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AN EXPERIMENTAL STUDY TO EVALUATE THE POTENTIATING EFFECT OF SELENIUM, ZINC, VITAMIN C AND VITAMIN E AS SUPPLEMENT TO SULFONYLUREAS ON STREPTOZOTOCIN INDUCED DIABETIC RATS

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ABSTRACT: Objectives: To study potentiation of hypoglycaemic effect of Glimepiride with combination of Selenium, Zinc, Vitamin C and Vitamin E on Streptozotocin induced diabetic rats and to compare potentiating hypoglycaemic effect of above-mentioned drugs with that of standard diabetic control group. **Methods:** Study was carried out in Research Laboratory, Department of Pharmacology, BIMS, Belagavi. Albino rats weighing 200-250g were used. Streptozotocin was administered intraperitoneally for induction of type 2 diabetes. Each diabetic rat was fed orally with test drugs once daily for 21 days. Blood glucose levels were monitored on first day and at end of study. **Results:** Administration of glimepiride caused a decrease in blood glucose levels which is statistically significant (Group 2 vs 3, p=0.004).Combination of glimepiride, selenium, vitamin C and E decreased blood glucose levels to lower level than glimepiride alone (Group 3 vs 4, p = 0.016). Combination of glimepiride, zinc, vitamin C and E decreased blood glucose levels to lower level than glimepiride alone (Group 3 vs 5, p = 0.006). Combination of glimepiride, selenium, zinc, vitamin C and E decreased blood glucose levels to lower level than glimepiride alone (Group 3 vs 6, p=0.004). **Conclusion:** Combination of insulin potentiating drugs like selenium, zinc and antioxidants like vitamin C and E with glimepiride caused a significant reduction in blood glucose levels than when drugs used individually. Thus, action of these drugs was synergistic.

INTRODUCTION: Diabetes mellitus is a group of metabolic disorders characterised by hyperglycaemia [1]. Factors contributing to hyper-glycaemia include reduced insulin secretion, decreased glucose utilization and increased glucose production. Type 2 diabetes mellitus is characterized by hyperglycaemia as a result of insulin resistance, inadequate secretion and excessive glucagon secretion.

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Oxidative stress reduces insulin secretion and increases resistance thus play a role in pathogenesis of diabetes [2]. The long-term complications of diabetes affect mainly blood vessels, and the kidneys, nerves and eyes [3]. Two distinct metabolic pathways have been implicated in the deleterious effects of persistent hyperglycaemia on peripheral tissues that are:

Formation of advanced glycation end products which bind to a specific receptor expressed on inflammatory cells, endothelium, and vascular smooth muscle. The detrimental effects are release of pro-inflammatory cytokines and growth factors from intimal macrophages, generation of reactive oxygen species in endothelial cells and enhanced proliferation of vascular smooth muscle cells and

synthesis of extracellular matrix [4]. Activation of protein kinase C which leads to production of proangiogenic vascular endothelial growth factor, implicated in neovascularization characterizing diabetic retinopathy and production of pro-inflammatory cytokines by the vascular endothelium [5].

Aim of therapy is glycaemic control by diet, regular exercises, medications which include oral antidiabetic drugs and insulin therapy and management of the complications of diabetes. Along with these add on like multivitamins, trace minerals and native herbal medicines are used.

Current treatment modalities are not very efficacious in preventing and/or delaying the progression of β-cell dysfunction and ultimate β-cell failure in patients with Type 2 diabetes. Hence, there is need for development of newer compounds which are potent and have lesser side effects for treating diabetes and to reduce the need for insulin injection.

Selenium is an essential trace element in human and animal nutrition. is a micronutrient with anti-inflammatory and antioxidant properties. It is essential for activity of glutathione peroxidase and selenoprotein P. These enzymes are involved in insulin regulation. It has been found to be beneficial in treatment of diabetes because of its insulin-mimetic actions [6].

Zinc is an essential mineral with antioxidant property. Zinc ions and its complexes have insulin like action. It stimulates glycolysis and inhibits gluconeogenesis, and is found to be beneficial in the treatment, as it delays the progression of diabetes. ZnT8 (zinc transporter 8) is identified as novel target autoantigen in patients with type1 DM and as a marker of insulin resistance in type 2 DM [7].

Vitamin C is a water-soluble antioxidant that prevents the increased production of free radicals induced by oxidative damage to lipids and lipoproteins in various cellular compartment and tissues as found in diabetes [8]. Vitamin E (α-tocopherol), a fat-soluble vitamin is a major lipid phase, free radical chain breaking antioxidant in the body [9]. Hence, the objective of study is to evaluate the potentiating effect of Selenium, Zinc, Vitamin C and Vitamin E assupplement to sulfonylureas.

MATERIALS AND METHODS: This study was carried out in Research Laboratory, Department of Pharmacology, Belagavi Institute of Medical Sciences, Belagavi. Institutional Animal Ethics Committee approval was taken (Ref No. BIMS/IAEC/PG05/2018). Albino rats of either sex weighing between 200-250 grams were obtained from the animal house registered to the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and maintained under good laboratory conditions. Streptozotocin (65mg/kg), Citrate buffer (pH - 4.5), normal saline (5ml/kg), glimepiride (0.1mg/kg/day), selenium (0.5µg/100g/day), zinc (99µg/100g/day), vitamin C (810µg/100g/day), vitamin E (135 µg/100g/day) were the test drugs used in experiment. Equipments like mouth gag, feeding tube, disposable syringes and needles, electronic weighing scale, glucometer and strips were used.

Grouping of Animals: Animals were randomly divided into 6 groups of 6 each.

Group 1: Normal control group were given normal saline.

Group 2: Diabetic control group were given normal saline.

Group 3: Diabetic standard group were given glimepiride.

Group 4: Diabetic group were given, glimepiride, selenium, vitamin C, vitamin E.

Group 5: Diabetic group were given, glimepiride, zinc, vitamin C, vitamin E.

Group 6: Diabetic group were given, glimepiride, selenium, zinc, vitamin C, vitamin E.

Under aseptic precautions a single dose of freshly prepared streptozotocin in citrate buffer (pH - 4.5) was administered intraperitoneally for induction of type 2 DM in rats. In a well restrained rat, 1mm of its tail end was cut and a drop of blood collected directly on the strip placed in glucometer for glucose estimation.

Diabetic rats with blood glucose levels in range 250-300 mg/dl were selected for study. Each diabetic rat was fed orally with test drugs by using feeding tube, once daily over a period of 21 days according to the group to which they belonged. Blood glucose concentration was monitored on first day and at the end of study. Groups 4, 5 and 6 were compared to group 3. After induction of diabetes, adequate amount of water and food was provided to rats. To prevent infection only 3 rats were housed in a cage. Antiseptic was applied to the tail after collection of blood. The basic data was expressed as Mean ± SD in each group. Difference between means was seen by using non-parametric Mann-Whitney *U* and Wilcoxon signed-rank tests.

RESULTS:

GROUP 1: NORMAL CONTROL – NO DIABETES

Rats	Initial reading	Final
1	98	97
2	96	99
3	100	96
4	97	95
5	99	103
6	101	99

Mean = 98.5000 / 98.1667, SD = 1.87083 / 2.85774

GROUP 2: DIABETIC CONTROL – GIVEN NORMAL SALINE

Rats	Initial reading	Final
1	278	288
2	290	299
3	285	300
4	298	304
5	266	299
6	280	301

Mean = 282.8333 / 298.5000, SD = 10.96206 / 5.46809

GROUP 3: DIABETIC RATS – GIVEN GLIMEPIRIDE

Rats	Initial reading	Final
1	263	174
2	298	198
3	285	186
4	300	197
5	275	166
6	290	184

Mean = 285.1667 / 184.1667, SD = 14.16216 / 12.59233

GROUP 4: DIABETIC RATS – GIVEN GLIMEPIRIDE, SELENIUM, VIT C & VIT E

Rats	initial reading	final
1	289	168
2	266	147
3	300	176
4	276	152
5	298	164
6	285	146

Mean = 285.6667 / 158.8333, SD = 13.03329 / 12.30312

GROUP 5: DIABETIC RATS – GIVEN GLIMEPIRIDE, ZINC, VIT C& VIT E

Rats	Initial reading	Final
1	280	156
2	266	143
3	272	146
4	302	170
5	298	162
6	287	154

Mean = 284.1667 / 155.1667, SD = 14. 23259 / 10.00833

GROUP 6: DIABETIC RATS – GIVEN GLIMEPIRIDE, SELENIUM, ZINC, VIT C & VIT E

Rats	Initial reading	Final
1	292	152
2	280	154
3	276	148
4	284	146
5	299	160
6	275	142

Mean = 284.3333 / 150.3333, SD = 9.47980 / 6.37704

COMPARISON OF GROUP 3 VS 4

Test	Initial Blood glucose	Final Blood glucose
Mann-Whitney U	17.500	3.000
Wilcoxon W	38.500	24.000
Z	0.80	2.887
P value	0.936	0.016

COMPARISON OF GROUP 3 VS 5

Test	Initial Blood glucose	Final Blood glucose
Mann-Whitney U	17.500	1.000
Wilcoxon W	38.500	22.000
Z	0.80	2.722
P value	0.936	0.006

COMPARISON OF GROUP 3 VS 6

Test	Initial Blood glucose	Final Blood glucose
Mann-Whitney U	16.500	0.0001
Wilcoxon W	37.500	21.000
Z	0.241	2.882
P value	0.810	0.004

COMPARISON OF GROUP 4 VS 5

Test	Initial Blood glucose	Final Blood glucose
Mann-Whitney U	17.000	14.500
Wilcoxon W	38.000	35.500
Z	0.161	0.561
P value	0.872	0.575

COMPARISON OF GROUP 4 VS 6

Test	Initial Blood glucose	Final Blood glucose
Mann-Whitney U	15.500	11.000
Wilcoxon W	36.500	32.000
Z	0.401	1.125
P value	0.688	0.261

COMPARISON OF GROUP 5 VS 6

Test	Initial Blood glucose	Final Blood glucose
Mann-Whitney U	17.500	12.000
Wilcoxon W	38.500	33.000
Z	0.080	0.964
P value	0.936	0.335

COMPARISON OF EFFECT OF DRUGS ON BLOOD GLUCOSE LEVELS OF DIABETIC RATS

Group	Initial blood glucose (mean rank)	Final blood glucose (mean rank)
I	3.50	3.50
II	20.33	33.50
III	22.17	26.83
IV	22.58	17.75
V	21.42	16.08
VI	21.00	13.33
Chi-square	14.819	29.898
P value	0.011	0.001

DISCUSSION:

Effect of Glimepiride on Blood Glucose Levels of Diabetic Rats: Glimepiride given to rats of group 3 at a dose of 0.1mg/kg/day caused a decrease in the levels of blood glucose which is statistically significant (Group 2 vs 3, p = 0.004, statistically significant). Study by Mwafy NS showed that administration of glimepiride to streptozotocin induced diabetic rats improved insulin, glucose levels and liver enzyme activities [10].

Effect of Glimepiride, Selenium and Antioxidants on Blood Glucose Levels of Diabetic Rats: On comparison between group 3 and 4 it was found that blood glucose levels decreased to lower level when a combination of drugs was used rather when glimepiride was used alone (Group 3 vs 4, p = 0.016, statistically significant). Study by Abdel Moneim *et al.* showed that selenium nanoparticles can alleviate hyperglycaemia and hyperlipidaemia in streptozotocin-induced diabetic rats [11].

Effect of Glimepiride, Zinc and Antioxidants on Blood Glucose Levels of Diabetic Rats: On comparison between group 3 and 5 it was found that blood glucose levels decreased to lower level when a combination of drugs was used rather when glimepiride was used alone (Group 3 vs 5, p = 0.006, statistically significant). Study by Beltramini M *et al.* showed that zinc pre-treatment reduces the occurrence of hyperglycaemic status and prevents the deleterious effects of oxidative stress [12].

Effect of Combination of all Drugs on Blood Gucose Levels of Diabetic Rats: On comparison between group 3 and 6 it was found that blood glucose levels decreased to lower level when a combination of drugs was used rather when glimepiride was used alone (Group 3 vs 6, p = 0.004, statistically significant)

Study by Kundusen S inferred that in STZ-induced diabetic Wistar rats given vitamin C in a dose dependent manner normalized blood glucose levels, serum biochemical parameters and decreased lipid Peroxidation that might be attributed to its antioxidant property [13].

Roldi PL *et al.* have reported that supplementation with vitamin E significantly reduced glycemia levels and glycated haemoglobin in streptozotocin induced diabetic rats [14].

Therefore, combination of these drugs could be synergistic leading to a potentiation of action in the decrease of blood glucose levels in diabetic rats.

CONCLUSION: From our study it is apparent that combination of insulin potentiating drugs like selenium, zinc and antioxidants like vitamin C, vitamin E with glimepiride caused a significant reduction in blood glucose levels than when these drugs are used individually. Thus, action of these drugs was found to be synergistic and their potentiating effects on control of blood glucose levels is vitally important when used as supplements to sulfonylureas (glimepiride) in the treatment of type 2 diabetes mellitus.

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REFERENCES:

1. Kumar V, Abbas AK and Aster JC: Robins Basic Pathology. 10th ed. Philadelphia: Elsevier 2018; 772-8.
2. Gonec A, Tokgoz D and Aslan S: Oxidative stress in relation to lipid profiles in different stages to chronic diseases. Indian J Biochem Biophy 2005; 42: 190-4.
3. Sheetz MJ and King GL: Molecular understanding of hyperglycaemia's adverse effects for diabetic complications. JAMA 2002; 288(20): 2579-88.

4. Sitt AW, Jenkins AJ and Cooper ME: Advanced glycation end products and diabetic complications. Expert opinInvestig Drugs 2002; 11(9): 1205-23.
5. Brownlee M: Biochemistry and molecular cell biology of diabetic complications. Nature 2001; 414(6865): 813-20.
6. Fontenelle LC, Feitosa MM, Morais JBS, Severo JS, Freitas TEC and Bessera JB: The role of selenium in insulin resistance. Braz J Pharm Sci 2018; 54(1): 1-11.
7. Yi B, Huang G and Zhou ZG: Current and Future Clinical Applications of Zinc Transporter-8 in Type 1 Diabetes Mellitus. Chin Med J 2015; 128: 2387-94.
8. Dawud FA, Eze ED, Ardja AA, Isa AS, Jimoh A and Bashiru M: Ameliorative effects of vitamin c and zinc in alloxan-induced diabetes and oxidative stress in wistar rats. Curr Res J Bio Sci 2012; 4(2): 123-9.
9. Garg MC and Bansal DD: Protective antioxidant effect of vitamin C and E in streptozotocin induced diabetic rats. Indian J Exp Biol 2000; 38: 101-3.
10. Mwafy NS and Yassin MM: Antidiabetic activity evaluation of glimepiride and Nerium oleander extract on insulin, glucose levels and some liver enzymes activities in experimental diabetic rat model. Pak J Bio Sci 2011; 14(21): 984-90. doi:10.3923/pibs.2011.984.990.
11. Abdel Moneim EA, Al-Quraishy S and Dkhil M: Anti-hyperglycemic activity of selenium nanoparticles in streptozotocin-induced diabetic rats. Int J Nanomedicine 2015; 10: 6741. doi:10.2147/IJN.S91377.
12. Beltramini M, Zambenedetti P, Raso M, Idrissi IM and Zatta P: The effect of Zn (II) and streptozotocin administration in the mouse brain. Brain Res 2006; 1109: 207-18.
13. Kundu Sen S, Gupta M, Mazumder UK, Haldar PK, Saha P and Bhattacharya S: Antihyperglycemic effect and antioxidant property of citrus maxima leaf in streptozotocin-induced diabetic rats. Diabetologia Croatica 2011; 40(4): 113-20.
14. Roldi PL and Pereira VFR: Vitamin E (α-tocopherol) supplementation in diabetic rats: effects on the proximal colon. BMC Gastroenterol 2009; 9: 88. doi:10.1186/1471-230X-9-88.

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