

EFFECTIVENESS OF THE NEPHRO ABHAYA (A PLANT BASED FORMULATION MANUFACTURED BY SDM PHARMACY) ON GLOMERULAR FILTRATION RATE IN PATIENTS OF CHRONIC DIABETIC NEPHROPATHY

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Article Received on
25 Feb. 2019,

Revised on 14 March 2019,
Accepted on 03 April 2019

DOI: 10.20959/wjpr20196-14751

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ABSTRACT

Objective: To investigate whether the medication with the plant based formulation Nephro abhaya is effective in improving the glomerular filtration rate in patients suffering from morbidity of basti marma / diabetic nephropathy thus improving the life expectancy of patients.

Design: Study Type - Interventional; Allocation - Randomized; Endpoint Classification - Efficacy Study; Intervention Model - Parallel Assignment; Masking: double blind (Subject, Investigator,); Primary Purpose – Treatment. **Setting:** 100 patients suffering from diabetic nephropathy attending the out patient department of Sri Dharmasthala Manjunatheshwara Ayurveda hospital, Udupi during the period January 2016 to January 2018. **Participants:** 97 patients with diabetic

nephropathy were randomly assigned 1:1 to oral administration of Nephro abhaya (n=50) or placebo (n=47). The randomization sequence was done by computer generated permuted block randomization with block size of 6 and is concealed using sealed sequentially numbered drug containers. **Main outcome measures:** Primary outcome measures - Cystatin c, eGFR, and microalbuminuria. Secondary outcome measures - serum creatinine, blood urea and HbA1c. **Results:** the initial value of Cystatin c in Nephro abhaya group at base line was 1.331 (\pm SE 0.0355) and which reduced 1.160 (\pm SE0.0355) after the medication. The initial mean value of eGFR in Nephro abhaya group was 56.693 ml/minU.73m² (\pm SE 2.152) that

improved to 69.739 ml/minU.73m² (\pm SE2.902) following medication thus recording an improvement to the tune of 13.383 ml/minU.73m². The mean value of microalbuminuria at base line in Nephro abhaya group was 92.420 mg/dl (\pm SE 14.021) that came down to 53.360 mg/ dl (\pm SE8.494) after 96 days of medication thus recording a mean reduction of 39.06 mg/ dl. Also this change was statistically significant as analyzed by paired t test showing p = 0.019. Conclusion: Nephro abhaya is effective in reducing the Cystatin c and improving the eGFR with out elevating the blood sugar level. The serum creatinine and blood urea level is also improved by the medication with Nephro abhaya. The observed improvement in the renal function, point towards the requirement of continuing the same for the longer duration for improving the life of ailing kidney.

Trial registration: RGU:R&D:Res.Wing:2014-15 DATED:13-03-2015

KEYWORDS: Prameha, Nephro abhaya, morbidity of basti marma, diabetic nephropathy.

INTRODUCTION

Santarpana nidana is characterized by excessive consumption of the food in combination with lack of physical activity. This, in turn, predisposes to the plethora of disease that includes prameha, hridroga, sthauilya, vatarakta, gulma and shonitadushti.^[1] Collectively these manifestations are called as metabolic syndrome in the conventional counterpart. Prameha initially begins with the predominant pathology of kapha dosha and eventually progresses to the predominant pathology of vatadosha through the significant vitiation of pitta dosha.^[2] Sequential morbidity of basti marma in a long run is usual and progress to terminal phase.^[3] This state is otherwise known as diabetic nephropathy. In the elderly, diabetic nephropathy today accounts for no less than 46% of chronic kidney disease.^[4] The estimated overall incidence rate of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in India are currently 800 per million populations and 150–200 per million populations, respectively.^[5] It is, therefore, necessary to identify patients with CKD at early stages, in particular, those with the greatest risk for CKD progression. Intensification of the treatment in those patients might slow the progression of the disease. In early stages of kidney disease, early detection is the key since there are typically no signs or symptoms and the disease is treatable and reversible. The glomerular filtration rate (GFR) is an important index of renal function in health and disease.^[6] With this understanding, this study is taken to evaluate the therapeutic effect of Nephro abhaya in patients suffering from pramehaja basti marmabhighata^[7] / diabetic nephropathy.

METHODS

Study design: This randomized placebo controlled clinical trial with blinding of patients and assessors was conducted at Sri Dharmasthala Manjunatheshwara Ayurveda hospital. All participants were provided written informed consent.

Patients, randomization, and treatment

Type II DM patients of both sex of age between 40 to 70 years with the history of more than five years of illness having $eGFR \leq 80\text{ml/min/1.73 m}^2$ were eligible for the study. Type II DM patients having thyroid dysfunction, under Corticosteroid therapy, cigarette smokers, elevated CRP and CBC counts were excluded from the study. The eligible patients were randomly allocated in a 1:1 ratio to Nephro abhaya and placebo treatment. The randomized sequence was generated by the computer with block sizes of six. For blinding the allocation was concealed and sealed, The Nephro abhaya and placebo in leha form of identical color and appearance were sealed in 250 g opaque containers. 6 bottles were given the same number and the numbering is made as per the randomization. The patients allocated to the Nephro abhaya group received a total of 6 containers of Nephro abhaya having same number. Similarly the patients of the placebo group received relevant placebo medicines. Participants received Nephro abhaya or placebo in a dose of 12 g twice daily before food for 96 days. All patients tolerated the dose very well and recorded no side effects.

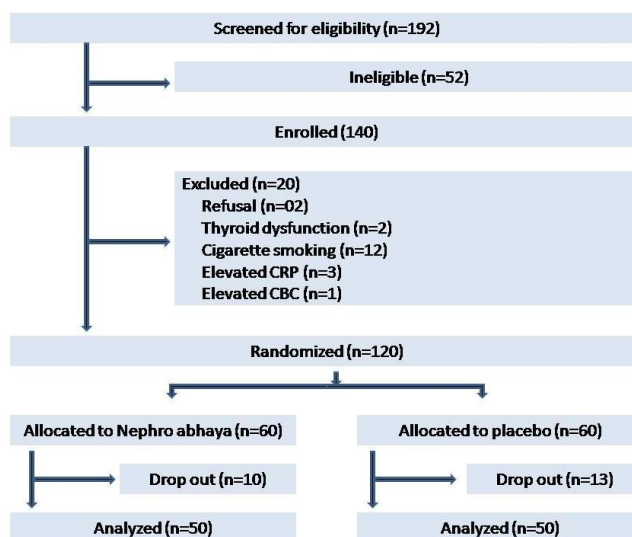


Fig. 1: Participant flow diagram.

Nephro abhaya: This is a Poly Herbal Ayurveda proprietary Medicine in Pharmaceutical Confectionary form. For the study the medicine is prepared at Sri Dharmasthala Manjunatheshwara Ayurveda pharmacy Udupi. Each 12 g of the Nephro Abhay is prepared

from – Dashamoola - Bilwamoola (*Aegle marmelos*), Agnimantha (*Clerodendrum phlomidis*), Shyonaka (*Oroxylum indicum*), Gambhari (*Gmelina arborea*), Patala (*Stereopermem suaveolens*), Shaliparni (*Desmodium gangeticum*), Prashnaparni (*Uraria picta*), Bruhati (*Solanum indicum*), Kantakari (*Solanum xanthocarpum*), Gokshura (*Tribulus terrestris*), Varuna (*Crteava nurvala*), Ushira (*Vetivera zizinooides*), Pashana bheda (*Berginia ligulata*), Punarnaava (*Boerhavia diffusa*), Guda (Jaggery), Haritaki (*Terminalia chebula*), Shunthi (*Zingiber officinalis*), Pippali (*Piper longa*), Maricha (*Piper nigrum*), Guduchi (*Tinospora cordifolia*), Gokshura (*Tribulus terrestris*), Ela (*Elattaria cardamomum*), Twak (*Cinnamomum zeylanicum*), Patra (*Cinnamomum tamala*), Ghrita (Clarified butter), Madhu (Honey). About the procedure Drugs from Dashamoola to Punarnava - are coarsely powdered and Chaturthavashesha Kashaya is prepared. Avaleha Paka is prepared by adding Jaggery to the above prepared Kashaya. When symptoms of proper paka are obtained, Prakshepaka dravya (comprising of drugs from Haritaki to Patra – finely powdered) - are added, stirred thoroughly and cooled. Ela and Honey is added to the avaleha when the mixture has sufficiently cooled down and packed for further use.^[8]

Procedures and outcomes

Primary Outcome Measures were changes in eGFR, microalbuminuria and Cystatin c after 96 days of administration of medicine or placebo. The value of eGFR expressed as % was measured using the MDRD equation in both groups at baseline and after 96 days following the intervention is recorded. The value of proteinuria was expressed in g/24hrs and was measured at baseline and compared to value at 96 days in both study groups. The value of Cystatin c was expressed as ratio and is compared from the base value to the value at 96 days Serum creatinine blood urea and HbA1c were the secondary outcome measures in both the arms. The HbA1c was recorded as % and average glucose level is expressed as g/dl is measured at baseline and is compared to the value at 96 days. The serum creatinine value is recorded as g/dl at base line and after 96 days. Similarly the value of blood urea expressed as g/dl is measured at base line and is compared to the value obtained after 96 days of intervention. The day of randomization and the first dose of leha is defined as day 0 and the day 96 is the time point of primary outcome of the clinical trial.

Statistical analysis

Initially it was planned to recruit 200 patients of diabetic nephropathy. But due to slow recruitment of patients it is decided to stop the recruitment of patients to 120 by October

2017. The data obtained are analyzed using sigma stat (version 3.5). Within the groups the data were tested reporting mean median minimum and maximum values, standard deviation as well as standard error. The continuous variables of primary outcome measure of Cystatin c, eGFR and microalbuminuria and the secondary outcome measures of Serum creatinine blood urea and HbA1c were compared for any change following treatment within the groups by adapting the paired t test and between the groups by the method of unpaired t test.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. We plan to disseminate the results of the research to all the scientific community, including trial participants.

RESULTS

120 patients included in the trial were recruited during the period from January 2016 to October 2017 from the OPD of Sri Dharmasthala Manjunatheshwara Ayurveda hospital Udupi. 60 each patients were randomly allocated into Nephro abhaya and placebo group. These patients received the medication as per the allocated group. 50 (83%) patients completed the study and follow-up until day 30 was complete in all these patients. 47 (78%) of patients completed the study in placebo group including 30 days of follow-up period.

Mean age of the patients was 61.22 years (SD±5.835) in Nephro abhaya group and 59.319 years (SD±5.876) in placebo group (Table 01). The mean duration of the diabetes mellitus was 16 years. Among the 97 patients 59% were men, 85% were married, 58% were Hindu, 38% had intermediate education, 27% were dependent upon clerical job, % were of lower middle class socioeconomic state, 39% had semi vegetarian diet, 43% of patients recorded moderate physical activity (Table 02).

Table 01: Age of 97 patients of diabetic nephropathy.

Profile	group	Mean	±SD	±SE	Max	Min	Median
AGE	NA	61.220	5.835	0.825	69.0	45.0	62.0
	PL	59.319	5.876	0.857	68.0	45.0	59.0

Table 02: Patient demographics.

Sl no	Profile	Category	Subjects					
			Nephro abhaya		Placebo		Total	
			No	%	No	%	No	%
1	Gender	Male	26	52	31	65	57	59
		Female	24	48	16	35	40	41
2	Marital status	Single	00	00	00	00	00	00
		Married	43	86	39	83	82	85
		Widowed	06	12	08	17	14	14
		Divorcee	01	02	00	00	01	01
3	Religion	Hindu	29	58	28	60	57	58
		Muslim	09	18	08	17	17	18
		Christian	07	14	09	19	16	16
		Jain	03	06	02	04	05	05
		others	02	04	00	00	02	02
4	Educational status	Postgraduate	05	10	05	11	10	10
		Graduate	10	20	12	26	22	23
		Intermediate	18	36	19	40	37	38
		High school	09	18	08	17	17	18
		Middle school	06	12	02	04	08	08
		Primary school	02	04	01	02	03	03
		Literate	00	00	00	00	00	00
	Occupation	Profession	04	08	03	06	07	07
		Semi-profession	06	12	06	13	12	12
		Clerical, Shop -owner	14	28	12	26	26	27
		Skilled worker	10	20	09	19	19	20
		Semi-skilled worker	11	22	09	19	20	21
		Unskilled worker	03	06	05	11	08	08
		Unemployed	02	04	03	06	05	06
5	Socio-economic class	Upper	05	10	8	17	13	13
		Upper middle	18	36	15	32	33	34
		Lower middle	20	40	21	45	41	42
		Upper lower	05	10	1	2	6	6
		Lower	02	04	2	4	4	4
6	Diet	lacto vegetarian	18	36	15	32	33	34
		lacto-ovo vegetarian	4	8	4	9	8	08
		Semi-vegetarian	20	40	18	38	38	39
		Non-Vegetarian	8	16	10	21	18	19
7	Physical Activity	Inactive	00	00	00	00	00	00
		Low	15	30	16	34	31	32
		Medium	20	40	22	47	42	43
		High	15	30	09	19	24	25

Comparison of baseline values between the groups

The mean Cystatin c at base line was 1.331 mg / dl (SE \pm 0.0361) in Nephro abhaya group and the same in placebo group was 1.214 mg / dl (SE \pm 0.0299). when the values are

compared between the groups at base line by unpaired t test the change observed was statistically significant with $p = 0.014$. The mean eGFR at base line in Nephro abhaya was 56.69 ml/minU.73m² (SE ± 2.152) and the same in placebo group was 63.18 ml/minU.73m² (SE ± 1.998), when compared with unpaired t test the meager change observed in eGFR is statistically insignificant with $p = 0.030$. The base line mean value of microalbuminuria in the Nephro abhaya group was 92.42 mg/dl (SE ± 14.02) and the same in placebo group was 53.36 mg/dl (SE ± 8.494). by the method of unpaired t test when baseline values of microalbuminuria was compared it showed statistically significant change with $p = 0.019$.

In the Nephro abhaya group the base line mean values of serum creatinine was 1.119 (\pm SE 0.0466) and the same in the placebo group was 1.105 (\pm SE 0.0449). When the mean values are compared at the base line there was no significance in the change observed between the group with $p = 0.822$. In regards to the blood urea the baseline mean value in the Nephro abhaya was 27.83 mg/dl (\pm SE 1.141) and the same in placebo group was 28.86 mg/dl (\pm SE 1.133). Also The difference in the mean values of the two groups is not great enough to reject the possibility that the difference is due to random sampling variability. There is not a statistically significant difference between the Nephro abhaya and placebo groups ($P = 0.522$). The mean HbA1c before the treatment in the Nephro abhaya was 9.100% (\pm SD 0.314) and the same in place group was 7.175% (\pm SD 0.214). The difference the mean HbA1c values between group when compared by the unpaired t test it was revealed that the change is statistically significant (Table 03).

Table 03: Comparison of baseline values between the groups.

Outcome (range)	Group (N)	Mean	\pm SD	\pm SE	Max	Min	Median	T*	P
C ystatin c (mg/dl)	NA(50)	1.331	0.256	0.0361	1.824	1.010	1.240	2.492	0.014**
	P(47)	1.214	0.205	0.0299	1.799	0.964	1.264		
eGFR (ml/minU.7 3m ²)	NA(50)	56.69	15.22	2.152	90.400	33.520	58.600	2.20	0.030***
	P(47)	63.18	13.70	1.998	84.68	34.03	64.240		
Micro albuminuri a (mg/dl)	NA(50)	92.42	99.14	14.02	558.00	16.000	56.000	2.383	0.019**
	P(47)	53.36	60.07	8.494	333.00	16.000	26.000		
serum creatinine	NA(50)	1.119	0.319	0.0466	2.000	0.700	1.100	0.225	0.822***
	P(47)	1.105	0.298	0.0449	1.700	0.800	0.950		
blood urea (mg/dl)	NA(50)	27.83	7.82	1.141	41.00	21.00	30.000	0.642	0.522***
	P(47)	28.86	7.52	1.133	48.00	20.00	26.000		
HbA1c	NA(50)	9.100	2.151	0.314	13.000	5.500	8.900	5.00	<0.001**
	P(47)	7.175	1.422	0.214	12.800	5.500	7.100		

* unpaired T Test; ** significant; *** not significant

Treatment effect on Cystatin c and comparison between the groups

Table 04 presents the results of primary outcome measure of Cystatin c. The initial value of Cystatin c in Nephro abhaya group at baseline was 1.331 (\pm SE 0.0355) and which reduced to 1.160 (\pm SE 0.0355) after the medication. This improvement was statistically significant with $p < 0.001$. On the other hand, the baseline value of 1.214 (\pm SE 0.0299) in Cystatin c of placebo group raised to 1.344 (\pm SE 0.0347) after the intervention. The paired t test recorded $p = 0.005$ thus revealing the statistically significant change after the intervention. Thus definite improvement was recorded in Nephro abhaya group. Further the analysis of statistical significance between the groups recorded significance with $P < 0.001$ confirming the improvement obtained by the medication with Nephro abhaya.

Treatment effect on eGFR and comparison between the groups

The initial mean value of eGFR in Nephro abhaya group was 56.693 ml/minU.73m² (\pm SE 2.152) that improved to 69.739 ml/minU.73m² (\pm SE 2.902) following medication thus recording an improvement to the tune of 13.383 ml/minU.73m². Paired t test also indicated statistically significant improvement with $p < 0.001$. Contrary to this the baseline mean values of eGFR in placebo group was 63.175 ml/minU.73m² (\pm SE 1.998) and the same came down to 54.792 ml/minU.73m² (1.945) following placebo treatment. This change following medication was statistically significant with $p = 0.003$. When the response was compared between the groups by the method of unpaired t test the change observed between the groups was not due to chance factor as $p < 0.001$ thus confirming the improvement in the eGFR by medication with Nephro abhaya (Table 04).

Treatment effect on microalbuminuria and comparison between the groups

The mean value of microalbuminuria at baseline in Nephro abhaya group was 92.420 mg/dl (\pm SE 14.021) that came down to 53.360 mg/dl (\pm SE 8.494) after 96 days of medication thus recording a mean reduction of 39.06 mg/dl. Also this change was statistically significant as analyzed by paired t test showing $p = 0.019$. Contrary to this mean increase of microalbuminuria to the tune of 38.936 mg/dl was recorded in placebo group from the baseline value of 54.064 mg/dl (\pm SE 9.004). This increase in microalbuminuria was also statistically significant with $p = 0.028$. More to add the improvement in the Nephro abhaya group was statistically significant in comparison to the Nephro abhaya group as showed by the unpaired t test with $p = 0.021$ (Table 04).

Treatment effect on serum creatinine and comparison between the groups

The baseline mean value of serum creatinine in Nephro abhaya was 1.119 mg /dl (\pm SE 0.0466) that came down to 1.055 mg /dl (\pm SE0.0387). However the improvement observed to the tune of 0.0638 mg /dl could not be substantiated by statistical significance by the paired t test. Contrary to this the initial mean value of serum creatinine was 1.105 mg /dl (\pm SE0.0449) and which increased to 1.175 mg /dl (\pm SE0.0514) following 96 days of intervention in placebo group; also this could not be substantiated by statistical significance test. When the change in the two groups were compared by the unpaired t test, it was revealed that the change may be due to chance factor as the p value was 0.064. (Table 04).

Treatment effect on blood urea and comparison between the groups

In the Nephro abhaya group the mean baseline value of serum creatinine was 27.830 mg / dl (\pm SE 1.141) that reduced to 25.149 mg / dl (\pm SE0.878) following medication with Nephro abhaya. This minimal change following treatment is statistically insignificant with $p = 0.066$ and may be due the chance factor. On the other hand the increase of 2.591mg/ dl in the creatinine level was observed in the placebo group from the initial mean score of 28.864 mg / dl (\pm SE1.133). Also statistical significance can be proved by the paired t test. More to add the minimal change observed between the group is statistically significant as analyzed by unpaired t test with p value <0.001 (Table 04).

Treatment effect on HbA1c and comparison between the groups

The mean HbA1c value was 9.100% (\pm SE0.314) in Nephro abhaya that increased to % 9.411 (\pm SE0.356) after the 96 days of medication. Also this change is not great enough to reject the possibility that the difference is due to random sampling variability as the p value =0.514. On the other hand the initial mean value of HbA1c in placebo group was 7.715% (\pm SE0.214) and which raised to 7.607% (\pm SE0.174) following placebo treatment again this change is also statistically insignificant. The change in two groups when compared reveals statistical significance with $p <0.001$ (Table 04).

Table 04: Treatment effect and comparison between the groups.

Outcome	GROUP	Mean value		BT-AT	With in group*		Between group**	
		BT (\pm SE)	AT (\pm SE)		T	P	T	P
Cystatin c (mg/dl)	NA(50)	1.331 (0.0361)	1.160 (0.0355)	0.172	3.388	0.001	3.713	<0.001
	P(47)	1.214 (0.0299)	1.344 (0.0347)	-0.131	-2.852	0.005		
eGFR (ml/minU.73m2)	NA(50)	56.693 (2.152)	69.739 (2.902)	13.045	-3.611	<0.001	4.224	<0.001
	P(47)	63.175 (1.998)	54.792 (1.945)	8.383	3.006	= 0.003		
Micro albuminuria (mg/dl)	NA(50)	92.420 (14.021)	53.360 (8.494)	39.060	2.383	= 0.019	2.348	= 0.021
	P(47)	54.064 (9.004)	93.000 (14.888)	38.936	2.238	= 0.028		
serum creatinine	NA(50)	1.119 (0.0466)	1.055 (0.0387)	0.0638	1.054	= 0.295	-1.875	= 0.064
	P(47)	1.105 (0.0449)	1.175 (0.0514)	-0.0705	-1.032	= 0.305		
blood urea (mg/dl)	NA(50)	27.830 (1.141)	25.149 (0.878)	2.681	1.862	= 0.066	-3.861	<0.001
	P(47)	28.864 (1.133)	31.455 (1.404)	-2.591	-1.436	0.155		
HbA1c	NA(50)	9.100 (0.314)	9.411 (0.356)	-0.311	-0.655	0.514** **	4.464	<0.001
	P(47)	7.175 (0.214)	7.607 (0.174)	-0.432	-1.565	0.121)		

* Paired t test; ** unpaired t test;

DISCUSSION

In this randomized double blind placebo controlled clinical study 50 patients were treated with Nephro abhaya for 96 days and is found to be effective in improving the eGFR and reducing the level of microalbuminuria in comparison to the placebo treatment. In almost all patients recorded improvement in the eGFR after medication with Nephro abhaya. Zingiber officinale R. rhizome is proved to be effective as carminative, anti-inflammatory, analgesic, antibiotic and antihypertensive. Animal experiments have proved that the ethanol extract of ginger is effective in the treatment of nephropathy induced by Carbon Tetrachloride through scavenging free radicals, improved kidney functions, inhibition of inflammatory mediators, and normalizing the kidney histopathological architecture. Also the literature admits that formulation made from combination of ginger and jiggery is very effective in the treatment of generalized edema. The same is considered in the formulation of Nephro abhaya with the addition of medication that is effective in diabetes mellitus. At the same time it also revealed

that the change in the serum creatinine blood urea and HbA1c is negligible by medication with Nephro abhaya.

Strengths and limitations of this study

Double blind RCT is considered as the gold standard in deriving clinical conclusion. Needless to say this double blind randomized design, with necessary concealment of allocation, blinding therapists and the assessors of outcome measures rules out the any possibility of bias in the result interpretation. The use of very sensitive outcome measures of Cystatin c, and eGFR gives clear picture of the response to the treatment with no any ambiguity of subjective errors in the evaluation. Contrary to this the prompt control of the blood sugar may have additional benefit in improving the GFR, this is not incorporated in the study. Patients with or without proper control of the sugar is included in the study. If the patients sugar is also well controlled along with the intervention with Nephro abhaya will give definitely better response. This need to be considered in further research designs in this regard.

CONCLUSIONS

Nephro abhaya is effective in reducing the Cystatin c and improving the eGFR with out elevating the blood sugar level. The serum creatinine and blood urea level is also improved by the medication with Nephro abhaya. The observed improvement in the renal function, point towards the requirement of continuing the same for the longer duration for improving the life of ailing kidney.

What is already known on this topic

Chronic patients of diabetes mellitus will develop diabetic nephropathy and the risk of the same may be minimized by the prompt control of the blood sugar.

What this study adds

Medication with Nephro abhaya improves the renal functioning in patients suffering from diabetic nephropathy.

Footnotes

We express the thanks to patients participated in the study and the laboratory personnel as well as doctor participants for meticulous data collection. Thanks to Sri Dharmasthala Manjunatheshwara Ayurveda hospital for its organizational support; and the pharmacy for the

production and blinding of the study drugs.

Funding

This study was completed by the funds provided by research chair rajiv Gandhi university of health sciences, Bangalore. Jayanagar 4th T block, Bangalore. Research committee is of university is involved in finalizing the research design and monitoring the research activities. However the research committee in not involved in result analysis plan and publishing of the article.

Ethical approval

This study was approved by the local research ethics committee.

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