Effect of Curcumin in the Amelioration of Pancreatic Islets in Streptozotocin-Induced Diabetic Mice

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Objective: *To evaluate the antidiabetic effect of curcumin and its potential in amelioration of pancreatic islets against damage under diabetic condition.*
Material and Method: *Diabetic mice were induced by injection of STZ (60 mg/kg body weight). Male mice were divided into 3 groups: group I was normal mice, group II was diabetic mice and group III diabetic mice were treated with curcumin (200 mg/kg body weight). The blood glucose levels and body weights were recorded every two weeks. After 4 weeks, 8 weeks and 12 weeks, the animals in each group were sacrificed. Histopathology of pancreatic tissues, pancreatic islets areas and numbers were observed under light microscope.*
Results: *The weight loss and the elevation of blood glucose levels were observed in diabetic mice and diabetic mice treated with curcumin at 4 weeks, 8 weeks and 12 weeks. The reduction of pancreatic islets areas and numbers were presented in diabetic mice and diabetic mice fed with curcumin at 4 weeks. At 8 weeks of diabetic mice, the numbers of pancreatic islets were decreased however the pancreatic islets hyperplasia was prominently investigated, whereas the noticeable increase in numbers of small pancreatic islets were observed in diabetic mice fed with curcumin. Histopathological observation at 12 weeks revealed the accumulation of lymphocytes in the shrunken pancreatic islets of diabetic mice, while an absent lymphocytes infiltration in the pancreatic islets and the increase in numbers of small islets of Langerhans appeared nearly the ducts in the pancreas of diabetic mice treated with curcumin at 12 weeks.*
Conclusion: *Curcumin treatment at 12 week can exert beneficial effect in diabetes mellitus, regarding the improvement of pancreatic islets. The islets of Langerhans neogenesis is characterize by the presentation of small islets increase in numbers nearly the ducts and no insulitis.*

Keywords: *Curcumin, Diabetes mellitus, Streptozotocin, Islet of Langerhans.*

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Diabetes mellitus is a complicated group of disorders characterized by hyperglycemia, that increase the global prevalence in the present century[1]. Diabetes mellitus type 1 (type 1 diabetes) is an autoimmune disorder caused by lymphocytic infiltration and beta-cells destruction within the pancreatic islets of Langerhans. The pancreatic beta-cells are lost in numbers and volume, then severe permanent insulin deficiency results[2].

There are efforts to search for alternative of drugs and herbal medicine that will be a new choice in diabetic treatment. Herbal plants have been the major source of drugs in Thai medical community. In Thailand, the plenty of herbs might provide a new oral hypoglycemic agent which is low cost without side effects and available medicine suitable for rural populations in developing countries. Medical plants like *Gymnema slyvestre*, *Allium sativum*[3] and *Aloe vera*[4] have been demonstrated for treatment of diabetes.

Curcumin is a naturally occurring yellow pigment powder extracted from the roots of the *Curcuma longa* plant (Turmeric). The potential beneficial effects of curcumin has been shown to exhibit anti-inflammatory[5], antioxidant[6], anti-tumor[7] and anti-diabetic activities[8,9]. Furthermore, curcumin has been demonstrated in protecting isolated islet against streptozotocin (STZ)-induced oxidative stress by scavenging free radicals[10]. However, its efficacy in ameliorative pancreatic islets from STZ-induced diabetic mice is still lacking.

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The present work was to investigate hypoglycemic activity of curcumin and its effect in improvement of the pancreatic islets in diabetic mice models.

Material and Method

Animals

The present work was approved by Srinakharinwirot Univeristy Medical Center Animal Care Committee. Young male mice weighting between 35-40 gm were obtained from Laboratory Animal Center, Mahidol University, Salaya, Nakonpathom. The animals were maintained in the room that was always kept at 25 $\pm$ 2°c with 12:12 hour light-dark cycle and the animal were provided standard diet and water throughout the experiment.

Experimental diabetic mice were induced by intravenous injection of 60 mg/kg body weight of STZ (Sigma, USA) in freshy citrate buffer (0.1 M, pH 4.5) whereas control mice were injected intravenous with the same volume of isotonic NaCl. Blood samples were obtained from tail at 72 h after an overnight fast by using the One Touch Ultra blood glucose monitoring system (LifeScan Inc. 2002, USA). Experimental animals with fasting blood glucose levels above 250 mg/dl were used as diabetic animals.

The animals were allotted into three experimental groups: group I (control), group II (diabetic mice) and group III (diabetic mice treated with curcumin), each containing 5 animals. In group II, diabetic mice were fed with corn oil 10 ml/kg body weight daily. Group III, diabetic mice were fed with curcumin 200 mg/kg body weight every day in single dose. Curcumin (Sigma, USA) was prepared by mixing 200 mg of curcumin powder in 10 ml of corn oil. These procedure were continued for 4 weeks, 8 weeks and 12 weeks.

Blood glucose levels and body weights were recorded every two weeks. Animal in each groups were sacrificed at the times to study (4 weeks, 8 weeks and 12 weeks) under sodium pentobarbital anesthesia.

Histological Study

The pancreatic tissues were dissected and immersed in Bouin's solution (Sigma, USA) for overnight. The pieces of pancreases were processed in graded series of 70%, 80%, 90% and absolute alcohol, then embedded in paraffin wax. Histological serial sections of 5 mm were cut using a microtome, mounted on glass slides and stained with hematoxylin-eosin (H&E) (Bio-Optica, Italy). The morphology and pathological alterations of the pancreas were observed and photographed under an Olympus (BX 50) light microscope.

Morphometric Study of the Pancreatic Islets

Every fifth pancreatic tissue section stained with H&E was selected for pancreatic islets morphormetric study. Ten pancreatic islets from each mouse, thus 50 islets for each group were chosen. The islets measurements were obtained by means of a calibrated eyepiece micrometer at x40 magnification. The area of islet was calculated by using the size (in mm) of the longest (r_1) and shortest (r_2) radii of all islet cross sections which was visible in the sections. The radii of all pancreatic islets were measured by using Image Pro Analysis software under an Olympus (BX 50) light microscope. Calculation of pancreatic islets area was analyzed by using the following formula:

$$\text{Islet area in } \mu m^2 = \mu m\,(r_1) \times \mu m\,(r_2) \times \pi$$

The Evaluation of Total Numbers of the Pancreatic Islets

Every fifth pancreatic tissue section stained with H&E was selected for evaluation of the pancreatic islets numbers. The total numbers of islets in each section were counted under light microscope at low power fields of eyepiece (10X) and calculated for evaluate average numbers of islets per pancreas.

Statistical analysis

Data were statistically analyzed using ANOVA, followed by Tukey's test. For all the tests, the results were expressed as mean $\pm$ standard error (SE). The value of $p < 0.05$ was considered to indicate statistical significance.

Results

The effect of curcumin (200 mg/kg body weight) in terms of their reducing blood glucose and improve pancreatic islets were observed. There were significant weight loss in diabetic mice and diabetic mice fed with curcumin, compared to control mice in each time (Table 1). However, there was no change significantly in body weight of diabetic mice compared with diabetic mice fed with curcumin. All levels of blood glucose in diabetic mice and diabetic mice fed with curcumin at 4 weeks, 8 weeks and 12 weeks increased significantly when compared to those of control mice (Fig. 1). Interestingly, blood glucose level (432 $\pm$ 16.44 mg/dl) of diabetic mice fed with curcumin in 12 weeks decreased significantly when compared with diabetic mice (505 $\pm$ 9.41 mg/dl).

Table 1. Comparisons in body weights at 4 weeks, 8 weeks and 12 weeks of control, diabetic and diabetic mice treated with curcumin (200 mg/kg body weight)

Group	Body weight (g), mean ± SE		
	4 weeks	8 weeks	12 weeks
Control	42.67 ± 0.18	44.47 ± 1.75	42.47 ± 0.20
Diabetic	36.96 ± 0.48*	37.08 ± 1.01*	37.15 ± 0.51*
Diabetic + Curcumin	36.23 ± 0.86*	36.92 ± 0.28*	37.50 ± 0.81*

Data are expressed as means ± SE, *p < 0.05 compared with control group in each time.

In order to determine whether the efficacy of curcumin to improve diabetic pancreatic islets, we evaluated areas of islets of Langerhans at 4 weeks, 8 weeks and 12 weeks (Fig. 2). Assessment of pancreatic islets areas of diabetic mice and diabetic mice fed with curcumin at 4 weeks and 12 weeks resulted in a significant decrease compared to those of control mice. The relative pancreatic islets areas in diabetic mice were similar to diabetic mice treated with curcumin at 4 weeks and 12 weeks. The areas of islets of Langerhans at 4 weeks and 12 weeks were not significant difference in diabetic mice compared with those of diabetic mice fed with curcumin. Interestingly, the pancreatic islets hyperplasia was present in diabetic mice at 8 weeks. As a result, there were significant increase in pancreatic islets area in diabetic mice (334 ± 10.31 mm^2) compared to control mice (220 ± 6.86 mm^2) and diabetic mice fed with curcumin (125 ± 6.66 mm^2). Nevertheless, the pancreatic islets area of diabetic mice treated with curcumin at 8 weeks were decreased significantly when compared to control mice.

For observation the islets of Langerhans neogenesis, the numbers of pancreatic islets per low power field were evaluated. A significant decrease in the numbers of pancreatic islets were seen in diabetic mice and diabetic mice fed with curcumin when compared to control mice in each time (Fig. 3). At 4 weeks, the reduction of pancreatic islets numbers were observed in diabetic mice (46 ± 3.28) and diabetic mice fed with curcumin (36 ± 3.46). The pancreatic islets numbers of diabetic mice at 8 weeks (32 ± 2.40) and 12 weeks (22 ± 2.65) were decreased significantly when compared to diabetic mice fed with curcumin at 8 weeks (50 ± 3.71) and 12 weeks (87 ± 2.03) respectively. At 12 weeks, the numbers of pancreatic islets in diabetic mice fed with curcumin (87 ± 2.03) increased in four folds compared to diabetic mice (22 ± 2.65).

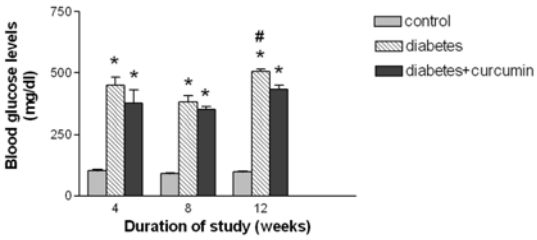

Fig. 1 Level of blood glucose in control, diabetic and diabetic mice treated with curcumin (200 mg / kg body wt) at 4 weeks, 8 weeks and 12 weeks respectively. Data are expressed as means ± SE, * p < 0.05 compared with control group in each time, # p < 0.05 compared with diabetic mice fed with curcumin in 12 weeks.

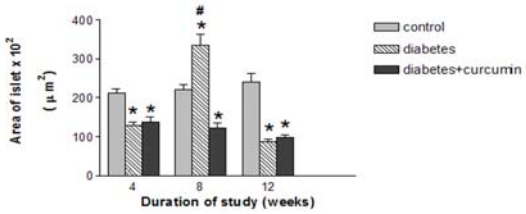

Fig. 2 Pancreatic islet area of control, diabetic and diabetic mice fed with curcumin at 4 weeks, 8 weeks and 12 weeks respectively. The results are expressed as means ± SE, * p < 0.05 compared with control mice in each time, # p < 0.05 compared with diabetic mice fed with curcumin in 8 weeks.

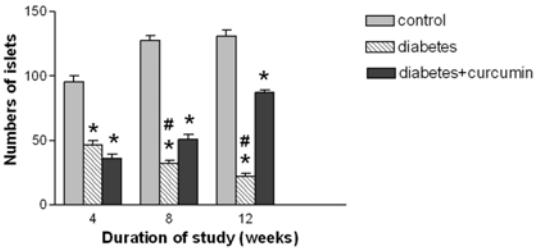

Fig. 3 Total numbers of pancreatic islets of control, diabetic and diabetic mice fed with curcumin at 4 weeks, 8 weeks and 12 weeks respectively. The results are expressed as means SE, * p < 0.05 compared with control mice in each time, # p < 0.05 compared with diabetic mice fed with curcumin in 8 weeks and 12 weeks.

Histopathological Study of the Pancreas

At 4 weeks, the pancreas of control mice showed elongated islets of Langerhans, with their lightly stained cellular nuclei. Interlobular ducts were

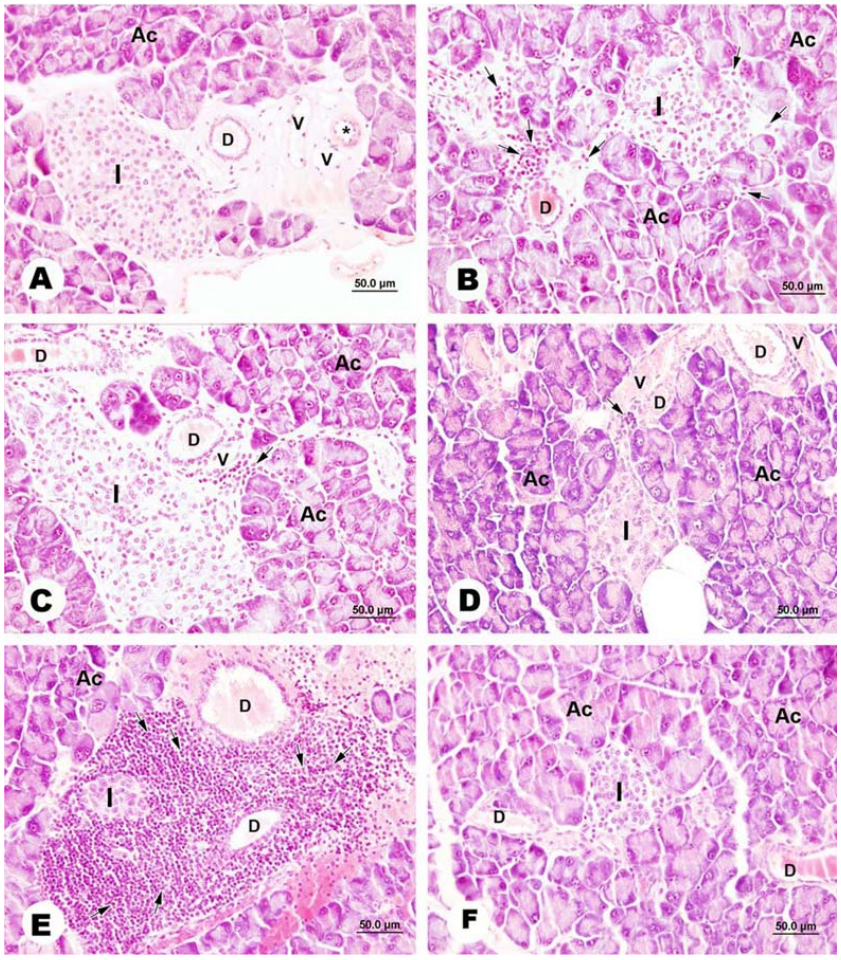

Fig. 4 Micrograph of pancreas stained with haematoxylin and Eosin (H&E) (magnification X40).
A&B. The pancreatic islets at 4 week. **A.** Control mouse shows normal islet of Langerhans (I). Surface area = 25,813 mm^2 **B.** Diabetic mouse presents shrunken islet, periductal and peripheral islet infiltration of lymphocytes (arrow). Surface area = 12,622 mm^2
C&D. The pancreatic islet at 8 weeks. **C.** Diabetic mouse demonstrates enlarged islet and diffuse lymphocytes (arrow) in stroma nearly vein (V). Surface area = 48,934 mm^2 **D.** Diabetic mouse treated with curcumin shows small islet (I) and diffusion of lymphocytes (arrow) in interductal stroma.
E&F. The pancreatic islets at 12 weeks. **E.** Diabetic mouse presents shrunken islet (I) and dense lymphocytes (arrow) infiltration. **F.** Diabetic mouse fed with curcumin shows small islet (I) and no lymphocytes infiltration.
(Ac = Acinar cell, D = pancreatic duct, I = islets of Langerhans, V = vein, * = Artery)

surrounded by dense connective tissue. There were veins and interlobular ducts nearly islets of Langerhans (Fig. 4A). In diabetic mice and diabetic mice fed with curcumin (figure not shown), the pancreatic islets were shrunk in sizes (Fig. 4B) when compared to the pancreatic islet of control mice at 4 weeks. There were diffusion of small lymphocytes at the periductular and interstitial stroma and few lymphocytes appeared around islets of Langerhans. At 8 week, the pancreatic islets of diabetic mice were enlarged and lymphocytes infiltration involved the islets and adjacent ducts and veins (Fig. 4C). In the pancreas of diabetic mice fed with curcumin showed small islets and aggregation of lymphocytes adjacent interlobular ducts. The pancreatic islets were enclosed by few lymphocytes infiltration (Fig. 4D). At 12 weeks, the pancreas of diabetic mice demonstrated heavy infiltration of lymphocytes in shrunken islets of Langerhans and periductal stroma (Fig. 4E). In the pancreas of diabetic mice fed with curcumin showed small pancreatic islets

with absent diffusion of lymphocytes in the islets and periductal stroma (Fig. 4F).

Discussion

It has been reported the effectiveness of curcumin in reducing secondary complications in STZ-induced diabetic animals[11]. Moreover, the curcumin has been demonstrated in prevention isolated beta-cell death and dysfunction induced by STZ[10,12]. Some studies also highlight its benefit in hypoglycemic agents[8,9] however, almost no reports present the importance role of curcumin for improvement pancreatic islets in diabetes. In the present study, we would like to evaluate the effect of curcumin that could influence pancreatic islets recuperation after the damage induced by STZ. The diabetic mice in this experiment were induced by STZ, alkylating agent, caused DNA damage in beta-cell and subsequent inhibition of insulin biosynthesis and secretion[13]. The curcumin treatment that relied to reduce glucose levels in STZ–treated mice were observed.

Our data show that there were significant increase in blood glucose levels in diabetic mice and diabetic mice fed with curcumin when compared to control mice at each time. These findings did not corroborate the previous observation in efficacy of curcumin in reduction of hyperglycemia[11]. Weight gain was noticed in control mice at time course of studies while the diabetic mice and diabetic mice treated with curcumin have weight loss. From the result, hyperglycemia did not help to gain body weight in diabetic mice and diabetic mice fed with curcumin. The reduction of body weight probably led to decrease gastrointestinal hormones release that participated in the stimulation of beta-cells proliferation[14]. Therefore, beta–cells proliferation could be impeded by the low level of gastrointestinal hormones. However, blood glucose levels in diabetic mice fed with curcumin (432 $\pm$ 16.44 mg/dl) decreased significantly when compared to diabetic mice (505 $\pm$ 9.41 mg/dl) at 12 weeks. Therefore, if diabetic mice were treated with curcumin in long time as more than 12 weeks, it would be expected that blood glucose levels might tend to decrease within normal levels. Although, the islets enlargement occurred in very young rats or hamsters[15] but there were found that between 1 and 7 month of age in rats, the beta-cells mass increased six to seven fold in females and males respectively[16]. After 7 month of age, growth of the beta–cell population was slow down considerably but still continued until 20 months, which were old age for rats[17]. This was clear for plasticity of the endocrine pancreas and its potent regenerative capacity in adult animals.

Histopathological examination from this work revealed the lymphocytes infiltration in the pancreatic islets of diabetic mice. Insulitis was an inflammatory infiltrate effecting the islets of Langerhans in type 1 diabetes[18]. In the diabetic mice at 4 weeks and 8 weeks, the histological finding of pancreas was characteristic as lesion of recent onset type 1 diabetes[18,19]. There was much morphological evidence of periinsulitis and lymphocytes accumulation adjacent to blood vessels and ducts in the pancreatic stroma. At 4 weeks, the pancreatic cellular evidence of diabetic mice fed with curcumin was similar to diabetic mice. The pancreatic islets areas were small and corresponded to decrease in numbers of pancreatic islets and there were no different between two groups. The decreasing in sizes and numbers of pancreatic islets was caused by beta-cells destruction in type 1 diabetes[20]. The hyperplasia of endocrine tissue were observed in the pancreas of diabetic mice at 8 weeks. Similar to our studies, islets hyperplasia has been reported in hyperglycemia obese *ob/ob* mice in response to the sustained hyperglycemia[21]. The evaluation of pancreatic islets areas in diabetic mice at 8 weeks, showed islets enlargement, suggesting that the expansion of beta-cell mass compensated for increased insulin demands in order to control blood glucose homeostasis[22]. Nevertheless, the blood glucose levels in diabetic mice at 8 weeks were still high relative to decrease in numbers of pancreatic islets resulted in insulin insufficiency. Although, the pancreatic islets of diabetic mice fed with curcumin at 8 weeks increased in numbers but decreased in pancreatic islets areas. Then the blood glucose of diabetic mice fed with curcumin at 8 weeks was presented in high levels. The cellular structure in the pancreas of diabetic mice fed with curcumin presented diffusion of lymphocytes at periductal pancreatic stroma like appeared in the pancreas of diabetic mice at 8 weeks. It was possibly that curcumin did not improve pancreatic islets damaged in diabetic mice at short time of treatment. At 12 weeks, pancreatic tissue in diabetic mice were presented as in prolonged duration of type 1 diabetes[19]. There were numerous lymphocytes infiltrated in the islets of Langerhans and accumulated nearly vascular and ducts. The morphometrical studies showed the reduction of pancreatic islets areas and numbers, suggesting that in prolonged duration of type 1 diabetes, the destruction of beta-cells resulted in shrunken islets and decrease in numbers of pancreatic islets. However, the

distribution of alpha, delta and pancreatic polypeptide cells in these islets were not disturbed[19]. Interestingly, the evidence in curcumin induced pancreatic islets recovery from the damage by STZ was found in 12 weeks. In diabetic mice treated with curcumin, the small pancreatic islets without insulitis were observed close to ducts and small islets were increased in numbers.

The islets neogenesis from ducts epithelium have been reported[23,24] and these studies supported our experiment that there were islets neogenesis in the pancreas of diabetic mice fed with curcumin at 12 weeks. Nevertheless, blood glucose levels in diabetic mice fed with curcumin at 12 weeks were still high. These probably presented the neogenesis of beta-cells started to proliferate. The recruitment were immature beta-cells so these cells could not function normally or were poorly functional. Here, our result has suggested that curcumin could influence pancreatic islets in STZ-induced diabetic mice recuperation after curcumin treatment for 12 weeks, together with the pancreatic islets neogenesis by increasing in numbers of small islets along the ducts and no insulitis. However the weight loss and hyperglycemia were demonstrated in diabetic mice treated with curcumin at 12 weeks. It might due to the condition that curcumin could not induce completely differentiated pancreatic islets in order to recover function at this time. Possibly, pancreatic islets neogenesis were completed and mature beta-cells were functioned in prolong curcumin treatment more than 12 weeks.

In conclusion, our study provides clear evidence of pancreatic islets growth to respond to curcumin treatment in diabetic mice at 12 week. The finding of this study is the presentation of pancreatic islets neogenesis by increasing in numbers of small pancreatic islets nearly the ducts. The curcumin might promote hormone or growth factors for pancreatic islets in diabetic mice neogenesis. Our observation is appropriate for the search of these factors and to study the implicated mechanisms in pancreatic islets modifications in the future that could lead to provide a new therapeutic of diabetes mellitus.

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ผลของขมิ้นชันที่ช่วยฟื้นฟู islets ในตับอ่อนของหนูที่ถูกเหนี่ยวนำให้เป็นเบาหวานด้วยสาร streptozotocin

มาลี จันทร์ภู่, หัทยา เพ็ชรพิบูลย์ไทย, บุษบา ปันยารชุน, วิภาวี อนุพันธ์พิศิษฐ์

วัตถุประสงค์: *เพื่อประเมินผลของขมิ้นชัน ในการต้านโรคเบาหวาน และประสิทธิภาพของขมิ้นชันในการฟื้นฟู islets ในตับอ่อนที่มีการเสียหายจากสภาวะโรคเบาหวาน*

วัสดุและวิธีการ: *หนูถูกเหนี่ยวนำให้เป็นเบาหวานโดยการฉีดสาร streptozotocin (60 mg/น้ำหนักตัว kg) หนูเพศผู้ถูกแบ่งออกเป็น 3 กลุ่ม กลุ่มที่ 1 เป็นหนูกลุ่มปกติ กลุ่มที่ 2 เป็นหนูที่เป็นโรคเบาหวาน และกลุ่มที่ 3 เป็นหนูที่เป็นโรคเบาหวานและได้รับการรักษาด้วยขมิ้นชัน (200 mg/น้ำหนักตัว kg) ทำการจดบันทึกน้ำหนัก และระดับน้ำตาลในเลือดของหนูทั้ง 3 กลุ่ม ทุก 2 สัปดาห์ หลังจากสัปดาห์ที่ 4, 8, และ 12 หนูในแต่ละกลุ่มได้ถูกนำมาศึกษาโครงสร้างของตับอ่อนจากนั้นทำการวัดพื้นที่และนับจำนวนของ islet ในตับอ่อนภายใต้กล้องจุลทรรศน์*

ผลการศึกษา: *หนูกลุ่มเบาหวานและหนูกลุ่มเบาหวานที่ได้รับการรักษาด้วยขมิ้นชัน มีน้ำหนักตัวลดลง และมีระดับน้ำตาลในเลือดสูงขึ้นในสัปดาห์ที่ 4, 8 และ 12 ในสัปดาห์ที่ 4 พบว่าพื้นที่และจำนวนของ islet ในตับอ่อนลดลงในหนูกลุ่มเบาหวานและหนูกลุ่มเบาหวานที่ได้รับการรักษาด้วยขมิ้นชัน ในสัปดาห์ที่ 8 หนูกลุ่มเบาหวานมีจำนวน islet ลดลง แต่สังเกตเห็นว่า islet ขยายใหญ่ขึ้น ในขณะที่ islet ที่มีขนาดเล็กนั้นมีจำนวนเพิ่มขึ้น ในหนูกลุ่มเบาหวานที่ได้รับการรักษาด้วยขมิ้นชัน การศึกษาทางจุลกายวิภาคในสัปดาห์ที่ 12 พบว่าในตับอ่อนของหนูที่เป็นเบาหวาน islets of Langerhans มีขนาดลดลงและมีกลุ่มเซลล์เม็ดเลือดขาว (lymphocyte) อยู่เป็นจำนวนมาก ในขณะที่ในตับอ่อนของหนูกลุ่มเบาหวานและได้รับการรักษาด้วยขมิ้นชันเป็นระยะเวลา 12 สัปดาห์นั้นไม่ปรากฏว่ามีเซลล์เม็ดเลือดขาวใน islets และพบว่า islets of Langerhans ขนาดเล็กมีจำนวนเพิ่มขึ้นและปรากฏอยู่ใกล้กับท่อภายในตับอ่อน*

สรุป: *การรักษาด้วยขมิ้นชันเป็นระยะเวลา 12 สัปดาห์ สามารถที่จะนำมาเป็นประโยชน์ในการรักษาโรคเบาหวานได้ เกี่ยวเนื่องจากการช่วยฟื้นฟู islets ในตับอ่อนให้มีการสร้าง islets of Langerhans เกิดขึ้นโดยพบว่ามี islets ขนาดเล็กมีจำนวนเพิ่มขึ้นปรากฏใกล้กับท่อภายในตับอ่อนและไม่มีการอักเสบของตับอ่อน*