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Research Article

EFFICACY OF DIPEPTIDYL PEPTIDASE-4 INHIBITOR WITH ZINC AND CHROMIUM PICOLINATE IN PATIENTS OF TYPE-II DIABETES MELLITUS

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ABSTRACT

In the present study, we have evaluated the effect of Zinc (Zn) and Chromium picolinate (CrPic) supplementation with sitagliptin in Type-II DM patients. A randomized controlled trial was conducted on 600 patients suffering from Type-II DM. Patients from four different hospitals of Punjab were divided into three groups comprising of 200 patients each. Group A was given sitagliptin (100mg), group B received Zn sulphate (10mg) for 12 weeks along with sitagliptin and group C received CrPic **(**200mcg) along with sitagliptin. Blood samples of the patients were collected before starting the treatment (zero time sample) and then after 12 weeks of the treatment, to monitor the changes in different study parameters. Blood sugar fasting (BSF) and Glycated hemoglobin (Hb_{A1c}) was measured by ion exchange chromatography by using a commercial kit (Sigma-Aldrich, St Louis, MO, USA). Analysis of variance (ANOVA) was used to compare the efficacy of all treatment groups. P value ≤ 0.05 was considered significant. Results indicated that all defined therapies have insignificant influence with respect to gender as *p = 1.000*. BSF and HbA_{1c} in group B was found effective in all treatments at all levels of study with *p=0.000*. Our study concludes that Zn supplementation with sitagliptin on glycemic control in patients with Type-II DM gave the best treatment option.

Keywords: BSF, CrPic, Hb_{A1C}, Type-II DM, Zinc

Introduction:

Type 2 diabetes mellitus, previously known as non-insulin-dependent diabetes mellitus, Diabetes mellitus (DM), is the most prevailing non-communicable, endocrine disorder characterized by hyperglycemia. The disease affects more than 150 million people throughout the world[1]. Currently it is one of the top ten causes of mortality worldwide [2]. Treatment prevents some of its devastating complications but does not usually restore normoglycemia or eliminate all the adverse consequences[3]. Various pathogenic procedures are involved in developing the disease. These include autoimmune damage to the β-pancreatic cells with subsequent abnormal insulin deficiency that ends in insulin resistance [4]. Symptoms of hyperglycemia include polydipsia, weight loss occasionally with polyphagia, polyuria, obesity, hypotension, nocturnal enuresis, and blurred vision. Impaired growth along with susceptibility to different infections may also possibly accompany hyperglycemia [5]. The diagnosis is often delayed until complications are present[6]. The current methods of treating diabetes remain inadequate, prevention is preferable [7]. There is growing evidence that β-cell dysfunction is crucial for the development and progression of T-II DM [8]. However, DM diagnosis is confirmed by performing various laboratory tests: Blood glucose testing including random (non-fasting) blood glucose test, fasting blood glucose (FBS) test, oral glucose tolerance test (OGTT) and gestational diabetic test and Urine analysis including ketouria and glycosuria[9].

To detect diabetes different tests are introduced including FBG, RBG, Hb_{A1c}. The main clinical feature of T-II DM is hyperglycemia, showing BSF>126 mg/dL or Hb_{Alc}> 7.9%. Both pharmacologic and non-pharmacologic therapies are essential for the management of T-II DM. DM not just stimulates oxidative stress, but it also declines cells ability to deal with this augmented oxidative burden. Amelioration of oxidative stress with antioxidants like Zinc (Zn) may help in reducing diabetic complications [10, 11]. Zinc plays a critical role in

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synthesis, storage and secretion of insulin under normal physiological and diabetic conditions due to its antioxidant properties. Decreased Zn level affects the ability of β-cells of pancreas to produce and secrete insulin and may also lead to the development of insulin resistance, a particular character of T-II DM [12, 13]. On the other hand, Chromium (Cr) is among trace minerals whose cellular mechanisms have not clearly been identified yet. This is the element that contributes in normal functioning of glucose and lipid metabolism but the element itself cannot be used owing to its poor absorption rate, so Chromium picolinate is efficient than other forms of the element due to its better absorption profile [14, 15]. CrPic increases the number of insulin receptors, receptor binding and receptor phosphorylation thus reducing insulin resistance. Oligopeptide low molecular weight chromium binding substance (apochromodulin) is an intracellular protein affecting insulin receptor. It is distributed extensively in the brain, liver, testicles, kidneys, intestine and spleen [16].

The objective of current study was to evaluate the effect of Zn and CrPic supplementation with sitagliptin in Type-II DM patients.

MATERIALS AND METHODS

Study design: This study included randomized controlled trial including outdoor diabetic clinics from four different hospitals of Punjab. i.e., Sheikh Zayed Hospital, Lahore; Diabetic Institute of Pakistan, Lahore; Akhuvat Foundation, Lahore; and Jinnah Hospital, Lahore

Sampling Techniques: The subjects were consented in written and randomized into three arms using block randomization. A block size of 10 randomly determined to avoid selection bias. For each center, three blocks were used to generate the random numbers. Randomization was central.

Sample Size: The study was conducted on 600 patients (n=600) suffering from T-II DM after fulfilling inclusion and exclusion criteria. Patients were divided into three groups; each comprising of 200 patients. Group A was given sitagliptin 100mg OD, Group B received Zn sulphate tablets of 10mg daily along with sitagliptin, and Group C received CrPic200mcg daily with sitagliptin for a period not more than 06 months.

Inclusion criteria: All the patients being participated the study met the following inclusion criteria:

- The patients suffering from T-II DM for more than 4 years having age not less than 30 years or greater than 60 years.
- Patients who never enrolled in any diabetes support or education programs or involved in similar programs in last 06 months.
- Patients have not taking vitamins or mineral supplements in the previous 02 months.
- Hb_{Alc} concentrations $\geq$ 8% and Hb level $\geq$12- 14 with no kidney disease.

Exclusion criteria: Subjects were excluded from the study that have:

- Hyper-vitaminosis or any cancer.
- Developed any cardiovascular disease during study duration.
- Any disability and any kind of Psychotic disease or gastrointestinal problems.
- Pregnancies or breast feeding.
- Consume more than 50-75mg of nicotine daily and/or taking alcohol.

Biochemical Assessment: Blood samples of all participants were collected at zero time intervals, after three months and at the end of treatment. Venous blood sample of 5ml was drawn after an overnight fasting of 10-14 hours and post-prandial (2 hours after lunch) before taking medications[10, 17].The blood samples were collected in EDTA containing sterile tubes. The biochemical markers of glycemic control assessed were blood sugar fasting (BSF) level and Glycated hemoglobin (Hb_{A1c}).

Statistical Analysis: Data was analyzed on SPSS version 22.0 software. One way ANOVA as applied using Tukey range test. The value of $p < 0.05$ as considered significant.

Ethical Consideration: It is submitted that the investigation was approved and that informed consent (in written) was obtained from Ethical Committee of Hajvery University, Lahore-Pakistan and from patients respectively.

RESULTS

This study enrolled 600 patients in total after taking informed consent. Both male and female patients were equal in number, i.e., 50%. For all

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enrolled subjects that were treated for type-II diabetes, the age presentation was 46.72±8.284 years. Out of these, 54% (324) patients have past medical history of type-II diabetes mellitus. All the subjects were divided into three groups A, B and C, each comprising of 200 patients with equal gender distribution. Group A receives sitagliptin, group B receives sitagliptin with zinc while Sitagliptin with zinc and chromium picolinate was administered to group C. Results indicated that all defined therapies have insignificant influence with respect to gender as *p = 1.000*. Blood sugar fasting (BSF) was observed at start, 03 months and 06 months of treatment. It was shown that group B was found effective in all treatments at all levels of study. After 06 months of therapy, group B (124.42±9.45) was observed most effective in lowering BSF as compared to group A (148.16±28.10) & C (127.30±8.42) with *p=0.000* as shown in figure 1.

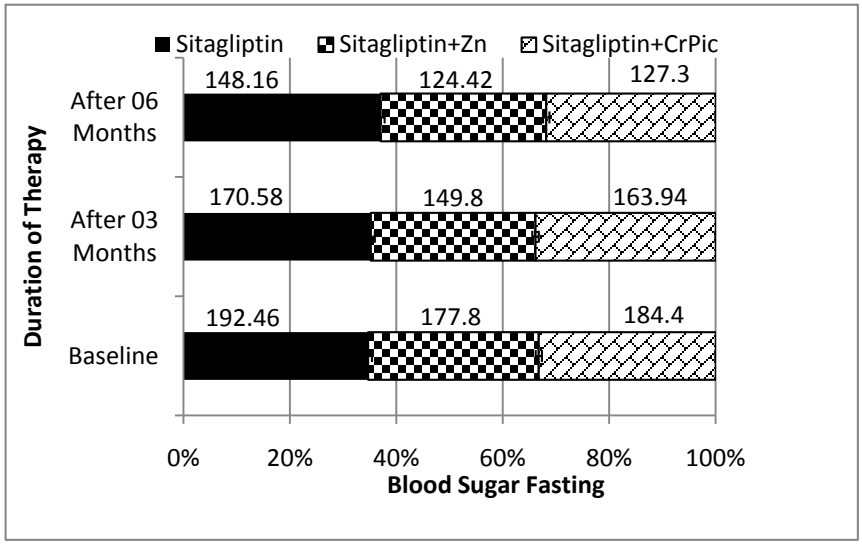

Figure 1: Graph shows the Blood sugar fasting levels during entire therapy period. Values given for BSF are in mmol/L.

HbA_{1c} was also assessed at start, 03 months and 06 months of treatment. Group B was found most effective in all treatment protocols at all levels of study. After 06 months of therapy, group B (7.02±1.07) was detected beneficial in lowering HbA_{1c} levels in relation to group A (7.79±0.26) & C (7.41±0.24) with *p=0.000* as shown in figure 2.

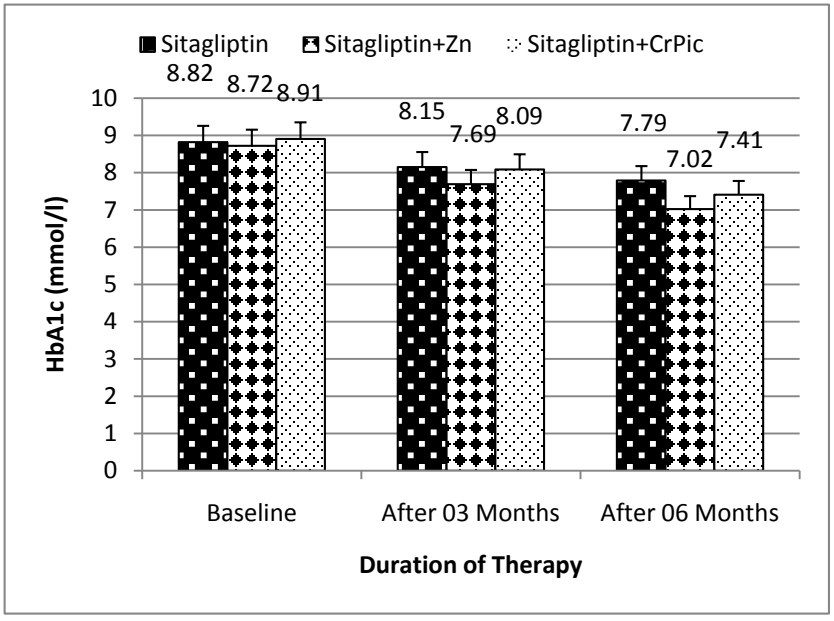

Figure 2: Graph shows the HbA_{1c} levels during entire therapy period.

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DISCUSSION

Type-II diabetes mellitus (type-II DM) is a widespread chronic disease characterized by hyperglycemia. Diagnosis of the disease is confirmed by performing various laboratory tests [18]. However, among them both blood sugar fasting (BSF) and glycated hemoglobin (Hb_{Alc}) tests are preferred. Type-II DM treatment is aimed to decrease insulin resistance and improves β-cell function. The oral hypoglycemic agents (OHAS) and insulin are mainly used for the management of the disease [19, 20]. The DPP-4 inhibitors may possibly be considered first-line drugs for the disease in future. Sitagliptin, also known as MK-0431 is a selective inhibitor of the enzyme DPP-4 [21, 22]. It is an orally active, cost effective, FDA-approved, novel drug for the treatment of type-II DM [23, 24]. Additionally, Zn improves tissue response to insulin [12, 25] and also increases the effectiveness of anti-diabetic drugs [26]. Similarly, Cr supplementation improves glycemic control in type-II DM patients due to increase in insulin action rather that secretion [27].

A total of 600 diabetes mellitus (DM) patients were enrolled in our study, among them 50% were males and 50% were females. There was insignificant influence of gender on the disease as p-value was 1.00. Demographic factors including gender, age and disease history in family, affect a person's health condition [28]. Gale & Gillespie (2001) has reported that in the last century the disease was more common in males than females but now it is equally common in both genders [29]. Zafar and his colleagues in 2011 also conducted a cross-sectional study in Rawalpindi to estimate the prevalence of type-II DM. A total of 1091 (males: 293, females: 798) respondents were selected in the study. From the data, it was found that the disease was more common in females (12.31%) than males (15.41%), with a total prevalence of 13.41% [30]. Doney et al. (2002) has also reported that the disease was significantly more common in males. However, females are more expected to transmit the disease to offspring [31]. In our study, patients with age ranging from 30 to 60 year were enrolled, the mean age was 46.72 ± 8.284 years. Formally, the disease was considered to develop only after the age of 40 years, so called "adult/maturity onset type diabetes mellitus" [32]. Researchers have reported that the disease is more common in adults or individuals with increasing age [33]. In the present study, 54% patients showed family history of type-II DM. This shows that the disease was more common in the patients with family history of the disease as also reported [34, 35].

In our six month study, in all three groups the drug, sitagliptin significantly treated the patients, either in monotherapy or with Zn and Chromium picolinate (CrPic) supplementation by normalizing BSF and Hb_{Alc} indices. Aschner et al. (2006) conducted a randomized study on patients receiving sitagliptin monotherapy. The study revealed that the drug provided effectual control in both BSF and Post prandial blood glucose (PPBG) levels [36]. Hanefeld et al. (2007) also carried out a randomized double-blind study to evaluate the effect of Sitagliptin monotherapy in type-II DM patients. In the study the drug improved glycemic control indices and was even well-tolerated [37]. Similarly, Solis-Herrera et al. (2013) conducted a study on treating type-II DM patients with the drug and concluded that it inhibits endogenous glucose production appreciably[38].

In the present study, patients were randomized into three groups. BSF values at start, 3 month and 6 month of the therapy for three treatment groups were assessed. Group B was found effective in lowering BSF value at different study level as compared to group A and C. Zn may help in reducing diabetic complications [10, 11]. It plays a critical role in synthesis, storage and secretion of insulin under normal physiological and diabetic conditions due to its antioxidant properties [12, 17,39]. Different studies have also reported that diabetes patients have lower serum Zn level as compared to non-diabetics [12, 40]. The administration of Zn improves tissue response to insulin [12, 25, 40] and also increases the effectiveness of OHAs like Metformin in type-II DM patients [26, 41]. This witnesses that Zn supplementation with sitagliptin provides much better results than sitagliptin mono-therapy. Likewise, Roussel et al. (2003) conducted a six month therapy to see the efficacy of Zn supplement in type-II DM patients and concluded that Zn supplementation was found beneficial for type-II DM patients of oxidative stress [39].

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However, in obese and lean thin subjects, in insulin sensitive and resistant subjects a consistent significant and fruitful effect of Cr was not observed [42]. Kleefstra et al. (2007) conducted a 6 months research on effectiveness of Cr in glycemic control of type-II DM in western population. Researchers reported that Cr was not found effective in improvement of glucose control in type-II DM western population [43]. Wang et al. (2007) has also reported that there is a controversy that Cr supplementation plays significant role in type-II DM patients. Our study also defines the same scenario[42].

Conclusion

Our study concludes that Zn supplementation with sitagliptin on glycemic control in patients with type-II DM gives best treatment option in the management of the disease. However, CrPic has poor control as an adjunct with sitagliptin and is as effective as sitagliptin alone.

Conflict of Interest statement: Authors declare no conflict of interest.

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