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Behavioral Study to Assess the Effect of Zinc Treatment in Combination with Paroxetine in Diabetic Mice

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Abstract: Major depression disorder in diabetic patients is highly prevalent and usually associated with poor glycemic control, poor coherence to anti-diabetic drugs and overall decrease in quality of life. Antidepressants use in those patients demonstrates variable clinical efficacy on depression and inconsistent effects on the blood glucose level. Paroxetine is one of the most potent selective serotonin reuptake inhibitors mediates its activity by, among others, inhibiting serotonin reuptake, modulating BDNF and glutamate receptors activities. On the other hand, Zinc involved in the synthesis, storage, and release of insulin and many other metabolic pathways, suggesting a potential value in blood glucose level regulation. Also, Zinc is a BDNF inducer and NMDA inhibitor; both involved in neuronal cell survival, differentiation, and plasticity supporting a likely antidepressant activity of zinc. Therefore, we hypothesized that addition of zinc to the antidepressants may enhance their efficacy and improve the blood glucose level in diabetes Mellitus. This study investigated the behavioral changes of zinc administration alone or in combination with paroxetine in diabetic and non-diabetic mice using the forced swimming test. The results showed a significant antidepressant activity of paroxetine or zinc either alone or in combination as it has been demonstrated in a decrease of immobility and increase of swimming behavior in diabetic and non-diabetic animals in comparison to the animals treated with paroxetine only. Interestingly, Paroxetine alone had no effect on the blood glucose but the addition of Zinc significantly improved the blood glucose level in diabetic- paroxetine treated mice. The present data support the notion that addition of zinc to paroxetine may offer additional antidepressant activity and improve hyperglycemic control in comorbid major depressive disorder.
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1. Introduction

Major depression disorder (MDD) is a common, severe, chronic and often life-threatening illness and it is more frequent in diabetic patients. The possibility of co-incidence between MDD and diabetes mellitus (DM) is more than twice that of non-diabetics [1, 2]. Comorbidity of DM and MDD representing a real clinical challenge as both are leading causes of disability worldwide [3, 4]. A number of studies have connected depression to poor self-care and inadequate glycemic control in diabetic patients as well as decreased adherence to medication which may contribute to increased diabetic complications, co-morbidity and mortality [5-7]. The high prevalence of comorbid depression and DM suggests that underlying causes of both are sharing common pathological pathways. Many mechanisms have been postulated for this comorbidity and the bidirectional impact between MDD and DM. The psychological burden with subsequent overproduction of cortisol promoting insulin resistance and visceral obesity is a major contributor. Also, biochemical and/or inflammatory changes related to DM may be involved in the pathological process [8, 9]. This biological component of the hypothesis speculates that the metabolic consequences of diabetes lead to neurochemical changes in the brain that increase susceptibility to stress and depression10. Both possibilities are supported by the sequential finding that DM typically precedes the onset of MDD [10, 11].

The relationship between antidepressants (ADs) use and DM is controversial and involve several factors and still remains a matter of debate. Recent studies have shown that ADs use in diabetic patients

associated with improved glycemic control. Whether this is related to a direct pharmacological effect of the ADs on blood glucose regulation or as a result of mood changes is not known [11, 12]. Particularly SSRIs have received a significant amount of evaluation in diabetic patients, examining their effects on depression as well as on diabetes outcomes and self-care. Fluoxetine, [13] sertraline, [14] and paroxetine [15] were found all effective in treating depression; fluoxetine and paroxetine were also associated with improved quality of life [16]. The efficacy of paroxetine for depression is comparable to that of older tricyclic antidepressants, with fewer side effects and lower toxicity [15, 32], therefore ADs should be assessed individually. Despite the devastating impact of depression in diabetic patients, the available treatments are either not effective enough in some patients or have many unpleasant effects [17].

Addition of another medication to the ADs regimen of diabetic patients with MDD has become a mutual intervention. Zinc plays an important role in the maintenance of blood glucose level, including the synthesis, storage and release of insulin [18]. Zinc has been found to enhance the effectiveness of insulin in vitro, and it has been seen that zinc deficiency may aggravate the insulin resistance in noninsulin dependent diabetes mellitus [19]. The development of hyperglycemia after dietary zinc deprivation, together with the occurrence of zinc deficiency in DM, suggest a role for zinc deficiency in the pathogenesis and progression of diabetes mellitus. On the other hand, it has been shown that zinc repletion could improve insulin sensitivity [18, 19].

Zinc acts also as a synaptic modulator in the central nervous system. Mostly the effect of zinc is connected with its action on glutamate receptors. Zinc is a very potent inhibitor of the NMDA receptor [20, 21]. Alterations in nervous zinc homeostasis are associated usually with behavioral disturbances, such as impaired learning and memory as well as cognitive function and with other neurological disorders (e.g. epilepsy, Alzheimer's disease) and furthermore, they are implicated in the pathophysiology and therapy of depression [22, 23].

Clinical observations demonstrated a decrease in blood zinc level in the patients suffering of depression. This reduced level was normalized only after antidepressant treatment [23, 24]. Chronic antidepressant therapy elevates zinc concentration in the rat hippocampus [24]. Collectively, several evidences strongly supports a direct relationship between zinc deficiency and the risk of depression and an inverse relationship between zinc supplementation and depressive symptoms. Also, chronic treatment with imipramine increases the potency of zinc to inhibit the NMDA receptor activity in the mouse cerebral cortex [25]. Moreover, Zinc is active in the forced swimming test, commonly used for evaluation of antidepressant activity [26]. In addition, zinc exhibits antidepressant activity in different animal models of depression, such as chronic mild stress and olfactory models of depression [27]. There is an association between antidepressants use in general and changes in the glycemic control [28–30]. Some antidepressants have been linked with increased risk of diabetes onset patients while others associated with improved glycemic control [31].

Thus, the purpose of this study is to investigate whether zinc either alone or in combination with Paroxetine (Pxt) influenced the animal behavior pattern in the FST. We will also assess the effects of zinc and/or Pxt on the glycemic control in diabetic mice as well as the spontaneous locomotors activity in these animals.

2. Material and Methods

All procedures were conducted according to the general Animal Care and Use Committee guidelines, and were approved by the Ethics Committee of the of King Khalid University (KKU). The experiments were carried out on male Albino Swiss mice (25–30 g). The animals were kept under a natural day–night cycle with free access to food and water. Each experimental group consisted of 8 animals. Zinc sulfate and Paroxetine hydrochloride were administered intra-peritoneal (IP), once daily for 14 days. In the last day of treatment, the animals received the same treatment three times approximately at 23.5, 7 and 1 h prior to the 5 min forced swim test. Control animals received vehicle (saline), we followed the methods of Hesham El Refaey et al. 2015[61].

2.1. Induction of diabetes and glucose monitoring

Two separate cohorts of mice were used. Eight-week-old, male Albino Swiss mice, housed in groups of 4–5 per cage, were used. To induce diabetes, mice received a single (IP) injection of 60 mg/kg STZ (Sigma-Aldrich, St. Louis, MO) prepared in 5 M sodium citrate, pH 4.5, or vehicle. Blood glucose levels were measured periodically, starting 2 days after STZ or vehicle injection, using a portable Freestyle glucometer (Abbott Laboratories, Abbott Park, IL). Blood was obtained via tail snip. Mice with blood glucose values 200 mg/dl were included in the STZ groups [62]. Glucose levels were measured on a two- day's basis, in the morning between 0800 and 1000, until the completion of the study. Behavioral testing for mice began 2 weeks after treatment with STZ. Mice (n=10–12 per group) underwent a series of behavioral tests.

2.2. Forced swimming test

The studies were carried out according to the method of Porsolt et al. [33]. Mice were dropped individually into glass cylinders (height 25 cm, diameter 10 cm) filled with water to a height of 10 cm, (maintained at 23–25°C), and left there for 6 min. The immobility time was measured during 5 min testing period. Mice were judged to be immobile when they remained floating passively in the water.

2.3. Locomotor activity

Locomotor activity was measured using photoresistor actometers (circular cages, 25 cm in diameter, two light sources, and two photoresistors). The animals were placed individually in an actometer for 10 min. Activity was measured at 5-min intervals to characterize dynamics of changes. The number of light beams crossed by an animal was recorded as the locomotor activity.

2.4. Data analysis

The obtained data were evaluated by the one way analysis of variance (ANOVA), followed by Dunnett's multiple comparisons test; $p < 0.05$ was considered significant.

3. Results

Zinc sulfate at doses of 10, 20, 30 and 40 mg/kg (respectively) was tested in the forced swimming test in mice and in the locomotor activity test. Zinc significantly reduced the immobility time in the forced swimming test at the dose of 30 and 40 mg/kg and had no effect at doses of 10and 20 mg/kg (Tab. 1).

Table (1) Effect of different doses of zinc administration on the immobility time in the forced swim test

Compound	Dose	Immobility time
Saline	-----	37.12 ± 5.91
Zinc sulfate	10 mg/kg	34.70 ± 7.32
Zinc sulfate	20 mg/kg	35.18 ± 5.64
Zinc sulfate	30 mg/kg	29.42 ± 4.16*
Zinc sulfate	40 mg/kg	27.40 ± 4.20*

Zinc sulfate was administered one hour before the test. The values represent the mean ± SD (N= 12 per group). (* $p < 0.05$) compared to saline treated animals by a 1-way ANOVA followed by Dunnett's Multiple Comparison post-test.

Therefore, the dose of 30 mg/kg was chosen for use in the combination studies of antidepressants with zinc. Zinc sulfate at dose of 30 mg/kg significantly reduced the immobility time and increased the swimming behavior of non-diabetic and diabetic animals in the forced swimming test (Fig.1, 2, 3).

The effects of Streptozotocin induced-diabetes on animals' behavior as compared to control non-diabetic mice are shown in Fig.1 The results show significant difference between non-diabetic and diabetic animal behavior in the FST. Diabetic animals spent significant much more time in the immobile behavior in comparison to non-diabetic animals. Also, there were a significant reduction in the swimming and climbing behavior as compared to non-diabetic mice Fig. (1).

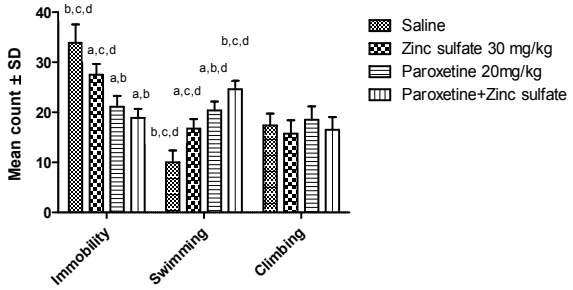

Fig-1. Effect of forced-swim test in non- diabetic and diabetic mice. Data are presented as mean ± S.D. of total number of intervals spent in each specific behavior (N= 12 per group), sampled every 5 sec, during a 5 min FST period. Significant differences within each behavior, as compared to (a) Non-diabetic, and (b) diabetic were determined by a t-student test ($P < 0.05$).

Fig-2. Effect of zinc sulfate (30 mg/kg) administration alone and/or in combination with Paroxetine (20 mg/kg) for 2 weeks in the forced-swim test in non-diabetic mice. In the last day, mice received their treatments three times following the initial 15 min pre-test swim, at 23.5, 7 and 1 h before the 5 min forced-swim test. Data are presented as mean ± S.D. of total number of intervals spent in each specific

behavior (N= 12 per group), sampled every 5 sec, during a 5 min FST period. Significant differences within each behavior, as compared to (a) saline treatment, (b) 30mg/kg zinc, (c) 20 mg/kg Paroxetine and (d) Paroxetine (20 mg/kg) + zinc (30mg/kg), were determined by a 2-way multivariate ANOVA, followed by Dunnett's Multiple Comparison posttest ($P < 0.05$).

In non-diabetic mice, Paroxetine administered alone at the dose of 20 mg/kg reduced the immobility time and increased the swimming and had no effect the climbing behavior (Fig.2). Combined administration of Prx (20 mg/kg) and zinc (30mg/kg) in the same study, induced statistically significant reduction of the immobility time in mice and increased the swimming durations as compared with either Prx or zinc treated animals as shown in Fig (2).

On the other hand, combined administration of zinc with Prx had no effect on the locomotors activity in mice Fig (5). In diabetic mice, Zinc (30mg/kg) significantly reduced the immobility time and increased the swimming activity in the forced swim test (Fig.3). Also, Paroxetine administered alone at the dose of 20 mg/kg reduced the immobility time and increased the swimming behavior durations (Fig.3).

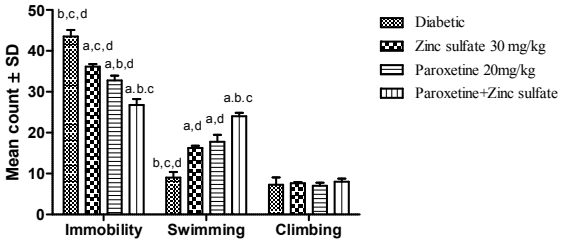

Fig-3. Effect of zinc sulfate (30 mg/kg) administration alone and/or in combination with Paroxetine (20 mg/kg) for 2 weeks in the forced-swim test on diabetic mice. Data are presented as mean ± S.D. of total number of intervals spent in each specific behavior (N= 12 per group), sampled every 5 sec, during a 5 min FST period. Significant differences within each behavior, as compared to (a) saline treatment, (b) 30mg/kg zinc, (c) 20 mg/kg Paroxetine and (d) Paroxetine (20 mg/kg) + zinc (30mg/kg), were determined by a 2-way multivariate ANOVA, followed by Dunnett's Multiple Comparison posttest ($P < 0.05$).

Combined administration of Prx (20 mg/kg) and zinc (30mg/kg) in the diabetic study, induced statistically significant reduction of the immobility time in mice and increased the swimming durations as compared with either Prx or zinc treated animals as shown in Fig (3). On the other hand, combined administration of zinc with Prx had no effect on the locomotors activity in diabetic mice, Fig (4).

Figure 4. Effect of different treatments on locomotor activity in the open-field test. Mice received saline (n = 11), Paroxetine (20 mg/kg; n = 10) and/or zinc sulfate (30 mg/kg) for two weeks by IP injection prior to the 10 min open-field test. Data are presented as mean ± S.D. number of crossings in the open-field test in response to saline or drug treatments. No significant difference was found between saline and zinc, paroxetine and zinc + paroxetine treated animals. Treated mice had no significant activity scores (* $p < 0.05$) compared to saline treated animals by a 1-way ANOVA followed by Dunnett's Multiple Comparison post-test.

Figure 5. Effect of different treatments on locomotor activity of diabetic mice in the open-field test. Mice received saline (n = 11), Paroxetine (20 mg/kg; n = 10) and/or zinc sulfate (40 mg/kg) by IP injection prior to the 10 min open-field test. Data are presented as mean ± S.D. number of crossings in the open-field test in response to saline or drug treatments. No significant difference was found between saline and zinc, paroxetine and zinc + paroxetine treated animals. Treated mice had no significant activity scores (* $p < 0.05$) compared to saline treated animals by a 1-way ANOVA followed by Dunnett's Multiple Comparison post test.

In non-diabetic mice, either Paroxetine administered alone at the dose of 20 mg/kg or zinc in 30mg/kg or their combined administration for two weeks had no significant effect on the blood glucose level in comparison to the normal mice Tab. (2).

Treatment / Blood glucose	Control group ±SD	Zinc sulfate ± SD	Paroxetine ± SD	ZnSo4 + Paroxetine ± SD
Non-diabetic	129.7 ± 4.5	119.8 ± 3.7	133.9 ± 3.9	123.9 ± 3.2
Diabetic	291.4 ± 3.4[b,d]	221.00 ± 4.6[a.c]	308.500 ± 4.65[b.d]	219.00 ± 4.13[a.c]

However, in the diabetic mice, zinc treatment either alone or in combination with paroxetine significantly lowered the blood glucose level as compared to the glucose level of the diabetic or paroxetine treated mice. On the other hand, paroxetine administration only have not shown significant effects on the blood glucose level as compared to the diabetic animals Tab. (2).

4. Discussions

The number of patients suffering of both diabetes and depression are exponentially increasing. Also, depression and diabetes demonstrated a bi-directional relationship and depression is usually associated with poor glycemic control. Certain ADs increase the risk of poor control while others improved the impact on glycemic control of the diabetic patients [28]. The efficacy of the different classes of ADs on diabetic patients is still questionable. Thus, the search for more effective therapeutic strategies represents one of the urgent priorities for the management of depression and its complications in diabetic patients.

Addition of another medication to the ADs regimen of diabetic patients with MDD represents a conventional intervention. Zinc has shown clinical beneficial effects in both diabetes and depression [18]. In the present study, we demonstrate the behavioral effects of zinc sulfate either alone or in combination with paroxetine administration in mice. Our data indicate that zinc administered at the dose of 30 mg/kg reduces the immobility time of mice in the forced swimming test and increased the swimming activity as has been shown before in Elrefaey et al. [61]. Concurrently, when zinc is given jointly with Prx. (20 mg/kg), a potent reduction in the immobility time is observed with concomitant increase in the swimming activity without change in the locomotors activity. Since these treatments (Prx plus zinc) do not affect locomotors activity, the results indicate potentiation of antidepressant- like activity by such combined treatments. These are in agreement with our previous study [61]. These results confirmed that zinc produced an antidepressant-like effect and demonstrated a zinc induced enhancement of the antidepressant activity of Prx without stimulation of locomotors activity [45].

Also, an increase in the swimming but not climbing parameter of the mice FST observed following zinc administration indicates the serotonin pathway participation in agreement with our study Elrefaey, et al. [61]. Therefore, this data suggests that the antidepressant-like effect of zinc seems to be mediated through an interaction with the serotonergic rather than the noradrenergic system [34]. Several studies have shown the synergistic effects of zinc with antidepressants. Zinc may indirectly release 5HT, which in turn activates 5HT receptors as a part of the mechanism of antidepressant activity [27, 34].

The effect of Zinc on swimming remains the same after 14 days of treatment. This may suggest that predominance of zinc effects as NMDA antagonist over the other time consuming effects like BDNF induction that require chronic administration [40].

Maes et al. [35] studied on MDD patients which they found that not only the zinc level was significantly lower in patients group, but also negatively correlated with the severity of depressive symptoms. In two further studies on 31 and 48 patients (respectively) diagnosed with MDD, they also confirmed previous observations [35, 36], which is consistent with the study by Swardfager et al. [37]. Moreover, growing evidence for the valuable effects of zinc therapy from clinical studies demonstrated that zinc supplementation significantly reduced depression severity and facilitated the outcomes in patients with the antidepressants treatment resistant [38, 39].

The potential mechanisms underlying the association between zinc and depression is multifactorial and involve the regulation of neurotransmitters, neurotrophic factors, signaling transductions and synaptic plasticity [45]. The co-localization of 5-HT1A receptors and Zn2+ in the nervous system proposes that Zn2+ released at nerve terminals may modulate signals generated by the 5-HT1A receptors prompting the effectiveness of antidepressant therapies that rely on 5-HT1A receptor activity [46]. Chronic administration of zinc increases the BDNF gene expression, which is a common effect shared by most of the clinically effective antidepressants. A possible role for zinc in depression is its role in induction of synaptic plasticity and synaptogenesis through transactivation of BDNF and its receptor Tyrosine Kinase B (Trk-B) [47, 48].

In addition, highest level of zinc in the brain can be found pre-dominantly within the vesicles of glutamatergic synapses. The term ‘gluzinergic neurons’ has been proposed for neurons that release zinc and glutamate [49, 50]. This glutamate-dependent mechanism associated with NMDA activation is likely

to be responsible for zinc-induced changes in BDNF gene expression. Apparently the release of zinc upon synaptic activity is followed by a massive increase in the local Zn2+ concentration in the synaptic cleft and subsequently an increase in the postsynaptic activity. This finally leads to increase in synaptogenesis which in part may explain the antidepressant activity of zinc [51, 52].

Furthermore, Zinc has found to modulate several crucial pathways, including Glycogen synthase kinase-3 (GSK-3) and mammalian target of rapamycin (mTOR). GSK-3 acts as an intermediate modulator in the 5-HT neurotransmission system, and balanced GSK-3 activity is vital for serotonin-regulated brain functions and behaviors [53]. Abnormalities in GSK-3β pathway are implicated in major depression as well as other psychiatric disorders. It has been demonstrated that the inhibition of GSK-3β is associated with the antidepressant activity [54]. Several studies have reported Zinc to be a potent GSK-3 inhibitors [55, 56]. Modulation of this pathway is hypothesized to be the main axes involved in both the rapid and delayed effects exerted by most antidepressants [54]. Particularly important, SSRI antidepressants, regulate GSK-3 by inhibiting its activity in different parts in the brain, which reinforces the importance of GSK-3 as a potential therapeutic target in neuropsychiatric diseases [53].

Also, Zinc has been found to induce its antidepressant activity on mTOR-dependent pathway through inhibition of NMDA receptors. It has been shown that single injection of Zinc induced an increase in the phosphorylation of mTOR 3 h after Zn treatment produced an antidepressant effect in the forced swim test FST [57, 58]. The characterization of the mTOR signaling pathway in depression and its action in response to zinc shows great potential for the identification of new therapeutic targets. Moreover, it was found that hippocampal mTOR signaling is necessary for the antidepressant effects of paroxetine [59]. These studies indicated that the antidepressant activity of Zinc contributes to the modulation of GSK-3 and mTOR signaling pathways.

Interestingly, both pathways have been involved in the antidepressant activities particularly SSRI which may explain the synergistic effect that has been seen in our study upon addition of zinc to paroxetine.

The present study extended to evaluate the effects of Zinc supplementation on diabetes in the depressed animals.

Zinc is important element in insulin synthesis and release as well as carbohydrate metabolism [41]. Oxidative stress plays a crucial role in the development and pathogenesis of diabetes and its complications. Zinc is a co-factor and essential structural part of key anti-oxidant enzymes such as superoxide dismutase, and Zinc deficiency impairs their synthesis, leading to increased oxidative stress [42]. Also, several studies have shown that diabetes is accompanied by hypozincemia [43]. In addition Zinc deficiency is more common in developing countries where diabetes mellitus is also showing an exponential increase in prevalence [44]. In this study we demonstrated that zinc treatment either alone or in combination with paroxetine significantly lowered the blood glucose level of diabetic animals as compared to the glucose level of the diabetic or paroxetine treated mice. This could be simply explained based on the role of zinc in insulin synthesis, carbohydrate metabolism and its anti-inflammatory as well as its antioxidant properties [46, 47]. Also, one of the astonishing in vivo features of zinc is its insulin-like effect and its potential link with insulin resistance and type 2diabetes. Zinc was found to stimulate lipogenesis and glucose transport in adipocytes [56]. Interestingly, it has been shown that zinc inhibits GSK-3 suggesting that its in- vivo insulin-like effects are mediated via direct inhibition of endogenous GSK-3 β signaling. On the other hand, mTOR is a key regulator of energy metabolism and function of both pancreatic islet β cells and immune cells. It seems that mTOR has both anti- and pro-diabetic effects [60]. This may explain in part the variable effects of antidepressants on the blood glucose level. Collectively, zinc as well as some antidepressants were found to share both GSK-3 and mTOR signaling proposing a common target in the management of depression and diabetes.

Thus, it could be assumed that zinc addition to paroxetine may augment its antidepressant activity and also improve the glycemic control of diabetes in the same time. It could be concluded from this study that zinc and Paroxetine combination may have a significant clinical application in psychiatric patients particularly in geriatric patients or other population where zinc level has shown dramatic decrease. Further studies are needed to assess the exact mechanism of chronic zinc administration in augmenting the activity of antidepressants as well as in improving glycemic control.

Conflict of interest

There is no conflict exists, “The Authors declare that there is no conflict of interest.”

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