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Reserach Article

# ROLE OF β- ENDORPHIN IN ZHONGWAN (CV12) ACUPOINT IN THE DIABETIC RATS- A HISTOLOGICAL STUDY

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**A B S T R A C T**

Acupuncture is used as an adjunct therapy throughout the World to treat various chronic ill disorders like systemic hypertension, diabetes. In our study, we investigated the effects of Acu-TENS therapy at Zhongwan (CV12) acupoint in Streptozotocin (45mg/kg/body weight/IP) induced diabetic rats and was compared with anti-diabetic drug (Pioglitazone 7.5mg/kg/body weight). Acu-TENS with low frequency (15HZ), high intensity, pulse width of 5 sec was used to stimulate the Zhongwan acupoint (CV12) for 5 minutes daily without anaesthesia for 60 days. Significant ($p \leq 0.01$) decrease in blood glucose level, the total cholesterol, triglycerides, low density lipid and with significant increase in high density lipid. Histopathological examination of pancreatic islets shows increased cellular density in Zhongwan acupoint treated rats and was compared with anti-diabetic drug. The anti-diabetic and lipolytic effect of Zhongwan(CV12) acupoint may be due to increase in insulin secretion through the mediation of β- endorphin.



## INTRODUCTION

Diabetes mellitus is an endocrine disorders characterized by hyperglycemia (increase blood glucose level) which disturbs the metabolism of carbohydrates, fat and protein (Ingle PV *et al*, 2011). The chronic complications of diabetes includes micro-vascular diseases (retinopathy, neuropathy, nephropathy) and macro-vascular diseases (dyslipidemia, hypertension, coronary heart disease, stroke, peripheral vascular disease). Type 2 (Non Insulin Dependent Diabetes Mellitus), is the common type of diabetes mellitus makes up about 90% of the cases (Shi Y, Hu FB, 2014), is due to the abnormal insulin secretion and inability of peripheral tissue to respond to insulin. The global prevalence of diabetes for all age groups was estimated to be 2.8% in 2000 and 4.4% in 2030.The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (Shamima Akter *et al*, 2014). In experimental diabetic model, chemical induction with streptozotocin diminished insulin production and causes high blood circulating glucose, which is similar as found in human diabetics. The altered physiological function of the pancreas from the action of streptozotocin provides the signs of abnormalities in pancreatic islets function and morphology in pancreas islets (Noman D Salih, 2015).

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Methods for controlling plasma glucose levels in patients with diabetes include diet control, exercise and medication. While medical treatment is convenient and effective, certain treatment can leads to serious side effects (Rizzos CV, 2009). Patients with poorly controlled type 2 diabetes who frequently use oral hypoglycemic agents often present with unstable glucose levels (Yu-Chen Lee *et al*,2011). Researchers have, therefore, searched for mild or complementary treatment methods with no side effects to increase insulin sensitivity (N.Ishizaki *et al*, 2009). Acupuncture therapy, herbal medicine, dietary supplementation, yoga therapy and hot tub therapy have been researched and explained the mechanism of anti-diabetic effects (Awanish Pandey *et al*, 2011).These therapies have become increasingly popular for last several years due to less adverse effects. Acupuncture, one of the oldest and most commonly used forms of alternative medicine has existed for more than 2500 years. Acupuncture therapy, though a Traditional Chinese Medicine (TCM), is now acknowledged all over the world mainly in U.S, Japan, Korea and India (Fitrullah and Addison Rousdy, 2017). The effectiveness of acupuncture in diabetes have observed both reducing the symptoms and long term complications of diabetes. According to the theory of ancient medicine, health is a state of balance between Yin and Yang, Qi and Xue and five elements of wood, fire, earth, metal and water (Connelly DM, 1994). Qi or life energy flows through the body in hypothesized channels called meridians and may be accessed at several hundred points. The traditional theory of acupuncture is based on the concept that an imbalance of yang

and yin, through the meridians, can be corrected by manipulation of identifiable points close to the skin. Each acupoint has distinct therapeutic actions. The stimulation of acupoints can be achieved by either a mechanical action of needling or electrical point stimulation. Acupuncture stimulates peripheral sensory nerves and their endings, increase cutaneous blood flow and microcirculation and releases neurotransmitters, neuropeptides and hormones. This explains acupuncture therapy may be effective in treating not only diabetes, but also in preventing and managing complications of diabetes (Zhi-Qi-Zhao, 2008). The effects of acupuncture on diabetes have been observed experimentally and clinically (Hironori Nakamura *et al*, 2014). Acupuncture can act on the pancreas to enhance insulin synthesis, increase the number of receptors on target cells, and accelerate the utilisation of glucose resulting in lowering of blood sugar (Rong-Tsung Lin, 2014). Obesity and physical inactivity are the specific risk factors for type 2 diabetes. Several studies have shown the lipolytic effect of acupuncture on obesity, which is the most modifiable risk factor for type 2 diabetes. It appears that the therapeutic effect of acupuncture on diabetes is not the result of its action on one single organ, but on multiple systems (Philip V.Peplow and G. David Baxter, 2012). Electro acupuncture (EA) is commonly used to stimulate the acupoints, an invasive technique with needle than manually. In this study, first time we shown that Transcutaneous electric nerve stimulation at acupoints (Acu-TENS) therapy, an non invasive method was selected to stimulate the acupoints, combines the advantages of electrical stimulation and acupuncture therapy. This study has designed to investigate the hypoglycemic effect of Zhongwan (CV12) acupoint on the histology of the pancreatic islets of Langerhans and biochemical parameters (fasting blood glucose level and lipid profile) in STZ- induced diabetic rats and acupuncture treated diabetic rats.

## MATERIALS AND METHODS

### *Animal*

Male albino wistar rats (200-250gm) were used for the study. They were well ventilated and housed at a controlled temperature with 12 hours light and dark cycles. Animals are fed with standard laboratory diet and water was given with ad libitum. Periodically assessed and compared the fasting blood glucose, food and water intakes of the rats. This study was approved by Institutional Animal Ethical Committee (Reg.no, 889/po/ac/05/CPCSEA/2011) of Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode.

### *Study Design*

Animals were divided into four groups with six animals in each group. The rats of I group were normal. Group II rats were induced diabetes with Streptozotocin (45 mg/kg/body weight) intraperitoneally. The induction of diabetes was conformed after 72 hours of Streptozotocin treatment by estimation of elevated fasting blood glucose level above ≥250 mg/dl included in the study. Group III of rats received Streptozotocin and treated with pioglitazone (7.5 mg/kg/body weight) given intra orally daily. Group IV of rats received Streptozotocin and treated with Zhongwan acupoint stimulation. Electrical stimulation was carried out for 3-5 minutes daily at frequency of 15Hz, pulse width 5s, intensity 15mA, using Acu-TENS unit without anaesthesia. The positive and negative charges are given through electrodes to the Zhongwan and Guanyuan acupoints respectively. The experiment was carried out for 60 days and blood sample was collected by rat tail and retro orbital venous plexus puncture. Fasting blood glucose and total cholesterol, triglycerides, low density lipid and high density lipid was measured and compared periodically between the groups. Histopathological changes in the pancreatic islets was assessed and compared between the groups. All animals were euthenesied by over dose anesthesia at the end of the treatment, for histopathological assement the pancreatic tissue specimens were collected and fixed in 10 % formalin, dehydrated in gradual ethanol (50-100%), cleared in xylene and embedded in paraffin sections (4-5µ) were prepared, stained with Heamatoxylin and Eosin.

### *Statistical Analysis*

The results were expressed as Mean± SD. The fasting blood glucose level were analysed by one-way ANOVA followed by Tukey post hoc test. The value of $p \leq 0.01$ was considered as statistically significant.

## RESULTS

A steady decrease and significant reduction of fasting blood glucose with ($p \leq 0.01$) was observed in Zhongwan (CV12) acupoint and oral anti-diabetic drug (pioglitazone, 7.5mg/kg/ body weight) treated diabetic rats after 60 days of treatment. The Zhongwan (CV12) acupoint stimulation restored its body weight. Graph1 shows fasting blood glucose level, Table1,2, 3 and 4 shows total cholesterol, triglycerides, high density lipid and low density lipid level.

**Table 1** Effects of Zhongwan (CV12) acupoint on Total Cholesterol (mg/dl)

| Groups | Total cholesterol level mg/dl (mean ±SD) | | |
|---|---|---|---|
| | $0^{th}$ day | $30^{th}$ day | $60^{th}$ day |
| I(Control) | 87.33±6.56 | 91.5±7.56 | 96.67±7.39 |
| II(STZ induced diabetic,45mg/kg/bwt) | 148.5±10.21 | 169.17±9.87 | 189.83±9.48 |
| III(pioglitazone,7.5mg/ kg/bwt) | 156.83±8.98 | 132.67±7.82 | 96.83±5.6 |
| IV(Zhongwan acupointwith 15hz) | 157.5±3.02 | 130.83±5.71 | 105.83±3.76 |

The results were expressed as Mean± SD. Comparison was done with one way ANOVA and Tukey test with ($p \leq 0.01$) to control and diabetic group.

**Table 2** Effects of Zhongwan (CV12) acupoint on Triglycerides (mg/dl)

| Groups | Triglycerides level mg/dl (mean ±SD) | | |
|---|---|---|---|
| | $0^{th}$ day | $30^{th}$ day | $60^{th}$ day |
| I(Control) | 53.17±4.02 | 54±38 | 54.33±2.42 |
| II(STZ induced diabetic,45mg/kg/bwt) | 142.83±9.39 | 154±8.25 | 161±6.57 |
| III(pioglitazone,7.5mg/k g/bwt) | 136.67±8.07 | 110.83±8.54 | 118.67±5.32 |
| IV(Zhongwan acupointwith 15hz) | 148.33±14.47 | 118.67±5.32 | 86.67±2.25 |

The results were expressed as Mean± SD. Comparison was done with one way ANOVA and Tukey test with ($p \leq 0.01$) to control and diabetic group.

**Table 3** Effect of Zhongwan (CV12) acupoint on HDL (mg/dl)

| Groups | HDL level mg/dl (mean ±SD) | | |
|---|---|---|---|
| | $0^{th}$ day | $30^{th}$ day | $60^{th}$ day |
| I(Control) | 47.83±4.58 | 48.83±4.12 | 50.5±3.51 |
| II(STZ induced diabetic,45mg/kg/bwt) | 33±5.69 | 24.83±7.31 | 20.33±4.37 |
| III(pioglitazone,7.5mg/kg/bwt) | 27±5.66 | 43.33±3.93 | 52.17±1.94 |
| IV(Zhongwan acupointwith 15HZ) | 24±6.03 | 37.5±4.14 | 45.5±2.17 |

The results were expressed as Mean± SD. Comparison was done with one way ANOVA and Tukey test with ($p \leq 0.01$) to control and diabetic group.

**Table 4** Effect of Zhongwan (CV12) acupoint on LDL (mg/dl)

| Groups | LDL level mg/dl (mean ±SD) | | |
|---|---|---|---|
| | 0th day | 30th day | 60th day |
| I(Control) | 30.48±10.47 | 31.9±9.31 | 37.97±7.64 |
| II(STZ induced diabetic,45mg/kg/bwt) | 86.93±14.03 | 96.87±45.6 | 137.3±11.78 |
| III(pioglitazone,7.5mg/kg/bwt) | 102.5±10.69 | 67.37±8.78 | 28.87±5.56 |
| IV(Zhongwanacupoint with 15HZ) | 103.83±5.57 | 69.6±4.91 | 43±4.62 |

The results were expressed as Mean± SD. Comparison was done with one way ANOVA and Tukey test with ($p \leq 0.01$) to control and diabetic group.

Treated diabetic rats with drug and Zhongwan acupoint stimulation significantly ($p \leq 0.01$) steady decrease in the total cholesterol, triglycerides, low density lipid and with significant ($p \leq 0.01$) increase in high density lipid.

### *Histopathological Examination*

GI showing normal architecture of pancreatic lobules with closely packed acinar cells. The rounded islets are interspersed between the acinar cells. The islets are lightly stained than the surrounding acinar cells. Streptozotocin (GII) induced diabetic group showed degenerative and necrotic changes in both exocrine and endocrine part. The islets are shrunken with severe vacuolation and reduction in number of cells. Pioglitazone (GIII) treated group revealed pancreas with nearly normal pancreatic lobular architecture. The large irregularly shaped islets with increased cellular density and reduction of vacuolation are noted. Wider interlobar and interlobular duct were observed.

**Figure 1** Zhongwan(CV12) acupoint stimulated with Acu-TENS of low-frequency(15HZ),High intensity and the pulse width of 5 sec, for 5 minutes daily without anaesthesia for 60 days

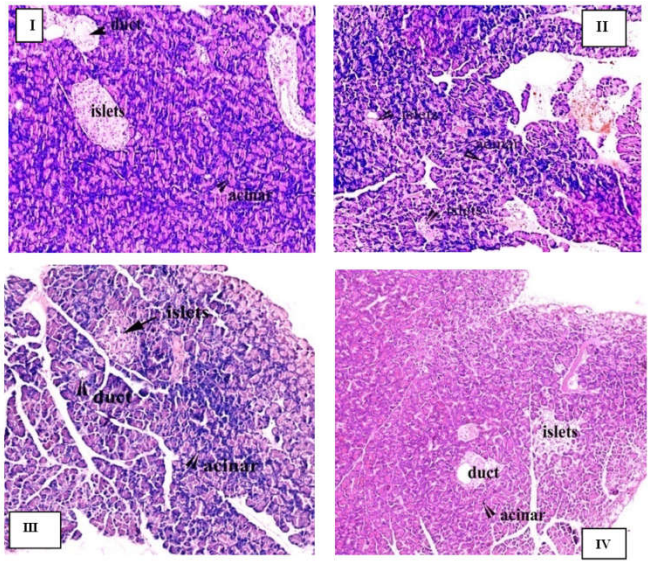



**Fig 2** Pancreatic islets at 60 days of treatment: H&E: X100: I (Control group)-islet appear normal; II(Diabetic group)- shrunken islets with necrosis; III(Pioglitazone treated group)-islets with increase cellular density; IV(Zhongwan acupoint treated group)-irregular shaped islets with increase cellular density.

Comparison with the standard anti diabetic treated group, the Zhongwan (GIV) acupoint treated group also showed recovery to near normal architecture with large irregularly shaped islets with increase in cellular density with less vacuoles and it was observed by using digital LEICA DMD 360 Microimaging Camera, German, Photomicroscopy. All the images of pancreas were captured at 400X and 100X, illustrated in figure 2 & 3.

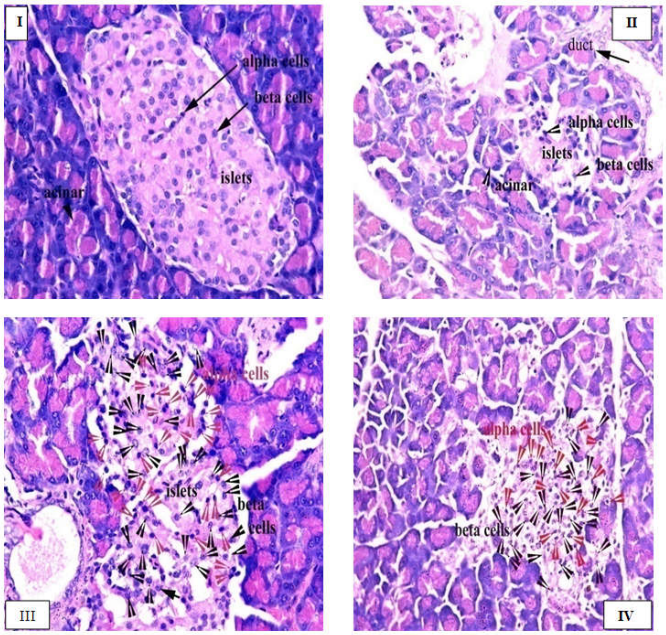
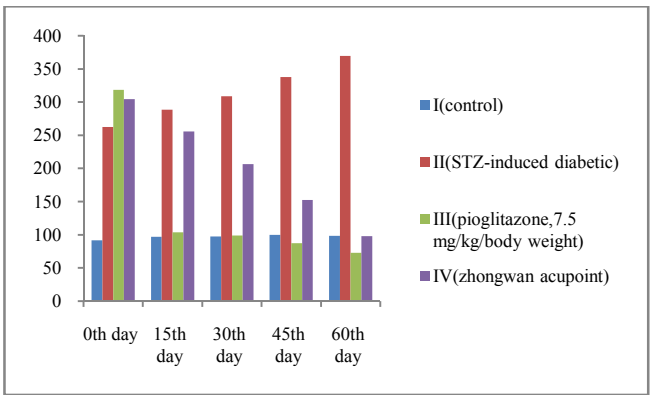



**Fig 3** Pancreatic islets at 60 days of treatment:H&E:X400: I (Control group)-normal distribution of alpha & beta cells; II(Diabetic group)- islets with only few surviving beta cells; III (Pioglitazone treated group)-islets with regeneration of beta cells(black arrow); IV (Zhongwan acupoiint treated group)-irregular islets with beta cell(black arrow) regeneration




**Graph 1** Effects of Zhongwan (CV12) on Fasting Blood Glucose Level (mg/dl).

The results were expressed as Mean± SD. Comparison was done with one way ANOVA and Tukey test with ($p \leq 0.01$) to control and diabetic group.

## DISCUSSION

Diabetes is one of a major public health problem throughout the World. Now a days the patients everyday medicines and insulin therapy is of a challenging role. Many of them are now a day showing interest towards adjunct therapy. Acupuncture therapy is practiced throughout the World due to its low cost and beneficial therapeutic effects for all diseases. The main concept of acupuncture is to stimulate Chi (life energy) through around 365 acupoints within 12 meridians in our body. There are numerous specific acupoints to treat diabetes but in

our study we selected Zhongwan(CV12) acupoints and proved the hypoglycemic effect of electrical acupuncture therapy in type 2 diabetes. An increase in evidence from scientific research is demonstrating the effectiveness of acupuncture for treating various diseases and revealing the mechanism of action. our study apprised the normal microanatomy of control rats pancreas with normal lobular architecture with rounded islets consists of lightly stained cells separated by blood capillaries. In streptozotocin induced diabetic rats pancreas shows marked histological changes with shrunken islets compared to normal islets. In the treated rats with antidiabetic drugs, the pancreas shows most of lobules with light stained islets with increased cellular density. In Zhongwan acupoint treated rats pancreas, shows mear normal architecture with islets of lightly stained beta cells and peripheral alpha cells are noted. In our study the increase in cellular density in islets of pancreas may be due to β-endorphin activation on the specific receptors in the pancreatic β cells. Skau M *et al*, (2001) concluded that increase in total volume can be caused by growth of existing islets and beta cells are the primary source for new beta cells. In another study has shown that exists adult pancreatic precursor can differentiate into cells with characteristic of islets β cells (Seaberg RM, 2004). Rong-Tsung Lin *et al*, 2014 explained the hypoglycemic effect of EA (2 HZ) and 15 HZ stimulation at Zhongwan acupoints was due to the increased secretion of endogenous beta endorphin from adrenal and from other sites respectively to increase the insulin secretion from pancreas. In our previous study, we reported the role of β endorphin in the hypoglycemic effect of Zhongwan acupoint in diabetic rats. Several studies showed that acupuncture regulates the lipid metabolism in various disorders. Electroacupuncture therapy in obese showed decrease in the level of serum total cholesterol, triglyceride and LDL cholesterol (Cabioglu MT, Ergene N, 2005). Richter *et al* (1983), explained the lipolithitic effect of β endorphin in rodants. Vetter *et al* (1993), explained in his study about the lipolithitic effect of β-endorphin on human fat tissues. In our study, we found that Zhongwan acupoint produced beneficial lipolytic effect may be due to role of β-endorphin. Dyslipidemia in diabetes is a major cause for morbidity, acupuncture therapy showed beneficial effects on lipid metabolism. According to the traditional Chinese medicine, the acupuncture therapy can be practiced either manual or electrical with needles. Zhi-Qi-Zhao (2008), mentioned that in electroacupuncture, stimulating current is delivered to acupoints via the needles connected to an electrical stimulator. Instead of insertion of acupuncture needles, a surface electrode on the skin over the acupoints is also described as electroacupuncture. Hence, in our study, we selected Acu-TENS apparatus to stimulate the abdomen (CV12) acupoint with surface electrode in rats which resulted hypoglycemic effect. Wu Zhiyuan *et al* (2015), explained the effect of TENS at specific acupoints (LI11, LI4, ST36, SP6) on type 2 diabetes patients for 30 minutes for each session and 5 times a week for 2 months. In our study, stimulation of Zhongwan acupoint for 5 minutes daily for 60 day treatment in diabetes rats shows a significant decrease in fasting blood glucose level (FBG). The Acu-TENS, a non-invasive technique having the beneficial effect to prevent risk of infection especially to the diabetic patients Shifen Xu *et al*, (2013). Some studies have shown that transcutaneous electrical muscle stimulation with a low stimulation frequency could be effective method to enhance glucose metabolism (Greenway F and Zheng J,2007 & Hamada T *et al* 2004).We selected Acu-TENS stimulator due its combined effect of both electrical and acupoints stimulation. Miyamoto *et al* (2012), used percutaneous electrical muscle stimulation with 4HZ for 30 minutes to decrease the glycemic index. In this study Acu-TENS with the frequency of 15 HZ (low frequency) produced a positive effect in reducing blood glucose level in type 2 diabetes and increase cellular density in pancreatic islets and also with improvement in lipid metabolism. Hence, Acu-TENS therapy at Zhongwan acupoint is an effective treatment for diabetes.

## CONCLUSION

This histopathological study concluded the effect of Acu-TENS therapy at Zhongwan acupoint on pancreatic islets of Langerhans in streptozotocin induced diabetic treated rats. The Zhongwan acupoint stimulation proved its hypoglycemic effect and with improvement on lipid profile. Acu-TENS electrical stimulation with low frequency and high intensity also induced mild muscle twitching which is similar to that of physiological process of physical exercise. Hence, this technique is used to the elderly diabetes patients who were not able to perform physical exercise. Moreover, the Acu-TENS application is non invasive uses only skin electrodes to stimulate the acupoints, this helps in preventing infection or inflammation than with the needle acupuncture therapy especially in diabetic patients. Here we suggest Acu-TENS therapy be a prior alternative therapy for diabetic patients.

**Conflict of Interest**

Conflict of interest declared none.

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