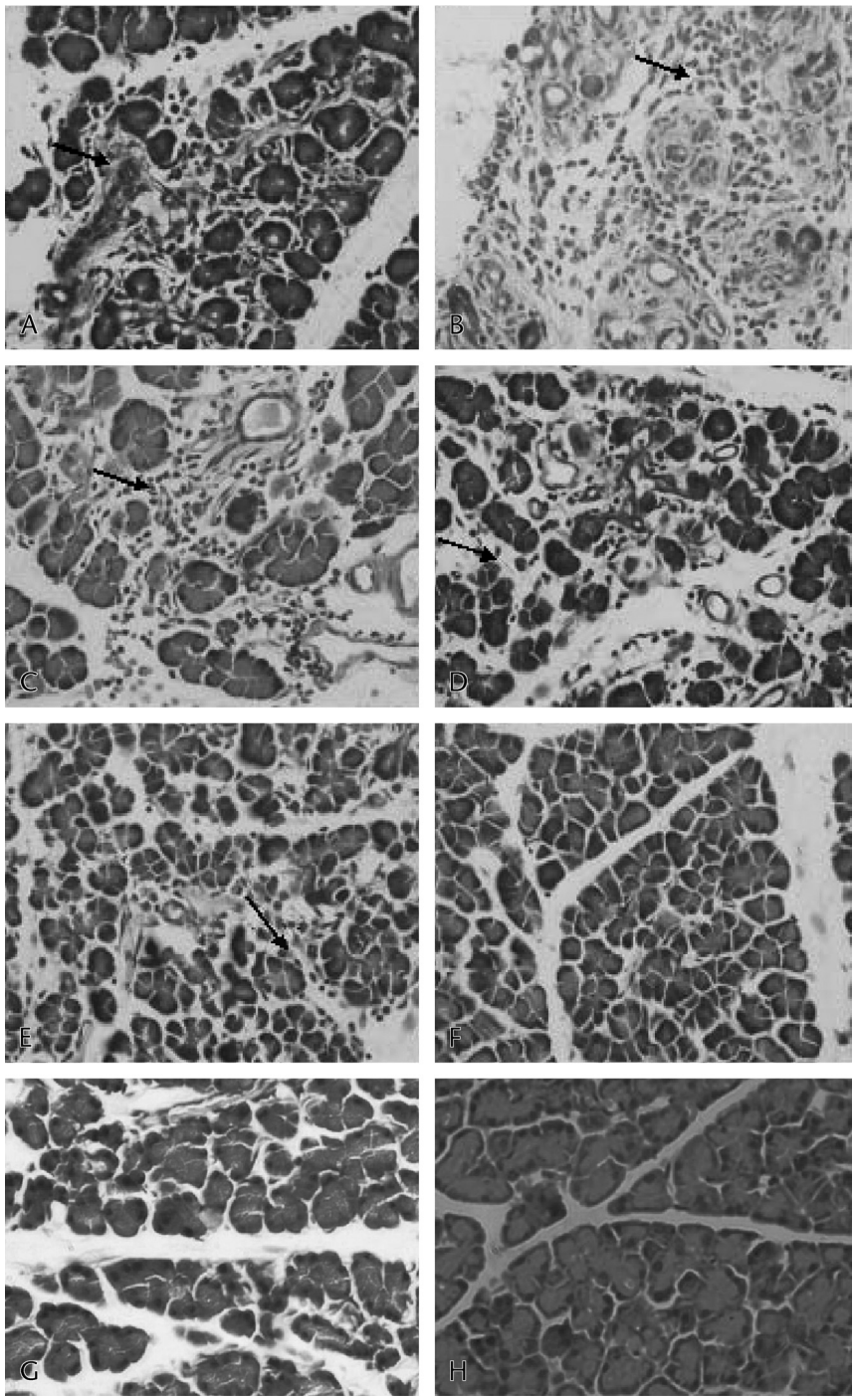

FIGURE 4. Representative imaging of pancreatic tissue hematoxylin-eosin staining in the exenatide and control groups. A, The change of pancreatic tissue fibrosis in the exenatide group (original magnification, ×400). B, The atrophic change of pancreatic tissue in the exenatide group (original magnification, ×400). C, Inflammatory cell infiltration of pancreatic tissues in the exenatide group (original magnification, ×400). D, The change of pancreatic tissue edema in the exenatide group (original magnification, ×400). E, Inflammatory cell infiltration of pancreatic intercellular substance in the exenatide group (original magnification, ×400). F, No pancreatic damage change in the control group (original magnification, ×400). G, The slight edema of pancreatic tissue in the exenatide female rat. H, No pancreatic damage change in the exenatide + inhibitor female rat.

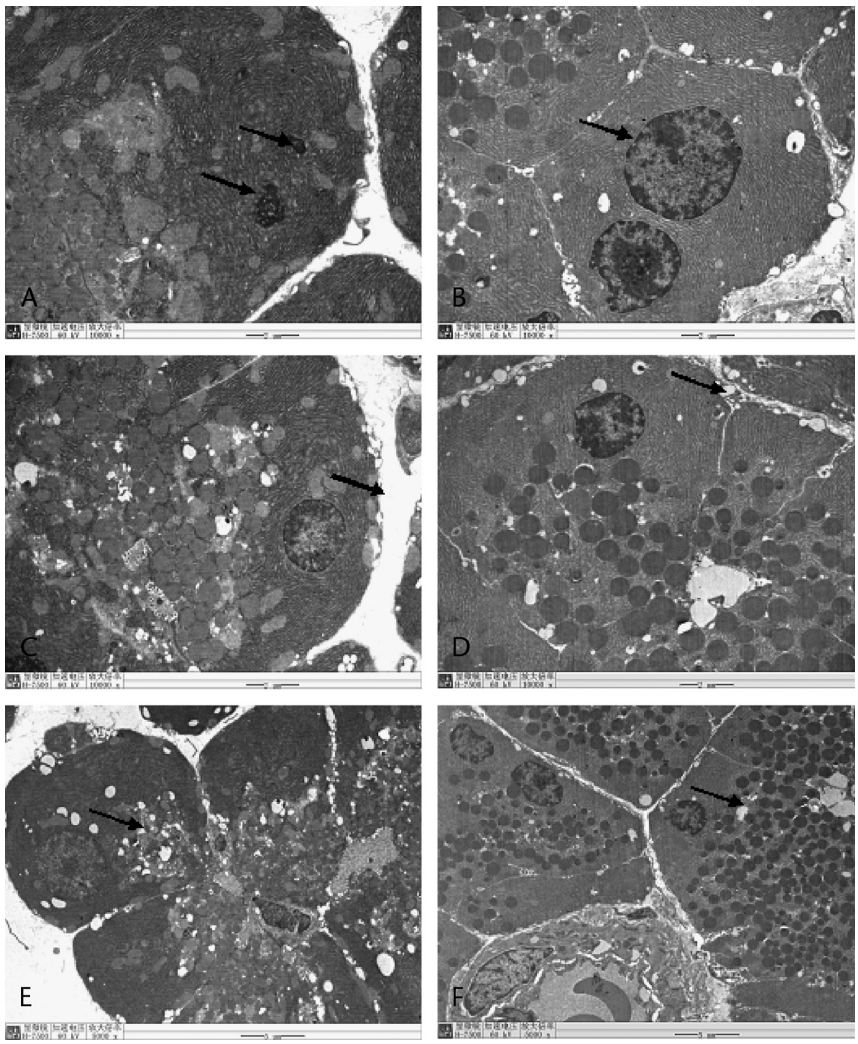

FIGURE 5. Images of SEM of pancreatic tissue from the exenatide and control groups. A, The change of pycnosis in acinar cells from the exenatide group (original magnification, ×10,000). B, Normal nuclei of acinar cells from the control group (original magnification, ×10,000). C, Widened gap of acinar cells from the exenatide group (original magnification, ×10,000). D, Normal gap of acinar cells from the control group (original magnification, ×10,000). E, Significantly increased acinar cell vacuoles from the exenatide group (original magnification, ×5000). F, A small amount of acinar cell vacuoles from the control group (original magnification, ×5000).

systemic inflammatory response of rats, the contents of serum IL-1, IL-6, and TNF-α in rats were determined, which exhibited no significant difference (Table 1). The possible reason is that the lesion in pancreatic tissue is a local chronic pancreatitis with a smaller lesion area, which is not enough to result in an obvious change of serum amylase and lipase levels and in a systemic inflammatory change.

There was a difference in body weight between no-damage exenatide treatment (10 rats) and control rats (15 rats) at 10 weeks for the first-stage experiment. In our second-stage experiment, we carefully examined the pancreas pathology and found that, besides the 6 rats with pancreas inflammation, other 10 rats with exenatide treatment had slight pancreas inflammation on the basis of lesion area, gland atrophy, fibrosis, edema, and inflammatory cells. The group with exenatide + inhibitor treatment (4 rats) had no pancreas inflammation. Actually, there was a difference in body weight between 10 rats with slight pancreas inflammation and 4 rats with exenatide + inhibitor treatment at 10 weeks.

We have included both male and female rats in our second-stage experiment. Exenatide treatment had effects on both male and female rats. One female in the group treated with 5 μg/kg exenatide for 8 weeks had inflammatory pancreas. One female

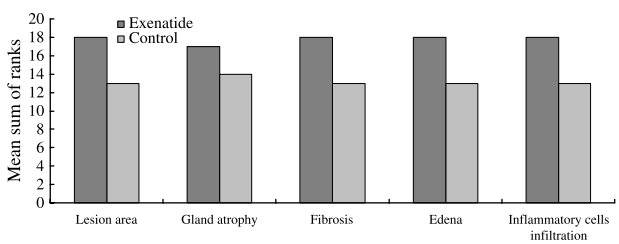

FIGURE 6. Statistical evaluation of pathological scores in the control (red bars) and exenatide (blue bars) groups were summarized. Tissue sections of the control (n = 15) and exenatide-treated (n = 15) rats were evaluated by 2 pathologists unaware of the identity of the slides. Statistically significant differences between the 2 groups were observed for lesion area ($P = 0.016$), fibrosis ($P = 0.016$), edema ($P = 0.016$), and inflammatory cell infiltration ($P = 0.016$).

in the group treated with 5 μg/kg exenatide for 10 weeks and treated for another 2 weeks without exenatide was found with inflammatory pancreas. It seemed that the effect of exenatide treatment on female rats (2/6) was slighter than that on male rats (4/6).

The pathological data in this study suggest that exenatide is a significant factor in producing pancreatic inflammation in pancreatic acinar cells and intercellular substance of exenatide-treated rats compared with control rats. Pancreatic effects were also confirmed biochemically in the previous study with exenatide-treated rats demonstrating significantly higher lipase values than those of the controls.[8] This information is valuable given the recent increase in the number of patients experiencing acute pancreatitis associated with the use of exenatide. In the study of Nachnani et al,[6] serum lipase revealed a 2-fold increase in the exenatide group compared with the control group, but serum amylase did not exhibit a significant increase. In the present study, no significant difference of serum amylase and lipase levels between the exenatide group and the control group was observed although both serum amylase and lipase levels had a slight increase (Fig. 2). There are several possible explanations for the association of pancreatitis with the use of exenatide. In 2007, the study of Wan et al[13] suggested that, maybe, exenatide stimulate exocrine and endocrine pancreatic secretions through local and central neurons of the vagus. Another explanation is that the lipoprotein and endocrine changes leading to weight loss may contribute to pancreatic effects.[14] Exenatide is known to cause human weight loss,[14] and indeed, the animals in the present study lost significant weight with 16% in the exenatide group (Fig. 1). In another study by Koehler et al,[15] they found that GLP-1 receptor activation increased the pancreatic mass and selectively modulated expression of genes associated with pancreatitis. In that study, although ductal GLP-1 receptor expression was not altered, it was postulated that the pancreatic effects could be related to increased GLP-1 concentrations.

The pathological evaluation of pancreatic tissue showed that 5 pancreatic tissue samples from the 15 rats administered with exenatide had typically chronic pancreatic inflammatory change, including interstitial edema, inflammatory cell infiltration, glandular atrophy, and fibrosis, but no obvious pancreatic tissue change was observed in the rats from the control group (Fig. 4). In the second-stage experiment, the damage rate in exenatide is 6 of 16 rats, the ratio being similar as that of the first-stage experiment. Except for glandular atrophy, pathological scores of pancreatic lesion, fibrosis, inflammation, and edema in the pancreatic tissue of the rats from the exenatide group exhibited a significant difference when compared with the control group (Fig. 6). In addition, ultrastructure change such as widened gap of acinar cells and inflammatory cell infiltration in pancreatic tissue from the rats administered with exenatide has complied with the pancreatic inflammatory change (Fig. 5). In the present study, exenatide-induced pancreatitis in rats was first confirmed by an ultrastructure evaluation of the pancreas. Although the study of Nachnani et al has shown that the differences between controls and exenatide-treated animals were not very striking, a slight difference in size and shape of the exocrine pancreatic cells and a more intense eosinophilic staining of the cellular secretion were counterweighed by a more intense basophilic stain in the pancreatic acinar cells of the controls.[6] They found that there were more pycnotic nuclei and evidence of moderate fibrotic changes in the vascular and the ductal walls of rats receiving exenatide.[6] Moreover, MPO as a neutrophil-specific enzyme can indirectly reflect infiltration number and activation degree of neutrophil cells in tissues, which is a clear evidence of tissue damage induced by local inflammation. Dry-wet ratio of pancreatic tissue also can indirectly reflect the change of vascular permeability and the degree of tissue edema. In this study, significantly increased MPO content and dry-wet ratio of pancreatic tissue in the rats administered with exenatide also supported that exenatide might induce pathological inflammatory change and edema of pancreatic tissue (Table 1 and Fig. 3).

The exenatide-induced pancreatic lesion during its clinical application has only been reported in recent years. Although there were no obvious evidences of exenatide-induced acute pancreatitis during its long-term application in our study, chronic inflammatory change in pancreatic tissue of the exenatide-treated rats was partly observed. At this point, it is different from the results of Nachnani et al. However, the pathways and mechanisms of exenatide-induced pancreatic histopathological damage are still not clear and need to be further explored. We speculate that exenatide possibly activates pancreatic stellate cells to induce fibrosis change while promoting insulin secretion of islet cells.

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