EFFECT OF ASCORBIC ACID SUPPLEMENTATION ON DIABETIC NEUROPATHY

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ABSTRACT

The important role of ascorbic acid is especially relevant in diabetes mellitus where plasma concentrations of ascorbic acid are reduced. This study was conducted to evaluate the effect of ascorbic acid administration on diabetic polyneuropathy. Twenty-two patients having non- insulin dependent diabetes mellitus (NIDDM) were included in the study with 10 healthy control subjects of matched age and sex. The patients received 500mg twice daily of ascorbic acid in addition to their usual antidiabetic therapy, and the study was conduced for three months. Before and after ascorbic acid treatment, the patients were assessed clinically for subjective and objective evidence of neuropathy with neurophysiological investigations including nerve conduction velocity estimation and H reflex latency study. Laboratory investigations included fasting and postprandial serum glucose, serum creatinine, liver function tests and serum ascorbic acid determinations. The results showed that diabetic patients had significantly reduced values of ascorbic acid in comparison to control healthy subjects ($P<0.05$). Ascorbic acid supplementation resulted in increased ascorbic acid levels reaching that of control subject ($p<0.05$). There was significant reduction of nerve conduction velocity in diabetic patients compared to control group($P<0.05$). There was non-significant change of nerve conduction velocity after ascorbic acid supplementation. H reflex latency was absent in a group of diabetic subjects having severe polyneuropathy (group A) and was delayed in another group

(group B). After ascorbic acid supplementation, H reflex latency showed mild significant improvement in group B ($P<0.05$). The study showed that early ascorbic acid supplementation in diabetic patients is advised in order to prevent or retard progression of diabetic complications including diabetic neuropathy.

INTRODUCTION

Oxygen free radicals and lipid peroxides have been implicated in the pathogenesis of a large number of diseases such as diabetes mellitus, cancer, infectious diseases, atherosclerosis, and in aging (Grankvist et al,1981; Yagi, 1984; Akkus, et al ,1996). Antioxidant deficiency e.g. vitamins A,C and E and excess peroxide mediated damage may appear early in non insulin dependent diabetes mellitus(NIDDM) before development of secondary complications (Sundaram et al, 1996).

The biological effects of free radicals are controlled in vivo by a wide range of antioxidants such as vitamins E and C, carotinoids , glutathione and antioxidant enzymes (Akkus et al ,1996). Ascorbic acid is of particular importance in diabetes, as the metabolism of ascorbic acid is known to be abnormal in human and experimental models of diabetes mellitus. Plasma concentrations of ascorbic acid were found to be reduced in diabetic humans and in diabetic rats (Yeu et al, 1989; Sinclair et al ,1994).

McAuliffe et al (1998) found that treatment with ascorbic acid restored plasma concentrations of ascorbic acid in diabetic subjects to normal levels and reduced microalbuminuria in patients having early diabetic nephropathy. They found that the degree of change in albumin excretion rate was inversely proportional to the rise of plasma ascorbic acid.

Antioxidant treatment has been shown to prevent nerve dysfunction in experimental diabetes , thus providing rationale of potential therapeutic value for diabetic patients. There are therapeutic trials of antioxidant treatment of diabetic neuropathy using thioctic acid (alpha lipoic acid) (Ziegler et al,1995). It has been proposed that alpha lipoic acid acts as an antioxidant and interferes with the pathogenesis of diabetic neuropathy (Nagamatsu et al, 1995).

So, the aim of this study was to investigate the possible effect of ascor-

bic acid supplementation in diabetic patients having neuropathy.

SUBJECTS AND METHODS

The study included twenty-two patients having NIDDM. The patients were recruited from the outpatient diabetic clinic of Mansoura University Hospital.

They were 8 males and 14 females. Their ages ranged from 40 to 61years. The duration of diabetes ranged from 4 to 16 years. Ten healthy subjects of matched age and sex were included in the study as control group. The mean height of the subjects in both groups was similar.

History taking and examination were done with stress on the duration of diabetes, type of therapy, other drug intake and history of sensory, motor or autonomic affection. Twenty patients complained of sensory symptoms in the form of burning and tingling sensations while 6 patients complained of motor manifestations in the form of distal weakness of both lower limbs. Autonomic dysfunction was present in 3 cases complaining of impotence.

Laboratory investigations included fasting and postprandial serum glucose estimation, serum creatinine, liver function tests and serum ascorbic acid estimation by the dinitrophenylhydrazine (DNPH) method (Omaye et al, 1979; Stankova et al,1984). Patients having abnormal liver or kidney functions or receiving medications apart from their usual antidiabetic treatment were excluded from the study.

Special neurophysiological investigations were done which included determination of median and lateral popliteal conduction velocity and H reflex latency studies from the soleus muscle.

Motor nerve conduction velocity was studied by the standard methods (Gohnson, 1980) by the use of Neuropack 2 Nihon Kohden, EMG/Evoked response recorder, model MEB/MEM, 7102/K.O2.

H reflex study

H reflex was studied according to Marya et al , 1986 and was identified by the already established criteria (Smorto and Basmajian,1977).

The tibial nerve was stimulated at the midpopliteal fossa , by a single

pulse from the EMG stimulator with the cathode bipolar stimulating electrode placed proximally, the optimum site for stimulation was identified from the lowest threshold for evoking the H response.

The latency from the stimulus artefact to the first deflection from the baseline was taken as the H reflex latency.

After performing the neurophysiological investigations, the patients received ascorbic acid tablets 500mg twice daily together with their usual antidiabetic therapy. The patients were followed for three months and instructed not to change their dietary habits. Then the previous investigations were repeated.

STATISTICAL ANALYSIS

Statistical analysis was done using "stat" computer program. The difference between patients and control was calculated using the student's t test. The effect of ascorbic acid treatment on diabetic patients was analyzed using the analysis of variance (anova). The results were considered significant at $P<0.05$.

RESULTS

Table (1) : shows fasting and postprandial serum glucose and ascorbic acid levels in diabetic patients compared to control group. Ascorbic acid levels were significantly lower in the diabetic patients compared to control group ($P<0.05$) , while fasting and postprandial serum glucose levels showed significantly higher values ($P<0.001$).

Table (2) : shows comparison of serum ascorbic acid and glucose levels before and after ascorbic acid administration. There was significant increase in serum ascorbic acid levels after treatment ($P<0.05$) while serum glucose levels showed non significant difference ($P>0.05$).

Table (3) : shows H reflex latency in the control group and diabetic subjects. H reflex was absent in 6 diabetic patients (considered as subgroup A, not shown in the table) and was delayed in the other 16 patients (considered as subgroup B) when compared to control group ($P<0.001$). This table also shows the effect of ascorbic acid administration on the H reflex latency time in group (B) diabetic patients where there were mild significant improvement after treatment

(P<0.05). but in group A there was no improvement after ascorbic acid treatment as H reflex was still absent (not shown in the table).

Table (4) : shows motor nerve conduction velocity in the total diabetic group, subgroup A and subgroup B in comparison to control group. There was markedly significant reduction in motor conduction velocity in subgroup (A) having severe polyneuropathy (P<0.001), mild significant reduction in the total diabetic group (P<0.05) and non significant reduction in subgroup B (P>0.05).

Table (5) : shows the effect of ascorbic acid administration on nerve conduction velocity in diabetic patients. There was non significant change in nerve conduction velocity in diabetic patients before and after treatment.

Table (1) : Serum ascorbic acid and fasting and postprandial serum glucose levels in diabetic patients before starting ascorbic acid treatment in comparison to control group.

Parameter / Group	Ascorbic acid (mg/dl)	Fasting serum glucose (mg/dl)	Postprandial serum glucose (mg/dl)
Control group (10)	M ± SD 1.139 ± 0.19	91.03 ±8.3	114.9 ±24.6
Diabetic Group (22)	0.998 ±0.06	160.7 ±51.6	220.8 ±70.2
P	<0.05	<0.001	<0.001

Table (2) : Serum ascorbic acid and fasting and postprandial serum glucose levels in diabetic patients before and after ascorbic acid treatment (anova test).

Group	Ascorbic acid (mg/dl)	Fasting serum glucose (mg/dl)	Postprandial serum glucose (mg/dl)
Diabetic patients before treatment	0.998 ±0.06	160.7 ±51.6	220.8 ±70.2
Diabetic patients after treatment	1.128 ±0.18	156.8 ±53.2	208.8 ±69.8
P	P <0.05	N.S	N.S

N.S. non significant

Table (3) : H reflex latency in diabetic subgroup B versus control group (t test) and in the same subgroup before and after ascorbic acid administration (anova test).

Group	H reflex latency (m/sec)	P (t-test)	$\bar{P}$ (anova)
Control group (10)	M 31.5 SD ±2.5		
Diabetic subgroup (B)before treatment	M 36.6 SD ±2.8	<0.001	
Diabetic subgroup (B) after treatment	M 32.4 SD ±6.2	N.S.	<0.05

P= The significance of difference between the diabetic subgroup and the control group (t-test).

$\bar{P}$=The significance of difference in H reflex latency time in diabetic subgroup (B) before and after treatment (anova).

Table (4) : Motor nerve conduction velocity in total diabetic group and subgroups versus control group.

Group	Median nerve conduction velocity (m/sec)	Lateral popliteal nerve conduction velocity (m/sec)
Control group (10)	M 56.8 ± S.D. 3.21	45.8 ± 2.41
Total diabetic group (22)	M 48.6 ± S.D. 8.7 P <0.05	38.29 ± 8.8 <0.05
Diabetic subgroup A (6)	M 36.7 ± ± S.D. 2.2 P 0.001	32.6 ± 6.4 <0.001
Diabetic Subgroup B (16)	M 52.4 ± ± S.D. 7.4 P N.S.	42.8 ± 6.2 NS

Table (5) : Nerve conduction velocity in total diabetic group and subgroups before and after ascorbic acid administration.

Group		Median nerve conduction velocity (m/sec)	Lateral popliteal nerve conduction velocity (m/sec)
Total diabetic Group (22)	before after	48.6±8.7 50.8±3 P N.S.	38.29±8.8 40.2±4.3 N.S.
GroupA (6)	before after	36.7±2.2 36.2±4.1 P N.S. N.S	32.6±6.4 32.1±4.4 N.S.
GroupB (16)	before after	52.4±7.4 53±6.2 P N.S. N.S.	42.8±6.2 43.4±4.2 N.S.

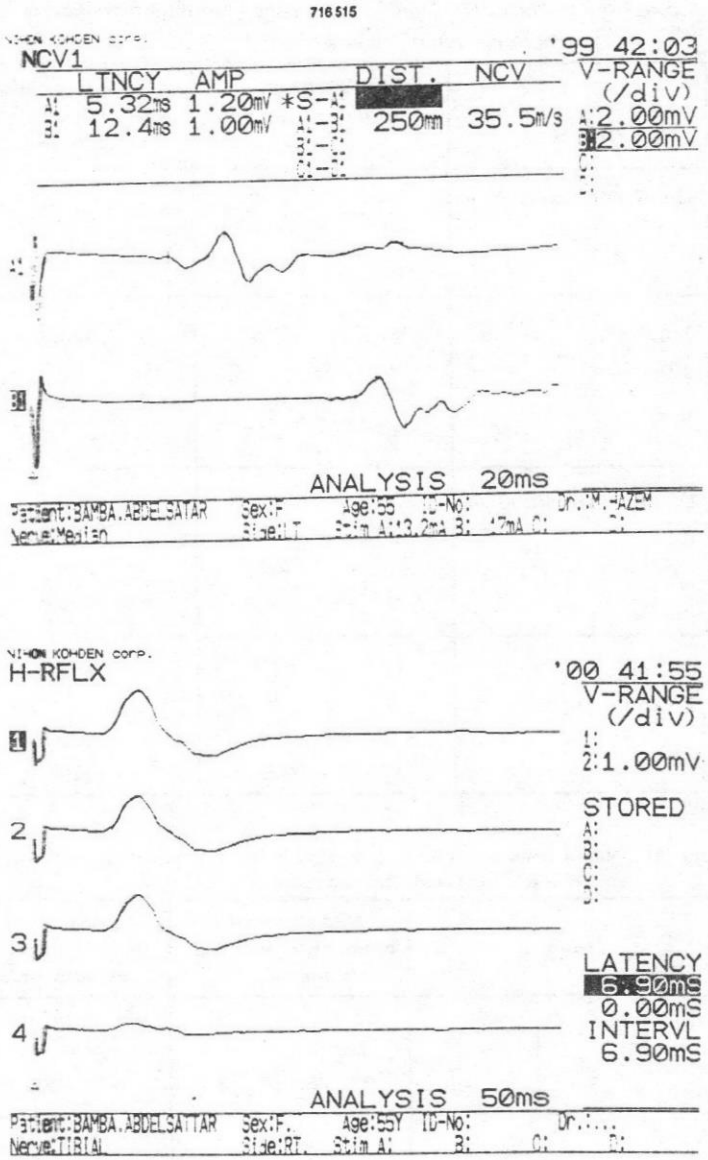

Fig. 1 : Delayed conduction velocity and absent H reflex in one patient of group A before ascorbic acid treatment .

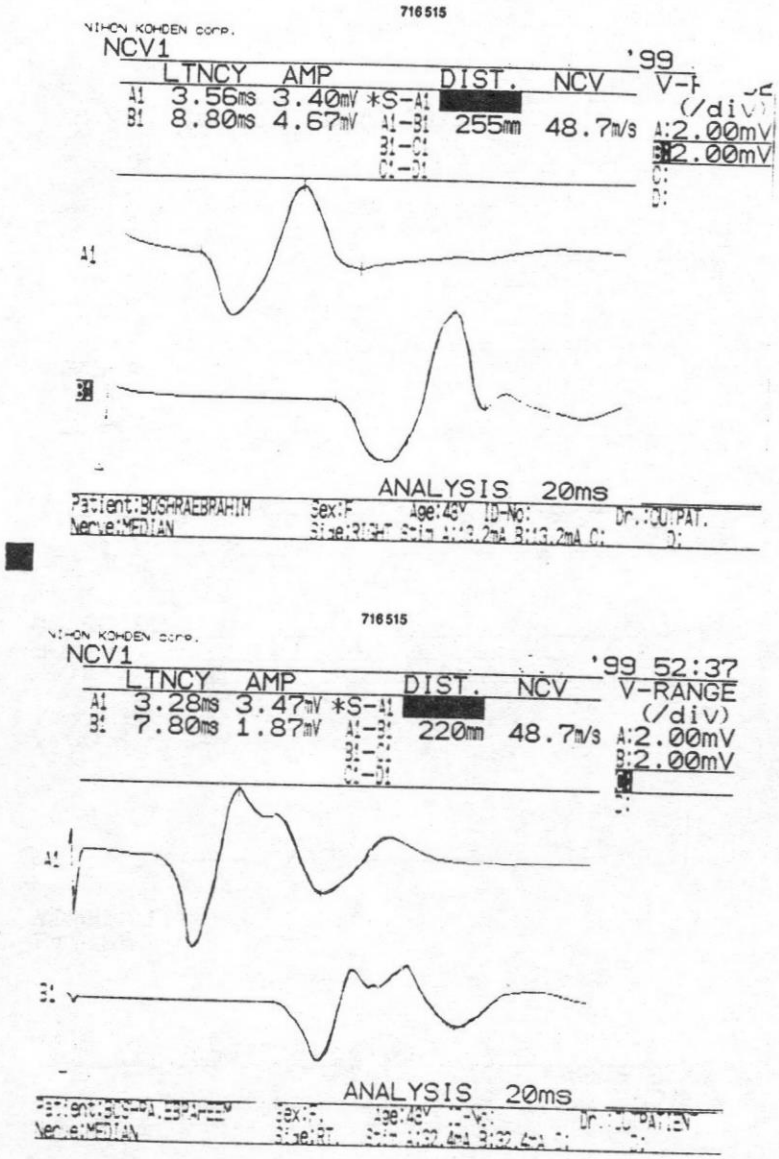

Fig. 2 : Median nerve conduction velocity in one patient of group B before and after ascorbic acid treatment .

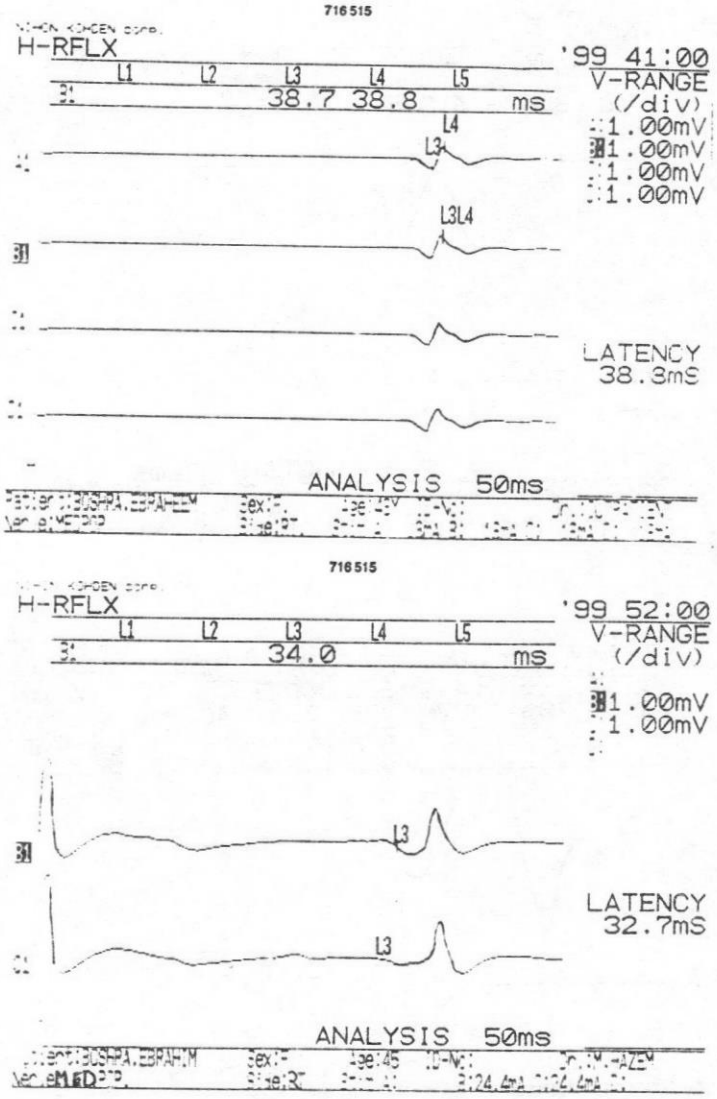

Fig. 3 : Improved H reflex latency in one patient of group B after ascorbic acid treatment in comparison with that before therapy .

DISCUSSION

Ascorbic acid metabolism is abnormal in both human and experimental diabetes. In this study, plasma ascorbic acid was lower in diabetic subjects compared to control healthy subjects (table 1) and was normalized after 1gm daily ascorbic acid supplementation for 3 months (table2). These results are in agreement with previous reports which found that the plasma and tissue concentrations of ascorbic acid are decreased in diabetic animals and humans (Som et al , 1981; Chen et al, 1983; Mclennan et al , 1988). More recently, Vijayalingam et al (1996) found that ascorbic acid is reduced by 20% in patients having impaired glucose tolerance and those having NIDDM.

Because ascorbic acid has many biological functions, abnormalities of ascorbic acid metabolism could be important in the pathogenesis of some diabetic complications (Yeu et al, 1989). Ascorbic acid plays an important role in the synthesis and modification of collagen. It is also important for regulation of many cellular biochemical processes including scavengering of free radicals (Barnes , 1976; Levine, 1986; Freeman and Crapo, 1982).

The mechanism of abnormalities of ascorbic acid metabolism in diabetes is not completely understood. Because human cannot synthesize ascorbic acid (as do rats), a change in the production rate cannot be a factor but other disturbances in its metabolism are possible. These disturbances may include shift in its equilibrium with dehydroascorbic acid, alteration of renal excretion, change of the half life and competition for cellular uptake with high glucose levels (Yeu et al, 1989).

A growing body of evidence suggests that cellular injury induced by intracellular alterations of defense systems against oxidative stress may be relevant in the pathogenesis of diabetic complications (Baynes, 1991). Increased free radical formation and changes in homeostatic variables related to endothelial damage have been found in NIDDM patients with microalbuminuria (Collier et al, 1992). Furthermore, impaired cellular scavengering activity against oxidative stress bas been demonstrated in diabetic patients (Yoshida et al, 1995). There is accumulating evidence suggesting that free radical mediated oxidative stress is implicated in the pathogenesis of diabetic neuropathy by

including neurovascular defects that result in endoneurial hypoxia and subsequent nerve dysfunction (Low and Nickander, 1991; Cameron and Cotter, 1994). Administration of physiological antioxidants including α- lipoic acid, which is a potent lipophillic free radical scavenger, resulted in prevention of neurovascular abnormalities associated with experimental diabetic neuropathy, providing a basis for potential therapeutic value in diabetic patients (Cameron et al, 1993 and 1994; Nagamatsu et al , 1995).

The aim of this study was to evaluate the possible value of ascorbic acid administration which is a hydrophillic antioxidant and its level is reduced in patients having diabetic neuropathy. Ascorbic acid supplementation in diabetic subjects was found to attenuate the progression of diabetic neuropathy (McAullife et al, 1998). This effect was not mediated by improvement in metabolic control. In this study (table2), ascorbic acid treatment did not affect serum glucose levels.

Electrophysiologic studies of the peripheral nerves are the most sensitive, reliable and reproducible measure of nerve function which also correlate with morphologic findings in nerve biopsy (Veves et al,1991). In this study , median and lateral popliteal conduction velocities were reduced in diabetic patients in comparison to control group (table 4). There was non significant change in nerve conduction velocity after ascorbic acid administration (table 5, fig.2).

On the other hand , H reflex latency (table3) was absent in group (A) which had severe polyneuropathy (markedly prolonged nerve conduction velocity in table 4) and was delayed in group (B) which had non significant change in motor conduction velocity in comparison to control group (table 4). These findings can be explained by the sensitivity of H reflex in detection of subclinical diabetic neuropathy than motor nerve conduction velocity (Marya et al,1986). The reason for greater sensitivity of H reflex is attributed to the longer pathway being tested, so that borderline abnormalities in conduction velocity are amplified. Also, the neuropathy may affect the proximal segments that are not measured by routine methods (Marya et al ,1986). In diabetic neuropathy, the histological studies showing Schwann cell damage leading to demyelination, have revealed involvement of proximal as well as distal

segments of the nerve. In some cases, axonal degeneration has been reported (Behse et al,1977).

The absence of H reflex represents a severe form of neuropathy and in all of the patients showing this feature, the motor conduction velocity is also abnormal (Marya et al,1986). In this study, subgroup A showing absent H reflex, had markedly prolonged conduction velocity in comparison to control group (table 4, $P<0.001$, fig. 1). On the other hand there was delayed H reflex latency time in subgroup B which had non significant prolongation in nerve conduction velocity (table 4).

An important feature of diabetic neuropathy is that the large diameter afferent fibres are affected earlier than the motor fibres (Lamontagne and Buchthal,1970). This may explain why motor conduction velocity studies have not been helpful in diagnosis of diabetic neuropathy in its early stage (Johnson,1980). Since the H reflex involves conduction in the proximal segments of both large diameter afferent and efferent fibres, its study may be helpful in the diagnosis of subclinical diabetic neuropathy (Wager and Beurger, 1974). In this study, after ascorbic acid supplementation, there was mild improvement in H reflex latency in subgroup B (table 3, fig. 3) while the nerve conduction velocity showed non significant change (table 5, fig. 2). These findings suggest that ascorbic acid supplementation would be beneficial only in patients with subclinical or early neuropathy but not in well established cases with markedly impaired nerve conduction velocity.

From the previous findings, it is clear that there is reduced ascorbic acid level in diabetic patients, which was restored to normal after ascorbic acid supplementation. Also, ascorbic acid supplementation resulted in improvement of patients having early neuropathy and not in those with advanced neuropathy. This beneficial effect of ascorbic acid supplementation can be explained by its antioxidant effect as oxidative stress has been also implicated in the pathogenesis of diabetic neuropathy (Low and Nickander, 1991). On the other hand, it is known that hyperglycemia is central to any pathogenetic scheme for development of human diabetic neuropathy. A complex chain of events, including glucose- induced activation of the polyol pathway, myoinositol depletion, impaired protein kinase activity and

decreased nerve Na-K ATPase activity, has been implicated in the development of a reduction in nerve conduction velocity (Stevens et al, 1995). Most studies have found that diabetic subjects have about 20-30% lower circulating ascorbic acid concentrations than people not having diabetes mellitus. Vitamin C supplementation had little impact on blood glucose concentration but was found to decrease cellular sorbitol concentration (Will and Byers, 1996). Also Wang et al, (1995) showed that ascorbic acid supplementation (1gm daily) led to the reduction of red cell sorbitol levels and red cell sorbitol/ plasma glucose ratio while fasting serum glucose showed non significant change. These findings suggested that the polyol pathway could be inhibited effectively by ascorbic acid. Cunningham (1998) stated that the roles of ascorbic acid as an aldose reductase inhibitor (decreasing cellular sorbitol levels) and as a water soluble antioxidant in body fluids are potentially very important as adjuncts to tight glycemic control in the management of diabetes.

In conclusion, this study suggests that ascorbic acid supplementation early in the course of diabetes is simple and may have long term benefits in preventing the occurrence or attenuating the progression of diabetic complications including neuropathy.

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تأثير حامض الاسكوربيك على إلتهاب الأعصاب الناتج عن مرض السكر

المشتركون فى البحث

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يمثل حامض الاسكوربيك أهمية خاصة فى مرضى السكر نظراً لأن نسبته تكون أقل فى هؤلاء المرضى. ولذا كان الغرض من هذه الدراسة هو تقييم تأثير تعاطى مرضى السكر لحامض الاسكوربيك على أصابتهم بإلتهاب الأعصاب الناتج عن السكر. إشتملت الدراسة على ٢٢ مريضاً بمرض السكر الغير المعتمد على الأنسولين وذلك بالإضافة إلى عشرة من الأصحاء كمجموعة ضابطة. وتم إعطاء هؤلاء المرضى ٥٠٠ مجم من حامض الاسكوربيك مرتين يومياً لمدة ٣ أشهر وتم عمل الفحوصات التى تشمل قياس نسبة حامض الاسكوربيك والسكر فى الدم وإلى جانب فحوصات قياس سرعة التوصيل فى الأعصاب إلى جانب الفعل المنعكس هـ وقد وجد أن نسبة حامض الاسكوربيك أقل فى هؤلاء المرضى عن المجموعة الضابطة كما أن سرعة التوصيل فى الأعصاب أبطأ فى هؤلاء عن المجموعة الضابطة ولم تتحسن بالعلاج بحامض الاسكوربيك ولكن ظهر تحسن فى الفعل المنعكس هـ مع العلاج بحامض الاسكوربيك ومن هذا يمكن التوصية بأن مرضى السكر يمكن أن يستفيدوا من إضافة ڤيتامين ج إلى علاجهم وذلك لتأثيرة فى منع أو تأخير الإصابة بمضاعفات السكر بما فيها إلتهاب الأعصاب .