A Study of Cardiac Autonomic Neuropathy among Type-II Diabetic Patients

B.V. Surendra[1*], N. S. Muthiah[2], M. V. Sailaja[2] and K. Prabhu[2]

[1]*Department of Physiology, Bharath Institute of Higher Education and Research, Chennai, India.*
[2]*Bharath Institute of Higher Education and Research, Chennai, India.*

Authors' contributions

This work was carried out in collaboration among all authors. Author NSM has given suggestions in doing the journal author MVS has done the review of literature. Author KP helped in doing statistics and author BVS written the article. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Background: Though very common, CAN is a least understood complication of diabetes which is often under diagnosed. In diabetes mellitus patients, CAN leads to silent myocardial infarction and sudden death. So by identifying CAN early, which is asymptomatic will help to delay or arrest its progression.

AIM: To find out the prevalence and the associated risk factors of Cardiac autonomic neuropathy (CAN) among type-II Diabetes Mellitus patients in a tertiary care hospital.

Materials & Methods: A total of 273 type-II diabetic participants were selected after taking into consideration of inclusion & exclusion criteria. The prevalence of CAN was assessed by ewings and clarkesnon invasive cardiac autonomic neuropathy reflex tests. The association of risk factors with the presence of CAN was analysed by using Pearson's chi square test. Data were analysed by using SPSS 16. The accepted level of significance was set below 0.05 (P<0.05).

Results: The prevalence of CAN among type-II diabetic patients in this study was found to be 34%. Prevalence of CAN increased in the participants with male gender, increased age, and increased BMI, increased duration of diabetes, poor glycaemic control,dyslipidimea, smokers and hypertension and it is statistically significant.

Conclusion: In this study it is observed that the prevalence of CAN increased with old age, male

---

*Corresponding author: E-mail: drsurendraphysiology@gmail.com;

gender, poor glycemic control, increased duration of diabetes, Dyslipidemia, higher BMI, Hypertension & smoking. So risk factors associated with the CAN be detected and treated at an early stage to further reduce morbidity and mortality.

1. INTRODUCTION

Diabetes is a metabolic disorder characterized by hyperglycemia that occurs either due to decreased insulin level or insulin resistance Diabetic Autonomic Neuropathy [1] can involve the entire autonomic nervous system (ANS). It is manifested by dysfunction [2] of one or more organ systems (e.g. cardiovascular, gastrointestinal, genitourinary, sudomotor, ocular)

Though very common, CAN is a least understood complication of diabetes which is often under diagnosed. Not only does it affect the survival and quality of life in diabetics [3-5]. it is also a major source of increased cost in the diabetic care. Currently, a general consensus exists that CAN is an independent risk factor for cardiovascular events [6]. Its high mortality rate is related to cardiac arrhythmias, silent myocardial ischemia, sudden death, perioperative cardiovascular, and cardio respiratory instability [7]. The autonomic fibres innervating heart and blood vessels are affected in CAN and causes disturbances in cardiovascular dynamics [8] and anatomy [9]. It is recommended by several professional bodies [10-12] to perform subclinical assessment of CAN by utilizing CARTs as soon as T2DM is diagnosed. Ewing's CARTs are considered as Gold standard in CAN therefore, consistently been used for its subclinical assessment [13-14]. Hyperglycemia, obesity, dyslipidemia, hypertension, and smoking which are the modifiable risk factors are among the proposed risk factors for Cardiac autonomic neuropathy [15,16-21]. No clear evidence supports glucose-lowering intervention to prevent CAN in type 2 diabetes [21]. On the other hand in the steno-2 trial, multifactorial therapy decreased the development of CAN upto 68% [22].

The present study was planned to find out the prevalence of Cardiac autonomic neuropathy and the risk factors associated with CAN among type-II Diabetes Mellitus participants in a tertiary care hospital.

2. MATERIALS AND METHODS

This cross-sectional study was conducted at department of General medicine OPD, Viswabharathi medical college from December 2019 to November 2020. 273 type-II DM patients with ≥ 3years of duration of both the sexes aged between 35-80 years were selected for this study by purposive sampling technique. Participants with other diseases associated with autonomic nervous system, Patients on drugs like sympathomimetics, and antiarrhythmics, patients with underlying cardiac illness, uncooperative and physically disabled patients were excluded from this study.

2.1 Study Protocol

A questionnaire which included socio-demographic details such as age, sex; anthropometric details such as height, weight; duration of diabetes, smoking & Hypertension history was administered to each patient.

Clinical and laboratory parameters such as BMI, Blood pressure, HbA1c, serum cholesterol, serum triglycerides were collected from each patient

BMI: by dividing weight in kilograms by the square of height in meters BMI was calculated.

Blood pressure: It was measured with a standard mercury manometer and if their blood pressure values were >140/90 mmHg or they were taking any antihypertensive drugs were considered to have arterial hypertension. Estimation of serum cholesterol, serum triglycerides, HbA1c: After an overnight fasting, venous blood was drawn in the morning. Using automatic analyzer Serum cholesterol and serum tryglicerides were measured and Glycosylated hemoglobin (HbA1c) was measured by the high-performance liquid chromatography.

Ewings Cardiovascular Reflex Tests (CRT): All the patients selected for study underwent Cardiovascular Reflex Tests (CRT) for evaluation of Cardiac autonomic neuropathy. Standard 12 lead ECG was taken and heart rate was measured by continuous ECG recording using lead II.

Instruments: 1. ECG instrument (CONTEC ECG300G) with paper speed of 25mm/sec

2. Diamond Sphygmomanometer BP instrument

All five Ewing`s tests were performed as following for the detection of DCAN (diabetic cardiac autonomic neuropathy):

I. Tests for assessing parasympathetic function
1) Heart rate response to deep breathing test:
2) Heart rate response to Valsalva maneuver
3) Heart rate response to standing
II. Tests for assessing sympathetic function:
1) Blood pressure response to sustained handgrip
2) Blood pressure response to standing

The results were then categorized into one of the four groups
Normal
Early CAN - One of three parasympathetic tests abnormal or two border line
Definite CAN- Two parasympathetic tests abnormal
Severe CAN- Two parasympathetic tests abnormal + one or both sympathetic tests abnormal

Statistical Analysis: Data analysis was done by using Software Package of Social Sciences (SPSS) trial version 16. Continuous data were analysed by using student unpaired t test. The association of risk factors with the prevalence of CAN was analysed by using Pearsons chi square test. The accepted level of significance was set below 0.05 (P<0.05).

3. RESULTS

A total of 273 type-II diabetes patients were included. Out of which 142 were males and 131 were females

Prevalence of CAN based on Ewings tests criteria: Fig. 1 is showing the Prevalence of CAN based on Ewings tests criteria. The prevalence of CAN is 34% among typ-2 diabetes mellitus patients.

Severity of CAN: Fig. 2 is showing the severity of CAN. Out of 93 T2DM participants with cardiac autonomic neuropathy, 36 (39%) individuals had 'early', 51 (55%) had 'definite' and 6 (6%) had 'advanced' Cardiac autonomic Neuropathy.

Comparison of continuous variables between CAN & Non CAN participants was described in Table 1.

The association between various risk factors and prevalence of CAN was described in Table 2.

4. DISCUSSION

In the present study, the prevalence of CAN was found to be 34%. DAN study in 2014 reported the prevalence of CAN among the type-II Diabetes as 35% [23]. Gupta and Gupta in 2017 [24] found that CAN was present in 54 patients (54%) out of 100 patients. Barthwal et al. in 1[25] reported prevalence of cardiac dysautonomia as 36.2% in Indian diabetic patients whereas Mathur and Gupta in 2006 [26] reported prevalence of CAN as 58%.

Our study reported increasing age as a risk factor for CAN. Similarly, Pappachan J et al. [27] &Refaie W et al. [28] in their studies reported increasing age as a risk factor for the development of CAN among diabetes patients.

Table 1. Comparison of continuous variables between CAN & NON CAN participants

Demographic variable		CAN positive Patients (n=93)	CAN Negative Patients (n=180)	P value
Age(Years)	Mean±SD	57.83±10.38	53.23±8.73	p< 0.001**
BMI (kg/m^2)	Mean± SD	27.83±3.68	24.18±3.67	P< 0.001**
Duration of Diabetes(Years)	Mean± SD	8.64±4.034	6.87±3.038	P< 0.001**
HbA1c (%)	Mean ± SD	6.48±.51	5.79±.44	P< 0.001**
SBP (mmHg)	Mean ± SD	134.28±15.98	127.34±16.58	P< 0.05*
DBP (mmHg)	Mean ± SD	84.30±9.36	80.68±10.09	P< 0.05*
Serum triglycerides (mg/dl)	Mean ± SD	141.3±25.55	132.85±19.03	P< 0.001**
Serum cholesterol (mg/dl)	Mean ± SD	201.32±41.6	174.56±31.6	P< 0.001**

the mean age, BMI, duration of diabetes, HbA1c, SBP, DBP, serum triglycerides& serum cholesterol were higher in CAN patients than non CAN patients
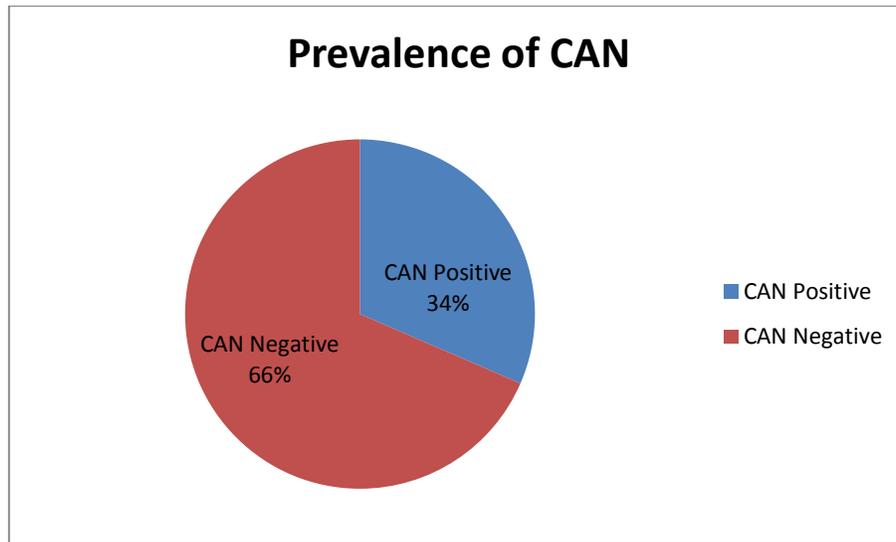
Prevalence of CAN

CAN Positive
34%

CAN Negative
66%

- CAN Positive
- CAN Negative

Fig. 1. Prevalence of CAN based on Ewings tests criteria

SEVERITY OF CAN

36

51

6

- EARLY
- DEFINITE
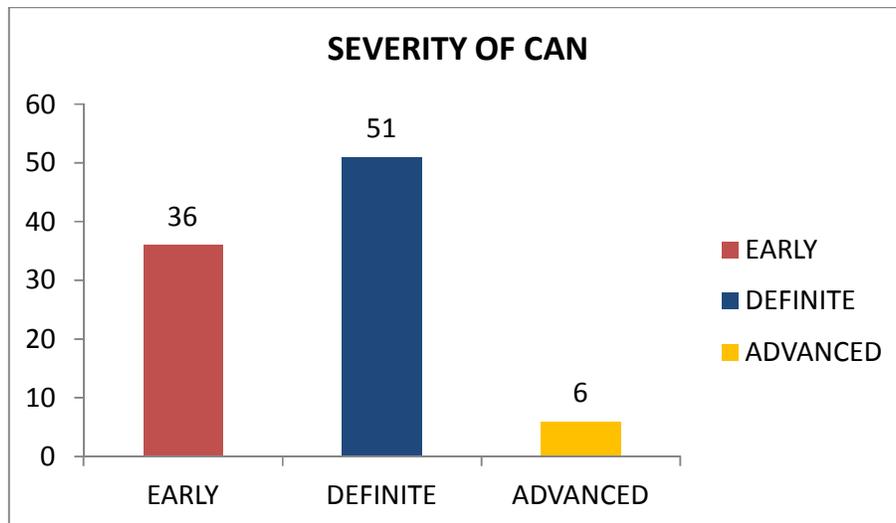- ADVANCED

EARLY   DEFINITE   ADVANCED

Fig. 2. Severity of CAN

Our study found that the male gender are more associated with CAN. This is in contrast with a study done by Sukl et al. [29] which reported that female gender as the risk factor for developing CAN.

Our study reported that poor glycemic control as a risk factor for CAN. Similarly, Haji Khan Khoharo et al. reported that the prevalence of CAN is associated with poor glycemic control [30].

Our study reported an increased duration of diabetes as a risk factor for CAN. Similarly, Ahire et al. [31] reported that CAN is associated with an increased duration of diabetes & David CL et al. [32] also reported an increase in CAN prevalence as the duration of diabetes is increased.

Our study reported that dyslipdimea as a risk factor for CAN. Similarly, Anca Moususianu et al. in their study reported that elevated triglyceride and cholesterol levels are associated with the prevalence of CAN [33]

Our study reported that obesity is a risk factor for CAN. Similarly, R. H. Straub et al. [34] & B.

Table 2. Association between various risk factors and prevalence of CAN

Demographic variable		NO can	CAN Positive	Total	P value
Age (years)	<40	0	16	16	P<0.001*
	40-49	17 (24.6%)	52 (75.4%)	69	
	50-59	36 (35.6%)	65 (64.4%)	101	
	60-69	27 (38.6%)	43 (61.4%)	70	
	≥70	13 (76.5%)	4 (23.5%)	17	
Gender	female	35 (26.7%)	96 (73.3%)	131	
	male	58 (40.8%)	84 (59.2%)	142	P<0.05*
BMI	<18.5	1 (16.7%)	5 (83.3%)	6	
(kg/m^2)	18.5-24.9	20 (15.4%)	110 (84.6%)	130	P< 0.001**
	25-29.9	46 (46.9%)	52 (53.1%)	98	
	≥30	26 (66.7%)	13 (23.3%)	39	
Duration of	<6	24 (23.8%)	17 (76.2%)	101	
Diabetes	6-10	44 (34.4%)	84 (65.6%)	128	P< 0.05**
(years)	>10	25 (56.8%)	19 (43.2%)	44	
HbA1c (%)	<6.5	33 (17%)	161 (83%)	194	
	≥6.5	60 (75.9%)	19 (24.1%)	79	P< 0.001**
Hypertension	Non-Hypertensives	36 (22.2%)	126 (77.8%)	162	
	Hypertensives	57 (51.4%)	54 (48.6%)	111	P< 0.001**
	≥200	58 (70.7%)	24 (59.3%)	82	
dyslipidemia	Absent	29 (16.2%)	150 (83.8%)	179	P< 0.001**
	Present	64 (68.1%)	30 (31.9%)	94	
Smoking	Non Smokers	40 (20.4%)	156 (79.6%)	196	
	Smokers	53 (68.8%)	24 (31.2%)	77	P< 0.001**

Prevalence of CAN increased in the participants with male gender, increased age, and increased BMI, increased duration of diabetes, poor glycaemic control, dyslipidimea, smokers and hypertension and it is statistically significant.

Bergstrom [35] in their study observed that the prevalence of CAN is associated with obesity.

Our study reported Hypertension as a risk factor for CAN. Similarly, Vincenza Spallone et al. [36] in their study found that the prevalence of CAN among diabetic patients is associated with an increase in Blood Pressure.

Our study reported smoking as a risk factor for CAN. Similarly Shai I *et al.* [37] reported that there is an increased prevalence of Cardiac Autonomic Dysfunction in individuals with smoking.

5. CONCLUSION

The prevalence of CAN in our study was found to be 34% and it is high. So these simple bedside tests are helpful in diagnosing the disease which enables to prevent its progression by appropriate interventions and it is concluded that risk factors are associated with the prevalence of CAN among type-II diabetes and therefore it highlights the importance of addressing not only glycaemic control but also modifiable risk factors like hypertension, dyslipidemia, smoking. So it is essential that risk factors associated with the progression and development of CAN be detected and treated at an early stage to further reduce morbidity and mortality.

In our study, the limitation of the study was the sample size which was not large enough to represent the whole population. so studies that include more subjects are required to confirm the findings of our study.

CONSENT AND ETHICAL APPROVAL

This study was approved by the Institutional Ethics Committee having approval number

VMC/IEC/2/2018 and informed consent form was obtained from the study participants.

ACKNOWLEDGMENTS

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sarah Wild , Gojka Roglic, Anders Green, Richard Sicree, Hilary King. Global Prevalence of diabetes: estimates for the 2000 and projections for 2030. Diacare. 2004;27(5):1047–1053.

2. Report and recommendations of the San Antonio Conference on diabetic neuropathy. Consensus Statement. ADA. Diabetes. 1988;37(7):1000–1004,

3. Aaron I Vinik , Raelene E Maser, Braxton D Mitchell, Roy Freeman. Diabetic autonomic neuropathy. Diacare. 2003;26 (5):1553–1579.

4. Maser RE, Mitchell BD,Vinik AI. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes. A meta-analysis. Diacare. 2003;26(6):1895-1901.

5. VinikAI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation. 2007; 115(3):387-397

6. Maser RE, Lenhard MJ. Cardiovascular autonomic neuropathy due to diabetes mellitus: clinical manifestations, consequences, and treatment. J Clin Endocrinol Metab. 2005;90(10):5896–5903,.

7. Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes a meta-analysis. *Diacare* 2003;26(6):1895–1901.

8. Kimura M, Toyoda M, Ono M, Saito N, Kaneyama N, Miyauchi M, et al. Detection of autonomic nervous system abnormalities in diabetic patients by 24□hour ambulatory blood pressure monitoring. Tokai J Exp Clin Med. 2018;43(3):97–102.

9. Hjortkjaer HO, Jensen T, Hilsted J, Mogensen UM, Corinth H, Rossing P, et al. Left ventricular remodeling and cardiac chamber sizes in long term, normo albumin uric type1 diabetes patients with and without cardiovascular autonomic neuropathy. J Diabetes Complications. 2019;33(2):171–177.

10. Andrew JM, Boulton Arthur I, Vinik Joseph C, Arezzo, Vera Bril, eva I. Feldman, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diacare. 2005;28(4):956–962.

11. Spallone V, Bellavere F, Scionti L, Maule S, Quadri R, Bax G, et al. Recommendations for the use of cardiovascular tests in diagnosing diabetic autonomic neuropathy. Nutr Metab Cardiovasc Dis. 2011;21(1):69–78.

12. Vincenza Spallone, Dan Ziegler, Roy Freeman, Luciano Bernardi, Simona Frontoni, Rodica Pop-Busui,,et al. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev. 2011;27(7):639–653.

13. Maser RE, Mitchell BD, Vinik AI, Roy Freeman. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes a meta-analysis. Diacare. 2003;26(6):1895–1901.

14. Jae-Seung Yun , Ji-Hyun Kim, Ki-Ho Song, Yu-Bae Ahn, Kun-Ho Yoon, Ki-Dong Yoo, et al. Cardio vascular autonomic dysfunction predicts severe hypoglycaemia in patients with type 2 diabetes: a 10- year follow-up study. Diacare. 2014;37(1):235–241.

15. Rodica Pop-Busui, Andrew JM. Boulton, Eva L. Feldman, Vera Bril, Roy Freeman, Rayaz A. Malik, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Diacare. 2017;40(1):136–154

16. Ayad F, Belhadj M, Pariés J, Attali JR, Valensi P. Association between cardiac autonomic neuropathy and hypertension and its potential influence on diabetic complications. Diabet Med 2010;27(7): 804–811

17. Andrew Moran, Walter Palmas, Lesley Field, Jyoti Bhattarai, Joseph E Schwartz, Ruth S Weinstocket al. Cardiovascular autonomic neuropathy is associated with micro albuminuria in older patients with type 2 diabetes. Diacare. 2004;27(4):972–977.

18. Maser RE, Lenhard MJ. An overview of the effect of weight loss on cardiovascular autonomic function. Curr Diabetes Rev. 2007;3(3):204–211.

19. Voulgari C, Psallas M, Kokkinos A, Argiana V, Katsilambros N, Tentolouris N, The association between cardiac autonomic neuropathy with metabolic and other factors in subjects with type 1 and type 2 diabetes. J Diabetes Complications. 2011;25(3):159–167

20. Serhiyenko VA, Serhiyenko AA, Cardiac autonomic neuropathy: risk factors, diagnosis and treatment. World J Diabetes. 2018;9(1):1–24

21. William Duckworth Carlos Abraira, Thomas Moritz, Domenic Reda, Nicholas Emanuele, Peter D Reaven, et al. VADT Investigators, Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129–139.

22. Gaede P, Vedel P, Parving HH, Pedersen O, Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet. 1999;353 (9153):617–622.

23. Jesper Fleischer Knud Yderstraede Elisabeth Gulichsen, Poul Erik Jakobsen ,Hans Henrik Lervang , Ebbe Eldrup , et al, Cardiovascular Autonomic Neuropathy Is Associated With Macro vascular Risk Factors in Type 2 Diabetes: New Technology Used for Routine Large-Scale Screening Adds New Insight. J Diabetes Sci Technol. 2014;8(4):874–880

24. Gupta S, Gupta N. The Prevalence of Cardiac Autonomic Neuropathy in Type 2 Diabetes Mellitus. JMSCR. 2017;5(7): 24635-39

25. Barthwal SP, Agarwal R, Khanna D, Kumar P. QTC prolongation in diabetes mellitus- an indicator of cardiac autonomic neuroapathy. JAPI. 1997; (45):15–17.

26. Mathur CP, GuptaD.QTC prolongation in diabetes mellitus-an indicator of cardiac autonomic neuropathy. JIACM. 2006;7(2): 130–162.

27. Pappachan J, Sebastian J, Bino B, Jayaprakash K, Vijayakumar K, Sujathan P, et al. Cardiac autonomic neuropathy in diabetes mellitus: prevalence, risk factors and utility of corrected QT interval in the ECG for its diagnosis. Postgrad Med J. 2008;84(990):205–210.

28. Refaie W. Assessment of cardiac autonomic neuropathy in long standing type 2 diabetic women. EHJ. 2014;66(1): 63–69.

29. Sukla P, Shrivastava SR, Shrivastava P S, Rao NL. Assessment of the cardiac autonomic neuropathy among the known diabeteics and age matched controls using non invasive cardiovascular reflex tests in a South-Indian population: A case-control study. Avicenna J Med. 2016;6(3): 81-85.

30. Haji KK, Shuaib A, Imran AS, Fatima Q. Cardiac AutonomicNeuropathy in Type-1 Diabetes Mellitus Patients and its Association with the duration of Disease and Glycemic Control. J Coll Physicians Surg Pak. 2009;19(4):232–235.

31. Ahire C, Sarode V, Jadhav K, Shreeram V, Gaidhani N. Prevalence of cardiac autonomic neuropathy in short and long-standing type 2 diabetics in western Maharashtra. Int J Basic Appl Med Res. 2014;3(4):252-259.

32. David CL, Henri KP, Gregg M and Aaron IV. 2012. Cardiac Autonomic Imbalance in Newly Diagnosed and Established Diabetes Is Associated with Markers of Adipose Tissue Inflammation. Exp. Diabetes Res. 2012;2012:878760.

33. Anca Moususianu, RodicaBslaGa, SeptimiuVoidszan, and ZoltánBajkó. Cardiovascular Autonomic Neuropathy in Context of Other Complications of Type 2 Diabetes Mellitus. Bio Med Research International. 2013;2013:1-8.

34. Straub RH, Thum M, Hollerbach C, Palitzsch KD, Schölmerich J. Impact of obesity on neuropathic late complications in NIDDM. Diacare. 1994;17(11):1290–1294.

35. Bergstrom B, Lilja B, Osterlin S, Sundkvist G. Autonomic neuropathy in non-insulin dependent (type II) diabetes mellitus. Possible influence of obesity, JIM. 1990;227(1): 57–63.

36. Vincenza Spallone M. Rosaria, Elina cicconetti,Guido Menzinger. Autonomic neuropathy and cardiovascular risk factors insulin dependent and non-insulin dependent diabetes. Diabetes Res Clin Pract.1997:34(3): 169-179

37. Iris Shai , Rui Jiang, Joann E

Manson, Meir J Stampfer, Walter C Willett, Graham A Colditz, et al. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diacare. 2006; 29(7):1585-1590.