Section: Miscellaneous

Original Research Article

A RANDOMIZED COMPARATIVE STUDY OF EFFICACY AND SAFETY OF EPALRESTAT AND METHYLCOBALAMIN IN PATIENTS WITH DIABETIC NEUROPATHY

C Preeth[1], P S Chakkaravarthi[2], S Saravana Kumar[3], V Gowtham[4]

[1]Assistant Professor, Department of Pharmacology, Government Thiruvarur Medical College, Tamil Nadu, India.
[2]Assistant Professor, Department of Cardiology, Government Thiruvarur Medical College, Tamil Nadu, India.
[3]Assistant Professor, Department of Pharmacology, Government Thiruvarur Medical College, Tamil Nadu, India.
[4]Assistant Professor, Department of Community Medicine, Government Thiruvarur Medical College, Tamil Nadu, India.

Received : 30/11/2023
Received in revised form : 29/01/2024
Accepted : 14/02/2024

Keywords:
Diabetes, Neuropathy, Epalrestat, Methylcobalamin.

Corresponding Author:
Dr. V Gowtham,
Email: doc.gowthampkm@gmail.com.

DOI: 10.47009/jamp.2024.6.1.350

Source of Support: Nil,

Conflict of Interest: None declared
Int J Acad Med Pharm
2024; 6 (1); 1771-1777

Abstract

Background: Diabetic neuropathies can lead to wide variety of sensory, motor and autonomic symptoms. Recently Epalrestat and Methylcobalamin are widely used in clinical practice to manage diabetic neuropathy. Hence, this study was undertaken to evaluate the efficacy and safety of Epalrestat with Methylcobalamin in patients with diabetic neuropathy. **Objectives**: To evaluate the efficacy and safety of combined effect of Epalrestat and Methylcobalamin in patients with diabetic neuropathy and to compare with individual effect of Epalrestat and Methylcobalamin in patients with diabetic neuropathy. **Materials & Methods**: Prospective randomized controlled, single blinded, parallel design study, was conducted for a period of one year from March 2021 to February 2022. A total of 165 participants were enrolled in the study. Data was collected and entered in excel and analysed in SPSS using appropriate statistics. **Results**: The overall mean age group of patients was in group A- 54 yrs, group B- 54 yrs and group C- 58 yrs accordingly. The proportion of male patients were high. The BMI and other laboratory parameters showed no statistically significant difference between the groups at each visit. In group A, 4% of patients and 7.8% in group B suffered with gastric discomfort. In group C, 6% suffered with nausea and vomiting. From VAS method, in group C, patients had significant reduction in pain score at 8th week and 12th week of therapy. All three groups had significant reduction in MNSI score by patient and health professional version. **Conclusion**: It was concluded that Combination of Epalrestat and Methylcobalamin treated patients were more efficacious and well tolerated with safety for the management of diabetic neuropathy than monotherapy of Epalrestat and Methylcobalamin. The combination therapy showed faster onset of relief of symptoms in MNSI patient version followed by physician version score and VAS pain intensity score.

INTRODUCTION

Diabetes is a national as well as global epidemic disease in terms of incidence, healthcare costs and overall complications as reported by the Center for Disease Control (CDC).[1] As per recent statistics, nearly 285 million people worldwide (6.6%) in the 20–79-year age group have diabetes in 2010 and by 2030, about 438 million people (7.8%) of the adult population, is actually expected to have diabetes.

The International Diabetes Federation (IDF) estimates the total number of people in India with diabetes to be 50.8 million in 2010, rising to 87.0 million by the year 2030.[2] Globally, as of 2013, an estimated 382 million people found to have diabetes worldwide, with type 2 diabetes in 90% of the cases.[3] This is almost equal to 8.3% of the adult's population, with equal rates occurring in both women and men.[4] Worldwide in 2012 and 2013 diabetes resulted in 1.4 to 5.1 million deaths per year, hence, the 8th leading cause of death.[5] The number of people with diabetes is actually expected to rise to 592 million by 2035.[6] The number of people with diabetes increased from 108 million in

ISSN (O): 2687-5365; ISSN (P): 2753-6556

1980 to 422 million in 2014.[7,8] The global prevalence of diabetes among adults over 18 years of age has actually increased from 4.7% in 1980 to 8.5% in 2014.[7] Diabetes prevalence is increasing more rapidly in middle- and low-income countries.

Diabetes is considered to be a major cause of blindness, heart attacks, kidney failure, stroke and lower limb amputation. In 2014, about 8.5% of adults aged 18 years and older were found to have diabetes. In 2015, diabetes was indicated as the direct cause of 1.6 million deaths and in 2012 high blood glucose was found to be the cause of another 2.2 million deaths. Half of all deaths are because of high blood glucose occur before 70 years of age. WHO projects diabetes as seventh leading cause of death in 2030.[9,10] Healthy diet, doing regular physical activity, maintaining a normal body weight and no tobacco use are effective ways to prevent or delay the onset of type 2 diabetes. Diabetes is treated and its consequences may be avoided or delayed with physical activity, diet, medication and regular screening and treatment for occurring complications.

Epalrestat is actually a carboxylic acid derivative that has the function as aldose reductase inhibitor. Epalrestat is found to have beneficial effects in diabetic neuropathy in many of the controlled clinical trials. In hyperglycemia, Epalrestat significantly dimishes the intracellular sorbitol accumulation by mechanism of an uncompetitive aldose reductase inhibition.

Methylcobalamin is actually the biologically active forms of vitamin B12. It is prescribed for the treatment of peripheral neuropathy, diabetic neuropathy, and used as a preliminary treatment for patients with amyotrophic lateral sclerosis. Unlike cyanocobalamin, Methylcobalamin is found to be active in the spinal fluid. Hence, it is able to heal the damaged nerve cells and helps in restoring the normal functions.

Diabetic neuropathies will result in various sensory, motor and autonomic symptoms. The most common is found to be the symmetrical distal sensory type, which is seen in the feet and it will progress to a complete loss of feeling. It is found to be most prevalent in elderly patients presenting with type 2 diabetes but may be seen in any type of diabetes, at any age beyond childhood.

Currently, Epalrestat and Methylcobalamin are found to be widely used in clinical practice to treat the patients with diabetic neuropathy. Previous studies showed that Epalrestat has a better efficacy and safety profile than Methylcobalamin in the treatment of diabetic neuropathy.[11] However, there are limited studies documenting the role of combination of both the drugs. Hence, this study was undertaken to evaluate the efficacy and safety of drug Epalrestat with Methylcobalamin in patients presenting with symptoms of diabetic neuropathy.

Aims and Objectives

This study was done with an aim to assess and compare the efficacy and safety of Epalrestat with Methylcobalamin in patients presenting with diabetic neuropathy

Objectives

To evaluate the efficacy and safety of combined effect of Epalrestat and Methylcobalamin in patients with diabetic neuropathy and to compare with individual effect of Epalrestat and Methylcobalamin in patients with diabetic neuropathy.

MATERIALS AND METHODS

This study was a prospective randomized controlled, single blinded, parallel design study, conducted in the Department of General Medicine at Government Thiruvarur Medical College and Hospital, Thiruvarur, between March 2021 to February 2022 for a period of 1 year. All the eligible diabetic patients with symptoms of neuropathy were included in the study. All the eligible subjects were recruited into the study consecutively by convenient sampling till the sample size is reached. Sample size was calculated based on previous study results. The other parameters considered for sample size calculation were 5% absolute precision and 95% confidence level. The sample size was calculated using software and found to be 165. Around 55 in each of the group.

Inclusion Criteria

1. Diabetic patients, both type 1 & type 2 with symptoms of neuropathy.
2. Age – 20 to 65 years.
3. HbA1C $\leq$ 9% $\pm$ 0.5% variation in the previous 3 months.
4. Patients who are on continued conventional therapy for treatment of Diabetes Mellitus.

Exclusion Criteria

1. Patients presenting with alcoholic neuropathy.
2. Patients presenting with Foot ulcer.
3. Patients presenting with Carpal tunnel syndrome.
4. Patients presenting with Cerebrovascular sequelae.
5. Patients presenting with hepatic and renal impairment.
6. Patients consuming antiepileptic and anti-depressant drugs.
7. Patients who are on any other medications that will have the effect on the symptoms of neuropathy

Based on the Inclusion and Exclusion criteria, about 165 diabetic patients with symptoms of neuropathy were randomly divided into three groups by block randomization method, i.e., Group A (55 patients) were given 150 mg of Epalrestat per day, Group B (55 patients) were given 1500 mcg of Methylcobalamin per day, Group C (55 patients) were given 150 mg of Epalrestat + 1500 mcg Methylcobalamin per day. They were treated with drugs for a period of 12 weeks and they were followed up on 4, 8 & 12 weeks. A total of 165 diabetic patients with neuropathy symptoms were

ISSN (O): 2687-5365; ISSN (P): 2753-6556

enrolled in our study program and followed parallel design of RCT.

The study was presented in the institutional human ethics committee and got the approval (No 007/IEC/GTMC/2021). Informed written consent was obtained and only those who are willing to sign the informed consent were included. The risks and benefits involved and the voluntary nature of participation were actually well explained to the participants before obtaining the consent. The confidentiality of the participants was maintained.

Data collection tools: All the relevant parameters were documented in a structured study proforma. The basic demographic details of the patients were observed for age, sex, family history. The vital parameters like blood pressure, weight & height were recorded. The patients were monitored for their blood glucose level, both fasting and postprandial and glycosylated hemoglobin at the initial visit to the hospital and after 3 months of treatment.

Efficacy Parameters

1. Visual Analog Scale of pain,[12] intensity based on 10 point scoring method - mild, moderate, severe, very severe, worst.

Score	Symptoms
0	No pain
1-2	Mild pain
3-4	Moderate pain
5-6	Severe pain
7-8	Very severe pain
8-10	Worst pain

2. Loss of sensation, burning sensation, numbness, muscle cramps, spontaneous pain, weakness, dizziness, loss of sensation of heat & cold assessed by Michigan neuropathy screening instrument score method. (Patient Version and Physician Version)
3. HbA1C at baseline & at the end of treatment.

Safety Parameters

1. Adverse events namely skin rash, hot flushes, etc.,
2. FBS value at baseline & at the end of treatment.
3. PPBS value at baseline & at the end of treatment.
4. LFT value at baseline & at the end of treatment.
5. RFT value at baseline & at the end of treatment.
6. CBC value at baseline & at the end of treatment.

Statistical Methods

Descriptive analysis was made using frequency and proportion for categorical variables and mean, standard deviation for continuous variables. The mean values were analysed between and within the study groups using ANOVA test. Categorical outcomes were analysed between study groups using the Chi-square test. P-value < 0.05 was considered statistically significant. IBM SPSS was used for statistical analysis.

RESULTS

About 165 were enrolled based on the inclusion and exclusion criteria. The recruited patients were randomized into 3 groups, A, B and C consisting of 55 patients each. Patients of group A received Epalrestat, group B received Methylcobalamin, group C received Epalrestat combined with Methylcobalamin. About 3 patients from group A, 2 from group B and 3 from group C were withdrawn from study because of complications and abnormal lab parameters. About 3 patients from group A, 2 from group B and 2 from group C were failed to follow up. Hence the number of patients completed study is 49 in group A, 51 in group B and 50 in group C.

The results are discussed below

The overall mean age group of patients were like in group A- 54 years, group B – 54 years and group C-58 years accordingly. The proportion of male diabetic neuropathy patients were high [group A (65%), group B (55%), group C (68%)] compared to female population in our study. [Table 1]

The BMI and FBS of all the groups of patients were observed at baseline, at 1st month, at 2nd month and 3rd month. The BMI and FBS did not have any statistically significant difference between the groups at each visit. The other laboratory parameters like PPBS, HbA1c, AST, ALT, serum albumin, serum total bilirubin, serum creatinine, serum urea, urine albumin and urine sugar were observed at baseline and 3rd month. All those parameters did not show any statistically significant difference between the groups at each visit. [Table 2 & 3]

In group A, 4% of patients suffered with gastric discomfort. In group B, 7.8% of patients suffered with gastric discomfort. In group C, 6% of patients suffered with nausea and vomiting. [Table 4]

From VAS method, in group C patients had significant ($p<0.001$) reduction in pain score (3.09) at 8th week of therapy while compared to baseline and very good reduction in pain score (1.49) was observed at 12th week of therapy. All three groups had significant ($p<0.001$) reduction in MNSI score by patient version, especially group C were shown to have very good reduction. Similarly, all three groups had significant ($p<0.001$) reduction in MNSI score by health professional version, especially group C were shown to have very good reduction. [Table 5]

In combination therapy, the majority of the patients had absence of muscle cramps, prickling feelings, burning pain especially at 12 weeks of therapy, though they were having presence of the same neurological problems at base line of therapy.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 1: Basic details of Participants

Parameter	Category	Group A (n=49)		Group B (n=51)		Group C (n=50)		p value
		N	%	N	%	N	%	
Age	Mean	54 years		54 years		58 years		0.84# (A)
	Standard Deviation	14 years		11 years		12 years		
Gender	Males	32	65%	28	55%	34	68%	0.77# (C)
	Females	17	35%	23	45%	16	32%	
#p >0.05 – There is no significant difference among the two groups C – Chi square test, A – ANOVA								

Table 2: BMI and Lab investigations of Participants

BMI							
Visit	Group A (n=49)		Group B (n=51)		Group C (n=50)		p value*
	Mean	S.D	Mean	S.D	Mean	S.D	
Baseline (1)	25.49	2.34	25.65	2.52	25.78	2.89	0.750 (A)
1st month	25.57	2.47	25.71	2.49	25.82	2.97	0.767 (A)
2nd month	25.51	2.38	25.63	2.76	25.69	2.67	0.762 (A)
3rd month	25.50	2.65	25.59	2.65	25.62	3.12	0.625 (A)
FBS							
Baseline (1)	161.17	14.76	165.53	13.51	164.18	12.37	0.263 (A)
1st month	160.76	13.34	165.37	14.52	163.41	14.28	0.262 (A)
2nd month	159.89	15.21	163.16	15.26	163.56	14.72	0.416 (A)
3rd month	157.87	14.29	161.59	14.47	162.892	13.67	0.191 (A)
PPBS							
Baseline	271.22	21.34	275.24	13.82	274.18	12.19	0.442 (A)
End of Study	270.34	18.41	273.39	14.84	270.45	14.25	0.552 (A)
HbA1c							
Baseline	7.67	0.34	7.85	0.62	7.76	0.69	0.293 (A)
End of Study	7.56	0.51	7.78	0.74	7.56	0.69	0.154 (A)
AST							
Baseline	33.78	19.27	32.28	17.74	33.36	13.73	0.90 (A)
End of Study	33.13	11.65	32.02	12.89	33.13	12.46	0.69 (A)
ALT							
Baseline	34.56	9.37	35.41	10.64	35.75	11.5	0.85 (A)
End of Study	33.13	13.65	35.12	10.89	34.59	9.46	0.69 (A)
Serum albumin							
Baseline	3.26	0.37	3.18	0.45	3.2	0.34	0.56 (A)
End of Study	3.29	0.52	3.22	0.49	3.25	0.57	0.80 (A)
Serum Total Bilirubin							
Baseline	0.76	0.08	0.73	0.07	0.74	0.07	0.51 (A)
End of Study	0.75	0.07	0.74	0.06	0.75	0.05	0.41 (A)
Serum creatinine							
Baseline	0.89	0.08	0.91	0.1	0.93	0.18	0.08 (A)
End of Study	0.86	0.09	0.89	0.07	0.91	0.08	0.47 (A)
Serum urea							
Baseline	16.23	0.17	16.75	0.12	16.54	0.18	0.33 (A)
End of Study	16.10	0.9	16.70	0.13	16.48	0.17	0.06 (A)
*p >0.05 – There is no significant difference among the two groups A- ANOVA							

Table 3: Urine Albumin and Sugar of Participants

Urine Albumin		Group A (n=49)	Group B (n=51)	Group C (n=50)	p value*
Baseline	nil	43	45	42	0.801(C)
	trace	6	6	8	
	present	0	0	0	
End of Study	nil	44	46	45	0.630(C)
	trace	4	5	4	
	Present	1	0	1	
Urine Sugar		**Group A (n=49)**	**Group B (n=51)**	**Group C (n=50)**	**p value***
Baseline	nil	43	45	40	0.054(C)
	trace	4	6	9	
	P	2	0	0	
	PP	0	0	1	
End of Study	nil	43	43	46	0.240(C)
	trace	5	7	3	
	P	1	0	1	
	PP	0	1	0	
#p >0.05 – There is no significant difference among the two groups, C – Chi square test					

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 4: Adverse drug reactions

S. No	Adverse drug reaction	Group A (n=49)	%	Group B (n=51)	%	Group C (n=50)	%
01	Diarrhoea	-	0	1	1.9	-	0
02	Erythema	-	0	-	0	-	0
03	Gastric Discomfort	2	4	4	7.8	2	4
04	Head ache	1	2	-	0	-	0
05	Hepatic Dysfunction	-	0	-	0	-	0
06	Hot flush	1	2	1	1.9	2	4
07	Itching	-	0	1	1.9	-	0
08	Nausea & Vomiting	1	2	3	5.9	3	6
09	Skin rash	1	2	-	0	1	2
10	Swelling	-	0	1	1.9	-	0

Table 5: Visual Analog Pain Score (VAS) & MNSI score

VAS		Group A (n=49)	Group B (n=51)	Group C (n=50)
Baseline/ Visit 1	Mean Score	6.39	6.28	6.34
	S.D	0.60	0.59	0.47
Visit 2	Mean Score	4.65	4.75	4.89
	S.D	0.43	0.45	0.39
Visit 3	Mean Score	4.12	3.98	3.09
	S.D	0.42	0.38	0.28
Visit 4	Mean Score	1.92	1.84	1.49
	S.D	0.11	0.13	0.10
p <0.001 – There is a significant difference in VAS among the two groups (ANOVA test)				
MNSI		**Group A (n=49)**	**Group B (n=51)**	**Group C (n=50)**
Baseline/ Visit 1	Mean Score	11	10	11
	S.D	1.63	1.19	1.77
End of 4th week	Mean Score	07	06	05
	S.D	0.58	0.52	0.61
p <0.001 – There is a significant difference in MNSI (by participants) among the two groups (ANOVA test)				
MNSI		**Group A (n=49)**	**Group B (n=51)**	**Group C (n=50)**
Baseline/ Visit 1	Mean Score	7.0	7.5	7.0
	S.D	0.68	0.78	0.64
End of 4th week	Mean Score	2.0	2.5	1.0
	S.D	0.17	0.19	0.92
p <0.001 – There is a significant difference in MNSI (by health professionals) among the two groups (ANOVA test)				

DISCUSSION

Diabetic neuropathies are nerve disorder; it is a common complication of diabetes caused by hyperglycaemia which can damage nerve fibers to whole body. Depends upon the types of nerves involved, which is categorized as peripheral, autonomic, proximal and focal neuropathies. The exact mechanism of diabetic neuropathy remains unknown. Several reports suggested that a variety of molecules are involved in the development of diabetic neuropathy, such as protein kinase C, polyol, aldose reductase, advanced glycation end products, reactive oxygen species, cytokines. Moreover, some risk factors like metabolite, autoimmune, inherited traits and life style, may contribute to the development of diabetic neuropathy. Methylcobalamin has an extended record as a nerve and it has been used in the treatment of neuropathy for a long time. Epalrestat is a relatively newer addition in this category that has gained the acceptance of the healthcare society as an effective treatment option for diabetic neuropathy, potentially preventing or ameliorating long term diabetic complications.[13]

Present study was conducted to compare the efficacy and safety of epalrestat, methylcobalamin alone and epalrestat in combination with methylcobalamin in treatment of patients with diabetic neuropathy. We have evaluated most common diabetic neuropathy complications including pain assessed by VAS scale of pain intensity based on 10 point scoring method, loss of sensation, burning sensation, numbness, muscle cramps, spontaneous pain, weakness, dizziness, loss of sensation of heat & cold assessed by Michigan neuropathy screening instrument score method and HbA1C at baseline & at the end of treatment.

The results of the present study showed combination group and Epalrestat monotherapy group gives very good improvement and comparably moderate improvement respectively in diabetic neuropathy symptoms compared to baseline. All the evaluated neuropathy symptoms showed statistically significant (P<0.001) and (P<0.01) in both groups. Despite the fact that, in combination group symptomatic relief was achieved much earlier with reduction in score values and was better compared to Epalrestat alone.

Improvement in diabetic neuropathy patients was investigated in terms of VAS (Visual analog scale) pain intensity score, MNSI (Michigan neuropathy screening instrument) score and HbA1C levels. In group C significant (p<0.001) reduction in pain score (3.09) was observed at 8th week onwards while compared to baseline and very good reduction in pain score (1.49) was observed at 12th week of

ISSN (O): 2687-5365; ISSN (P): 2753-6556

therapy. All three groups had significant ($p<0.001$) reduction in MNSI score by patient version, especially group C were shown to have very good reduction. Similarly, all three groups had significant ($p<0.001$) reduction in MNSI score by health professional version, especially group C were shown to have very good reduction. The MNSI diabetic patient version score was evaluated on the basis of higher score out of maximum 13 points indicates more neuropathic symptoms as well as MNSI physician version score greater than 2 points out of 10-point scale were considered neuropathic.[14] With respect to HbA1C, both group A & C were shown very slight amount (7.56%) of reductions compared to baseline, which is not merely significant. The demographic profiles were not statistically significant. Blood glucose profiles like FBS, PPBS, HbA1C and BMI were measured before and after study, which also not significant. The serum profiles like AST, ALT, serum albumin and urine albumin & urine sugar were measured before and after study period, but which were not observed any significant difference. Serum urea, creatinine and total bilirubin were measured baseline and end of study, which were showed statistically not significant difference between the groups and within groups at baseline and at the end of study.

The synergistic effect of Epalrestat and Methylcobalamin may be linked to their complementary mechanisms of neuroprotection. Epalrestat helps to prevent neuronal degeneration by reducing the accumulation of toxic sorbitol and decreasing the oxidative stress while Methylcobalamin helps to recover neuronal injury. Methylcobalamin is one of the biologically active forms of vitamin B12. It is used in the treatment of peripheral neuropathy, diabetic neuropathy, and as a preliminary treatment for amyotrophic lateral sclerosis. Unlike cyanocobalamin, methylcobalamin is active in the spinal fluid. Due to this property, it is able to help heal the damaged nerve cells and restores normal functions. In clinical studies, Methylcobalamin showed improvement in the somatic and autonomic symptoms with regression of signs of diabetic neuropathy such as pain and paresthesia.[15,16]

Epalrestat is a carboxylic acid derivative that acts as aldose reductase inhibitor. Epalrestat is proven to have beneficial effects in diabetic neuropathy in many controlled clinical trials. In hyperglycemia, Epalrestat significantly reduces intracellular sorbitol accumulation by an uncompetitive aldose reductase inhibition. Epalrestat improves motor and sensory nerve conduction velocity and subjective neuropathy symptoms in patients with diabetic neuropathy.[13,1718] So this combination of Epalrestat and Methylcobalamin treated patients were more efficacious and well tolerated with safety for the management of diabetic neuropathy than monotherapy of Epalrestat and Methylcobalamin. The combination therapy showed faster onset and quick relief of symptoms. Apart from this as per our observation, in general people with diabetes who smoke and drink alcohol are more likely to develop neuropathy. Hyperglycemia promotes the synthesis of an endogenous protein kinase C activator, diacylglycerol. This excess protein kinase C activation induces ischemia and promotes vascular permeability and thickening of the basement memberane and causes neuropathy.[19-21] So, inactivation of protein kinase C indirectly reduces the risk of diabetic neuropathy.

The wellbeing and safety of both drugs was assessed based on the occurrence of adverse events reported by the patients who received the medicine. All three groups were well tolerated and do not generate any safety concern.

CONCLUSION

From our study, it was revealed that Combination of Epalrestat and Methylcobalamin treated patients were more efficacious and well tolerated with safety for the management of diabetic neuropathy than monotherapy of Epalrestat and Methylcobalamin. The combination therapy showed faster onset of relief of symptoms in MNSI patient version followed by physician version score and VAS pain intensity score. All three groups had no significant difference between baseline and end of study with respect to HbA1C levels. There was no statistically significant change between the groups and within groups at base line and end of study with respect to BMI, FBS, PPBS, AST, ALT, serum albumin, urea, creatinine, total bilirubin, urine albumin and urine sugar.

Conflict of Interest: Nil
Funding Source: Nil.

REFERENCES

1. Keecia DK, Jocelyn DJ, Jessica W. Micro vascular and macro vascular complications of diabetes mellitus. American Journal of Pharmaceutical education, 2005; 69: 1-8.
2. Ramachandran A, Das AK, Joshi SR, et al., Current status of diabetes in India and need for novel therapeutic agents. Journal of the Association of Physicians of India, 2010; 58: 7-9.
3. Melmed, Shlomo, Williams, et al., Textbook of endocrinology (12th ed.). Philadelphia: Elsevier/Saunders: 1371–1435.
4. Vos T, Flaxman AD, Naghavi M, et al., Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study. TheLancet, 2010; 380: 2163–96.
5. The top 10 causes of death Fact Sheet N°310, World Health Organization, October 2013.
6. IDF DIABETES ATLAS (6 ed.), International Diabetes Federation, 2013.
7. John WS, Diana F, Karen LG. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Medicine, 2006; 3(11): e442.
8. Sarwar N, Gao P, Seshasai SR, Gobin R, et al., Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet, 2010; 26 (375):2215-2222.
9. Bourne RR, Stevens GA, White RA, Smith JL, et al., Causes of vision loss worldwide, 1990-2010: a systematic analysis. Lancet, 2013; 1: 339-349.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

10. USRDS annual data report: Epidemiology of kidney disease in the United States. United States Renal Data System. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2014:188–210.
11. Maladkar M., Rajadhyaksha G, Vengataswamy N, Hariharan S., et al., Efficacy, safety, and tolerability of epalrestat compared to methylcobalamine in patients with diabetic neuropathy. International Journal of diabetes in developing countries 2009; 29(1); 28-34.
12. Metapress. A Fast Growing Resource for Young Entrepreneurs. Metapress, https://metapress.com/ (2023, accessed 12 September 2023).
13. Itagaki I, Shimizu K, Kamanaka Y, Ebata K, et al., The effect of an aldose reductase inhibitor (epalrestat) on diabetic nephropathy in rats. Diabetes Research and Clinical Practice, 1994; 25:147-154.
14. Hotta N, Kakuta H, Koh N, Fukasawa H, et al., In-vitro retinal and erythrocyte polyol pathway regulation by hormones and an aldose reductase inhibitor. Diabetes Research and Clinical Practice, 1991; 14: 29-35.
15. Ramirez MA and Boria NL. Epalrestat: an aldose reductase inhibitor for the treatment of diabetic neuropathy. Pharmacotherapy 2008; 28: 646-55.
16. Yaqub BA, Siddique A, Sulimani R. Effects of methylcobalamin on diabetic neuropathy. Clinical Neurology and Neurosurgery. 1992; 94(2):105-11.
17. Sun Y, Lai M.S and Lu CJ. Effectiveness of vitamin B12 on diabetic neuropathy: Systematic review of clinical controlled trials. Acta Neurologica Taiwanica, 2005; 14: 48-54.
18. Dyck PJ, Karnes J, O'Brien PC, Swanson CJ. Neuropathy Symptom Profile in health, motor neuron disease, diabetic neuropathy, and amyloidosis. Neurology, 1986;36:1300-8.
19. Borghini I, Ania LA, Regazzi R, et al., Alpha, beta II,delta and epsilon protein kinase C isoforms and compound activity in the sciatic nerve of normal and diabetic rats. Journal of Neurochemistry, 1994; 62: 686-96.
20. Hempel A, Maasch C, Heintze U, et al., High glucose concentration increase endothelial cell permeability via activation of protein kinase C alpha. Circulation Research, 1997;81:363-71.
21. Mara L. The Polyol Pathway as a Mechanism for Diabetic Retinopathy: Attractive, Elusive, and Resilient. Experimental Diabetes Research, 2007, 1-31.

ISSN (O): 2687-5365; ISSN (P): 2753-6556