

Diabetic Neuropathy- A Chance Toward a Better Treatment

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Diabetic Neuropathy - A Chance Towards A Better Treatment

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Review

HISTORICAL PERSPECTIVE

¹ Diabetic neuropathy is the most important and commonest diabetic complication, afflicting over 50% of all diabetics. Center of Indonesia's data and information informed, during 2011, diabetic neuropathy affects >50% of diabetic patients with amputation numbers ranging from 15-30%. These problems led to a high number of disabilities, declining productivity and huge costs.

¹⁰ Multiple pathogenic of hyperglycemia contribute to diabetic complications. Additional experiments indicate that diabetic neuropathy is not simply the result of nerve cells being damaged directly by hyperglycemia. The clinical manifestations, underlying pathology and aetiology are varied and complex. There remains much debate and controversy to prove effective treatments for diabetic neuropathy.

To uncover these problems, we did some studies in 2007-2015 with the objective to determine a good approach to treat diabetic neuropathy. Since the research about "Correlation among the duration of suffering DM and diabetic neuropathy degree", "Comparison of diabetic neuropathy degree based on the state of diabetes", "Management of ulcus diabeticum - a study of antibiotics and diet counseling effectivity", "Efficacy of diabetic foot exercise in the diabetic neuropathy based on the diabetic neuropathy scale and the diabetic neuropathy examination", "Susceptibility pattern and antibiotic therapeutic effectivity", "Pattern development of diabetic foot", "Pattern of serum levels changes of nerve growth factor, brain derived neurotrophic factor and neurotrophin-3 after performing diabetic foot exercise", and "Diabetic foot exercise induced serum neurotrophin-3 in diabetic neuropathy".

Those studies and some other data shown a peripheral effect of intervention can be a good chance for diabetic neuropathy therapeutic strategies in the future.

Keywords : Diabetes ; Neuropathy ; Diabetic Neuropathy ; Pathogenesis ; Treatment

1. Introduction

Diabetic people suffer much morbidity and premature mortality because of chronic diabetic complications, which include cardiovascular and cerebrovascular disease, retinopathy, and neuropathy¹. Diabetic neuropathy is the most common and important diabetic complication, afflicting over 50% of all diabetics, and is the leading cause of nontraumatic limb amputations with a high number of disabilities, declining productivity and huge costs¹. Indonesia's data and information centers of the Basic Health Research also informed, during 2011, diabetic neuropathy affects more than 50% of diabetic patients with amputation numbers ranging from 15-30%^{2,3}.

Diabetic neuropathies are a heterogeneous group of disorders with different mechanisms. They can be proximal or distal, focal or diffuse, using pathological changes with great impact on the quality of life of the patients. Multiple pathogenic effectors downstream of hyperglycemia contribute to chronic diabetic complications. The findings indicate that the incidence of diabetes neuropathy increases with the duration and severity of disease, and that strict glycemic control can delay its development and progression. Hyperglycemia is known to underlie most, but not all, diabetic complications. The clinical manifestations, underlying pathology, and aetiology of human diabetic neuropathy are varied and complex. There remains much debate and controversy on the pathophysiology of the condition. Some of the interventions clinical trials have failed to prove effective. To date we have no evidence-based and effective treatment(s) for human diabetic neuropathy^{4,5}.

Symptomatic therapy has become available, and better and newer treatment modalities based on etiologic factors are being explored with significant impact on morbidity and mortality. A number of mechanical measures for the treatment of diabetes neuropathy have been examined but it is unclear whether these have salutary effects over and above those of placebo. In addition, there is the suggestion that surgical unentrapment of nerves might make symptoms relieved, but this form of intervention has not yet been endorsed universally. A number of research have been done, but it is unclear whether these treatments are the most effectively. Some treatment approaches can augment current studies and lead to new discoveries to identify more effective therapeutic methods^{6,7,8,9}.

To uncover these problems, we did some studies in 2007 – 2015 with the objective to determine a good approach to treat diabetic neuropathy. Since the research about "Corelation among the duration of suffering DM and diabetic neuropathy degree" (2007), "Comparation of diabetic neuropathy degree based on the state of diabetes" (2008), "Management of ulcus diabeticum - a study of antibiotics and diet counseling effectivity" (2010), "Efficacy of diabetic foot exercise in the diabetic neuropathy based on the diabetic neuropathy scale and the diabetic neuropathy examination" (2013), "Susceptibility pattern and antibiotic therapeutic effectivity" (2014), "Pattern development of diabetic foot" (2015), "Pattern of serum levels changes of nerve growth factor, brain derived neurotrophic factor and neurotrophin-3 after performing diabetic foot exercise" (2015), and "Diabetic foot exercise induced serum neurotrophin-3 in diabetic neuropathy" (2015).

2. Research's Data

2.1. Study-1

We did a research in title "Corelation among the duration of suffering DM and diabetic neuropathy degree" (Aulia M & Wahyuliati T, 2007). We investigated 36 subjects by cross sectional design. The result shown a significant association between long suffering

from diabetes with diabetic neuropathy rates. The longer suffer from diabetes, the more severe degree of neuropathy occurred anyway.

2.2. Study-2

We investigated 64 subject in research “Comparison of diabetic neuropathy degree based on the state of diabetes” (Susanti R. & Wahyuliati T., 2008). We pooled the subject in poorly, moderate, and well controlled of Diabetes mellitus. The study found, the diabetic patients with moderate and poorly controlled of diabetes mellitus more suffer from diabetic neuropathy significantly compared to well-controlled of diabetes mellitus.

2.3. Study-3

We did a prospective cohort study, pre test – post test group design in “Management of ulcus diabeticum - a study of antibiotics and diet counseling effectivity” (Wahyuliati, Inayati H, Dewi A, 2010). We investigated 38 subjects with no significant differences in terms of age, random blood glucose, duration of DM, recurrence rate and duration of ulcer, score of DNS, DNE and wagner.

Clindamycin, cefadroxil, ceftriaxon, amoxicillin, ciprofloxacin and cefotaxime which been used in the study were not influenced significantly effective for the treatment ($p > 0.05$). Only three antibiotics has $RR > 2$, it can be considered effective clinically. That were clindamycin ($RR=2.571$), ciprofloxacin ($RR=2.880$), cefotaxim ($RR=2.306$).

Diet counseling had a significant result to control random blood glucose ($RR= -2,139$; $p.0,032$) and also to reduce the number of ulcus recurrent ($RR= -2,157$, $p.0,047$).

The study concluded Clindamycin, Ciprofloxacin and Cefotaxim could be considered clinically effective. Diet counseling has a significant result to control random blood glucose and reduce the number of ulcus recurrent.

2.4. Study-4

We investigated 26 subjects in research “Efficacy of diabetic foot exercise in the diabetic neuropathy based on the diabetic neuropathy scale (DNS) and the diabetic neuropathy examination (DNE)” (Arif D, Ciputra T, Wahyuliati T., 2013) with a quasi experimental control group design. Twenty six subjects were divided into two groups, 13 subjects in the intervention group and 13 subjects on the control group. The result of statistical calculation by DNS was $p=0,002$ ($<0,05$) at intervention group and control group was $p=0,212$ ($>0,05$) and $NNT = 2$. The results of the statistics calculation for intervention group by DNE was $p=0,004$ ($<0,05$) and for control group $p=0,636$ ($>0,05$). The number needed to treat (NNT) is 2. The study concluded, diabetic foot exercise was able to reduce the degree of diabetic neuropathy were significantly both by diabetic neuropathy scale and the diabetic neuropathy examination.

2.5. Study-5

We did a prospective cohort , pre test – post test random control group design in “Susceptibility pattern and antibiotic therapeutic effectivity” (2014). There were 38 subjects, 26% men and 74% women. No significant differences in terms of age, initial GDS, the DM duration , the ulcers duration, ulcer recurrence rate and baseline score of DNS, DNE and wagner. The proportion of antibiotics which were prescribed including Clindamycin, Cefadroxil , Ceftriaxon, Amoxicillin Ciprofloxacin and cefotaxime (see table 1-4) :

Table 1. List of Antibiotic

Antibiotic	n	%
Clindamycin	5	13.2
Cefadroxil	2	5.3
Ceftriaxon	11	28.9
Amoxicillin	7	18.4
Ciprofloxacin	9	23.7
Cefotaxime	4	10.5
Total	38	100

Tabel 2. The effectiveness of antibiotics based on DNS Score

Antibiotic	DNS		
	RR	95% CI	p
Clindamycin	1,432	-0,8475 – 4,0475	0,245
Cefadroxil	0,511	-4,0475 – 0,8475	0,315
Ceftriaxon	0,028	-1,9960 – 1,11596	0,871
Amoxicillin	0,450	-2,1700 – 1,2557	0,294
Cyprofoxacin	1,800	-1,0094 – 2,2539	0,514
Cefotaxim	0,280	-1,8124 – 2,1124	0,871

Tabel 3. The effectiveness of antibiotics based on DNE score

Antibiotik	DNE		
	RR	95% CI	P
Clindamycin	2,571	-1,0901 – 2,6901	0,210
Cefadroxil	0,961	-2,6901 – 1,0901	0,311
Ceftriaxon	1,800	-1,9275 – 1,8275	0,264
Amoxicillin	1,200	-1,8371 – 2,0970	0,881
Cyprofoxacin	1,808	-1,5045 – 2,3215	1,000
Cefotaxim	2,306	-2,3154 – 2,9564	0,502

Tabel 4. The effectiveness of antibiotics based on Wagner score

Antibiotic	Wagner		
	RR	95% CI	P
Clindamycin	2,291	-1,6200 – 3,0200	0,141
Cefadroxil	1,025	-1,0200 – 1,6200	0,210
Ceftriaxon	0,720	-0,6873 – 1,0146	0,410
Amoxicillin	0,720	-0,5524 – 1,2953	0,410
Cyprofoxacin	2,880	-0,1911 – 3,5689	0,099
Cefotaxim	0,720	-1,0084 – 1,1084	0,410

Tables above shown, antibiotics therapy were not influenced significantly the effectiveness of treatment according to the DNS, DNE and Wagner ($p > 0,05$). The relative risk of each antibiotic therapy were computed and results showed: Clindamycin (RR = 2.571) and Cefotaxim (RR = 2.306) based on DNE scores; Clindamycin (RR = 2.291) and Ciprofloxacin (RR = 2.880) based on Wagner. The RR > 2 can be considered as clinically effective. Cyprofloxacin is the most sensitive antibiotics, followed by Clindamycin and Cefadroxyl as much as 60.5% and 57.8% respectively. Six antibiotics did not significantly effective for diabetic ulcers therapy based on DNS, DNE and Wagner. Clindamycin, Ciprofloxacin and Cefotaxim might be considered clinically effective.

2.6. Study-6

We did a prospective cohort study on "Pattern development of diabetic foot based on the DNS, DNE and Wagner Classification (Wahyuliati T & Inayati H, 2015). Has been

studied 38 subjects, there are 26% men and 74% women. No significant differences in terms of age, initial GDS, the DM duration, the ulcers duration, ulcer recurrence rate and baseline score of DNS, DNE and wagner classification.

The study found a significant correlation between neuropathy variable (DNS and DNE) and angiopathy variable (wagner) with $p < 0,05$. The higher score of DNS correlated with the higher wagner classification ($p 0,042$), and the higher score of DNE correlated with the higher wagner classification ($p 0,037$).

The study concluded a significant correlation between neuropathy and angiopathy variable. The higher score of DNS correlated with the higher wagner classification, and the higher score of DNE correlated with the higher wagner.

2.7. Study-7

We did a true experimental study with randomized pre test – post test control group design on “Pattern of serum levels changes of nerve growth factor, brain derived neurotrophic factor and neurotrophin-3 after performing diabetic foot exercise” (Wahyuliaty T, Pranoto A, Wibowo S., 2015). A total of 36 subjects meeting the inclusion and exclusion criteria were included in the exercise group or the control one with age matched systematic random sampling method.

4 The study found, exercise group had a significant improvement on the score of ABI ($p.0.002$), systolic blood pressure ($p.0.014$), diastolic blood pressure ($p.0.055$), DNS ($p.0.01$), DNE ($p.0.001$). Increase of serum level of NGF ($p.0.157$), decrease of serum level of BDNF ($p.0.059$), and increase of serum level of NT-3 ($p.0.049$).

Control group has a result respectively on ABI ($p.0.131$), systolic blood pressure ($p.0.668$), diastolic blood pressure ($p.0.216$), DNS ($p.1.00$), DNE ($p.0.543$), increase of NGF ($p.0.402$), decrease of BDNF ($p.0.803$), and increase of NT-3 ($p.0.264$).

5 The comparison results of the two groups have significant different on the score of ABI ($p.0.01$), systolic blood pressure ($p.0.01$), diastolic blood pressure ($p.0.01$), DNS ($p.0.01$), DNE ($p.0.01$), increase of NGF ($p.0.04$), decrease of BDNF ($p.0.01$), and increase of NT-3 ($p.0.01$).

The study concluded diabetic foot exercise has a peripheral affect on a clinically significant improvement based on ABI scores, systolic and diastolic blood pressure, DNS and DNE. A significant increase in serum levels of NGF, a significant decrease in BDNF serum levels is as reductive compensation from the influence of peripheral foot exercise work. The most affected Neurotrophin level is NT-3 which is more increased being compared to NGF and BDNF.

2.8. Study-8

We did a true experimental study with randomized pre – post test control trial on “Diabetic foot exercise induced serum neurotrophin-3 in diabetic neuropathy” (2015). A total of 36 subjects meeting the inclusion and exclusion criteria were included in the exercise group or the control one with age matched systematic random sampling method.

4 The result found, exercise group had a significant improvement on the score of ABI ($p.0.002$), systolic blood pressure ($p.0.014$), diastolic blood pressure ($p.0.055$), DNS ($p.0.01$), DNE ($p.0.001$) and increased of serum level of NT-3 ($p.0.04$).

Control group had result respectively on ABI ($p.0.131$), systolic blood pressure ($p.0.668$), diastolic blood pressure ($p.0.216$), DNS ($p.1.00$), DNE ($p.0.543$), and increase of NT-3 ($p.0.264$).

5 The comparison results of the two groups had a significant different on the score of ABI ($p.0.01$), systolic blood pressure ($p.0.01$), diastolic blood pressure ($p.0.01$), DNS ($p.0.01$), DNE ($p.0.01$), and increased of NT-3 ($p.0.01$).

The study concluded, diabetic foot exercise had a peripheral affect on a clinically significant improvement based on ABI scores, systolic and diastolic blood pressure, DNS and DNE, and increase of serum level of NT-3

3. Conclusion

Thus, it can be concluded that in patients with diabetic neuropathy, a peripheral effect on the treatment like diabetic foot exercise has a clinically significant improvement based on ABI scores, systolic and diastolic blood pressure, DNS and DNE. A significant increase in serum levels of NGF, a significant decrease in BDNF serum levels are as reductive compensation from the influence of peripheral exercise foot work. The most affected Neurotrophin level is NT-3 which is more increased being compared to NGF and BDNF.

Therapeutic strategies in the future might consider a peripheral factors to improve diabetic neuropathy, when a systemic approach shown an unsatisfied result. Diabetic foot exercise and other local or peripheral intervention like intra-muscular injection for synthetic NT-3 and ointment can be a chance towards a better treatment.

4. Suggestion

Accordingly, the study suggests (1) clinicians to include appropriate physical exercise suitable for the patients' condition. Low impact workout such as diabetic foot exercise can still be applied, especially in patients with severe conditions. (2) nurses, gymnastics groups, health counselors, and various stakeholders in health care systems to always manage to implement physical exercise including diabetic foot gymnastics in any effort to improve health status. (3) patients and societies to perform actively even the low impact exercise like diabetic foot gymnastics as proven to provide benefits. (4) therapeutic strategies in the future to consider neurotrophic factors particularly NT-3 level given as the least affected by diabetic foot exercise, for instance, an intra-muscular injection for synthetic NT-3 or an ointment.

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