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Effect of inhibition of α-glucosidase on age-related glucose intolerance and pancreatic atrophy in rats

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Abstract

Oral administration of α-glucosidase inhibitor reduces postprandial serum glucose and insulin concentrations; thus, α-glucosidase inhibitor is used for the treatment of diabetes mellitus worldwide. In our study, we have evaluated the effect of α-glucosidase inhibitor, acarbose, on age-related glucose intolerance and pancreatic atrophy in the Long-Evans Tokushima Otsuka (LETO) rat. The first group of rats received a standard rat diet (control). The second group received a diet containing acarbose (150 mg/100 g food) from 12 to 28 weeks and then switched to a standard rat diet until 72 weeks of age (A12-28W). The third group was administered the same diet containing acarbose from 12 to 72 weeks of age (A12-72W). Fasting serum glucose and insulin concentrations gradually increased with increasing age in the control group, but these increases were completely prevented (A12-72W) or delayed (A12-28W) by acarbose treatment. In addition, acarbose treatment prevented the deterioration in insulin resistance with increasing age. At 72 weeks of age, pancreatic wet weight and DNA content in the A12-72W group were significantly higher than those in the control group. Although most islets were enlarged, and some portions of pancreatic tissue contained fatty and connective tissue in the control group, these alterations were mild in the A12-28W group and remained minimal in the A12-72W group. Our study suggests that acarbose is useful in the prevention of age-related glucose intolerance and pancreatic atrophy.

1. Introduction

Although the treatment of type 2 diabetes mellitus has become increasingly sophisticated during the last decade [1-3], normalization of blood glucose levels is seldom achieved [4]. Because type 2 diabetes mellitus often has an insidious onset associated with the presence of hyperglycemia for many years before the diagnosis, some patients already have vascular complications at diagnosis, and numerous patients later develop micro- and/or macroangiopathy. Therefore, the worldwide increase in type 2 diabetes mellitus is a major health concern as it is associated with excess morbidity, mortality, and substantial health care costs [5]. The prevention of type 2 diabetes mellitus is thus regarded as a pertinent health care issue.

The α-glucosidase inhibitor, acarbose, retards carbohydrate digestion by inhibiting α-glucosidases that hydrolyze disaccharides and oligosaccharides into monosaccharides in the small intestine and thereby reduces postprandial glucose and insulin responses [6,7]. Therefore, the α-glucosidase inhibitor is generally used for the treatment of type 2 diabetes mellitus in combination with diet or other antidiabetic agents [8-13]. In addition, previous studies also reported that acarbose is effective for the treatment of type 1 diabetes mellitus [14] and impaired glucose tolerance (IGT) [15]. Recently, the randomized controlled prospective trial, the Study TO Prevent Non–Insulin Dependent Diabetes Mellitus (STOP-NIDDM), demonstrated the potential efficacy of acarbose in preventing or delaying progression of IGT to type 2 diabetes mellitus [16].

Aging in both humans and animals is associated with elevated fasting and postprandial plasma insulin concentrations, suggesting an insulin-resistant state [17-20]. Indeed, there is a high prevalence of IGT and type 2 diabetes mellitus in the elderly [21]. The interaction of many factors associated with aging, including increased adiposity, decreased physical activity and muscle volume, medications, and insulin secretory defects, may contribute to

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alterations in glucose tolerance. Because acarbose improves insulin sensitivity in subjects with glucose intolerance through the combined effects of decreased glucose toxicity and reduced down-regulation of the insulin receptor [15], administration of acarbose seems to be an appropriate therapy for age-related glucose intolerance. However, the effect of acarbose on age-related glucose intolerance has been poorly defined to date. A recent study [22] reported that acarbose was unable to reverse beta-cell dysfunction in the elder people with IGT. However, this study was conducted only for 6 weeks, and the effect of acarbose on progression to IGT with advancing age was not examined. On the other hand, the pancreas undergoes a continuous aging process leading to alterations such as atrophy, fatty infiltration, fibrosis [23], and thereby results in dilation of pancreatic duct [24]. However, the effect of acarbose on the alterations in the pancreas with aging has not been examined. Because acarbose does not induce hypoglycemia and has a good safety profile [25], and it has been used most widely among α-glucosidase inhibitors, we designed the present study to assess the effects of acarbose treatment on age-related glucose intolerance and alterations in the pancreas in the Long-Evans Tokushima Otsuka (LETO) rat.

2. Materials and methods

2.1. Animals

Male LETO rats aged 5 weeks were supplied by the Otsuka Pharmaceutical (Tokushima, Japan). Long-Evans Tokushima Otsuka rat strain was established in the Tokushima Research Institute of Otsuka Pharmaceutical from an outbred colony of Long-Evans rats that had been purchased from Charles River Canada (Montreal, Canada) [26]. The LETO line originated from the same colony of spontaneously diabetic strain, the Otsuka Long-Evans Tokushima Fatty (OLETF) rats, and the genetic profiles of LETO rats were similar to those of OLETF rats. Although the LETO line has not shown diabetes mellitus, serum insulin concentrations tended to increase with aging [26]. The rats were maintained in a temperature-controlled (23°C ± 2°C) and humidity-controlled (55% ± 5%) room with a 12-hour light-dark cycle (lights on at 7:00 AM) and received humane care according to the guidelines at our institution. This experimental protocol was approved by our institutional animal welfare committee.

2.2. Administration of acarbose

Standard rat diet consisting of 54.8% carbohydrate, 23.4% protein, 5.1% fat, 3.6% dietary fiber, and 13.1% others (wt/wt) (15.046 kJ [3.596 kcal/g] diet; Oriental Yeast, Tokyo, Japan) was powdered, and α-glucosidase inhibitor, acarbose (a generous gift from Bayer Pharmaceutical, Osaka, Japan), was added and thoroughly mixed to a final concentration of 150 mg/100 g food. Acarbose concentration was selected based on the data from our previous studies [27-30]. The drug-diet powder mixture was reconstituted into pellets with a normal appearance.

2.3. Experimental protocol

Rats were randomly divided into 3 groups at 12 weeks of age. The first group received a standard rat diet throughout the entire experimental period (control). The second group received the diet containing acarbose from 12 to 28 weeks and then switched to a standard diet until 72 weeks (A12-28W). The third group received the same acarbose diet from 12 to 72 weeks of age (A12-72W). All groups of rats were allowed free access to food and water throughout the experimental period. The body weight and food intake were measured weekly, and fasting serum glucose and insulin concentrations were determined every 4 weeks. At 12, 36, 52, and 70 weeks of age, intravenous glucose tolerance test (IVGTT) was performed. For IVGTT, rats were fasted overnight, and anesthesia was induced by sodium pentobarbital (50 mg/kg body weight, IP), and then a bolus dose of 0.2 g/kg body weight glucose was injected into the jugular vein. Blood samples were collected before and at 5, 10, 30, and 60 minutes after glucose loading to determine serum concentrations of glucose and insulin. The areas under the curve (AUCs) for insulin and glycemic response to intravenous glucose load were evaluated.

At 72 weeks of age, the rats were fasted overnight and anesthetized with pentobarbital (50 mg/kg body weight). Blood samples were taken from jugular vein for determination of serum cholesterol and triglyceride (TG) and plasma cholecystokinin (CCK) concentrations. The abdomen was opened to remove the pancreas and adipose depots. The pancreas was cleared of lymph nodes and fat and weighed. White adipose depots were collected from the retroperitoneum, mesentery, and epididymis and then weighed. A splenic portion of the pancreas was frozen at −80°C until measurement of pancreatic contents of DNA, protein, enzymes, and insulin.

2.4. Histologic examination

A duodenal portion of the pancreatic tissue was fixed overnight in 4% buffered neutral paraformaldehyde solution, embedded in paraffin, and deparaffinized by standard procedure. Thin sections (5 μm) were stained with hematoxylin-eosin for light microscopic examination. Immunohistochemistry for tumor necrosis factor α (TNF-α) was performed using goat antimouse TNF-α antibody in 1:10 dilution (Santa Cruz Biotechnology, Santa Cruz, CA). The primary antibody was visualized using the labeled streptavidin-biotin method available as a commercial kit (Dako, Carpinteria, CA) according to the instructions provided by the manufacturer [30]. Volume density of islets was quantified by using an Axiophot microscope (Carl Zeiss, Eching, Germany) connected to an interactive image analysis system (IBAS, Carl Zeiss). For each pancreatic specimen, 8 nonoverlapping fields of hematoxylin-eosin staining (n = 6) were randomly selected at a magnification

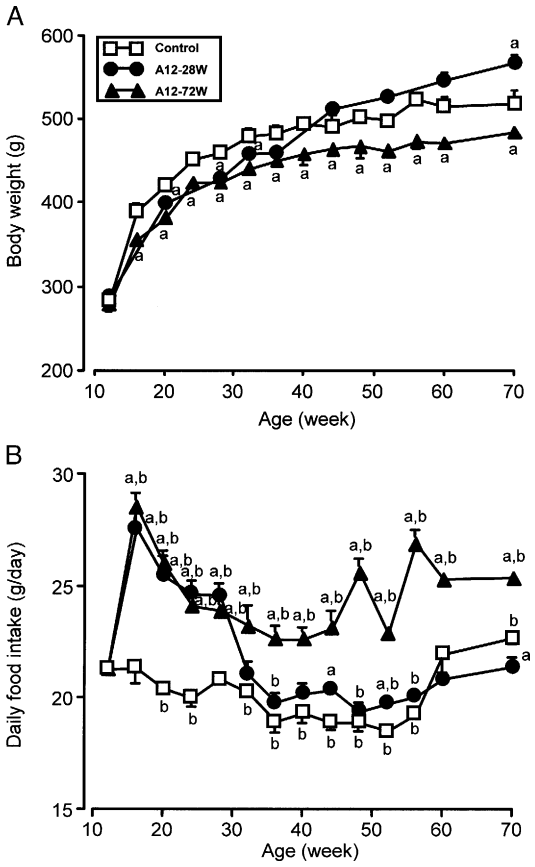

Fig. 1. Serial changes in body weight (A) and daily food intake (B) in rats treated with or without acarbose. Data are presented as mean ± SEM of 7 to 9 rats. [a]Significant difference vs control value at corresponding time point. [b]Significant difference vs value at 12 weeks of age in the same group. The control group (□) was given standard rat diet. The A12-28W group (●) received a diet containing acarbose from 12 to 28 weeks of age and then switched to standard rat diet until 72 weeks of age. The A12-72W group (▲) was maintained on a diet containing acarbose from 12 to 72 weeks of age.

×100. Volume density of islets was indicated as a percentage of total specimen using the following equation: total cross sectional area of islets/total area of specimen.

2.5. Assays

The pancreas was homogenized in a 0.15 mol/L sodium chloride solution using a motor-driven, Teflon-coated glass homogenizer. The homogenates were filtered through 3 layers of gauze and then sonicated for 1 minute. The aqueous phase was used for protein, enzymes, and DNA assay. Insulin was extracted by a modified method of Davoren [31]. Protein concentration in the pancreatic homogenate was measured using the method of Lowry et al [32] with bovine serum albumin (BSA) as a standard. Pancreatic DNA was measured fluorometrically by the reaction between 3,5-diaminobenzoic acid and deoxyribose sugar using calf thymus DNA as a standard [33]. Insulin concentrations in serum and pancreatic homogenates were determined by radioimmunoassay [34] using a commercially available kit (ShionoRIA, Shionogi Pharmaceutical, Osaka, Japan) with crystalline insulin of the strain of rats (Novo Industria, Copenhagen, Denmark) as a reference standard. Serum glucose concentration was determined by the glucose oxidase method using a commercially available kit (Glucose-E reagent; International Reagents, Kobe, Japan) [35]. Plasma CCK concentration was measured by a sensitive and specific radioimmunoassay using antiserum OAL-656 with CCK-8 as a standard [36]. Serum cholesterol and TG concentrations were analyzed enzymatically using commercially available kits (Wako Pure Chemical, Tokyo, Japan).

2.6. Evaluation of insulin resistance

Insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-R) calculated with the following formula: fasting insulin (mU/mL) × fasting glucose (mmol/L)/22.5, as described by Matthews et al [37]. Homeostasis model assessment of insulin resistance was calculated at 12, 36, 52, and 70 weeks of age.

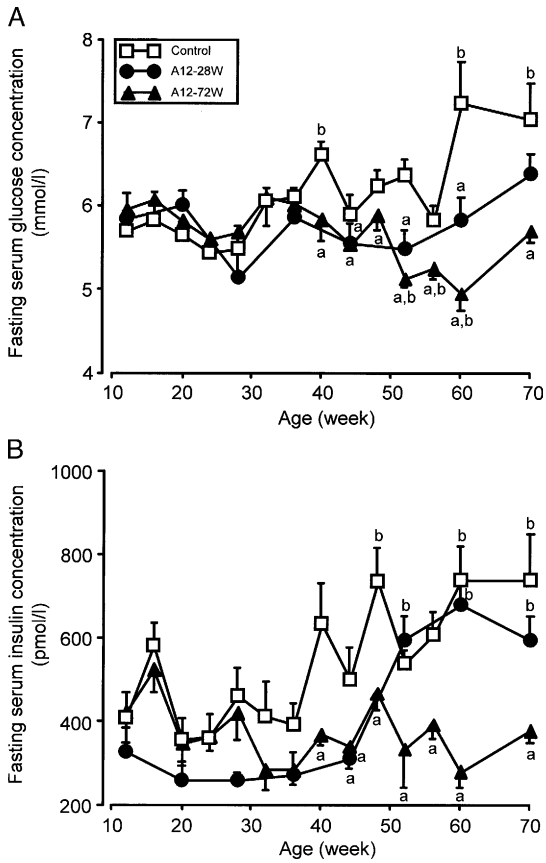

Fig. 2. Serial changes of fasting serum glucose (A) and insulin (B) concentrations in rats treated with or without acarbose. Data are presented as mean ± SEM of 7-9 rats. [a]Significant difference vs control value at corresponding time point. [b]Significant difference vs value at 12 weeks of age in the same group. The control group (□) was given standard rat diet. The A12-28W group (●) received a diet containing acarbose from 12 to 28 weeks of age, and then switched to standard rat diet until 72 weeks of age. The A12-72W group (▲) was maintained on a diet containing acarbose from 12 to 72 weeks of age.

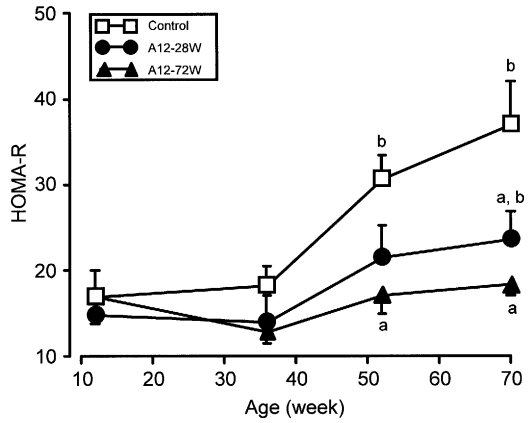

Fig. 3. Serial changes of HOMA-R in rats treated with or without acarbose. Data are presented as mean ± SEM of 7 to 9 rats. [a]Significant difference vs control value at corresponding time point. [b]Significant difference vs value at 12 weeks of age in the same group. The control group (□) was given standard rat diet. The A12-28W group (●) received a diet containing acarbose from 12 to 28 weeks of age and then switched to standard rat diet until 72 weeks of age. The A12-72W group (▲) was maintained on a diet containing acarbose from 12 to 72 weeks of age.

2.7. Statistical analysis

Each experiment was performed in 7 to 9 rats, and results are expressed as the mean ± SEM. Statistical analysis was performed by analysis of variance followed by Fisher exact test using StatView (Abacus concepts/Brain Power, Berkeley, CA). Differences with $P < .05$ were considered to be statistically significant.

3. Results

3.1. Body weight and daily food intake

There was a significant body weight gain with increasing age in all the experimental groups of rats. However, acarbose treatment slightly, but significantly lowered body weight compared with that in the control group. The body weight gain in the A12-28W group gradually increased after switching to the standard diet (Fig. 1A).

The food intake in the control group gradually decreased until 52 weeks of age, but thereafter it gradually increased. The food intake in the A12-28W and A12-72W groups immediately and markedly increased after switching to acarbose diet, but returned to the control levels in the A12-28W group after withdrawal of acarbose diet (Fig. 1B).

3.2. Fasting serum glucose and insulin concentrations

Fasting serum glucose concentration in the control group gradually increased with age. Indeed, significant differences

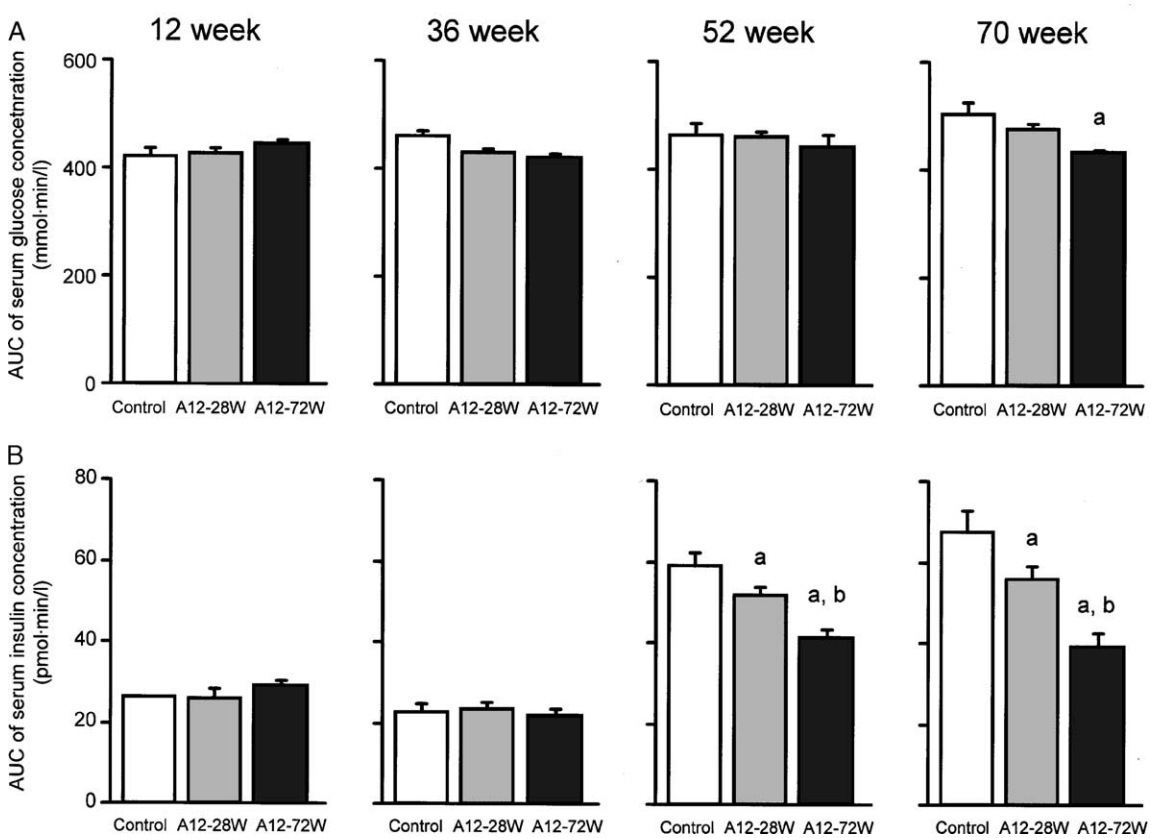

Fig. 4. The areas under the response curves of serum glucose (A) and insulin (B) during an IVGTT in rats treated with or without acarbose. The AUCs are presented as mean ± SEM of 7 to 9 rats. [a]Significant difference vs control group. [b]Significant difference vs A12-28W group. The control group was given standard rat diet. The A12-28W group received a diet containing acarbose from 12 to 28 weeks of age and then switched to standard rat diet until 72 weeks of age. The A12-72W group was maintained on a diet containing acarbose from 12 to 72 weeks of age.

Table 1
Effect of acarbose treatment on pancreatic weight and pancreatic contents of protein, DNA, enzymes and insulin, and plasma CCK concentration at 72 weeks of age

	Control	A12-28W	A12-72W
Pancreatic weight (mg)	1308.0 ± 48.5	1382.7 ± 46.6	1509.4 ± 58.6[a]
(mg/100 g BW)	249.8 ± 7.8	243.9 ± 8.8	321.7 ± 18.2[a,b]
Pancreatic protein, DNA, enzyme, and insulin contents			
Protein (mg per pancreas)	204.0 ± 6.2	208.6 ± 9.9	235.6 ± 12.3
DNA (mg per pancreas)	6.7 ± 0.2	7.1 ± 0.2	7.7 ± 0.3[a]
Protein/DNA (mg/mg DNA)	30.8 ± 1.6	29.5 ± 1.0	31.0 ± 2.0
Amylase (10^3 × SU per pancreas)	51.0 ± 3.2	30.2 ± 3.3[a]	16.1 ± 2.1[a,b]
Lipase (10^3 × U per pancreas)	13.1 ± 2.0	14.7 ± 0.8	16.0 ± 2.2
Trypsinogen (mg per pancreas)	4.8 ± 0.8	6.1 ± 0.2	7.2 ± 1.1
Insulin (mmol per pancreas)	6.9 ± 0.6	7.1 ± 0.4	5.1 ± 0.5[a,b]
Plasma CCK concentration (pmol/L)	1.9 ± 0.6	1.8 ± 0.6	1.7 ± 0.6

Values are mean ± SEM of 7 to 9 rats. Control was given standard rat chow throughout the entire experimental period. A12-28W received a diet containing acarbose from 12 to 28 weeks of age and then switched to standard rat chow until 72 weeks of age. A12-72W was maintained on a diet containing acarbose from 12 to 72 weeks of age.
[a] Significant difference vs control.
[b] Significant difference vs A12-28W.

were observed at 40, 60, and 70 weeks when compared with the concentration recorded at 12 weeks of age. However, the increase was completely prevented in the A12-72W group, or delayed in the A12-28W group (Fig. 2A).

Fasting serum insulin concentration in the control group gradually increased after 40 weeks of age. However, serum insulin concentration in the A12-72W group remained at similar level to that recorded at 12 weeks of age until the end of the experimental period, whereas it gradually increased after 52 weeks of age in the A12-28W group (Fig. 2B).

Although insulin resistance estimated by HOMA-R in the control group deteriorated with age, the increase in HOMA-R was prevented in the A12-72W group and was reduced in the A12-28W group (Fig. 3).

3.3. Serum glucose and insulin response to IVGTT

Although there were no significant differences in AUCs of glycemic response to intravenous glucose load among 3 experimental groups until 52 weeks of age, the AUC of glycemic response in the A12-72W group was slightly but significantly lower than that in the control group at 70 weeks of age (Fig. 4A). On the other hand, AUCs of insulin response in acarbose treatment groups significantly decreased compared with that in the control group after 52 weeks of age (Fig. 4B). In the control group, although the AUC of the glycemic response slightly increased with advancing age, the AUC of insulin response markedly increased with aging.

3.4. Pancreatic wet weight and pancreatic contents of protein, DNA, enzymes, and insulin, and plasma CCK levels

At 72 weeks of age, pancreatic wet weight and DNA content in the A12-72W group were significantly increased in comparison to those in the control group. Acarbose treatment markedly decreased pancreatic content of amylase compared with that in the control group. Pancreatic insulin content in the A12-72W group was significantly decreased when compared with that in the control and A12-28W groups (Table 1). Although the differences were not significant, pancreatic content of protein, trypsinogen, and lipase in the A12-72W group was higher than those in the A12-28W and control groups. There was no significant difference in plasma CCK concentrations among the 3 experimental groups at 72 weeks of age (Table 1).

3.5. Concentrations of serum lipid and weight of the adipose depots

Serum cholesterol and TG concentrations in the A12-72W group were slightly, but not significantly, decreased compared with those in the control group (Table 2). However, the total weight of abdominal white adipose depots in the A12-72W group significantly decreased compared with those in the control and A12-28W groups. In the A12-28W group, although the total amount of

Table 2
Effect of acarbose treatment on fasting plasma cholesterol and TG concentrations, and abdominal adipose depots at 72 weeks of age

	Control	A12-28W	A12-72W
Serum lipid levels (mg/dL)			
Cholesterol	90.3 ± 5.6	107.5 ± 6.8	86.3 ± 2.9[a]
TG	39.8 ± 6.9	38.5 ± 3.5	37.2 ± 3.5
Depots of abdominal fat (g)			
Mesenteric	7.6 ± 0.6	10.6 ± 0.9[b]	4.5 ± 0.3[a,b]
Retroperitoneal + epididymal	21.7 ± 1.3	20.7 ± 1.0	13.5 ± 1.2[a,b]
Total	29.3 ± 1.8	31.3 ± 1.9	18.0 ± 1.2[a,b]

Data are mean ± SEM of 7 to 9 rats. The control group was provided with standard rat chow throughout the entire experimental period. The A12-28W group received a diet containing acarbose from 12 to 28 weeks of age and then switched to standard rat chow until 72 weeks of age. The A12-72W group was maintained on a diet containing acarbose from 12 to 72 weeks of age.
[a] Significant difference vs A12-28W.
[b] Significant difference vs control.

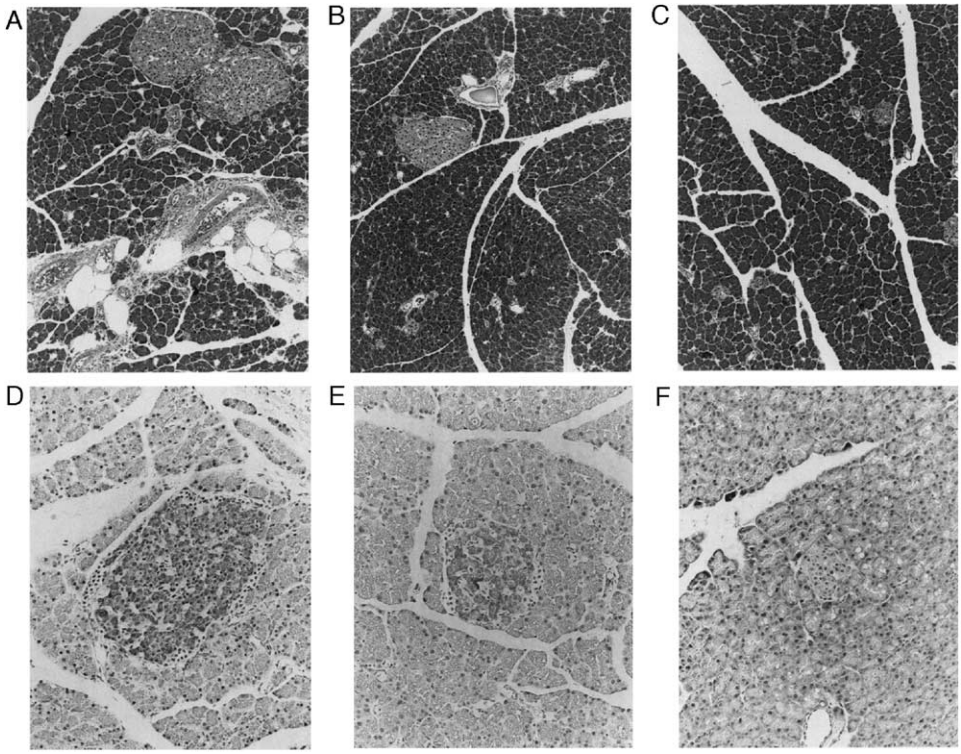

Fig. 5. Representative light microscopic appearances of the pancreas at 72 weeks of age (A-C). Immunohistochemistry for TNF-α in the pancreas (D-F). Sections of the pancreas in the control group contain adipose and connective tissue, and most islets were enlarged (A). In A12-28W, some islets were enlarged, but areas of fatty and connective tissue were rarely observed (B). In A12-72W, histologic alterations in exocrine and endocrine pancreas remained minimal (C) (original magnification ×100). Tumor necrosis factor α was expressed in most islets in the control group (D) and A12-28W group (E), but was rarely noted in the A12-72W (F) (original magnification ×200). The control group was given a standard rat diet. The A12-28W group received a diet containing acarbose from 12 to 28 weeks of age and then switched to standard rat chow until 72 weeks of age. The A12-72W group was maintained on a diet containing acarbose from 12 to 72 weeks of age.

abdominal fat depots was similar to those in the control group, mesenteric fat weight significantly increased compared with that in the control group (Table 2).

3.6. Histologic findings

Histologic examination revealed that fatty and connective tissue infiltrated into exocrine pancreas, and most islets were enlarged in the control group (Fig. 5A). Although some islets became larger, fatty and connective tissue replacements were mild in the A12-28W group (Fig. 5B). However, theses alterations remained minimal in the A12-72W group (Fig. 5C). Immunohistochemistry revealed that TNF-α expression was noted in the islets in the control (Fig. 5D) and A12-28W groups (Fig. 5E), but was only scantily present in the A12-72W group (Fig. 5F). Quantitative analysis of the volume density of islets, using IBAS, demonstrated that the islets became markedly larger with age in the control and A12-28W groups, but not in the A12-72W group (Table 3).

4. Discussion

We have shown in the present study that acarbose treatment prevented or delayed the exaggeration of age-related glucose intolerance. The increases in serum insulin concentrations at fasting and postglucose load with aging were prominent in the control group, although the increases in serum glucose concentrations remained mild. In addition, insulin resistance estimated by HOMA-R was markedly exaggerated, and volume density of islets became larger with advancing age in the control group. These results suggest that insulin resistance play a central role in age-related glucose intolerance. Serum insulin concentrations seemed to be increased to compensate for insulin resistance, as previous studies have shown [17-20]. Since acarbose

Table 3
Effect of acarbose treatment on volume density of islets at 12 and 72 weeks of age

Groups (%)	12 wk	72 wk
Control	0.64 ± 0.21	5.53 ± 1.16[a]
A12-28W	0.67 ± 0.21	2.91 ± 0.71[a]
A12-72W	0.60 ± 0.19	0.70 ± 0.19[b,c]

Values are mean ± SEM of 7 to 9 rats. The control group was provided with standard rat chow throughout the entire experimental period. The A12-28W group received a diet containing acarbose from 12 to 28 weeks of age and then switched to standard rat chow until 72 weeks of age. The A12-72W group was maintained on a diet containing acarbose from 12 to 72 weeks of age.

[a] Significant difference in the same group.
[b] Significant difference vs control at the same weeks.
[c] Significant difference vs A12-28W at the same weeks.

prevented hyperinsulinemia and exaggeration of HOMA-R, acarbose prevented glucose intolerance by maintaining insulin sensitivity. It is conceivable that acarbose maintained insulin sensitivity largely through decreased postprandial serum glucose and insulin concentrations. In addition, insulin resistance is closely associated with obesity, in particular, abdominal adiposity [20,38]. These findings indicate that the decreased body weight gain and abdominal fat deposition by acarbose treatment also participated in maintaining insulin sensitivity. On the other hand, mesenteric fat depot in the A12-28W group significantly increased compared with that in the control and A12-72W groups at 72 weeks of age. In the A12-28W group, absorption of carbohydrates and delivery of monosaccharides into the portal system might have markedly increased after withdrawal of acarbose treatment. Moreover, food intake had remained at higher levels than that in the control group for a long period after withdrawal of acarbose treatment. Therefore, it is likely that the mesenteric fat depot increased and thereby insulin resistance ensued in the A12-28W group.

Although many studies have examined the effect of aging on insulin secretory function, there is a great deal of variability in the outcome of these studies [39]. In our study, insulin secretory function evaluated by the insulinogenic index at IVGTT was unaltered with increasing age in the control group, and acarbose treatment showed no influence on the insulinogenic index (data not shown).

In line with our former studies [28,40], acarbose treatment significantly decreased amylase content in the pancreas. Previous studies [41,42] reported that carbohydrate-rich diets increase the synthesis of pancreatic amylase, whereas low-carbohydrate diets decrease pancreatic amylase because of adaptation to the diet. It is likely therefore that the reduction of amylase in the pancreas in the A12-72W and A12-28W groups is the consequence of deficient absorption of carbohydrates resulting from inhibition of α-glucosidases. On the other hand, pancreatic lipase and trypsinogen contents tended to increase in acarbose treatment groups compared with the control group. These alterations could be attributable to the relatively increased absorption of protein and fat due to inhibition of α-glucosidases in the acarbose-treated groups. Because the decrease in pancreatic amylase content may delay carbohydrate digestion, and thereby reduce postprandial glucose and insulin responses, lowered amylase content in the pancreas, together with acarbose in the gut, played some roles in the maintenance of glucose tolerance in the acarbose-treated groups. In addition, pancreatic amylase content still significantly decreased in A12-28W compared with that in the control group at 72 weeks of age, even after withdrawal of acarbose treatment. It is likely therefore that glucose tolerance was maintained after withdrawal of the treatment in the A12-28W group.

A recent study demonstrated that pharmacologic intervention with acarbose in patients with IGT can slow the progression of type 2 diabetes mellitus [16]. Because acarbose treatment prevented the progression to IGT with aging, our study suggests that acarbose treatment is effective to prevent or delay the onset of IGT in subjects not only with old age, but also with other risk factors for type 2 diabetes such as obesity, physical inactivity, and a strong familial history of this condition.

Pancreatic weight and pancreatic exocrine function decrease with advancing age [23,43]. However, acarbose treatment significantly increased pancreatic weight and DNA content without altering protein/DNA in the A12-72W group when compared with those in the control group at 72 weeks of age. These results suggest that acarbose treatment prevents age-related pancreatic atrophy mainly through the stimulation of hyperplasia. Because acarbose treatment prevented hyperglycemia and hyperinsulinemia, it is likely that maintenance of insulin sensitivity and glucose tolerance play important roles in prevention of pancreatic atrophy in the A12-72W group. Although insulin sensitivity was significantly improved in the A12-28W group, pancreatic weight was not significantly increased compared with those in the control group. A possible explanation is that immunoreactivity for TNF-α was expressed in most islets in the control and A12-28W groups, but not in the A12-72W group. Because TNF-α is a major mediator of cell death through necrosis and/or apoptosis [44], it may have stimulated pancreatic atrophy in the control and A12-28W groups.

In our study, supplementing the diet with acarbose resulted in a significant increase in food consumption, although there was a reduction in body weight gain. These findings are similar to those from our previous study in the diabetic strain OLETF rats [29,30], but are in contrast to our former reports that showed unchanged body weight gain and food intake in Wistar rats [27,28]. Because we used the same dose of acarbose in the same rat diet, this disparity in these effects is probably due to the difference of the species of rats.

In conclusion, we have demonstrated that acarbose is useful to prevent glucose intolerance and pancreatic atrophy with advancing age in rats. Our results suggest that acarbose treatment is beneficial for elderly populations to prevent the development of IGT or pancreatic atrophy.

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