The Influence of Supplemental Vitamin C on Glycosylated Hemoglobin in Patients with Type 2 Diabetes Mellitus

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There is evidence implying the influence of vitamin C on prevention of hemoglobin glycation. The aim of the present study was to investigate the effect of vitamin C on the level of glycosylated hemoglobin (HbA1c) in patients with type 2-diabetes.

Materials and Methods: 18 patients with type 2 diabetes (14 females, 4 males) were enrolled in a clinical trial study. 1000 mg of supplemental vitamin C (divided into 4 doses) per day was given to the subjects for 6 weeks. Body mass index (BMI), a 3-day diet recall, fasting plasma glucose and glycosylated hemoglobin were measured before and after the administration of supplemental vitamin C. Data were analyzed by paired t-test.

Results: Body weight and BMI were slightly higher at the end of study, as compared to before. Glycosylated hemoglobin level decreased significantly at the end of study 11.8±1.48 vs, 10.2±1.28%, ($p<0.015$). Fasting plasma glucose did not change.

Conclusion: Our findings indicate that vitamin C as a result of its structural similarity to glucose can compete with it to reduce hemoglobin glycosylation in patients with type 2-diabetes.

Key Words: Diabetes mellitus, Vitamin C, Fasting blood glucose, Glycosylated hemoglobin, Body mass index

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Introduction

Diabetes mellitus is one of the most common metabolic disorders worldwide, leading to different complications. It has been shown that the control of diabetes prevents the occurrence of complications, including microvascular (renal and ocular), dermatologic and neurologic injuries.[1,2]

Measurement of serum levels of glycosylated hemoglobin is one of the best indicators used to monitor diabetes.[3] It has been established that even in a tightly controlled follow-up, periods of hyperglycemia occur in diabetic patients, leading to nonenzymatic glycation of long half-life serum proteins.[4] Furthermore, structural proteins with long half-lives (e.g. collagen and basement membrane proteins) are prone to glycosylation.[5]

Based on the evidence from various studies, nonenzymatic glycosylation of proteins contributes to the pathogenesis of vascular complications in diabetes.[6] HbA1c is one of the glycosylated products, known as an indicator of the glycosylation level of proteins which is influenced by different factors including vitamin C. Eriksson et al demonstrated that serum levels of glycosylated hemoglobin decreased significantly following administration of 2 grams of vitamin C for 3 months in patients with type 2 diabetes.[7] It was shown by Yue et al that serum levels and

urinary excretion of vitamin C in diabetic patients were inversely related to serum levels of glycosylated hemoglobin.[8]

The reduction of glycosylated hemoglobin can reflect the decrease of total glycosylation of proteins. Considering the different complications attributed to glycosylated protein compounds and the evidence confirming the influence of vitamin C on reduction of the protein glycosylation process, this study was devised to investigate the influence of vitamin C on the serum level of glycosylated hemoglobin in patients with type 2 diabetes mellitus. The aim of our study was to determine whether vitamin C could reduce serum levels of HbA1c in patients with type 2 diabetes mellitus.

Materials and Methods:

18 patients with type 2 diabetes were enrolled in a before after clinical trial study. The diabetic patients were diagnosed using the WHO protocol, FBS>140 mg/dl - evaluated in 2 separate measurements.[9] Inclusion criteria consisted of informed consent, no administration of supplemental vitamin C prior to the study, regular physical activity, and regular diet and dosage of anti-diabetic medications throughout the study.

Subjects were examined by a physician and those suspected of gout, thalassemia, renal failure, and cystinuria were excluded. Pregnancies, breastfeeding, taking of medications interacting with vitamin C metabolism (anticoagulants, barbiturates, disulfidates and salicylates) were also among criteria for those excluded.

The height and weight of patients were measured before and after the study by a nutritionist using a seca scale. Body mass index (BMI) was calculated dividing weight (kg) by height to the power of 2 (m^2). A 3-day diet recall was one of the methods used to investigate the diet before and after the study.

One-gram vitamin C per day, divided into 4 doses, was administered to the patients for 6 weeks. Fasting blood glucose and glycosylated hemoglobin of patients were determined before and after the study, using the GOD-PAP enzymatic method (Pars azmoon Co, Tehran, Iran) and the calorimetric method (Mahsa yaran co, Isfahan, Iran) respectively. Data were analyzed by paired t-test using SPSS software (ver 6, for win). $P<0.05$ was considered as significant.

Results

All 18 patients completed the study. Mean age of subjects was 50±5 years. Mean weight of subjects was 63.8±7 and 64.3±6 Kg in the beginning and end of the study respectively ($p=0.03$). Mean dietary consumption before and after the study did not differ significantly (Table 1). Mean BMI of patients was 25.1±3 kg/m^2 in the beginning and 25.3±3 kg/m^2 at the end of the study ($p=0.003$). After controlling for the effect of weight and BMI alterations, the changes of glycosylated hemoglobin remained significant ($P=0.0001$). Mean fasting blood glucose and glycosylated hemoglobin are given in table 2. As shown, the level of glycosylated hemoglobin decreased significantly following administration of vitamin C while fasting blood glucose did not.

Table 1. The resuls of recall of a 3-day diet in patients with non-insulin dependent diabetes mellitus

Variables	Energy (Kcal)	Carbohydrate (g)	Protein (g)	Fat (g)	Fiber (g)	Vitamin C (mg)
Beginning of the study	1050±320*	180±60	40.7±16.7	19±10.2	9.7±0.2	42±25
End of the study	1037±35.8	172±46	38.5±13.8	21±9.6	9.4±3.67	43±41

* Non - significant for all variables

Table 2. Comparison of glycosylated hemoglobin and fasting blood glucose before and after the study

Variables	Before	After	P value
Glycosylated hemoglobin (%)	11.8±1.48	10.2±1.28	0.015
Fasting blood glucose (mg/dL)	164±45	171±45	NS

NS: non-significant

Discussion

Our findings indicate that supplemental vitamin C significantly reduced HbA1c level in the patients studied. As fasting blood glucose did not change significantly, the reduction of HbA1c level could not be attributed to the alteration of blood glucose level. This finding is in agreement with the study of Eriksson et al, in which 2 grams of vitamin C or 600 mg of magnesium were given blindly to 56 patients with type 2 diabetes for 3 months and thereafter the level of glycosylated hemoglobin was observed to decrease significantly in the patients taking vitamin C.[7]

The same results were obtained by Stolba et al and Khatami et al.[9,10] Stalba et al investigated the influence of ascorbic acid on the process of glycosylation of albumin in bovine serum and observed that ascorbic acid significantly reduced glycosylation. Khatami et al, confirming the influence of vitamin C on the reduction of glycosylation, conducted the same research in vitro. Some studies performed on fructosamine (an indicator applied to monitor diabetes) have shown that supplemental vitamin significantly reduced the level of glycosylated proteins.[12,13]

Furthermore, in a study performed by Davie et al, levels of glycosylated albumin and hemoglobin were found to decline in subjects taking 1 gram of vitamin C per day for 3 months.[14] On the contrary, giving 500 mg vitamin C as well as placebos to 50 diabetic patients for 4 months, Bishop et al found no significant difference in glycosylated hemoglobin levels between groups taking vitamin C and those taking placebos, which can be explained by the low dose of vitamin C administered. No correlation was demonstrated between the dose of supplemental vitamin C and glycosylated hemoglobin in diabetic patients in a study performed by Shoff et al.[16]

Bensch et al showed that influence of vitamin C on glycosylation reaction is exerted by competition with glucose. In other words, vitamin C can compete with glucose in vitro to react with amine groups of proteins as a result of structural similarity to glucose, hence inhibiting the process of glycolysis.[17]
Overall, this study implies that vitamin C can reduce the glycosylation of hemoglobin in vivo in patients with type 2 diabetes.

In conclusion, considering the importance of glycosylated proteins in the pathogenesis of vascular complications in diabetes and the inhibitory effect of vitamin C on the glycosylation of proteins, which was confirmed in this study, it would seem that further studies to investigate the long term influence of vitamin C on the glycosylation of the proteins with short and long half-lives are called for to see whether the products of the reaction of vitamin C with proteins may give rise to other complications. If not, the administration of vitamin C can be considered in the prevention of long-term complications of non-insulin dependent diabetes mellitus. It is also recommended that more enhanced methodology be used for further investigations.

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