Thi-Qar Medical Journal (TQMJ):Vol.(26),No.(2),2023
Web Site: https://jmed.utq.edu Email: utjmed@utq.edu.iq
ISSN (Print):1992-9218

The Association between Elevated Serum Gamma Glutamate Transferase Level and Diabetic Peripheral Neuropathy in Patients with Type 2 Diabetes Mellitus

Abdulkareem Mohammed Abdulkareem Alhashimi (MBChB, Diploma Internal Medicine, FICMS Internal Medicine)

Talib Hussein Kamoona (MBChB, CABM)

Abstract

Background: diabetes mellitus is a common disorder worldwide. Type 2 is the commonest form of this disorder. Patients with DM type 2 have a higher susceptibility to develop certain complications including diabetic peripheral neuropathy which often leads to foot ulceration and consequently amputation. One of the major contributers to the development of this complication is the oxidative stress. Gamma glutamyl transferase (GGT) is an enzyme that increases in level with increasing oxidative stress.

Aim of the Study: To determine the strength of association between serum GGT and the presence of diabetic peripheral neuropathy, and to detect whether elevated serum GGT can be used as an early marker for the development of diabetic peripheral neuropathy.

Methodology: This study is a case-control study that included a total of 60 participants: 30 patients of type 2 DM with peripheral neuropathy (cases) and 30 patients of type 2 DM without peripheral neuropathy (controls). Data was collected from Al-Sadr Medical City and Middle Euphrates Center for Neurological Sciences (Al-Najaf – Iraq) during the period from November 2017 through January 2018.

Results: Statistical analysis of the data shown that there is a strong statistical significance indicating significant relationship between elevated serum GGT levels and the presence of peripheral neuropathy in study population ($\chi 2 = 13.07$, d.f = 1 , $P < 0.001$).

Conclusion: Elevated level of serum GGT is associated with diabetic peripheral neuropathy in patients with type 2 DM.

Keywords: Diabetes mellitus; Gamma-glutamyltransferase; neuropathy

1.1 Introduction

Diabetes mellitus is a common chronic metabolic disorder whose prevalence is increasing globally, resulting in growing public health burden of this disease all around the world.[1] several factors have been attributed to this rapid increase including aging, physical inactivity and increasing prevalence of obesity.[2] A high rate of this rise in prevalence is estimated to be in the Middle-East.[3] Iraqi population, especially elderly, are highly affected by this disease. Iraq Family Health Survey Report (IFHS 2006/7); a nationally representative survey conducted in 2006 and 2007 by Iraqi Ministry of Health (MoH), Central Organization for Statistics & Information Technology (COSIT) and the World Health Organization (WHO) showed that prevalence rate of DM in Iraq is 143.8 per 1000 persons in people aged 50 years or older.[4]

Type 2 DM is the most common type of DM, which is characterized by elevated glycemic level (hyperglycemia), insulin resistance and relative insulin deficiency.[5] It was first described in 1988 as part of metabolic syndrome.[6] Patients of type 2 DM have higher susceptibility to various forms of short-term and long-term complications, which increases their morbidity and mortality. This could be attributed to the insidious onset and later recognition of type 2 DM in comparison to type 1 DM.[7] These complications include cardiac disorders, nephropathy, retinopathy and neuropathy.[8] In the Middle East more than 50% of patients with DM type 2 are affected by diabetic neuropathy, with early involvement of the distal lower extremities.[9]

Diabetic peripheral neuropathy is one of the most common complications of DM, and may lead to foot ulceration and consequently, amputation. Therefore, early diagnosis can be effective to prevent or reduce the incidence of foot ulcers and amputation in the future.[2] Diabetic neuropathy is defined by *The American Diabetes Association* as “The presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.”[10] Diabetic peripheral neuropathy is characterized by a variety of symptoms involving numbness, paresthesia and sensory loss.[2, 11] Nerve conduction studies shows that about 10-18% of DM patients already have neuropathy at the time of diagnosis, indicating that development of peripheral nerve injury occurs in early disease stages.[12] One of the major contributors to the development of diabetic complications is Oxidative stress (OS) by the formation of reactive oxygen species (ROS).[13]

Gamma glutamyl transferase (GGT) is a transferase enzyme that is bound to the cell membrane. It can protect cells against oxidative stress by making cysteine available for intracellular glutathione regeneration.[14] Therefore, an increase in the level of GGT may be a marker of oxidative stress.[15] Also, elevated level of serum GGT is associated with excessive deposition of fat in the liver (non-alcoholic fatty liver disease) that may lead to hepatic insulin resistance, contributing to the systemic insulin resistance and its related hyperinsulinemia.[16] Therefore, GGT level could be a reflection of metabolic alterations and may be considered as a marker for insulin resistance syndrome.[17]

Several methods are employed to detect diabetic peripheral neuropathy; including symptoms analysis, neurological physical examination and NCV studies. But a precise diagnosis requires a combination of these methods, rather than a single confirmative one. [18, 19] In this study the evaluation of the existence of peripheral neuropathy was performed using nerve conduction velocity studies (NCV).

Oxidative stress is one of the contributors to the pathophysiology of nerve injury that leads to the progression of diabetic neuropathy. [13] This occurs through certain defects in vascular and metabolic pathways. The increased level of blood glucose leads to increase in the production of nicotinamide adenine dinucleotide that leads to overloading the chain responsible for electron transport, resulting in OS and poly adenosine diphosphate(ADP)-ribose polymerase (PARP) activation. This activation leads to inducing inflammation and neuronal dysfunction.[2]

Direct measurement of OS is difficult, therefore; serum markers of OS are valuable ways to estimate oxidative stress, because they are relatively easy and inexpensive.[19] Serum GGT is thought to be associated with OS. Several facts supports this assumption, including the fact that serum GGT can be predicted by the dietary heme iron level and dietary antioxidants level (particularly vitamin C and β-carotene), and also the fact that serum GGT can predict the level of C-reactive protein (CRP) as a marker of inflammation. [20]

1.2 Aim of the Study

To determine the strength of association between serum level of GGT and the presence of diabetic peripheral polyneuropathy, and to detect whether elevated serum GGT can be used as a predictor marker of OS that cause the development of diabetic peripheral polyneuropathy.

2.1 Patients and Methods

This study is an analytical case-control study, that was carried out from November 2017 through January 2018. It included a total of 60 patients from Al-Sadr Medical City and Middle Euphrates Center for Neurological Sciences (Al-Najaf - Iraq) who were already diagnosed with DM type 2 by fasting blood sugar (FBS) and HbA_1c level, and underwent further investigation and clinical examination for the assessment of the presence of peripheral neuropathy.

The inclusion criteria for the study were patients with type 2 DM who had the disease for at least 5 years, with age of 40 years or older. Patients who had a history of chronic alcohol consumption were excluded from the study to reduce the confounder effect of alcohol on the level of serum GGT.[17] Other exclusion criteria included patients with demyelinating disorders, muscular disorders, and intake of medications that affect peripheral nerves.

Patient information were collected using specially constructed interview questionnaire, comprised of the basic demographic information of the patients, clinical history of the participants (including detailed history of DM), and symptoms that are associated with peripheral neuropathy (numbness & paresthesia). The patients also had the following clinical, biochemical, and biometric information collected: height and weight; which were further used to calculate body mass index (BMI), blood pressure, fasting blood sugar (FBS), glycosylated hemoglobin (HbA1c), serum gamma-glutamyl transferase (GGT) and neurological physical examination for tactile sensation, vibration sensation, joint position sensation and ankle jerk. Serum GGT level was determined using Knight & Russell's method. Serum GGT level of 9-48 IU/L was considered normal.

The evaluation of the existence of peripheral neuropathy was performed using nerve conduction velocity studies (NCV) by utilizing the nerve conduction velocity and the amplitude of action potential. The device used is the Micro Medic (Italy 2002). Diabetic peripheral neuropathy was defined in this study as a positive nerve conduction study (slow nerve conduction velocity and/or reduced amplitude of action potential) and a positive neurological physical examination with no apparent cause for peripheral neuropathy other than DM. [18]

2.2 Statistical Analysis

SPSS Software version 23.0 was used to perform statistical analysis. Qualitative data are presented as number and percentage, and continuous numerical data are presented as mean ± standard deviation. Comparison of study groups was carried out using chi-square test for categorical data, and using Student's t-test for continuous data. P value of < 0.05 was considered statistically significant.

3.1 Results

This research included a total of 60 participants: 30 patients of type 2 DM with peripheral neuropathy (cases) and 30 patients of type 2 DM without peripheral neuropathy (controls). The demographic characteristic of the study groups are compared in table 1. There has been statistically significant relationship between duration of DM in years and presence of peripheral neuropathy (P=0.016). Age and gender distributions are summarized in figures 2 and 3, respectively. Biochemical and clinical characteristics, including signs and symptoms, of the study groups are compared in table 2.

Table(1) Demographic characteristics of the participants

Age (Years)	**Range**	**43 – 66**	**45 – 63**	**0.502**
	Mean ± SD	**56.2 ± 6.1**	**55.2 ± 5.3**	
Gender	**Male**	**22 (73.3%)**	**21 (70.0%)**	**0.774**
	Female	**8 (26.7%)**	**9 (30.0%)**	
BMI (Kg/M^2)		**25.5 ± 2.1**	**25.2 ± 1.5**	**0.531**
Hypertension		**20 (66.7%)**	**20 (66.7%)**	**1.000**
Smoking		**9 (30.0%)**	**9 (30.0%)**	**1.000**
Smoking Duration (Years)		**26.7 ± 6.6**	**24.3 ± 5.2**	**0.417**
Duration Of DM (Years)		**12.5 ± 4.8**	**9.9 ± 3.3**	**0.016**

Thi-Qar Medical Journal (TQMJ):Vol.(26),No.(2),2023
Web Site: https://jmed.utq.edu Email: utjmed@utq.edu.iq
ISSN (Print):1992-9218

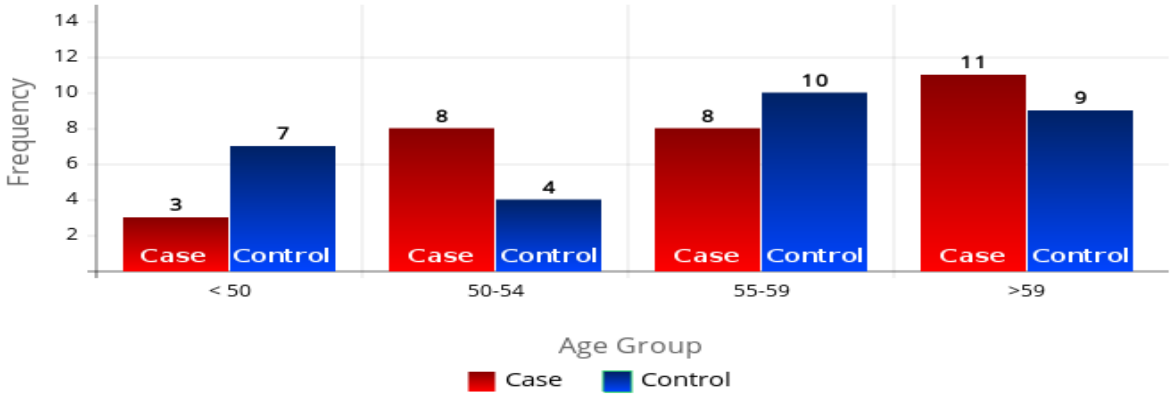

Figure (1) Age distribution of the study subjects

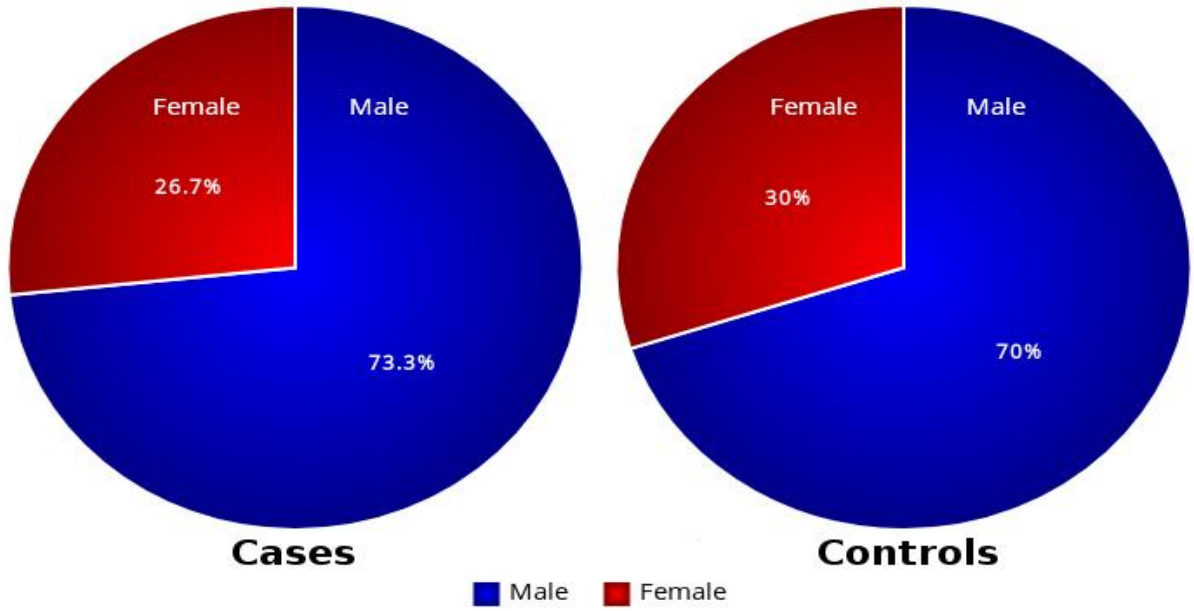

Figure (2)Gender distribution of the study subjects

Thi-Qar Medical Journal (TQMJ):Vol.(26),No.(2),2023
Web Site: https://jmed.utq.edu Email: utjmed@utq.edu.iq
ISSN (Print):1992-9218

Table(2)Biochemical and clinical characteristics of the participants

Hba1c (%)		9.33 ± 0.98	8.80 ± 0.63	0.016
FBS (Mg/Dl)		137.9 ± 12.6	135.3 ± 6.0	0.320
BP (Systolic) (Mmhg)		140.8 ± 6.8	136.5 ± 12.7	0.106
(Diastolic) (Mmhg)		81.3 ± 7.2	82.0 ± 9.5	0.761
Symptoms	Numbness	15 (50.0%)	6 (20.0%)	0.015
	Paresthesia	19 (63.3%)	5 (16.7%)	< 0.001
Signs	Loss Of Tactile Sensation	30 (100%)	-	< 0.001
	Loss Of Vibration Sensation	5 (16.7%)	-	0.020

The presence of positive symptoms (numbness and paresthesia) in control group (Table 2) could be attributed to other forms of neuropathy, such as B_{12} deficiency, hypothyroidism, chronic inflammatory demyelinating polyneuropathy (CIDP), and uremia, which are known to occur more frequently in patients with diabetes.[10]

Figure 3 compares Body-Mass Index (BMI) between cases group and control group, there was no statistically significant relationship between BMI and peripheral neuropathy (χ^2=1.15, d.f=2, P=0.562).

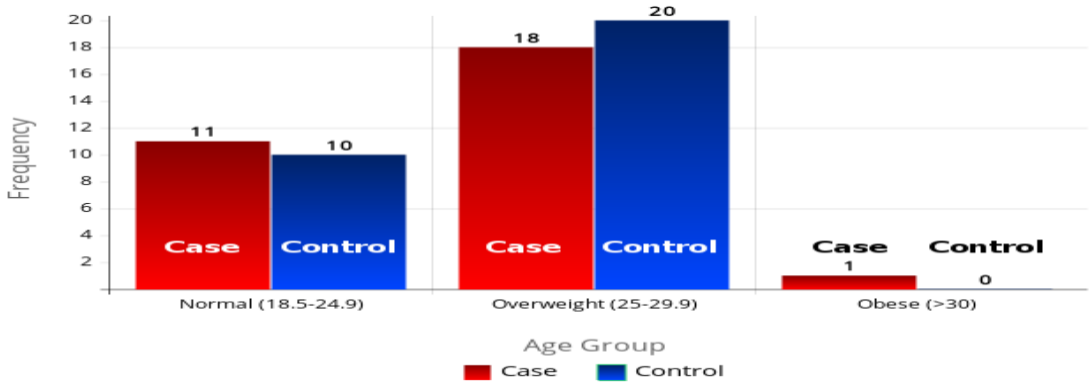

Figure (3)BMI distribution of the study subjects

Table 3 compares the levels of serum GGT between patients with diabetic peripheral neuropathy (cases) and patients without peripheral neuropathy (controls). There is a strong statistical significance indicating significant relationship between elevated serum GGT levels and presence of peripheral neuropathy ($\chi^2 = 13.07$, d.f = 1 , $P < 0.001$).

An independent sample t-test was conducted to compare mean serum GGT between cases and controls. There was a significant difference in the mean of serum GGT level between cases (M=55.17, SD=10.48) and controls (M=35.03, SD=16.22); t(49.6)=5.71, P<0.001.

Table (3)Distribution of serum GGT levels in study groups

Distribution of serum GGT levels in study groups

Serum GGT Level		Cases (n=30)	Controls (n=30)	Total (n=60)
Normal (9-48 IU/L)	Frequency	8 (26.7%)	22 (73.3%)	30 (50.0%)
	Mean ± SD	41.8 ± 2.7	27.2 ± 10.6	31.1 ± 11.2
Elevated (>48 IU/L)	Frequency	22 (73.3%)	8 (26.7%)	30 (50.0%)
	Mean ± SD	60.1 ± 7.5	56.6 ± 5.4	59.1 ± 7.1
Total	Frequency	30 (100%)	30 (100%)	60 (100%)
	Mean ± SD	55.2 ± 10.5	35.0 ± 16.2	45.1 ± 16.9
$\chi^2 = 13.07$, d.f. = 1 , $P < 0.001$				

The presence of patients with elevated level of serum GGT in control group and presence of patients with normal level of serum GGT despite having diabetic peripheral neuropathy are explained by the unimodal distribution for most of the biologic characteristics of the human populations.[21]

4.1. Discussion

This study investigated the possibility of considering serum GGT as a marker for oxidative stress that contributes to the development of diabetic peripheral neuropathy in patients with type 2 DM. A comparison was made between cases and controls regarding certain characteristics (Table 1). There was a statistically significant relationship between duration of DM and incidence of peripheral neuropathy, which is consistent with current scientific knowledge.

Another comparison was made between study groups regarding certain clinical and biochemical characteristics (Table 2). No significant difference was observed between the two groups

regarding blood pressure level (P=0.11 for systolic, P=0.76 for diastolic) or fasting blood sugar (P=0.32). However, there was a statistically significant difference between study groups regarding HbA1c (P=0.016) which can be explained by the fact that both HbA1c and the development of peripheral neuropathy are positively associated with increased duration of disease.

Comparing serum GGT level between study groups; it has been found that there is a statistically significant association between elevated serum GGT level and the presence of diabetic peripheral neuropathy in the study participants. This association statistically was highly significant with p-value of less than 0.001.

In a similar study conducted in Kurdistan region of Iraq at University of Sulaimani and Sulaimani Diabetic Center during the period of March 2012 through February 2013, the results were similar regarding association between serum GGT and diabetic peripheral neuropathy with P value of 0.002.[11] However, the mean serum GGT level for either group was higher in the Kurdistan region as compared to this study (65.7±5.54 vs 55.17±10.48 respectively) for cases and (40.6±3.98 vs 35.03±16.22 respectively) for controls. This can be explained by the wider range of age for study participant in the Kurdistan study (44-72 years) as compared to this study (43-66), which prolong the duration of exposure to the oxidative stress resulting from DM.

Another study conducted in India by SRM Medical College Hospital and Research center in 2012 have shown similar result, with mean serum GGT of 57.4 for cases, and a P value of 0.001 [14]

This association between elevated serum GGT level and the presence of diabetic peripheral neuropathy was also confirmed by a study done in Daegu Medical Center – South Korea from January 2009 to November 2009, with a mean GGT level of 66.1 IU/L among cases, and a mean GGT level of 26.6 IU/L among controls, with a P-value of less than 0.001.[2]

There are some limitations in this study, first; peripheral neuropathy due to causes other than DM could not be excluded completely; and second; these results may represent only the age groups included in the study, and further research with wider range of age of the participants might be needed to generalize the results for the entire population.

5.1. Conclusion

This study results and findings give the conclusion that serum GGT level is associated with diabetic peripheral neuropathy, and can be used as an early marker for the development of diabetic peripheral neuropathy in patients with type 2 DM.

5.2 Recommendations

1. Regularly checking serum GGT level in patients with type 2 DM as a suggestive early biomarker for the development of peripheral neuropathy.
2. Further studies are necessary for the confirmation of the relationship between serum GGT and diabetic peripheral neuropathy in a larger study population.
3. The use of strict and specific guidelines for neurological examination and other tests used to detect peripheral neuropathy in order to avoid misleading or inaccurate results.

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047-1053.

2. Cho H. The Association between Serum GGT Concentration and Diabetic Peripheral Polyneuropathy in Type 2 Diabetic Patients. Korean Diabetes Journal. 2010;34(2):111-118.

3. Hossain P, Kawar B, El Nahas M. Obesity and Diabetes in the Developing World — A Growing Challenge. New England Journal of Medicine. 2007;356(3):213-215.

4. Iraq Family Health Survey 2006/7. Prevalence of non communicable diseases and risk factors in Iraq, A step wise approach. National survey implemented by Ministry of Health, Directorate of Public Health and Primary Health Care and Ministry of Planning and Development Cooperation in collaboration with World Health Organization (WHO)/Iraq-Baghdad, 2006/7.

5. Olokoba A, Obateru O, Olokoba L. Type 2 Diabetes Mellitus: A Review of Current Trends. Oman Medical Journal. 2012;27(4):269-273.

6. Piero M, Nzaro G, Njagi J. Diabetes mellitus – a devastating metabolic disorder. Asian Journal of Biomedical and Pharmaceutical Sciences. 2014;04 (40):1-7.

7. Azevedo M, Alla S. Diabetes in sub-saharan Africa: Kenya, Mali, Mozambique, Nigeria, South Africa and Zambia. International Journal of Diabetes in Developing Countries. 2008 ;28(4):101-8.

8. M. Wilson N, E. Wright D. Inflammatory Mediators in Diabetic Neuropathy. Journal of Diabetes & Metabolism. 2012;01(S5).

9. Bhat M. Diabetic Neuropathy - A Review. European Journal of Biomedical and Pharmaceutical Sciences. 2015;2(5):1583-1602.

10. Boulton A, Vinik A, Arezzo J, Bril V, Feldman E, Freeman R et al. Diabetic Neuropathies: A statement by the American Diabetes Association. Diabetes Care. 2005;28(4):956-962.

11. Abdullah Q, Omer S, Mohammed M. Diabetic polyneuropathy: role of oxidative stress and inflammation. World journal of pharmacy and pharmaceutical sciences. 2015;4(2): 88-101.

12. Al-Ani Y. Predicting Microvascular Complications in Diabetic Patients. Iraqi Journal of Medical Sciences. 2011;9(3):195-205.

13. de M. Bandeira S, da Fonseca L, da S. Guedes G, Rabelo L, Goulart M, Vasconcelos S. Oxidative Stress as an Underlying Contributor in the Development of Chronic Complications in Diabetes Mellitus. International Journal of Molecular Sciences. 2013;14(2):3265-3284.

14. Jyothirmayi B, Sanjayseth, Kaviarasi S, William E. Study of serum GGT levels and lipid profile in diabetic peripheral neuropathy, International Journal of Pharma and Bio Sciences. 2012;3(4):(B)995-1000

15. Whitfield J. Gamma-glutamyl transferase. Critical Reviews in Clinical Laboratory Sciences. 2001;38:263–355.

16. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M et al. Nonalcoholic Fatty Liver Disease: A Feature of the Metabolic Syndrome. Diabetes. 2001;50(8):1844-1850.

17. Meisinger C, Löwel H, Heier M, Schneider A, Thorand B. Serum γ-glutamyltransferase and risk of type 2 diabetes mellitus in men and women from the general population. Journal of Internal Medicine 2005;258:527-35.

18. Herder C, Lankisch M, Ziegler D, Rathmann W, Koenig W, Illig T et al. Subclinical Inflammation and Diabetic Polyneuropathy: MONICA/KORA Survey F3 (Augsburg, Germany). Diabetes Care. 2009;32(4):680-682.

19. Boulton A, Malik R, Arezzo J, Sosenko J. Diabetic Somatic Neuropathies. Diabetes Care 2004;27(6):1458-86

20. Lee D, Gross M, Jacobs D. Association of Serum Carotenoids and Tocopherols with γ-Glutamyltransferase: The Cardiovascular Risk Development in Young Adults (CARDIA) Study. Clinical Chemistry 2004;50(3):582-8

21. Gordis L. Epidemiology. Philadelphia, Pennsylvania: Elsevier Saunders; 2014.