Injection of Subcutaneous Glucose 10% in Small Shots is Effective in Treatment of Diabetic Neuropathic Pain

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ABSTRACT

Objectives: The aim of this study is to show that if subcutaneous glucose 10% 0.5 ml injection around inflamed nerves can relieve diabetic neuropathic pain in comparison to control. Design: Observational cohort prospective study 2 months trial. Materials and Methods: Observational cohort prospective study with the following of 100 patients of type 1 and type 2 diabetes mellitus in 2 groups each group 50 patients, each group 30 males, and 20 females,35 patients with type 2 diabetes and 15 patients type 1 diabetes all have diabetic peripheral neuropathy, the second group is considered as control. Conclusion: Diabetic neuropathy is considered as a great problem affecting most of the diabetic patients with moderate to severe pain. Subcutaneous glucose injection around inflamed nerves is considered as a new option for the treatment of neuropathic pain and muscle pain.

Keywords: Diabetes mellitus, diabetic neuropathy, glucose 10%, pain

INTRODUCTION

Diabetes mellitus is considered as the biggest global burden in the last years. With increasing prevalence due to modern lifestyles with no exercise, reaching more than 400 million cases all over the world, which put a great impact on productivity? The increase in diabetes occurrence is related to increased age, in which more than 20% of peoples over 60 years have diabetes [1].

Diabetes mellitus is one of the most important causes of peripheral neuropathy at this time, which is mostly in the form of distal symmetrical polyneuropathy in more than 90% of patients which may be presented as small fiber damage with a burning sensation or with large fiber damage with numbness [2].

Distal symmetrical polyneuropathy begins distally from the toes and progress proximally in a slow fashion to include the feet then the legs. The most frequent complication is the foot infections, foot ulcers and there is a risk of leg amputation in diabetic patients with diabetic neuropathy [3]. Diabetic neuropathy pain is burning and may lead to an electric
shock sensation [4]. The pain is moderate to severe increasing at night in which may cause insomnia and may lead to low mood and anxiety [5].

It is considered as a great problem as About 30% of diabetic patients suffered pain from peripheral neuropathy which is more common in type 2 diabetes than type 1 [6].

Diabetic neuropathy is considered as a serious problem as it is present in most diabetic patients, and also is present in the prediabetes stage before the occurrence of hyperglycemia [7].

When diabetes mellitus is diagnosed about 7-8% of patients have neuropathy, after 20 years of diabetes, more than 50% of patients have neuropathy. [8].

Diabetic neuropathy is a consequence of the inability to repair nerve damage which leads to sensory loss. Inflammation, ischemia and metabolic factors are responsible for the pathogenesis of diabetic neuropathy [9].

A strong relationship is present between the period of diabetes and diabetic neuropathy [10]. Good glucose control by intensive insulin therapy could prevent diabetic neuropathy in type 1 diabetes [11]. But in type 2 diabetes, it is not evident if strict glucose control could prevent diabetic neuropathy [12].

Diabetic neuropathy takes place due to prolonged hyperglycemia which results in increased glycolysis rate which leads to an increased level of reactive insulin species resulting in damage of cells and impairing mitochondrial function. Also, prolonged hyperglycemia shifting glucose metabolism to the polyl pathway which leads to oxidative stress which increases cytokine levels and decreasing nitric oxide level impacting the endothelial function resulting in hypoxia of nerves [13]. Hyperglycemia cause formation of advanced glycation end products which leads to nerve damage and vascular injury [14].

Treating symptoms of neuropathy is the target of many clinicians and is guided by choosing a safe and effective drug [15].

The pain of diabetic neuropathy can be controlled by systemic FDA approved drugs like pregabalin, Duloxetine, and gabapentin or by topical drugs like capsaicin and lidocaine. Also, some dietary supplement may be used for treating diabetic neuropathy like alpha-lipoic acid and acetyl-L-carnitine [16].

Prolotherapy is considered as a new option for the treatment of neuropathic pain and muscle pain. Glucose as an irritant material may be injected in the site of pain and in the tendons [17]. How glucose control neuropathic pain is a marvelous thing in which glucose hyperpolarize nerves by acting on potassium channels, and so diminishing nociceptive pain fibers transport [18]. Glucose solution is thought to give rise to inflammatory action giving rise to chemical inflammatory mediators including ILGF, EGF, PDGF, TGF-beta and CTGF resulting in stimulation of the healing process [19].

One of the mechanisms proposed to explain the pain-relieving effect of hyperosmolar glucose is blocking vanilloid type 1 receptor permitting the entrance of Ca2+ and Na+. Entrance of sodium result in action potential and nociception calcium entrance leads to the liberation of
substance P and calcitonin gene-related peptide [20], and so preventing entrance of sodium and potassium could decrease neuropathic pain [22].

**MATERIALS AND METHODS**

Observational cohort prospective study with the following of 100 patients of type 1 and type 2 diabetes mellitus in 2 groups each group 50 patients, each group 30 males, and 20 females, 35 patients with type 2 diabetes and 15 patients type 1 diabetes all have diabetic peripheral neuropathy, the second group is considered as control. The ages of all patients are between 20 and 50 years.

The first group was on subcutaneous glucose 0.5 ml per site around subcutaneous nerves in the foot region both on palm and sole, which is repeated every 2 weeks for 2 months.

The aim of the study is to show if subcutaneous glucose 10% has a pain-relieving effect on peripheral diabetic neuropathy pain.

Pain severity was evaluated by using the Visual Analogue Scale (VAS) which is a numerical rating scales, with a straight horizontal line of 100 mm. which is directed from the left with severe pain to the right with no pain. 1-3 = mild pain, 4-6 = moderate pain, 7-10 = severe pain.

The evaluation of neuropathy was done by using the Michigan Neuropathy Screening Instrument (MNSI) after translation to the Arabic language, which consists a 15 self-administered questionnaires and examination lower extremities which comprise inspection and examination of vibratory senses and ankle reflexes. A score which is more than 7 was suggested to be abnormal.

**Inclusion Criteria**

1. Patients 20 years to 50 years with type 1 or type 2 diabetes who have symptoms of symmetrical peripheral neuropathic pain.
2. Female patients are not pregnant.
3. Patient has a pain score of at least 5 on the Visual Analogue Scale (VAS).
4. Patients are on their antidiabetes medication.
5. Patents are not on any medication for peripheral neuropathy.
6. Patient must be able to complete questions on the Michigan Neuropathy Screening Instrument (MNSI).

**Exclusion Criteria**

1. Patient has conditions that could affect the evaluation of painful DPN, or non-diabetic neurologic disorders.
2. Patient has skin conditions in the area affected by the neuropathy that could alter sensation.
3. Patient with history of drug abuse.
4. Patients on any drug for diabetic neuropathy like pregabalin or gabapentin.
5. No side effects were monitored during the period of treatment.

**RESULTS**

Patients group was compared to the control group before and 2 months after treatment of subcutaneous 10% glucose. Analysis of that was done using GraphPad. Paired ‘t’ test was done to analyze pre-post changes within the group and between the 2 groups.
**Table 1:** Patients received sc glucose v/s control on vas scale.

| Table format: | Group A | Group B |
|--------------|---------|---------|
|               | patients on subcutaneous glucose | control |
|               | before | 2 months after | before | 2 months after |
| 1              | Title  | 9         | 1      | 9         |
| 2              | Title  | 8         | 1      | 8         |
| 3              | Title  | 7         | 0      | 6         |
| 4              | Title  | 6         | 0      | 6         |
| 5              | Title  | 6         | 1      | 8         |
| 6              | Title  | 7         | 0      | 8         |
| 7              | Title  | 9         | 0      | 7         |
| 8              | Title  | 8         | 1      | 9         |
| 9              | Title  | 5         | 0      | 7         |
| 10             | Title  | 9         | 0      | 6         |
| 11             | Title  | 6         | 1      | 8         |
| 12             | Title  | 7         | 0      | 8         |
| 13             | Title  | 6         | 0      | 6         |
| 14             | Title  | 8         | 0      | 7         |
| 15             | Title  | 8         | 0      | 6         |
| 16             | Title  | 9         | 0      | 6         |
| 17             | Title  | 9         | 1      | 6         |
| 18             | Title  | 6         | 0      | 6         |
| 19             | Title  | 8         | 0      | 7         |
| 20             | Title  | 9         | 1      | 9         |
| 21             | Title  | 8         | 0      | 6         |
| 22             | Title  | 7         | 1      | 6         |
| 23             | Title  | 7         | 0      | 6         |
| 24             | Title  | 6         | 1      | 8         |
| 25             | Title  | 6         | 0      | 9         |
| 26             | Title  | 8         | 1      | 7         |
| 27             | Title  | 7         | 1      | 7         |
| 28             | Title  | 8         | 0      | 8         |
| 29             | Title  | 9         | 1      | 9         |
| 30             | Title  | 7         | 0      | 7         |
| 31             | Title  | 5         | 0      | 8         |
| 32             | Title  | 5         | 1      | 7         |
| 33             | Title  | 7         | 1      | 6         |
| 34             | Title  | 6         | 0      | 6         |
| 35             | Title  | 9         | 1      | 6         |
| 36             | Title  | 7         | 0      | 7         |
| 37             | Title  | 6         | 1      | 6         |
| 38             | Title  | 6         | 0      | 5         |
| 39             | Title  | 8         | 1      | 6         |
| 40             | Title  | 9         | 1      | 7         |
| 41             | Title  | 9         | 2      | 7         |
| 42             | Title  | 6         | 0      | 8         |
| 43             | Title  | 8         | 1      | 7         |
| 44             | Title  | 7         | 0      | 5         |
| 45             | Title  | 7         | 0      | 6         |
| 46             | Title  | 9         | 1      | 8         |
| 47             | Title  | 9         | 2      | 5         |
| 48             | Title  | 9         | 1      | 8         |
| 49             | Title  | 8         | 0      | 7         |
| 50             | Title  | 9         | 0      | 8         |
Table 2: Patients on sc glucose v/s c on MNSI questionnaire.

| Table format Grouped | Group A on sc glucose | Group B control |
|----------------------|-----------------------|-----------------|
|                      | before | after | before | after |
| 1 Title              | 6      | 2     | 6      | 6     |
| 2 Title              | 7      | 3     | 7      | 7     |
| 3 Title              | 8      | 3     | 8      | 8     |
| 4 Title              | 6      | 2     | 6      | 6     |
| 5 Title              | 6      | 3     | 6      | 6     |
| 6 Title              | 8      | 3     | 8      | 8     |
| 7 Title              | 7      | 2     | 7      | 7     |
| 8 Title              | 8      | 2     | 8      | 7     |
| 9 Title              | 7      | 2     | 7      | 8     |
| 10 Title             | 6      | 3     | 8      | 8     |
| 11 Title             | 6      | 2     | 6      | 6     |
| 12 Title             | 8      | 3     | 8      | 7     |
| 13 Title             | 9      | 3     | 9      | 9     |
| 14 Title             | 8      | 3     | 8      | 7     |
| 15 Title             | 6      | 2     | 6      | 6     |
| 16 Title             | 7      | 3     | 7      | 7     |
| 17 Title             | 8      | 3     | 8      | 8     |
| 18 Title             | 6      | 2     | 6      | 8     |
| 19 Title             | 7      | 3     | 7      | 7     |
| 20 Title             | 6      | 2     | 6      | 6     |
| 21 Title             | 6      | 3     | 6      | 6     |
| 22 Title             | 7      | 2     | 7      | 7     |
| 23 Title             | 7      | 3     | 7      | 6     |
| 24 Title             | 8      | 3     | 8      | 8     |
| 25 Title             | 6      | 2     | 6      | 6     |
| 26 Title             | 6      | 2     | 6      | 6     |
| 27 Title             | 8      | 2     | 8      | 8     |
| 28 Title             | 7      | 3     | 7      | 8     |
| 29 Title             | 8      | 3     | 8      | 8     |
| 30 Title             | 7      | 3     | 7      | 7     |
| 31 Title             | 8      | 3     | 8      | 8     |
| 32 Title             | 6      | 2     | 6      | 8     |
| 33 Title             | 7      | 3     | 7      | 7     |
| 34 Title             | 7      | 3     | 7      | 7     |
| 35 Title             | 5      | 2     | 5      | 5     |
| 36 Title             | 7      | 2     | 7      | 7     |
| 37 Title             | 8      | 3     | 8      | 7     |
| 38 Title             | 8      | 3     | 8      | 8     |
| 39 Title             | 6      | 2     | 6      | 6     |
| 40 Title             | 7      | 2     | 7      | 7     |
| 41 Title             | 5      | 2     | 5      | 5     |
| 42 Title             | 7      | 2     | 7      | 7     |
| 43 Title             | 6      | 2     | 6      | 6     |
| 44 Title             | 8      | 3     | 8      | 8     |
| 45 Title             | 7      | 2     | 7      | 7     |
| 46 Title             | 8      | 3     | 8      | 8     |
| 47 Title             | 7      | 3     | 7      | 7     |
| 48 Title             | 8      | 3     | 8      | 8     |
| 49 Title             | 8      | 3     | 8      | 8     |
| 50 Title             | 6      | 2     | 6      | 6     |
**Table 3:** t test patients on sc glucose v/s control on vas score with p value less than 0.0001.

| Unpaired t test                  |        |
|---------------------------------|--------|
| 1. Table Analyzed               | Data 1 |
| 2.                                |        |
| 3. Column B                      | control|
| 4. vs.                           | vs.    |
| 5. Column A                      | patients on subcutaneous glucose |
| 6.                                |        |
| 7. Unpaired t test              |        |
| 8. P value                       | <0.0001|
| 9. P value summary              | ****   |
| 10. Significantly different (P < 0.05)? | Yes    |
| 11. One- or two-tailed P value?  | Two-tailed |
| 12. t, df                        | t=18.52, df=98 |
| 13. How big is the difference?   |        |
| 14. Mean of column A             | 4.010  |
| 15. Mean of column B             | 7.440  |
| 16. Difference between means (B - A) ± SEM | 3.430 ± 0.1852 |
| 17. 95% confidence interval      | 3.062 to 3.798 |
| 18. R squared (eta squared)      | 0.7777 |
| 19. F test to compare variances |        |
| 20. F, DFn, Dfd                  | 1.976, 49, 49 |
| 21. P value                      | 0.0188 |
| 22. P value summary              | *      |
| 23. Significantly different (P < 0.05)? | Yes    |
| 24. Data analyzed                |        |
| 25. Sample size, column A        | 50     |
| 26. Sample size, column B        | 50     |
**Table 4:** pts on sc glucose v/s control on MNSI questionnaire with p value less than 0.0001.

| Unpaired t test |  |
|-----------------|---|
| Table Analyzed  | Data 1 |
| Column B       | control |
| vs.            | vs. |
| Column A       | on sc glucose |
| **Unpaired t test** |  |
| P value        | <0.0001 |
| P value summary| **** |
| Significantly different (P < 0.05)? | Yes |
| One- or two-tailed P value? | Two-tailed |
| t, df          | t=13.50, df=98 |

**How big is the difference?**

| Mean of column A | 4.820 |
| Mean of column B | 7.000 |
| Difference between means (B - A) ± SEM | 2.180 ± 0.1615 |
| 95% confidence interval | 1.866 to 2.500 |
| R squared (eta squared) | 0.6503 |

**F test to compare variances**

| F, Df1, Df2 | 1.468, 49, 49 |
| P value     | 0.1834 |
| P value summary | ns |
| Significantly different (P < 0.05)? | No |

**Data analyzed**

| Sample size, column A | 50 |
| Sample size, column B | 50 |

**Table 5:** One sample t test for patients before and after sc glucose on vas scale with p value less than 0.0001.

| One sample t test | A patients on subcutaneous glucose |  |
|-------------------|------------------------------------|---|
| Theoretical mean  | 0.000 |
| Actual mean       | 4.010 |
| Number of values  | 50 |
| **One sample t test** |  |
| t, df             | t=37.35, df=48 |
| P value (two tailed) | <0.0001 |
| P value summary   | **** |
| Significant (alpha=0.05)? | Yes |

**How big is the discrepancy?**

| Discrepancy | 4.010 |
| SD of discrepancy | 0.7592 |
| SEM of discrepancy | 0.1074 |
| 95% confidence interval | 3.794 to 4.226 |
| R squared (partial eta squared) | 0.9681 |
Table 6: One sample t test for patients on sc glucose v/s control on MNSI questionnaire with p value less than 0.0001.

| One sample t test | A on sc glucose |
|-------------------|-----------------|
| 1 Theoretical mean | 0.000           |
| 2 Actual mean     | 4.820           |
| 3 Number of values| 50              |
| 5 One sample t test | 1, df  |
| 7 P value (two tailed) | <0.0001 |
| 8 P value summary | ****         |
| 9 Significant (alpha=0.05)? | Yes |
| 11 How big is the discrepancy? | |
| 12 Discrepancy    | 4.820           |
| 13 SD of discrepancy | 0.7267  |
| 14 SEM of discrepancy | 0.1038  |
| 15 95% confidence interval | 4.613 to 5.027 |
| 16 R squared (partial eta squared) | 0.9782 |

Figure 1: Patients on sc glucose v/s control on vas score show significant decrease in pain scores in patients receiving glucose.

Figure 2: Patients on sc glucose v/s control on MNSI showing significant improvement in neurological scores.
Table 7: Patients on sc glucose before and after treatment.

| Unpaired t test |  |
|-----------------|---|
| 1 Tabe Analyzed | Data 1 |
| 2 | |
| 3 Column B | Data Set-B |
| 4 vs. | vs. |
| 5 Column A | Data Set-A |
| 6 | |
| 7 Unpaired t test |  |
| 8 P value | <0.0001 |
| 9 P value summary | **** |
| 10 Significantly different (P < 0.05)? | Yes |
| 11 One- or two-tailed P value? | Two-tailed |
| 12 t, df | t=37.26, df=98 |
| 13 | |
| 14 How big is the difference? |  |
| 15 Mean of column A | 7.520 |
| 16 Mean of column B | 0.5000 |
| 17 Difference between means (B - A) ± SEM | -7.020 ± 0.1884 |
| 18 95% confidence interval | -7.304 to -6.546 |
| 19 R squared (eta squared) | 0.9341 |
| 20 | |
| 21 F test to compare variances |  |
| 22 F, DFn, Dfd | 4.272, 49, 49 |
| 23 P value | <0.0001 |
| 24 P value summary | **** |
| 25 Significantly different (P < 0.05)? | Yes |
| 26 | |
| 27 Data analyzed |  |
| 28 Sample size, column A | 50 |
| 29 Sample size, column B | 50 |

Figure 3: Patients on sc glucose before and after treatment on vas score showing significant decrease of pain scores.
Table 8: Patients on sc glucose before and after treatment on MNSI questionnaire.

| Unpaired t test |         |
|-----------------|---------|
| 1. Table Analyzed | Data 1  |
| 2.               |         |
| 3. Column B      | Data Set-B |
| 4. vs.           | vs.     |
| 5. Column A      | Data Set-A |
| 6.               |         |
| 7. Unpaired t test |   |
| 8. P value       | <0.0001 |
| 9. P value summary | **** |
| 10. Significantly different (P < 0.05)? | Yes |
| 11. One- or two-tailed P value? | Two-tailed |
| 12. t, df        | t=29.79, df=98 |
| 13. How big is the difference? | |
| 14. Mean of column A | 7.020 |
| 15. Mean of column B | 2.540 |
| 16. Difference between means (B - A) ± SEM | 4.460 ± 0.1504 |
| 17. 95% confidence interval | -4.778 to -4.182 |
| 18. R squared (eta squared) | 0.9096 |
| 19. F test to compare variances | |
| 20. F, DFn, Dfd | 3.461, 49, 49 |
| 21. P value       | <0.0001 |
| 22. P value summary | **** |
| 23. Significantly different (P < 0.05)? | Yes |
| 24. Data analyzed | |
| 25. Sample size, column A | 50 |
| 26. Sample size, column B | 50 |

Figure 4: Patients on sc glucose before and after treatment on MNSI scores showing significant improvement on MNSI scores.
The results show that subcutaneous 10% glucose shots showed significant reduction in Pain using VAS scale with mean of 7.520 to mean of 0.5000 with p-value less than 0.0001 in the group who were on sc glucose as seen in Table 5 and Fig. 3, and in comparison to the control group as in Table 1, 3 and Fig. 1.

In MNSI score with a mean of 7.020 to mean of 2.540 significant p-value less than 0.0001 as seen in Table 4 and Fig. 4 in patients who were on sc glucose, and in comparison to the control group as seen in Table 2 and 4 and Fig. 2.

DISCUSSION
Diabetic neuropathy is prevalent in most type 1 and type 2 patients, in which presented mainly by pain, which is caused mainly by chronic hyperglycemia. Treatment is by controlling hyperglycemia and drugs decreasing pain [22].

Diabetic neuropathy results due to nerve injury and tissue damage. Pain and temperature nerve fibers are the most affected [23].

Also, microcirculation is affected leading to muscle atrophy, foot infection, and foot ulcers [24]. Diabetic neuropathic pain is mainly localized to the foot [25].

Available treatment for diabetic neuropathy is only for relieve of symptoms and don't have any effect on the progress of the disease. These drugs may lead to many side effects which cannot be afforded by a large number of patients [26].

There are also trials for using other managements for diabetic neuropathy like a cold laser, acupuncture [27], transcutaneous electrical nerve stimulation (TENS). All of these procedures for pain relieve is still not guaranteed as effective [28].

Hypertonic glucose injection is used for pain relieve in various chronic musculoskeletal conditions. Usually, a small volume of hypertonic glucose (0.5 ml) is injected in painful sites as around inflamed nerves [29].

In this trial glucose, 10% was injected in painful sites in the foot in the palm and sole regions.

My finding in this study shows that subcutaneous glucose 10%, when injected by 0.5 ml in various painful sites in the foot, led to relieve of neuropathic pain in diabetic neuropathy and also led to improvement in nerve functions.

The restriction of my study is the few patients sample size. While the inclusion of a small number of patient’s limits and restricts the extrapolation of our findings to the general population.

CONCLUSION
As diabetic neuropathy is considered as a great problem affecting most of the diabetic patients with moderate to severe pain, subcutaneous glucose injection around inflamed nerves is considered as a new option for the treatment of neuropathic pain and muscle pain.

The data used to support the findings of this study are included in the article.

Conflicts of Interest
There is no conflict of interest to declare.

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Contributions
"Mahmoud Younis wrote the manuscript and researched data, reviewed/edited the manuscript, discussion and reviewed/edited the manuscript."
"Dr. Mahmoud Younis is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis."
REFERENCES

1. Carrillo-Larco RM, Barengo NC, Albites-Flores L, Bernabe-Ortiz A (Feb 2019), “The risk of mortality among people with type 2 diabetes in Latin America: A systematic review and meta-analysis of population-based cohort studies”, *Diabetes Metab. Res. Rev.*, Volume 33, pp. 31–39.

2. Tesfaye S, Boulton AJ, Dickenson AH (2013), “Mechanisms and management of diabetic painful distal symmetrical polyneuropathy”, *Diabetes Care*, Volume 36, pp. 2456–2465.

3. Boulton AJ, Kirsner RS, Vileikiyte L (2004), “Clinical practice. Neuropathic diabetic foot ulcers”, *N Engl J Med.*, Volume 351, pp. 48–55.

4. Bansal V, Kalita J, Misra UK (2006), “Diabetic neuropathy”, *Postgrad Med J.*, Volume 82, pp. 95–100.

5. Gore M, Brandenburg NA, Dukes E, Hoffman DL, Tai KS, Stacey B (2005), “Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep”, *J Pain Symptom Manage*, Volume 30, pp. 374–385.

6. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A (Mar 2009), “Neuropathic pain in diabetes, prediabetes and normal glucose tolerance: the MONICA/KORA Augsburg Surveys S2 and S3”, *KORA Study Group.Pain Med.*, Volume 10, Issue 2, pp. 393–400.

7. Papanas N, Vinik AI, Ziegler D (2011), “Neuropathy in prediabetes: does the clock start ticking early?”, *Nat Rev Endocrinol.*, Volume 7, Issue 11, pp. 682–690.

8. Vinik AI, Ziegler D (2007), “Diabetic cardiovascular autonomic neuropathy”, *Circulation*, Volume 115, pp. 387–397.

9. Gerald Charnogursky, Norma Lopez (2014), “Neurologic Aspects of Systemic Disease Part II, in Handbook of Clinical Neurology”.

10. Chong MS (2007), “Review Diabetic painful neuropathy: current and future treatment options”, *Hester J Drugs*, Volume 67, Issue 4, pp. 569–585.

11. Albers JW, et al. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. *Diabetes Care*. 2010 May; 33(5):1090-6. DOI: 10.2337/dc09-1941. Epub 2010 Feb 11.

12. Albers JW, Herman WH, Pop-Busui R, Feldman EL, Martin CL, Cleary PA, Waberski BH, Lachin JM (2010 May), “Diabetes Control and Complications Trial /Epidemiology of Diabetes Interventions and Complications Research Group”, *Diabetes Care*, Volume 33, Issue 5, pp. 1090–1096.

13. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassaï B, Erpeldinger S, Wright JM, Gueyfier F, Cornu C (26 Jul, 2011), “Effect of intensive glucose lowering treatment on all-cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials”, *BMJ*, Volume 343, d4169.

14. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D (Jan 2017), “Diabetic Neuropathy: A Position Statement by the American Diabetes Association”, *Diabetes Care*, Volume 40, Issue 1, pp. 136–154.

15. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL (Jun 2012), “Diabetic neuropathy: clinical manifestations and current treatments”, *Lancet Neurol*, Volume 11, Issue 6, pp. 521–534.
16. (Aug 2012), “Management of painful diabetic neuropathy: guideline guidance or jungle?”, Spallone V Curr Diab Rep., Volume 12, Issue 4, pp. 403–413.
17. National Library of Medicine, or “Vancouver style” (International Committee of Medical Journal Editors): DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - Record No. T115259, Diabetic Peripheral Neuropathy.
18. Rabago D, Best TM, Zgierska AE, et al. (2009), “A systematic review of four injection therapies for lateral epicondylitis: prolotherapy, polidocanol, whole blood and platelet-rich plasma”, Br J Sport Med, Volume 43, pp. 471–481.
19. Burdakov D, Jensen LT, Alexopoulos H, et al. (2006), “Tandem-pore K+ channels mediate inhibition of orexin neurons by glucose”, Neuron, Volume 50, pp. 711–722.
20. Jensen KT, Rabago DP, Best TM, et al. (2008), “Longer term response of knee ligaments to prolotherapy in a rat injury model”, Am J Sports Med, Volume 36, pp. 1347–1357.
21. Lyftogt J (2007), “Subcutaneous prolotherapy treatment of refractory knee, shoulder and lateral elbow pain”, Aust Musculoskeletal Med, Volume 12, pp. 110–112.
22. Verones B, Oortgiesen M (2001), “Neurogenic in ammation and particulate matter (PM) air pollutants”, Neurotoxicology, Volume 22, pp. 795–810.
23. Anne K Schreiber, Carina FM Nones, Renata C Reis, Juliana G Chichorro, Joice M Cunha (15 Apr 2015), “Diabetic neuropathic pain: Physiopathology and treatment”, World J Diabetes, Volume 6, Issue 3, pp. 432–444, DOI: 10.4239/wjd.v6.i3.432.
24. Irina G Obrosova (2009), “Diabetes and the peripheral nerve. Biochimica Biophysica Acta (BBA) - Molecular Basis of Disease”, Volume 10, pp. 931–940.
25. Bharara M, Cobb JE, Claremont DJ (2006), “Thermography and thermometry in the assessment of diabetic neuropathic foot: a case for furthering the role of thermal techniques”, Int J Low Extrem Wounds, Volume 5, Issue 4, pp. 250–260.
26. Abeer A, Yamany, Hayam M. Sayed (2012), “Effect of low level laser therapy on neurovascular function of diabetic peripheral neuropathy”, Journal of Advanced Research, Volume 3, Issue 1, pp. 21–28.
27. Davies M, Brophy S, Williams R, Taylor A (2006), “The prevalence, severity and impact of painful diabetic peripheral neuropathy in type 2 diabetes”, Diabetes Care, Volume 29, Issue 7, pp. 1518–1522.
28. De Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ (2001), “Association of depression and diabetes complications: a meta-analysis”, Psychosom Med, Volume 63, pp. 619–630.
29. Dworkin RH, O’Connor AB, Backonja M, Farris JT, Finnerup NB, Jensen TS, et al. (2007), “Pharmacologic management of neuropathic pain: evidence-based recommendations”, Pain, Volume 132, Issue 3, pp. 237–251.
30. Rabago D, Best TM, Beamsley M, Patterson J (2005), “A systematic review of prolotherapy for chronic musculoskeletal pain”, Clin. J. Sport Med., Volume 15, Issue 5, pp. 376–380.