ORIGINAL PROF-614

ROLE OF ANTITOXIDANT ALPHA LIPOIC ACID IN SYMPTOMATIC DIABETIC NEUROPATHY

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ABSTRACT

Two hundred subjects of diabetes mellitus of both sexes between 25-60 years of age were included in this study, fifty normal healthy males and females of same age group were included as controls. These subjects were divided into three groups, controls, diabetic patients without neuropathy and diabetic patients with symptomatic neuropathy. The patients of last group treated with alpha lipoic acid 600 mg/day for 12 weeks. Fasting blood, glucose, cholesterol and C S F proteins were estimated, peripheral nervous system was examined to assess sensory (Q.S.T) as well as motor components (E.Q.X). E M G was carried out on all these subjects. In the diabetic patients the biochemical abnormalities determined in terms of fasting blood glucose, serum cholesterol and C S F proteins showed a linear relationship with physiological abnormalities detected by E M G and study of nervous system. Supplementation of alpha lipoic acid in this study reverted most of the biochemical and physiological parameters to near normal by better control over blood glucose level, relieving pain, numbness, paresthaesias and restoration of reflexes. Thus treatment of diabetes with antidiabetics along with supplements of antioxidant alpha lipoic can prevent number of complications in diabetic neuropathy and even help in reversal of most of the symptoms.

INTRODUCTION

Neuropathy is a complication of long standing neglected diabetes[1]. Nerve conduction studies in diabetic subjects concluded that abnormalities of sensory nerve conduction are the most consistent sub clinical alterations indicating that sensory fibers are usually first to be affected[2]. Occurrence of peripheral neuropathy is the apparent initial manifestation of diabetes and the failure in majority of patients for closer control of hyperglycaemia to produce improvement in the disease has led to the idea that peripheral neuropathy is the direct expression of underlying defects of diabetes and does not result from metabolism and hormonal effects[3]. In experimental diabetes the flow of protein molecules through the exoplasm is delayed which supports the idea of disorder in the nerve fiber itself with or without direct involvement of Schwan cells[4]. Control of diabetes

improves the nerve function and thereby support the hypothesis that diabetic neuropathy has metabolic component[5].

Diabetic neuropathy presents a variable clinical picture of progressive symmetrical sensory neuropathy, neuropathic arthropathy, mononeuropathy and diabetic amyotrophy. Diabetic neuropathy remains a definitive distinguishing characteristic of diabetic state exhibiting a variety of pattern and nerve involvement in affected patients[6]. Sometimes neuropathic features often provide the first clue to diabetes mellitus and decreased glucose tolerance[7].

Myoinositol depletion is responsible for decreased Na.K. ATPase activity in nerves of diabetic animals. A cyclic metabolic defect involving sorbitol, myoinositol and Na.K. ATPase has been held responsible for degenerative changes in diabetic neuropathy[8].

Alpha lipoic acid is a sulfur containing antioxidant that prevent free radical damage, energizes metabolism, protects genetic material, slows ageing and help to protect against heart disease. It not only protects the nervous system but it regenerates the nerves. It also interacts with other antioxidants like vitamin C and E[9]. Alpha lipoic acid is unique, that it is both water and fat soluble thus it can be used throughout the body. In its metabolic role alpha lipoic acid is fundamental coenzyme in two vital reactions that lead to production of cellular energy (ATP)[10].

Administration of lipoic acid has been shown to result in significant increase of insulin stimulated glucose disposal in type II diabetes[11]. He further studied that patients of diabetic neuropathy treated with 500 mg of lipoic acid for more than ten days, the metabolic clearance ratio for glucose is increased by about 50% [12]. Lipoic acid enhances the disposal of glucose due to its enhanced effect on glucose transport that involves its stimulatory effect on GLUT I and GLUT 4, glucose transports which are involved in cellular insulin signaling pathways[13].

Intravenous alpha lipoic acid has been used successfully but oral supplements nonetheless proved partially helpful in treating at least one form of diabetic neuropathy[14]. Principal uses of alpha lipoic acid are in the treatment of diabetes and AIDS[15]. Alpha lipoic acid has also been shown to improve antibody response in immuno suppressed animals.

Alpha lipoic acid is found naturally as a prosthetic group in alpha lipoic acid dehydrogenase complex of mitochondria so plays fundamental role in carbohydrate metabolism. High doses of alpha lipoic acid i.e. 600 mg per day have provided new and consistent evidence for its therapeutic use in the treatment of insulin resistence and diabetic neuropathy[16].

Alpha lipoic acid is a natural antioxidant slowly being recognized as having unique abilities in the therapy and prevention of large number of diseases[17]. Lipoic acid has been used successfully for treating diabetic neuropathy which has caused nerve damage for the last 25 years in Germany[18].

MATERIALS & METHODS

Two hundred subjects of both sexes between 25-60 years of age were selected and divided into following groups;

1. Controls : Normal healthy sex and age matched individuals without any family history of diabetes mellitus.
2. Diabetic patients without neuropathy
3. Diabetic patients with symptomatic neuropathy. Diabetic patients with symptomatic neuropathy given alpha lipoic acid 600 mg/day for twelve weeks.

Four ml of fasting venous blood samples were collected, it was allowed to clot and then contrifuged to separate the serum which was used for analysis of blood glucose and cholesterol.

One ml of C S F was collected through lumber puncture in a storage tube and was analyzed on the same day. E.M.G was carried out on Racia EMG 21-P on all the subjects. Blood glucose was estimated by orthotoluedene method of Winter and Jacobs 1971. Total cholesterol was estimated by Lieberman and Burchard method 1890. Total proteins in C.S.F. were estimated by Pyrogallol Red method McEleny et al 1982

RESULTS

Electromyography was carried out in both controls and diabetic patients suffering from diabetic neuropathy but having no symptoms. In the control group I mean amplitude ± S.D was 516.65 ± 144.21 uv, mean duration was 9.81 ± 2.36 m sec and mean phases were 3.6 ± 0.66. Diabetic patients without evidence of neuropathy were compared with control and the results are shown in group II, the man amplitude was 523.36 ± 118.92 uv, mean duration was 10.07 ± 1.16 m sec and mean phases were 3.7 ± 0.73. The increase in the values was not significant statistically. Diabetic patients with symptomatic neuropathy did showed significant increase in the values as shown in group III. Mean amplitude was 1763.04 ± 234.51 uv, mean duration was 27.71 ± 2.97 m sec and mean phases were 7.75 ± 0.63. After lipoic acid supplementation these values returned to near normal as shown in group IV, mean amplitude was 536.29 ± 106.21 uv, mean duration was 11.67 ± 1.10 m sec and mean phases were 3.9 ± 0.69.

Table-I. Amplitude of electromyogram (EMG).
(Results shown as mean ±SD in uv. No of subjects in parentheses).

Group		Amplitude	P value
I	Controls	516.65 ±144.12 (50)	-
II	Diabetic patients without neuropathy	523.36 ±118.92 (50)	II Vs I P<.05
III	Diabetic patients with symptomatic neuropathy	1763.04 ±234.51(50)	III VsI P<.001
IV	Diabetic patients with symptomatic neuropathy after giving lipoic acid supplements	536.29 ±106.21 (50)	IV VsI P<.001

P>0.05 Non significantP<.01 SignificantP<.001 Highly significant

Table-II. Duration of electromyogram (EMG).
(Results shown as mean ±SD in mSec. No of subjects in parentheses).

Group		Duration	P value
I	Controls	9.81 ±2.36 (50)	-
II	Diabetic patients without neuropathy	10.07 ±1.16 (50)	II Vs I P<.05
III	Diabetic patients with symptomatic neuropathy	27.71 ±2.97 (50)	III VsI P<.001
IV	Diabetic patients with symptomatic neuropathy after giving lipoic acid supplements	11.67±1.10 (50)	IV VsI P<.001

P>0.05 Non significantP<.01 SignificantP<.001 Highly significant

Fasting blood glucose in controls was 78.67 ± 5.76 mg/dl while in diabetic patients without neuropathy the levels were 201.55 ± 27.20. After lipoic acid supplementation the levels decreased to 129.12 ± 12.02 mg/dl as shown in table IV. Fasting serum cholesterol levels in controls were 188.10 ± 17.63 mg/dl, in diabetic patients without neuropathy 237.05 ± 38.32 and in diabetic patients with symptomatic neuropathy 284.00 ± 22.95 mg/dl while after giving lipoic acid supplements the values obtained were 242.00 ± 32.40 mg/dl, as shown in table V. C.S.F proteins in controls were 29.1 ± 4.64 mg/dl, in diabetic patients without neuropathy 58.15 ±16.53 in diabetic patients with symptomatic neuropathy 75.40 ± 15.06 mg/dl while after lipoic acid supplements the values declined to 44.28 ± 9.92 mg/dl as shown in Table VI.

Table-III. Phases of electromyogram (EMG).
(Results shown as mean ±SD. No of subjects in parentheses).

Group		Phases	P value
I	Controls	3.6 ±0.66 (50)	-
II	Diabetic patients without neuropathy	3.7 ±0.73 (50)	II Vs I P<.05
III	Diabetic patients with symptomatic neuropathy	7.75 ±0.63 (50)	III VsI P<.001
IV	Diabetic patients with symptomatic neuropathy after giving lipoic acid supplements	3.9±0.69 (50)	IV VsI P<.001

P>0.05 Non significantP<.01 SignificantP<.001 Highly significant

Table-IV. Fasting blood glucose levels.
(Results shown as mean ±SD in mg/dl. No of subjects in parentheses).

Group		Blood glucose	P value
I	Controls	78.67 ±5.76 (50)	-
II	Diabetic patients without neuropathy	201.55±27.93 (50)	II Vs I P<.05
III	Diabetic patients with symptomatic neuropathy	255.15±27.20 (50)	III VsI P<.001
IV	Diabetic patients with symptomatic neuropathy after giving lipoic acid supplements	129.00±12.02 (50)	IV VsI P<.001

P>0.05 Non significantP<.01 SignificantP<.001 Highly significant

Table-V. Total serum cholesterol levels.
(Results shown as mean ±SD in mg/dl. No of subjects in parentheses).

Group		Serum cholesterol	P value
I	Controls	188.10±17.63 (50)	-
II	Diabetic patients without neuropathy	227.05±38.32 (50)	II Vs I P<.05
III	Diabetic patients with symptomatic neuropathy	284.00±22.95 (50)	III VsI P<.001
IV	Diabetic patients with symptomatic neuropathy after giving lipoic acid supplements	242.00±32.40 (50)	IV VsI P<.001

P>0.05 Non significantP<.01 SignificantP<.001 Highly significant

Table-VI. Total proteins levels in C.S.F.
(Results shown as mean ±SD in mg/dl. No of subjects in parentheses).

Group		C.S.F Proteins	P value
I	Controls	29.1 ±4.64 (50)	-
II	Diabetic patients without neuropathy	58.15±16.53 (50)	II Vs I P<.05
III	Diabetic patients with symptomatic neuropathy	75.40±15.06 (50)	III VsI P<.001

Table-VI. Total proteins levels in C.S.F.
(Results shown as mean ±SD in mg/dl. No of subjects in parentheses).

Group		C.S.F Proteins	P value
IV	Diabetic patients with symptomatic neuropathy after giving lipoic acid supplements	44.28±9.92 (50)	IV VsI P<.001

P>0.05 Non significantP<.01 SignificantP<.001 Highly significant

DISCUSSION

Peripheral neuropathy is a disease of the nerves. Duration and poor control of the metabolic disease are the main factors responsible for development and onset of neuropathy. About 15% of the patients with diabetes mellitus ultimately develop neuropathy[19] however it is difficult to make an accurate estimate of prevalence of symptomatic nerve involvement in diabetes but the defects demonstrable by electrophysiological studies, reflex abnormalities, sensory loss or automonic dysfunction occur in majority of patients. It is evident that diabetic neuropathy occurs in persons who have had diabetes for long time and do not control or cannot control their blood sugar very well, seem to be more prone to get diabetic neuropathy. Evidence of neuropathy is based on loss of vibration sense and deep reflexes and sensory receptions. In the present study sensory system and reflexes were evaluated by manual techniques and E.M.G. was carried out to establish the functional defects and biochemical estimation of fasting blood glucose, cholesterol and C.S.F proteins were carried out on all the subjects.

After the clinical examination median motor, peroneal motor and sural sensory nerve conduction velocities were carried out in all the subjects. A patient was considered to have abnormal nerve conduction when atleast no measured attribute (nerve conduction velocity, F wave latency or amplitude) were abnormal in at least two anatomically distinct nerves.

The precise pathogenetic mechanism responsible for the progressive loss and damage of nerve fiber underlying clinical diabetic polyneuropathy remains controversial and may involve direct metabolic and micro vascular ischaemic insult[20]. The results of DCCT 1995 research group conclusively established that intensive diabetic management in patients of diabetes mellitus markedly reduces the risk for developing clinically overt, objectively confined diabetic neuropathy as this therapy normalize glucose levels which prevents or slows the progression of diabetic neuropathy[21].

Ziegler 1997 found that supplementation with alpha lipoic acid caused an amerlioration of neuropathy. It is more interesting that dose of oral antidiabetics and insulin decreased markedly due to addition of alpha lipoic acid which according to Packer 1995 helps in the uptake and utilization of glucose by the cells[22]. The same results have been obtained in this study.

Gosh 1996 found that E.M.G had a wide application in clinical medicine and research so E.M.G was performed to delineate the peripheral nerve abnormality. In symptomatic diabetic neuropathy highly significant improvement ($P < .001$) was observed in E.M.G findings after lipoic acid supplements. These results are in accordance with those of Thurslon 1984[23].

Diabetic neuropathy has a metabolic component in a study by Graffe 1981, two important indicators of metabolic derangement like fasting blood glucose and cholesterol were estimated in this study and findings were further strengthened by estimation of C.S.F proteins. After lipoic acid supplementation in this study blood glucose, chlesterol and C.S.F proteins decreased significantly ($P < .001$) showing a better metabolic control.

CONCLUSION

It is concluded from the study that biochemical abnormalities determined in terms of fasting blood glucose, serum cholesterol and C.S.F proteins and study of nervous system. It is a modern concept that brain does not need insulin for glucose utilization, however in vitro studies by Heller & Hess 1960 on nerve trunk showed that insulin stimulates utilization of glucose and lipogenesis within the nerve tissue and it is true that peripheral nervous tissue is sensitive to and dependent on insulin. This explains why long standing diabetes is

injurious to peripheral and even central part of nervous system. But the effects of alpha lipoic acid in this study reverted most of the biochemical and physiological parameters to near normal by better control over blood glucose level, relieving pain, numbness, paresthaesis and restoration of reflexes. Thus effective treatment of diabetes with anti diabetics and supplements of this so called universal antiosidant alpha lipoic acid can prevent number of complications in diabetic neuropathy and even help in reversal of most of the symptoms.

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