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RESEARCH ARTICLE

Role of Corticosteroid and CNS Neurotransmitters in Correlation between Diabetes and Depression

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ABSTRACT

Diabetes and Depression are highly prevalent conditions with severe impact on health outcomes. It was found that the prevalence of depression was significantly higher among patient with type 2 diabetes (T2D) but an exact mechanistic link between these two diseases is not yet clear. HPA axis hyperactivity leads to hypercortisolemia and alteration in corticosteroid metabolism which may play a key role in the development of depression in diabetes. Objective: To study the role of Corticosteroids in depressive diabetic mice. Materials and method: Total six groups each having six animal. T2D was induced by High Fat Diet (HFD) and Streptozotocin (STZ) (10 mg Kg-1, i.p.). Depression was induced by changing light & dark cycle (22:02 hr). Mifepristone (100 mg Kg-1, p.o., b.i.d.) was administered on day 49 to 53. FBG, Corticosterone level, and Forced Swimming test were performed to judge the status of the disease. Neurotransmitters level were also measured at the end of a study. Results: Serum Corticosterone, as well as Fasting Blood Glucose (FBG) level, was significant increases in diabetic, depressive and depressive diabetic group while decrease FBG level and serum corticosterone in mifepristone treated group. Immobility was significantly increased in depressive and depressive diabetic group and significantly decrease in Mifepristone received animals. Conclusion: It was concluded that Corticosteroids might be a link between diabetes and depression.

KEYWORDS

Diabetes, depression, corticosterone, fasting blood glucose level, mifepristone

INTRODUCTION

Depression is serious medical condition that affects thoughts, feelings and the ability to function in everyday life. Approximately 340 million people worldwide suffer from depression.[1] It was estimated that depressive disorders were higher in women (4930 per 100,000) than men (3199 per 100,000) and that globally depressive disorders were the fourth leading cause of disease burden in women and seventh leading cause in men.[2] An interaction between genetic predisposition and life history appear to determine a person's level of risk. Episodes of depression may then be triggered by stress (due to hyper activity of HPA axis), difficult life events, side effects of medications or other environmental factors. It is suggested that stress of chronic diseases increases the risk of depression. Several studies suggest that diabetes doubles the risk of depression compared to those without the disorder.[3]

The most serious of the clinical metabolic disturbances – i.e. visceral obesity, hypertension and dyslipidemia – are concurrent risk factors for type 2 diabetes.[4,5] In recent years, alterations in corticosterone (cortisol in human) metabolism have been suggested to play a pathogenic role in metabolic disturbances,[6] and some perturbations of the hypothalamic-pituitary– adrenal (HPA) axis have been found in diabetic patients.[7,8] Richardson and Tayek (2003) were found that hypercortisolemia due to HPA axis hyperactivity

was observed in individual patent with type 2 diabetes.[9] Hypercortisolemia is accompanied by increased sympatho-adrenal tone. In patients with type 2 diabetes, counter-regulation is known to start at normoglycemic thresholds, indicating elevated sympathetic neural outflow which is key factor for depression.[10,11] Thus, HPA axis hyper-activity leads to hypercortisolemia which might play a key role in the development of depression in type 2 diabetes. In light of above facts, the present investigation is carried out to study role of corticosterone in development of depression in diabetic mice.

MATERIALS AND METHODS

Animals: Healthy female Swiss Albino mice, weighing 20-40 g, procured from Zydus Research Centre, Ahmadabad, India.

Study Groups: Mice were randomly divided into seven groups (Table 1) (n=6)

Table 1: Group distribution

Groups	Detail of Groups	No. of animal
I	Control Group (NPD)	6
II	HFD + STZ (10 mg Kg^{-1}, i.p.) Group (DM)	6
III	Depression Group (NPD)	6
IV	DM + Depression Group	6
V	DM + Mifepristone (100 mg Kg^{-1}, p.o., b.i.d.)	6
VI	Depression + Mifepristone (100 mg Kg^{-1}, p.o., b.i.d) (NPD)	6
VII	DM + Depression + Mifepristone (100 mg Kg^{-1}, p.o., b.i.d)	6

The animals were housed in standard polypropylene cages and maintained under controlled room temperature (22±2 ℃) and humidity (55±5%) with 12:12 h light and dark cycle. All the mice were fed with commercially available normal pellet diet (NPD) and water ad libitum, prior to the dietary manipulation. The protocol (KBIPER/2012/329) was approved by Institutional (K. B. Institute of Pharmaceutical Education and Research) Animal Ethics Committee (IEAC) under the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) before carrying out the project.

a) Induction of Type 2 diabetes

Table 2: Composition of High Fat Diet (HFD) [13]

Ingredients	Weight (gm)	Kcal %
Powdered NPD	200	724
Lard	260	2340
Casein	135	540
Sucrose	245	980
Vitamin and mineral mix	5	20
DL-methionine	3	12
Corn starch	150	600
Sodium chloride	1	0
Soya bean oil	5	45
Total	1004 gm	5261 Kcal

A dietary fat constituent such as lard is rich in Saturated Fatty Acid (SFA). Subsequent HFD feeding increased adiposity, insulin resistance and hyperglycaemia. Low-dose STZ injection further augments hyperglycaemia.[12] All animals except group I (control) & III

(Depression) were fed HFD (Table 2) from day 0 to day 53.

On day 28, single dose of STZ (10 mg kg -1, i.p.; selected based on pilot study) (freshly prepared by dissolving 26 mg in 75 ml 0.05 M citrate buffer at pH 4.5) was administered in all HFD groups. Mice of control group were injected with the equivalent volume of saline. The induction of diabetes was confirmed by measuring the Fasting Blood Glucose (FBG) level on day 32 (after 72 hrs of STZ administration). Mice with fasting blood glucose level > 14 mmol L-1 were considered diabetic and were included for further study.

b) Induction of Depression

All the animals of group III, IV, VI, VII were exposed to 22:02 h light/dark cycle from day 32 to day 53 (three weeks) for induction of Depression and Forced Swimming Test (FST) was performed to confirm the induction of depression.[12]

c) Administration of Mifepristone

All the animals of group V, VI, VII were administered Mifepristone (100 mg Kg-1, p.o., b.i.d.) [14] from day 49 to day 53.

Evaluation Parameters

a) Measurement of Fasting Blood Glucose (FBG)

The Fasting Blood Glucose level was measured in all the animals on day 0, 28, 32 and 53. Mice were fasted for 24 hours, blood was collected from retro orbital plexus under anaesthesia; serum was separated by centrifugation (C24 REMI Centrifuge, India) at 5000 round per minute (rpm) for 15 minutes and was analyzed for glucose (GOD-POD) at 505 nm in UV-Visible Spectrophotometer (V-530, JASCO, Japan) using commercially available diagnostic kits (Span diagnostics Ltd, Surat, India).

Procedure: 20 µl of serum and standard glucose solution (100 mg/dl) was pipette into the different test-tubes, 1500 µl of working glucose reagent was added to each test tube. The test tubes were incubated at room temperature (15-30°C) for 30 min. Thereafter 1500 µl purified water was added. Then absorbance of standard and test was measured against reagent blank at 505 nm. Concentration of test sample was determined using the following formula:[15]

$$\text{Serum glucose } (\frac{\text{mg}}{\text{dl}}) = \frac{\text{Absorbance of test x 100}}{\text{Absorbance of standard}}$$

b) Forced swimming test (FST)

The FST was performed in all the animals on day 32 and day 53. Mouse was forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm) filled with water (25±1◦C) up to 19 cm; the total duration of immobility during a 6 min was recorded by stop watch. Mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water.[16]

c) Measurement of Corticosterone

The corticosterone level in serum was measured in all the animals on day 0, 28, 32 and 53. Blood was collected from retro orbital plexus under anaesthesia in the morning in between 6:00 a.m to 8:00 a.m. Serum was separated by centrifugation (C24 REMI Centrifuge, India) at 5000 rpm for 15 min. Serum (0.1 ml) was diluted with 0.2 ml freshly prepared chloroform-methanol mixture (2:1,v/v) and further extracted with 3 ml chloroform. The sample was vertexed for 30 sec and centrifuge (C24 REMI Centrifuge, India) at 2000 rpm for 10 min. The chloroform layer was carefully removed with the help of syringe with a long 16 gauge needle attached to it. The chloroform layer treated with 0.3 ml of 0.1N NaOH by vertexing and remove NaOH immediately. Chloroform layer vertexed with 30N H2SO4 vigorously. After phase separation, chloroform layer on the top was removed using syringe and discarded. The tube containing H2SO4 layer was kept in dark for 60 min. and thereafter fluorescence measurement was carried out using spectrofluorophotometer (RF 5301, SHIMADZU, Japan) with excitation and emission wavelength at 472 nm & 523.2 nm respectively. Equivalent volume of the isolation media without serum was used as blank.[17]

d) Measurement of Neurotransmitter

[Nor epinephrine (NE), Dopamine (DA) & 5-Hydroxytryptamine (5-HT)]

The neurotransmitter (NE, DA & 5-HT) level in brain was measured in all the animals on day 54. Mice were scarified by cervical dislocation and their brain were removed and homogenized in 5 ml of homogenizing buffer (0.32M sucrose solution). Homogenate were then subjected to centrifugation (3500 gyrun per min) for 35 min.[18] Nor epinephrine and Dopamine measurement was performed using reagent. Versene (prepared by dissolving 4 gm EDTA in 95 ml of distilled water & adjust the pH between 6.0 and 6.5 with 10N NaOH then make up the volume up to 100 ml with distilled water) & fluorescence was measured using spectro-fluorophotometer (RF 5301, SHIMADZU, Japan) at excitation & emission wavelength 385 nm & 485 nm for NE & excitation & emission wavelength 320 nm & 385 nm for DA. 5-HT measurement was performed using o-pthaladehyde & fluorescence was measured at excitation & emission wavelength 360 nm & 470 nm.[19]

Statistical analysis

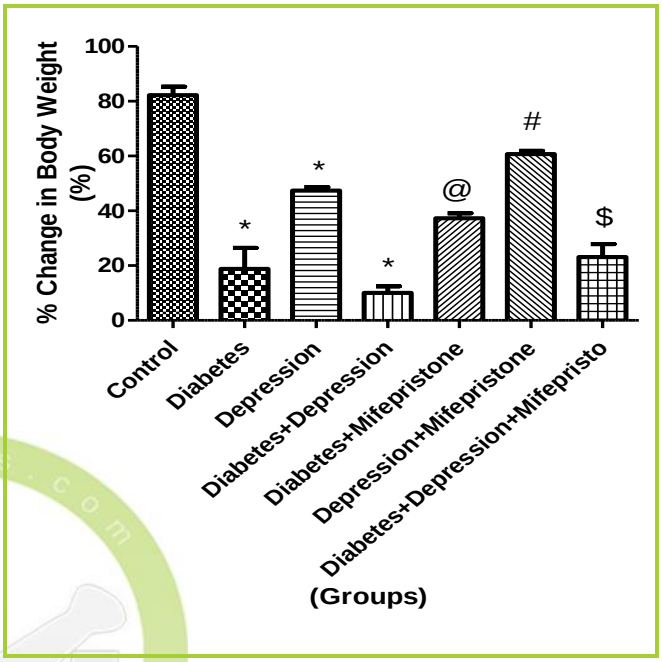
Data were expressed as Mean ± SEM for 6 animals. One way ANOVA followed by Tukey test and One way ANOVA followed by Dunnet's test was performed to check the significant difference among group. Multiple linear regression was applied to check the correlation between diabetes & depression.

RESULT

1) % Change in Body Weight

Body Weight of animal was measured on Day 0, 14, 28, 42, 53. Change in body weight (%) was observed (Figure-1) significantly ($p<0.05$) decrease in diabetic group (18.81±7.613), depressive group (47.35±1.237) & depressive diabetic group (10.05±2.412) compared to control group (82.24±3.086). Mifepristone treated diabetic group (37.33±1.783), Mifepristone treated depressive group (60.68±1.192) & Mifepristone treated depressive diabetic group (23.17±4.708) showed significantly ($p<0.05$) increase in % body weight compared to diabetic group, depressive group and depressive diabetic group.

Figure 1: Change in body weight (%) on Day 53



Each bar in the graph represents Mean ± SEM, n=6

***** Significantly different from control group at $p<0.05$

@ Significantly different from diabetic group at $p<0.05$

Significantly different from depressive group at $p<0.05$

$ Significantly different from depressive diabetic group at $p<0.05$

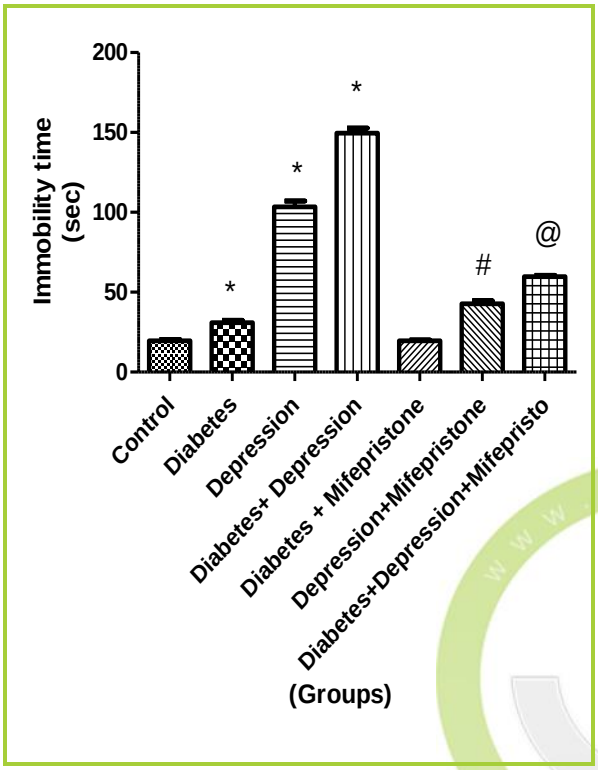
(One way ANOVA followed by Tukey's test)

(2) Forced Swimming Test

Immobility time was significantly ($p<0.05$) increase in diabetic group (30.83± 1.621), depressive group (103.3±3.827) as well as depressive diabetic group (149±3.181) compared to control group (19.50±0.991). Mifepristone treated depressive group (42.83±1.778) & Mifepristone treated

depressive diabetic group (59.83±0.749) showed significantly ($p<0.05$) decrease in Immobility time compared to depressive group and depressive diabetic group *(Figure-2)*.

Figure 2: Immobility time on Day 53



Each bar in the graph represents Mean ± SEM, n=6

***** Significantly different from control group at $p<0.05$

Significantly different from depressive group at $p<0.05$

@ Significantly different from depressive diabetic group at $p<0.05$

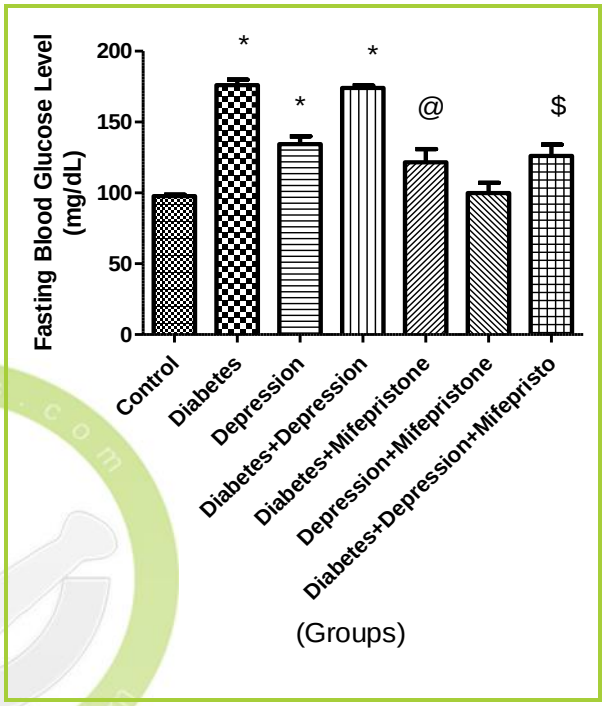
(One way ANOVA followed by Tukey's test)

(3) Fasting Blood Glucose Level

Fasting Blood Glucose (FBG) Level was measured on Day 0, 28, 32 and 53. Fasting Blood Glucose (FBG) Level was significantly ($p<0.05$) increase in diabetic group (176.04±3.943), depressive group (134.49±5.435) and depressive diabetic group (174.02±1.780) as compared to Control group (97.78±1.021).

Fasting Blood Glucose level was significantly ($p<0.05$) decrease in Mifepristone treated diabetic group (121.66±9.190) as well as Mifepristone treated depressive diabetic group (126.13±7.867) as compared to diabetic group and depressive diabetic group *(Figure-3)*.

Figure 3: Fasting Blood Glucose (FBG) level on Day 53



Each bar in the graph represents Mean ± SEM, n=6

* Significantly different from control group at $p<0.05$

@ Significantly different from diabetic group at $p<0.05$

$ Significantly different from depressive diabetic group at $p<0.05$

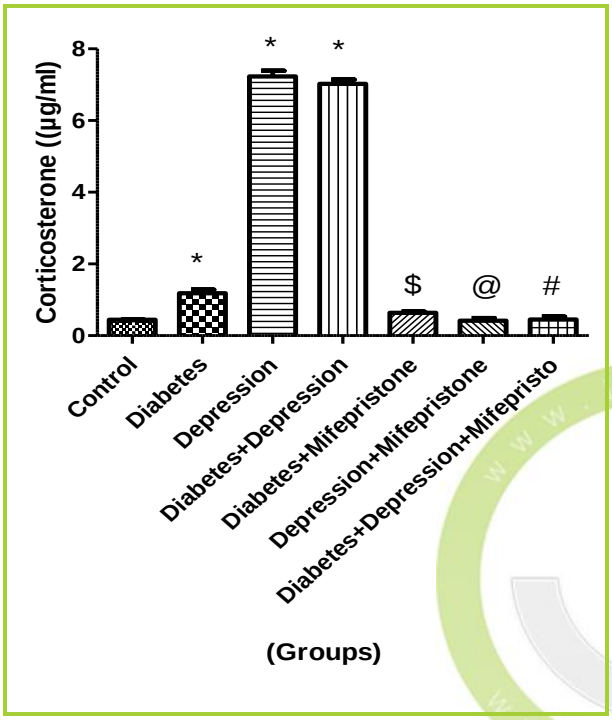
(One way ANOVA followed by Tukey's test)

4) Serum Corticosterone Level

Serum Corticosterone level was measured on Day 0, 28, 32 and 53. Serum Corticosterone level was significantly ($p<0.05$) increase in diabetic group (1.18±0.100), depressive group (7.25±0.169) and depressive diabetic group (7.33±0.350) as compared to Control group (0.452±0.005). Mifepristone treated diabetic group (0.63±0.036), Mifepristone treated

depressive group (0.41±0.076) & Mifepristone treated depressive diabetic group (0.452 ±0.079) showed significantly ($p<0.05$) decrease in serum corticosterone level as compared to diabetic group ,depressive group & depressive diabetic group respectively. (Figure-4).

Figure 4: Serum Corticosterone Level on Day 53



Each bar in the graph represents Mean ± SEM, n=6

***** Significantly different from control group at $p<0.05$

$ Significantly different from diabetic group at $p<0.05$

@ Significantly different from depressive group at $p<0.05$

Significantly different from depressive diabetic group at $p<0.05$

(One way ANOVA followed by Tukey's test)

5) Level of Neurotransmitters:

A) 5-Hydroxytryptamine (5-HT)

5-HT level was measured on Day 54. There was a significant ($p<0.05$) increase in 5-HT level in diabetic group (2.257±0.088), depressive group (1.390±0.317), depressive diabetic group (2.25±0.011), Mifepristone treated diabetic group(2.083±0.121), Mifepristone treated depressive group (2.227±0.177) & Mifepristone treated depressive diabetic group(2.430±0.228) as compared to control group(0.346±0.023) (Figure-5).

Figure-5: (A) 5 HT Level

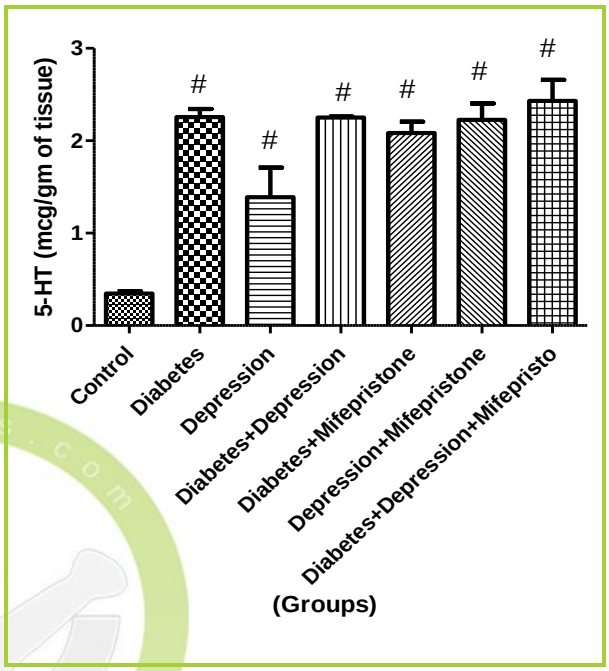


Figure-5: (B) NE level

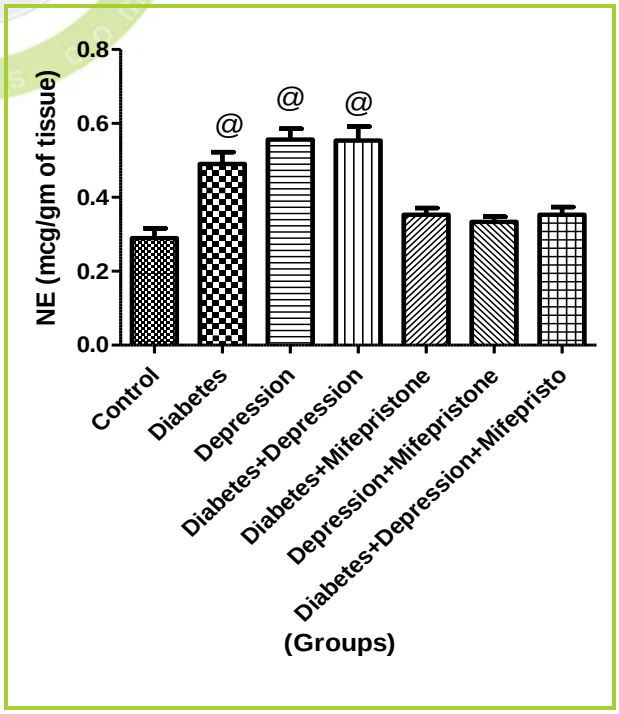
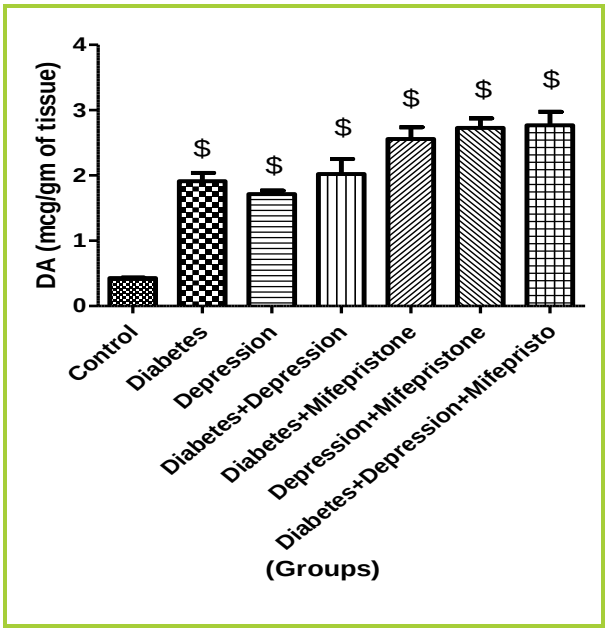


Figure-5: (C) DA level



Each bar in the graph represents Mean ± SEM (n=6), #, @and $ Significantly different from control group at p<0.05 (ANOVA followed by Dunnett's test)

B) Nor Epinephrine (NE)

NE level was measured on Day 54. There was a significant (p<0.05) increase in 5-HT level in diabetic group (0.49±0.032), depressive group (0.556±0.029), depressive diabetic group (0.553±0.038), Mifepristone treated diabetic group(0.6±0.030),Mifepristone treated depressive group (0.6±0.020) & Mifepristone treated depressive diabetic group(0.553±0.020) as compared to control group (0.29±0.029) (Figure-5).

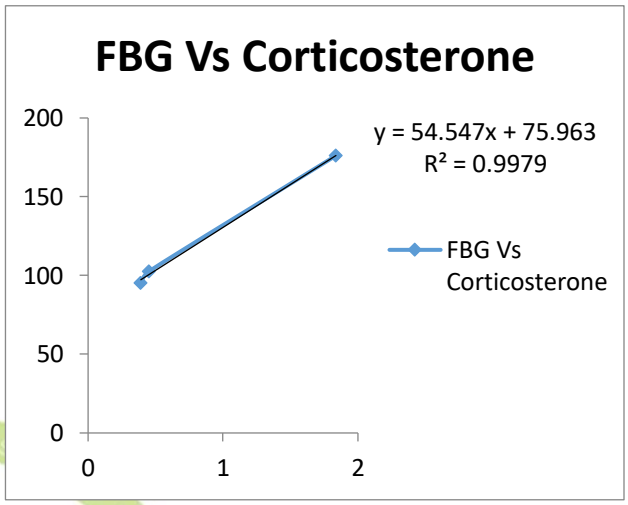
C) Dopamine (DA)

DA level was measured on Day 54. There was a significant (p<0.05) increase in 5-HT level in diabetic group (1.913±0.123), depressive group (1.713±0.054), depressive diabetic group (2.023±0.228), Mifepristone treated diabetic group (2.56±0.177),Mifepristone treated depressive group (2.727±0.147) & Mifepristone treated depressive diabetic group (2.770±0.205) as compared to control group (0.426±0.008) (Figure-5).

6) Correlation between Diabetes & Depression

There is positive and significant correlation between diabetes & depression (R^2 = 0.997).

Figure 6: Correlations between Diabetes & Depression



DISCUSSION

Depression is the major co-morbid psychological disorder with diabetes.[20,21] The probability of depression in diabetic patients is approximately double that of those without diabetes.[20] It was found that the prevalence of depression was significantly higher among patients with type 2 diabetes than those without diabetes[22] but exact mechanistic link between these two diseases is yet not clear. Since corticosteroid has a key role in insulin resistance[23] and also in depression, present investigation focus on corticosteroid as a link between diabetes and depression. Present investigation focused on corticosteroid as a link between diabetes and depression.For undergoing the study, diabetic (T2D) symptoms were induced in mice by high fat diet fed-STZ injected model which have been proposed as the better model for T2D.[24-26] A low fat diet is not enough to induce Insulin resistance (IR). Only high fat diet requires very long time to produce IR whereas only STZ administration causes T1D. High fat diet with STZ injection causes pancreatic β-cell damage as well as permanent IR. Thus, the pathogenesis of high fat diet-STZ induced diabetes is likely similar to the

pathogenesis in human, however, the dose and composition of diets largely affect the success of the induction of T2D in experimental animal. Depression was induced by changing light & dark cycle which causes mainly psychological stress (fear of drowning and suffocation) and consequently also physical stress (vigorous activity to come out).[27] High fat diet fed animal showed elevated body weight initially due to leptin resistance.[25] Diabetic, Depressive and depressive diabetic groups showed decrease in body weight compared with normal control group. Lipolysis due to insulin resistance and stress induced anorexia is major reasons for decreased body weight in diabetic group and depressive group respectively. There was significant increase in body weight in Mifepristone received groups.

Mifepristone is potent progesterone as well as glucocorticoid receptor antagonist. The advantage of Mifepristone over other anti-steroid agents is that it has no mineralo-corticoid action.[28] It showed dose-dependent action in body and 200 mg/kg, p.o. dose has anti-glucocorticoid action.Behavioral immobility reflects a state of despair in the mice and is one of the valuable parameter in assessing the depressive state.[29] Present investigation showed increase in immobility time in Diabetic, Depressive and depressive diabetic groups when compared with normal control group. Present investigation showed that there was a significant change in immobility time of diabetic, depressive and depressive diabetic group as compare to normal control group. Mifepristone treated animal shows decrease immobility time as compared to disease control group. Fasting blood glucose (FBG) level was found to be increased due to insulin resistance. There was a significant increase in FBG level in Diabetic group, Depressive group and Depressive diabetic group compared with normal control group. On the other hand, there was a significant decrease in FBG level in Mifepristone received animals due to its action on insulin resistance.[30]

Hypothalamic-Pituitary-Adrenocortical (HPA) axis plays major role in the etiopathogenesis of major depression. HPA axis abnormality was found in depression that leads to hypercorticosteronemia and thereby elevated corticosterone level.[28] A significant elevated corticosterone level was found in diabetic group, depressive group and diabetic depressive group compared with control group. Mifepristone, being a glucocorticoid receptor antagonist, restored elevated corticosterone level in Mifepristone received diabetic group, depressive group and diabetic depressive group.

The monoamine hypothesis of depression predicts impairment in central monoaminergic function. The lesion may comprise deficiencies in the absolute concentrations of norepinephrine and/or serotonin (5-HT). The studies have shown a correlation between depletion of monoamine level and depressive symptoms.[31] But Contrary to this, higher 5-HT, NE and DA level was observed in all the groups except control group in our study. This is in accordance with previous reports. Palanza, 2001[32] reported that female mice show higher level of 5-HT in depressive status. Further, Alvaro, 2011[33] and Strickland et al, 2002[34] also observed higher 5-HT level in female suffering from MDD. 5-HT or its agonists are reported to induce hyperglycemia in rats.[30] Increased 5-HT level might be one of the causes for increase in blood sugar level in depressive group in our study. Likewise, as per study of Wurtman, 2002, elevated NE level is associated with HPA axis abnormality.[33-34] The raised DA level might be due to either lack of N-methyl transferase in rodent's brain or psycho-depressive status. Furthermore correlation coefficient (R2 Value) between FBG and Corticosterone is 0.997, between FBG and 5-HT is 0.817, between FBG and NE is 1.000 & between FBG and DA is 0.995. These results indicate that there is positive and significant correlation between diabetes & depression.

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