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EFFECT OF VITAMIN E ON BLOOD GLUCOSE LEVEL IN RABBITS AND ITS POSSIBLE INTERACTION WITH COMMONLY USED ANTI DIABETIC AGENTS

Chandra Veer Singh and Rakesh C. Verma *

Pharmacology, Academic Block, UP Rural Institute of Medical Sciences & Research, Saifai, Etawah, Uttar Pradesh, India

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Correspondence to Author:
Rakesh C. Verma

Assistant Professor, Pharmacology, Academic Block, UP Rural Institute of Medical Sciences & Research, Saifai, Etawah - 206130, Uttar Pradesh, India

E mail: rakeshverma.kgmu@gmail.com

ABSTRACT: Effect of Vit. E on blood glucose and its possible interactions with oral antidiabetic agents (i.e. glimepiride, gliclazide and metformin) in rabbits have been reported in the present study. The study was performed on albino rabbits in which hyperglycemia was induced by giving glucose. We observed that Vit.E significantly lowered the blood glucose level but on co-administration with oral antidiabetic agents it antagonized the effect of the latter drugs. It is therefore advisable not to give inadvertent amount of Vit.E to diabetic patients just in a belief that antioxidants are helpful to diabetics and do not produce adverse effects.

INTRODUCTION: Diabetes is a syndrome known to human beings since ancient times. In Ebers Papyrus of Egypt (1500 BC) clinical descriptions of polyuric conditions resembling diabetes mellitus is present. Charak from India (200 A.D.) distinguished both obese & thin patients having sugary urine.

Diabetes mellitus is a metabolic disorder of multiple aetiology characterised by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. Diabetes is the single most important metabolic disease which can affect nearly every organ system in the body.

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Chronic hyperglycemia resulting from diabetes has profound effects on nearly every system of the body. The toxic effects of hyperglycemia may result from accumulation of nonenzymatically glycosylated products [1, 2], increased sorbitol production in tissues, formation of diacylglycerol leading to activation of protein kinase C or by free radical generation.[3, 4]

Oxygen derived free radicals especially superoxide may have role in destruction of β cell in type 1 diabetes also.[3] Therefore antioxidants may have role in retarding or preventing the pathological process of diabetes mellitus by reducing the formation of free radicals.[6, 7, 8, 9, 10]

It is important to note that diabetes may alter the pharmacokinetics and pharmacodynamics of pharmaceutical agents. Antidiabetic drug therapy requires a continued supervision for optimal blood sugar level in patients because strict blood sugar regulation can prevent many of the complications of diabetes like retinopathy, nephropathy,

neuropathy and vascular derangements. Avoidance of hypoglycemia is also important because that is also dangerous and can lead to convulsions coma and death.

It is therefore necessary to know interactions of various pharmacological agents with antidiabetic agents because knowledge of such an interaction enables the prescriber to avoid or minimize such an interaction by adjustment of doses and schedule of drug administration or by using an alternative drug. Various drugs have known interaction with antidiabetic agents, some causing hypoglycemia, some hyperglycemia and altering the response of diabetic patients to their existing therapeutic regimens.[11, 12, 13] Salicylates, indomethacin, ethanol, clofibrate, sulfonamides and pentamidine enhance the hypoglycemic effect while glucocorticoids, diuretics, diazoxide, phenytoin, heparin and nicotine antagonizes the effect of antidiabetic agents.

It was therefore decided to undertake a study to explore the possibilities of drug interactions between antioxidants and antidiabetic agents.

The aim of the present study is –

1) To assess if Vit.E per se had any effect on blood sugar level.

2) To evaluate the possible effect of this antioxidant on the modification of blood sugar levels produced by commonly used antidiabetic agents.

Various drugs included in the study are the ones which are at present commonly employed (Vit. E, gliclazide, glimepiride and metformin).

MATERIALS AND METHODS:

Present study was conducted on healthy albino rabbits of either sex weighing 1.5 - 2.0 kg. Study was approved by the meeting of IAEC held on 16th Aug, 2010 (circular No. 38/ AH/ RIMS&R/ 2010-11). Animals were made available to Department of Pharmacology by Central Animal House. They were maintained on standard pellet diet and water ad libitum.

Estimation of blood glucose level was done by using glucose oxidase - peroxidase method. Due to specificity of enzymes the enzymatic method is the most accurate.

For this study rabbits were divided into 8 groups of 5 rabbits in each.

Group I: Rabbits of this group were given 25 gm of glucose powder orally. This group shows normal pattern of blood glucose level after a glucose load and served as control.

Group II: Rabbits of this group were given vitamin E (80 IU/kg/d) orally for 7 days and 25 gm of glucose powder orally on 7th day. This group shows effect of vitamin E on blood glucose level.

Group III: Rabbits of this group were given glimepiride (0.2 mg/kg) orally and 25 gm of glucose powder. This group shows normal pattern of antidiabetic action of glimepiride.

Group IV: Rabbits of this group were vitamin E (80 IU/kg/d) for 7 days and glimepiride (0.2 mg/kg) plus 25 gm of glucose powder were added on 7th day. This group shows effect of vitamin E on the pattern of blood glucose levels produced by glimepiride.

Group V: Rabbits of this group were given gliclazide (8 mg/kg) orally and 25 gm of glucose powder. This group shows normal pattern of antidiabetic action of gliclazide.

Group VI: Rabbits of this group were vitamin E (80 IU/kg/d) for 7 days and gliclazide (8 mg/kg) plus 25 gm of glucose powder were added on 7th day. This group shows effect of vitamin E on the pattern of blood glucose levels produced by gliclazide.

Group VII: Rabbits of this group were given metformin (100 mg/kg) orally and 25 gm of glucose powder. This group shows normal pattern of antidiabetic action of metformin.

Group VIII: Rabbits of this group were vitamin E (80 IU/ Kg/d) for 7 days and metformin (100 mg/kg) plus 25 gm of glucose powder were added

on 7th day. This group shows effect of vitamin E on the pattern of blood glucose levels produced by metformin.

- Rabbits were fasted overnight and during the study but were allowed water during this period.
- Samples were collected just before administration of drug and glucose (0 hr.) and after 2, 4 and 6 hrs. of administration.
- All drugs and glucose were given orally through nasogastric tubes, those not soluble in water ere rendered soluble with the help of gum acacia.

Observations:

TABLE 1: BLOOD GLUCOSE LEVELS OF RABBITS RECEIVING 25 gm GLUCOSE POWDER AFTER OVERNIGHT FASTING.

S. No.	Blood glucose level (mg%) Time interval (hrs.)			
	0	2	4	6
1.	104.2	297.4	129.2	112.7
2.	111.0	288.8	133.1	108.5
3.	103.7	291.3	126.9	99.8
4.	98.9	302.0	119.3	118.0
5.	106.0	293.5	117.2	97.8
Mean	104.62	294.6	125.14	107.36
S.E. +	1.98	2.33	3.0	3.82

TABLE 2: BLOOD GLUCOSE LEVELS OF RABBITS RECEIVING VITAMIN E (80 I.U./kg/d) FOR 7 DAYS AND 25 gm GLUCOSE POWDER AFTER OVERNIGHT FASTING.

S.No.	Blood glucose level (mg%) Time interval (hrs.)			
	0	2	4	6
1.	103.0	316.0	163.3	120.7
2.	96.3	292.0	133.0	98.3
3.	107.8	304.0	138.6	79.8
4.	99.2	280.0	117.8	91.0
5.	98.6	289.7	123.7	104.0
Mean	100.98	296.2	135.28	98.76
S.E. ±	2.02	6.28	7.89	6.83

TABLE 3: BLOOD GLUCOSE LEVELS OF RABBITS RECEIVING GLIMEPIRIDE (0.2 mg/kg) AND 25 gm GLUCOSE POWDER AFTER OVERNIGHT FASTING

S. No.	Blood glucose level (mg%) Time interval (hrs.)			
	0	2	4	6
1.	104.2	112.0	101.8	98.3
2.	108.0	116.3	104.5	102.7
3.	112.9	127.1	98.3	104.9
4.	99.3	110.4	109.7	93.6
5.	102.0	109.8	112.0	90.5
Mean	105.28	114.96	105.26	98.00
S.E. ±	2.38	3.28	2.51	2.70

TABLE 4: BLOOD GLUCOSE LEVELS OF RABBITS RECEIVING VITAMIN E (80 I.U./ Kg/d) FOR 7 DAYS AND GLIMEPIRIDE (0.2 mg / kg) PLUS 25 gm GLUCOSE POWDER AFTER OVERNIGHT FASTING.

S.No.	Blood glucose level (mg%) Time interval (hrs.)			
	0	2	4	6
1.	102.0	148.2	103.8	92.0
2.	93.5	161.0	127.6	87.6
3.	107.6	138.7	113.0	84.3
4.	89.3	129.2	122.7	81.2
5.	91.0	131.9	117.0	96.9
Mean	96.68	141.82	116.82	88.4
S.E. ±	3.50	5.83	4.10	2.78

TABLE 5: BLOOD GLUCOSE LEVELS OF RABBITS RECEIVING GLICLAZIDE (8 mg/kg) AND 25 gm GLUCOSE POWDER AFTER OVERNIGHT FASTING.

S. No.	Blood glucose level (mg%) Time interval (hrs.)			
	0	2	4	6
1.	107.2	101.7	79.4	81.3
2.	100.0	91.4	76.0	90.3
3.	94.9	86.3	73.7	84.8
4.	98.8	88.0	81.2	91.7
5.	92.7	107.0	92.0	79.6
Mean	98.72	94.88	80.46	85.54
S.E. ±	2.50	4.05	3.17	2.39

TABLE 6: BLOOD GLUCOSE LEVELS OF RABBITS RECEIVING VITAMIN E (80 I.U./ kg/d) FOR 7 DAYS AND GLICLAZIDE (8 mg / kg) plus 25 gm GLUCOSE POWDER AFTER OVERNIGHT FASTING.

S. No.	Blood glucose level (mg%) Time interval (hrs.)			
	0	2	4	6
1.	89.7	117.0	93.6	90.5
2.	93.0	123.8	74.8	96.3
3.	97.3	120.3	96.0	87.6
4.	100.0	133.3	89.9	93.0
5.	91.6	109.8	94.0	102.0
Mean	94.32	120.84	89.66	93.88
S.E. ±	1.89	3.88	3.85	2.49

TABLE 7: BLOOD GLUCOSE LEVELS OF RABBITS RECEIVING METFORMIN (100 mg/kg) AND 25 gm GLUCOSE POWDER AFTER OVERNIGHT FASTING

S. No.	Blood glucose level (mg%) Time interval (hrs.)			
	0	2	4	6
1.	112.0	197.8	128.1	98.7
2.	108.3	186.4	118.7	101.3
3.	104.7	201.7	131.3	100.0
4.	113.9	211.9	124.8	103.8
5.	118.1	201.0	129.4	112.0
Mean	111.4	199.76	126.46	103.16
S.E. ±	2.30	4.10	2.21	2.37

TABLE 8: BLOOD GLUCOSE LEVELS OF RABBITS RECEIVING VITAMIN E (80 I.U./ kg/d) FOR 7 DAYS AND METFORMIN (100 mg / kg) plus 25 gm GLUCOSE POWDER AFTER OVERNIGHT FASTING.

S. No.	Blood glucose level (mg%) Time interval (hrs.)			
	0	2	4	6
1.	97.8	197.0	109.7	79.0
2.	103.0	164.8	117.0	93.5
3.	107.3	153.7	123.6	104.0
4.	93.8	145.0	113.7	88.7
5.	98.0	139.8	127.0	100.0
Mean	99.98	160.06	118.2	93.04
S.E. ±	2.34	10.18	3.17	4.39

TABLE 9: STATISTICAL COMPARISON BETWEEN THE GROUP RECEIVING VIT. E PLUS GLUCOSE POWDER AND CONTROL GROUP (RECEIVING ONLY GLUCOSE POWDER)

Group receiving Vit. E plus glucose powder (n = 5)	Time interval (hrs.) 0	2	4	6
Mean blood glucose (mg%)	100.98	296.2	135.28	98.76
SD ±	4.52	14.04	17.64	15.27
Control group (receiving glucose powder only) (n = 5)	**Time interval (hrs.) 0**	**2**	**4**	**6**
Mean blood glucose (mg%)	104.62	294.6	125.14	107.36
SD ±	4.43	5.21	6.71	8.54
't' value	1.67	0.43	1.20	1.09
'p' value	> 0.05	> 0.05	> 0.05	> 0.05

TABLE 10: STATISTICAL COMPARISON BETWEEN THE GROUP RECEIVING GLIMEPIRIDE PLUS VIT. E PLUS GLUCOSE POWDER AND THE GROUP RECEIVING GLIMEPIRIDE AND GLUCOSE POWDER.

Group receiving glimepiride, Vit. E and glucose powder (n = 5)	Time interval (hrs.) 0	2	4	6
Mean blood glucose (mg%)	96.68	141.82	116.82	88.4
SD ±	7.84	13.05	9.18	6.22
Group receiving glimepiride and glucose powder (n = 5)	**Time interval (hrs.) 0**	**2**	**4**	**6**
Mean blood glucose (mg%)	105.28	114.96	105.26	98.0
SD ±	5.32	7.33	5.61	6.04
't' value	2.02	4.01	2.40	2.48
'p' value	> 0.05	< 0.05	> 0.05	> 0.05

TABLE 11: STATISTICAL COMPARISON BETWEEN THE GROUP RECEIVING GLICLAZIDE PLUS VIT. E PLUS GLUCOSE POWDER AND THE GROUP RECEIVING GLICLAZIDE AND GLUCOSE POWDER

Group receiving gliclazide, Vit. E and glucose powder (n = 5)	Time interval (hrs.) 0	2	4	6
Mean blood glucose (mg%)	94.32	120.84	89.66	93.88
SD ±	4.23	8.69	8.62	5.57
Group receiving gliclazide and glucose powder (n = 5)	**Time interval (hrs.) 0**	**2**	**4**	**6**
Mean blood glucose (mg%)	98.72	94.88	80.46	85.54
SD ±	5.59	9.06	7.09	5.34
't' value	1.40	4.62	1.84	2.41
'p' value	> 0.05	< 0.01	> 0.05	> 0.05

TABLE 12: STATISTICAL COMPARISON BETWEEN THE GROUP RECEIVING METFORMIN PLUS VIT. E PLUS GLUCOSE POWDER AND THE GROUP RECEIVING METFORMIN AND GLUCOSE POWDER.

Group receiving metformin, Vit. E and glucose powder (n = 5)	Time interval (hrs.) 0	2	4	6
Mean blood glucose (mg%)	99.98	160.06	118.2	93.04
SD ±	5.24	22.80	7.10	9.83
Group receiving metformin and glucose powder (n = 5)	**Time interval (hrs.) 0**	**2**	**4**	**6**
Mean blood glucose (mg%)	111.4	199.76	126.46	103.16
SD ±	5.14	9.17	4.94	5.30
't' value	3.48	3.61	2.13	2.02
'p' value	< 0.05	< 0.05	> 0.05	> 0.05

DISCUSSION: The aim of the present study was to see the effect of vitamin E on blood glucose level and its possible interactions with oral antidiabetic agents. Present study was conducted on healthy albino rabbits of either sex weighing 1.5 - 2 Kg.

There were 8 groups in the present study each group comprising of 5 rabbits. The rabbits were fasted overnight. Blood samples (0.5 ml) were withdrawn by disposable syringe each time from marginal pinna vein. Samples were taken in fluoride vials. Samples were centrifuged for 10 minutes at 3000 r.p.m. Supernatant was taken for estimation of blood glucose level. The estimation was done by glucose oxidase - peroxidase method. The observations obtained are shown in tables.

Table 1 shows blood glucose levels in fasted rabbits and at 2, 4 and 6 hrs. following administration of 25 gm glucose powder orally. The mean of blood glucose levels at 'O' hour (just before glucose) i.e. fasting value was found to be 104.62 mg%. The fasting values were found to be raised i.e. 294.6 mg% after 2 hrs., 125.14 mg% after 4 hrs. and 107.36 mg% after 6 hrs. following administration of glucose. These observations indicated that the blood glucose levels were significantly raised ($p < 0.001$) (about three times higher) than the fasting values following administration of larger dosage of glucose after 2 hrs. These values declined gradually reaching almost equal to fasting values after 6 hrs. This group served as control for the study.

Table 2 shows blood glucose levels in fasted rabbits following administration of vitamin E and glucose powder. Vitamin E was given in dose of 80 I.U./Kg/d for 7 days and 25 gm glucose powder was added on 7th day. The mean of blood glucose levels at '0' hr. (just before the administration of drug and glucose) was 100.98 mg%. It became 296.2 mg% after 2 hrs., 135.28 mg% after 4 hrs. and 98.76 mg% after 6 hrs. following administration of drug and glucose. These values are compared statistically with control group in **Table 9** which shows that the effect of Vitamin E on blood glucose level is not significant ('p' value > 0.05) throughout the period of observation.

Table 3 shows blood glucose level of fasted rabbits following administration of 25 gm of glucose powder and glimepiride (0.2 mg/kg) orally. The mean of blood glucose levels at '0' hr. (fasting) was 105.28 mg%, which became 114.96 mg% after 2 hrs., 105.26 mg% after 4 hrs. and 98.0 mg% after 6 hrs. following administration of drug and glucose. On comparison to Table 1 it was found that glimepiride exhibit significant hypoglycemia at 2 and 4 hrs.

Table 4 shows blood glucose level of fasted rabbits following administration of Vitamin E, glucose powder and glimepiride. Vitamin E was given in dose of 80 I.U./Kg/d for 7 days regularly and 25 gm glucose plus glimepiride (0.2 mg/kg) were added on 7th day and blood samples were taken. Mean blood glucose level at '0' hr (fasting) is 96.68 mg% which becomes 141.82 mg% at 2 hr., 116.82 mg% at 4 hr. and 88.4 mg% at 6 hr. following administration of drugs and glucose.

The values of **Table 3** and **4** were compared statistically in Table 10, which shows that Vitamin E antagonizes the hypoglycemic effect of glimepiride at 2 hrs. significantly ($p < 0.05$).

Table 5 shows blood sugar levels of fasted rabbits following administration of glucose (25 gm) and gliclazide (8 mg/kg). The mean of blood glucose levels at '0' hr. (fasting) was 98.72 mg% which became 94.88 mg% at 2 hrs., 80.46 mg% at 4 hrs. and 85.54 mg% at 6 hrs. following administration of drug and glucose. Gliclazide produced significant hypoglycemia at 2, 4 and 6 hrs.

Table 6 shows blood glucose levels of fasted rabbits following administration of vitamin E, glucose and gliclazide. Vitamin E was given in dose of 80 I.U./kg/d for 7 days regularly, glucose 25 gm and gliclazide (8 mg/kg) were added on 7th day and blood samples were taken. Mean of blood glucose levels at '0' hr. (fasting) was 94.32 mg% which became 120.84 mg% after 2 hrs. 89.66 mg% after 4 hrs. and 93.88 mg% after 6 hrs. following administration of drugs and glucose. Values of **Table 5** and **Table 6** are compared in **Table 11.** Vitamin E was found to antagonize the effect of gliclazide at 2 hrs. significantly ($p < 0.05$).

Table 7 shows blood glucose levels following administration of glucose powder (25 gm) and metformin (100mg/kg) in fasted rabbits. The mean of blood glucose levels at '0' hr. (just before administration of drug and glucose) was 111.4 mg% which becomes 199.76 mg% after 2 hrs., 126.46 mg% after 4 hrs. and 103.16 mg% after 6 hrs. Metformin produced significant hypoglycemia at 2 hrs. as compared to control group.

Table 8 shows blood glucose levels following administration of vitamin E, glucose and metformin in fasted rabbits. Vitamin E was given in dose of 80 I.U./Kg/day for 7 days regularly, glucose powder (25 gm) and metformin (100mg/kg) were added on 7th day and blood samples were taken. The mean of blood glucose levels at '0' hr. (just before administration of drug and glucose) was 99.98 mg% which became 160.06 mg% at 2 hrs., 118.2 mg% at 4 hrs. and 93.04 mg% at 6 hrs. These values were compared with those of **Table 7** in **Table 12**. It was evident from the observations that vitamin E when co-administrated with metformin, the effect of metformin was found to be enhanced at 2 hrs. significantly ($p< 0.05$).

CONCLUSION: We observed that in studied conditions Vit. E did not produce any significant effect on blood glucose levels. Administration of Vit. E exhibited antagonistic effects on glimepiride's effect on blood glucose levels. However these effects in studied conditions were found to be significant at 2 hrs only.

Vitamin E co-administration with gliclazide in studied conditions had produced significant antagonistic effects at 2 hrs.

Administration of Vit. E with metformin and glucose was found to antagonize the effect of metformin significantly at 2 hrs.

Thus it is evident from the present study that antioxidants e.g. Vit. E in spite of its inherent vital properties have some inevitable effects on the action of oral antidiabetic agents.

These antioxidants may modulate or reduce the ultimate effects of these drugs (in co-administered therapy). Therefore it is advisable to prescribe and use the oral antidiabetic agents carefully with utmost precautions in patients suffering from diabetes mellitus to avoid the adverse effects of drugs in co-ordination therapy with antioxidants.

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