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HIGH DOSE THIAMINE THERAPY FOR TYPE 2 DIABETES WITH MICROALBUMINURIA PATIENTS: A RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED STUDY

Medicine

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ABSTRACT

Background: Diabetic nephropathy is the single most common cause of chronic renal failure. Despite protective treatment with ACE inhibitors and angiotensin receptor blockers, many patients progress to end stage renal disease. Thiamine and benfotiamine have been proposed as protective agents for diabetes complications.

Objective: Present study was conducted to see the effect of thiamine on urinary albumin excretion (UAE) in patients with type 2 diabetes and nephropathy.

Methods: The study was a hospital based follow-up study where Patients with type 2 diabetes and UAE equivalent to 30-300mg/24h, were randomly assigned to 12 weeks of thiamine (300mg/day) (n= 36) or placebo (n=37).

Results: Compared with placebo, thiamine treatment resulted in significant decrease in UAE ($p < 0.05$) and remained constantly low after another 8weeks follow up ($p < 0.001$).

Conclusion: In patients with type 2 diabetes, high dose thiamine treatment for 12 weeks causes regression of UAE, so it can prevent early stage diabetic nephropathy.

KEYWORDS

Diabetic nephropathy, Thiamine, Urinary albumin excretion,

INTRODUCTION

Diabetic nephropathy is the single most common cause of chronic renal failure, accounting for 45% of patients receiving renal replacement therapy, and is a rapidly growing problem worldwide.[1] The pathophysiology of diabetic nephropathy includes albuminuria as a consequence of glomerular endothelial damage and further progression due to tubule-interstitial inflammation and fibrosis[2]. Despite protective treatment with ACE inhibitors and angiotensin receptor blockers, many patients progress to end stage renal disease[3].

Diabetic nephropathy develops progressively over 5-40 years of diabetes[4]. A novel strategy to counter biochemical dysfunction linked to the development of diabetic nephropathy is high dose thiamine therapy[5]. High dose thiamine therapy prevents the development of diabetic nephropathy in experimental diabetics without improvement of glycemic control[6]. Experimental diabetics was associated with thiamine deficiency characterized by a marked decrease in plasma thiamine concentration and decreased activity and expression of the thiamine dependent enzyme transketolase in renal glomeruli[7]. Type 1 and Type 2 diabetic patients showed similar decrease in plasma thiamine concentrations[8].

Thiamine and benfotiamine have been proposed as protective agents for diabetes complications[6]. Benfotiamine is a lipophilic thiamine derivative with high bioavailability[9]. In animal studies, both compounds had beneficial effects on micro vascular complications, including diabetic nephropathy [10].

In this study the effect of oral high dose supplements of thiamine on urinary albumin excretion (UAE), a marker of early stage diabetic nephropathy, in type 2 diabetic patients with microalbuminuria was evaluated.

MATERIALS AND METHODS:

It was a hospital based follow up Study conducted from June 2009 to Dec 2009, in a tertiary care teaching hospital in Rajasthan. Participants who were presented at diabetic clinic with type 2 diabetes, age 30-65 years, active diabetic nephropathy (UAE 30-300mg/24hr), glycated haemoglobin (A1C) $\leq$ 12.5% and BMI 19-40kg/m^2 were included. However, those individuals with renal impairment by causes other than diabetes, significant co-morbidities, pregnancy, lactation and hypersensitivity or use of thiamine-containing supplements were excluded.

In total 100 patients were screened. Eligible patients were included after written informed consent was received. The trial was approved by the Institutional medical ethics committee. After initial examination and applying exclusion criteria, 20 cases were excluded. Patients were randomized to oral thiamine 100mg three times daily (Group A) or placebo for 12 weeks (Group B) with an 8 week follow up period. Participants were evaluated at baseline and after 12 and 20 weeks for assessment of consistent effect of thiamine. From group A, 4 patients and group B, 3 patients were excluded due to loss to follow up in first or second visit Finally, in group A 36 patients and group B 37 patients were included in the study.

Each time 24-hour urine and blood samples were collected from each patient for urine albumin excretion (UAE) in 24 hours, plasma thiamine, glucose, HbA1C, lipid profile, serum creatinine and glomerular filtration rate (GFR). All laboratory measurements were performed according to standard procedures. Thiamine concentration was measured in whole blood and plasma by high performance liquid chromatography.

STATISTICAL ANALYSES:

The collected data was entered in MS excel and analysed using SPSS, version 10.0. Variables with normal distribution are presented as means ± SD. while skewed data were presented as median (inter-quartile range). Changes were analyzed by ANOVA for repeated measurements. Results were considered statistically significant with P value < 0.05.

RESULTS:

Mean age was 53.156.02 and 55.006.22 in control and study group respectively while duration of diabetes was 8.783.12 and 9.804.13 years in control and study group. Mean BMI was 27.962.22 in control and 26.113.56 in study group.

Comparison between study and control group in baseline characteristics and results at 12 and 20 weeks are shown in Table1. There was no significant difference in any clinical, biochemical variables at baseline between study and control group.

In patients receiving thiamine therapy decreased median urine albumin excretion was observed in comparison to patients receiving placebo. Although there was no significant effect of thiamine supplementation on glycaemic controls.

Change in UAE between baseline and 12 weeks was – 27mg/24h in the study group and – 8mg/24h in the control group.Total cholesterol was also found to have reduced by thiamine therapy. Similarly, the therapy also reduced LDL but the changes were not consistent after 8 weeks washout period.

DISCUSSION:

In present study, 12 weeks treatment with high dose thiamine resulted in decrease in 24h UAE. Thus, thiamine derivatives provide protective effects in early diabetic nephropathy.

These findings were found similar to those of a pilot study of 40 patients with type2 diabetes in which 12 weeks of 300mg/day of thiamine resulted in a significant decrease in UAE by 17.7mg/24h[11]. In that study, baseline UAE was 44mg/24h in the thiamine and 51mg/24h in the placebo group which is approximately three times lower than in our study.

It is important to realise that thiamine is supposed to antagonize detrimental effects of hyperglycaemia. Yet, in two large intervention studies, it took years of lowering A1C before a difference in UAE was found between strict metabolic control and standard therapy[12,13]. Our study may therefore have been too short to demonstrate the effect of thiamine.

Thornalley et al in their study showed that accumulation of triosephosphates arising from high cytosolic glucose concentrations in hyperglycemia is the trigger for biochemical dysfunction leading to the development of diabetic nephropathy-a common complication of diabetes associated with a high risk of cardiovascular disease and mortality.[8] Stimulation of the reductive pentosephosphate pathway by high-dose therapy with thiamine and the thiamine monophosphate derivative benfotiamine countered the accumulation of triosephosphates in experimental diabetes and inhibited the development of incipient nephropathy. High-dose thiamine and benfotiamine therapy increased transketolase expression in renal glomeruli, increased the conversion of triosephosphates to ribose-5-phosphate, and strongly inhibit the development of microalbuminuria. This was associated with decreased activation of protein kinase C and decreased protein glycation and oxidative stress-three major pathways of biochemical dysfunction in hyperglycaemia. Benfotiamine also inhibited diabetes-induced hyperfiltration. This was achieved without change in elevated plasma glucose concentration and glycated haemoglobin in the diabetic state[8]. Rabbani et al described that high-dose supplements of thiamine prevent the development of microalbuminuria in experimental diabetes[11].

Conclusion:

The study concludes that high doses of thiamine can prevent diabetic nephropathy in initial stage.

Recommendation:

In conclusion, longer term intervention studies and/ or intervention studies in earlier stages of diabetic nephropathy are necessary to discern whether thiamine has an effect on the development of diabetic nephropathy.

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TABLE – 1 baseline characteristics and changes in parameters and clinical characteristics over time

Parameters	Thiamine (n = 36)					Placebo (n = 37)				
	Baseline	12 weeks	P value	20 weeks	P value	Baseline	12 weeks	P value	20 weeks	P value
Plasma Thiamine (mg/kg)	7.10±7.16	73.32±72.12	<.001	8.58 ±8.50	< 0.02	11.88±6.57	12.22±6.53	<0.9	13.29±6.72	<0.4
Urinary Albumin Excretion (mg/24hr)	128.82 ±57.43	101.37 ±49.08	<0.05	83.58 ±46.27	< 0.001	131.26±45.95	122.73±46.01	<0.5	119.42±46.28	<0.1
Plasma Glucose (mg/dl)	192.98 ±73.87	170.21 ±47.70	< 0.1	166.17 ±49.18	< 0.001	145.75±30.77	137.68±25.95	<0.4	140.34±21.38	<0.6
Glycated Haemoglobin (%)	8.42 ±1.30	8.10 ±1.19	< 0.4	7.97 ±1.11	< 0.1	8.07±0.78	7.86 ±0.68	<0.5	7.81±0.63	<0.1
Total Cholesterol (mg/dl)	209.74 ±47.84	193.87 ±45.51	< 0.2	189.44 ±34.88	< 0.001	209.75±46.17	195.0±38.47	<0.2	191.74±35.86	<0.1
Low Density Lipids (mg/dl)	129.73 ±39.36	121.26 ±37.08	< 0.2	118.66 ±33.08	< 0.05	133.48±17.19	126.65±16.81	<0.1	126.95±17.39	<0.2
High Density Lipids (mg/dl)	44.79 ±11.64	38.68 ±13.20	< 0.05	42.25 ±5.95	< 0.1	47.28±12.12	47.14±8.91	<0.9	47.45±9.17	<0.5
Triglycerides (mg/dl)	135.77 ±35.19	130.11 ±29.73	< 0.5	128.94 ±33.51	< 0.02	151.83±29.62	146.11±25.44	<0.4	144.82±23.60	<0.1
Blood Urea (mg/dl)	36.60 ±13.02	35.13 ±12.49	< 0.8	34.70 ±11.53	< 0.1	45.83±9.42	45.68±9.03	<0.9	44.55± 8.79	<0.5
Serum Creatinine (mg/dl)	1.20 ±0.52	1.19 ±0.44	< 0.9	1.15 ±0.42	< 0.2	1.24±0.30	1.22±0.21	<0.9	1.21±0.26	<0.4
Glomerular Filtration Rate (ml/min)	70.68 ±21.72	70.02 ±19.64	< 0.9	72.18 ±21.53	< 0.5	64.51± 11.55	64.81±12.42	<0.9	66.21±11.18	<0.5

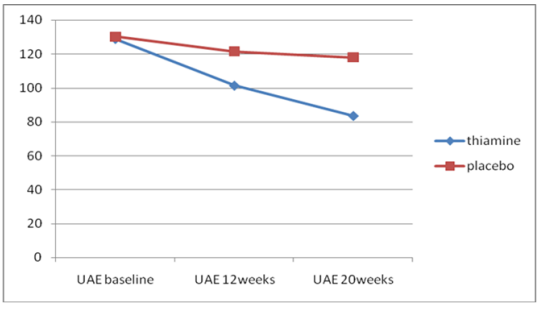

Figure 1: Changes in UAE between baseline and control group

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