Original Article

Retinal microvascular abnormalities and cognitive dysfunction in older patients with Type-2 diabetes mellitus patients at tertiary care hospital

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ABSTRACT

The main of the study was to determine whether several parameters of retinal microvascular abnormality were related to cognitive ability also to estimated cognitive impairment in people with Type 2 diabetes mellitus. A prospective study was carried out for a period of 6 months (October 2017–March 2018) at the Department of Medicine in Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab, India. Data were collected from patient case sheets, laboratory tests reports, and patient interviews into the specially designed data collection form after taking the written consent from the patient diagnosed with diabetic retinopathy. Among 70 study participants, 67.1% were males and 32.9% were females. The mean age of the patients was found to be 66.37 years. The majority of 68.5% were from the urban area. The test of proportion for addiction showed that 34.7% were addicted to alcohol and 25.7% were addicted to smoking. A large number of study population up to 38.6% suffered diabetes from 11 to 15 years and 34.3% had early macular edema due to retinopathy. Surprisingly, the majority of study participants up to 47.1% were found not having a cognitive impairment, 12.9% had a mild cognitive impairment, 21.4% had a moderate cognitive impairment, and 18.6% were found having severe cognitive impairment. The Pearson correlation between duration of diabetes, stage of binocular digital retinal photography, and cognitive impairment was found to be strong ($r = 0.760, 0.772$) and statistically significant ($P < 0.01$) at 95% confidence interval. This study has found that the prevalence of retinal microvascular abnormalities was higher in males as compared to their female counterparts. People living in the urban area are more likely to be affected by it than people living in a rural area. There was a strong correlation between duration of diabetes, stage of binocular digital retinal photography, and cognitive impairment; this suggests that the peoples with a history of diabetes and retinal microvascular abnormalities are prone to reduced cognitive ability and cognitive decline. However, further investigation is required to confirm the direction and potential causal nature of the association between retinal microvascular disease and cognitive decline.

Keywords: Cognitive dysfunction, diabetic retinopathy, elderly population, retinal microvascular abnormalities, Type-2 diabetes mellitus

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INTRODUCTION

Diabetes mellitus (DM) is one of the oldest diseases known to man, which was the first reported in Egyptian literature about

3000 years ago. The term "diabetes" was first coined by Araetaeus of Cappodocia (81-133 AD). Mellitus (honey sweet) was added by Thomas Willis (Britain) in 1675 when he detected sweetness in the urine. It is said that it was first noticed by the ancient Indians; Shushrutha had named it as "Madhumeha."[1] Avicenna is the famous Arabian physician who first described the complications and progression of the disease.[2] Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[3] The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[4] According to IDF,[5] the number of people with diabetes in the world in 2013 was 382 million, which is going to increase to almost 592 million by 2035. India has the similarity of being home to a large number of people suffering from diabetes. According to IDF, 65.1 million adults in India suffered from diabetes in a year.[6,7] It has been predicted that the prevalence of diabetes in the adult population in India will be 6% by the year 2025.[8,9]

Cognitive function

Cognition or cognitive function is defined as the conscious mental activity that is not principally sensory or emotional, comprising a large range of higher brain functions related to the selection, acquisition, storage, manipulation, and organization of information.[10,11] Different aspects of mental function can be conceptualized, measured, and sometimes correlated with underlying neuroanatomical systems.[12,13] The realistic approach taken by most people when measuring cognitive function is to use validated neuropsychological tests (also referred to as cognitive or mental tests), which have been derived using comparisons between patients with circumscribed brain lesions and normal controls.[14]

Cognitive dysfunction associated with Type 2 DM (T2DM)

Cognitive dysfunction, with its wide range, from mild cognitive impairment (MCI) through dementia, is one of the chronic complications of DM.[15,16] T2DM is associated with a range of adverse consequences, including a higher risk of cognitive impairment and dementia, which is increasingly becoming recognized.[17-19] Both diabetes and cognitive impairment occur more commonly at an older age. It has been estimated that the risk of developing Alzheimer's disease is doubled and that of vascular dementia tripled in T2DM.[20,21] The pathways underlying these associations may be multiple.

There is strong evidence that T2DM increases the risk of dementia in the form of multi-infarct dementia, AD, and mixed type dementia. There are some close associations between diabetes and vascular dementia of above 100–160% compared to AD, which is about 45–90%.[15,22] The long-term risk of dementia increases in patients with diabetes by a factor of two. T2DM also increases the risk of progression of MCI to dementia.[23,24] Even in the pre-diabetic states; there is an increased risk of AD and dementia which are not related to the future development of diabetes.[15,25] About 80% of people with AD may have diabetes or impaired fasting glucose. There is a faster deterioration of cognition in diabetic patients rather than non-diabetic elderly ones.[9,26,27] The results of the Edinburgh T2D study that was conducted for evaluation of this correlation were published in 2013. At baseline, any clinical and subclinical macrovascular diseases, including cardiovascular event history, carotid intima-media thickness, ankle-brachial index, and serum N-terminal pro-brain natriuretic peptide were evaluated. Seven neuropsychological tests were also done at baseline, and after 4 years. They found that stroke and subclinical markers of cardiovascular and atherosclerosis are associated with cognitive decline in older patients with T2D.[4,22,28] Retinal microvascular abnormalities in T2DM range from mild, non-proliferative changes to proliferative diabetic retinopathy, and reflect the severity of the condition and the degree of glycemic control.[22,28] Retinal vasculature shares embryological origins, physiological characteristics, structure, and size with cerebral vasculature,[29,30] and thus provides a potential means to investigate further the relationship between diabetes and cognitive function. Investigations into associations between retinal imaging measurements and cognitive function in T2DM have been relatively few. Kadoi *et al.*[31-33] found that diabetic retinopathy was associated with cognitive impairment 6 months after coronary artery bypass surgery.

MATERIALS AND METHODS

The main of this prospective study was to determine whether several parameters of retinal microvascular abnormality were related to cognitive ability also to estimate cognitive impairment (based solely on cognitive test performance) in people with T2DM. This study was carried out for a period of 6 months (October 2017–March 2018) at the Department of Medicine in Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab, India. A total of 70 study participants were recruited in the study based on inclusion criteria and exclusion criteria given below.

Inclusion criteria

The following criteria were included in the study:

- Patients diagnosed with DM with complications (retinopathy) both admitted inpatient and outpatient follow-up
- Both the genders with age between 51 and 75 years.

Exclusion criteria

The following criteria were excluded from the study:

- Patients aged <50 years
- The patient is not willing to participate in the study
- Pregnant and lactating mothers.

Data were collected from patient case sheets, laboratory tests reports, and patient interviews into the specially designed data collection form after taking the written consent from the patient diagnosed with diabetic retinopathy. The data were analyzed by using SPSS ver. 25.

RESULTS

The study enrolled 70 patients. Among the total study population, 67.1% of the patients were found to be males and 32.9% of patients were females. The mean of age (mean ± standard deviation) of the

patients was 66.37 ± 1.406 years. The majority of patients up to 28.6% belonged to the age group of 71–75 years. Out of the 70 studied patients, most of them up to 68.5% were from the urban areas. Only 31.5% were from rural areas. The test of proportion for addiction showed that 34.7% were addicted to alcohol and 25.7% were addicted to smoking cigarettes. Details are shown in Table 1.

A large proportion of the study population up to 38.6% suffered diabetes from 11 to 15 years followed by 32.9% from 6 to 10 years, 21.4% from 16 to 20 years, and 7.1% from 21 to 25 years, respectively. Details are shown in Figure 1.

Out of the 70 studied patients, the majority of patients up to 34.3% had early macular edema, followed by 24.3% advance macular edema, 20.0% developed the new vessels and bleeding due to retinopathy, 20.0% bleeding and edema, and only 1.4% of patients suffered from severe bleeding [Table 2].

Cognition impairment among study participants was assessed using Borkowski verbal fluency test. Among 70 studied patients, surprisingly the majority of study participants up to 47.1% were found not having a cognitive impairment, 12.9% had a MCI, 21.4% had moderate cognitive impairment, and 18.6% were found having severe cognitive impairment. Details are shown in Figure 2.

The Pearson correlation between stage of binocular digital retinal photography and cognitive impairment was found to be strong, $r = 0.772$ and statistically significant ($P < 0.01$) at a 95% confidence interval. Details are shown in Table 3.

The Pearson correlation between duration of diabetes and cognitive impairment was found to be strong, $r = 0.760$ and statistically significant ($P < 0.01$) at a 95% confidence interval. Details are shown in Table 3.

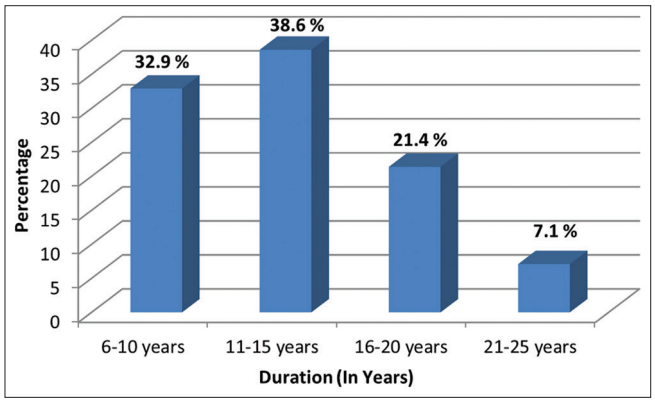

Figure 1: Duration of diabetes mellitus Type-2 in the study population

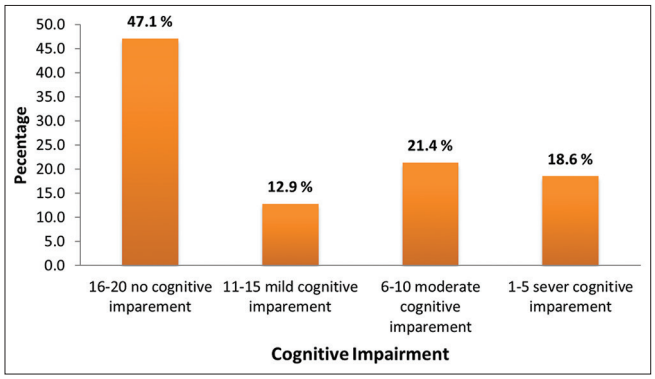

Figure 2: Cognitive impairment among the study population

DISCUSSION

We acknowledge that this type of study has certain limitations such as small sample size and there may be presence confounding factors because of this the results cannot be generalized to the overall population. For analysis of cognition dysfunction, this study has only focused on verbal fluency, not on the other domains of cognitive function affected by the disease. However, it should closely approximate the relationship between retinal microvascular abnormalities and cognitive dysfunction in the case of the scenario in the Punjab region. In this representative population of older people with T2DM, majority of the study participants up to 67.1% was found to be males as compared to their female counterparts up to 32.9% which is also similar to findings were reported in a study conducted in United Kingdom which suggested that a significant dose-response relationship was found only in men and for individual tests of verbal fluency, information processing speed, and mental flexibility (but not memory and nonverbal reasoning). These associations persisted after adjustment for estimated premorbid cognitive ability (vocabulary scores), suggesting that in men, DR was not only associated with cognitive ability in later life but also with increased estimated lifetime cognitive decline.[34] The test of proportion showed most of the patients

Table 1: Socio-demographic characteristics of the study population (*n*=70)

Age distribution of patients (in years)	Frequency (*n*=70)	Percentage (%)
51–55	10	14.3
56–60	10	14.3
61–65	14	20.0
66–70	16	22.9
71–75	20	28.6
Gender distribution of patients		
Male	47	67.1
Female	23	32.9
Locality distribution of patients		
Urban	48	68.5
Rural	22	31.5
Addiction		
Alcohol	25	34.7
Smoking	18	25.7

Table 2: Stage of binocular digital retinal photography observed in the study population

Stage of binocular digital retinal photography	Frequency (*n*=70)	Percentage (%)
Early macular edema	24	34.3
Adv. Macular edema	17	24.3
New vessels and bleeding	14	20.0
Bleeding and edema	14	20.0
Severe bleeding	1	1.4
Total	70	100

Table 3: Correlation between stage of binocular digital retinal photography and cognitive impairment

Correlation	Stage of binocular digital retinal photography	Cognitive impairment
Stage of binocular digital retinal photography		
Pearson correlation	1	0.772**
Sig. (one-tailed)		0.000
n	70	70
Cognitive impairment		
Pearson correlation	0.772**	1
Sig. (one-tailed)	0.000	
n	70	70

**Correlation is significant at the 0.01 level (one-tailed)

Table 4: Correlation between duration of diabetes and cognitive impairment

Correlations	Duration of diabetes	Cognitive impairment
Duration of diabetes		
Pearson correlation	1	0.760**
Sig. (one-tailed)		0.000
n	70	70
Cognitive impairment		
Pearson correlation	0.760**	1
Sig. (one-tailed)	0.000	
n	70	70

**Correlation is significant at the 0.01 level (one-tailed)

28% were significantly higher in the age group of 71–75 years, which was also reported in various other studies.[17,18,20,28,35,36] The prevalence of diabetic retinopathy was higher in urban patients than the rural patients which were also reported in a study conducted in South India,[13,37] lifestyle and ethnicity can be a major factor in this difference. Surprisingly, this factor has not been well studied by various studies conducted in India and other parts of the world. Only a few study participants were found to be addicted to alcohol 34.7% and smoking 25.7%, which is similar to findings reported by other studies.[37-41] A large proportion of the study population up to 38.6% suffered DM from 11 to 15 years. The Pearson correlation between duration of diabetes and cognitive impairment was found to be strong, $r = 0.760$ and statistically significant ($P < 0.01$) at a 95% confidence interval. The Duration of DM is age related which affects cognitive behavior. Such duration of diabetes is normally calculated by subtracting age at diagnosis from the current age. Because people with diabetes may have the disease many years before diagnosis, the true duration of diabetes is often difficult to estimate precisely and may, therefore, be underestimated.[33,34,42-52] Despite these difficulties, there is increasing evidence from recent studies suggesting a longer duration of diabetes may be an important risk factor for cognitive dysfunction in older people with T2DM.[2,3,11,24,25] The Pearson correlation between stage of binocular digital retinal photography and cognitive impairment was found to be strong, $r = 0.772$ and statistically significant ($P < 0.01$) at 95% confidence interval which is similar to the findings of other studies [Table 4].[4,7,15,16,19,21,22,31,34,53]

Direction for future research

- Assessment of the relationship between the residence/locality of patients with T2DM and retinal microvascular abnormalities should be explored
- In further studies, the administration of a number of tests for each major cognitive domain should be considered as opposed to the use in the present study of only a single marker of verbal fluency domain
- Studies on preventive strategies should also be considered as a direction for future research.

CONCLUSION

This study has found that the prevalence of retinal microvascular abnormalities was higher in males as compared to their female counterparts. People living in urban areas are more likely to be affected by it than people living in rural areas. There was a strong correlation between duration of diabetes, stage of binocular digital retinal photography, and cognitive impairment; this suggests that the peoples with a history of diabetes and retinal microvascular abnormalities are prone to reduced cognitive ability and cognitive decline. However, further investigation is required to confirm the direction and potential causal nature of the association between retinal microvascular disease and cognitive decline.

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REFERENCES

1. Sharma A, Sharma P, Anghore D. Diabetes and its Complications. 1st ed. Moga: Lambert Academic Publishing; 2017.
2. Joshi N, Sharma A, Baldi A, Sharma DK. Drug utilization study in patients attending emergency department at a tertiary care hospital in Punjab: A prospective observational study. Pharmaspire 2018;10:95-7.
3. Sharma A, Baldi A, Sharma DK. Assessment of drug-related problems among diabetes and cardiovascular disease patients in a tertiary care teaching hospital. Pharm Aspire 2018;10:7-12.
4. Sharma A, Kaur T, Vishal B, Rathore MS, Chhabra M, Gaur A. Drug utilization study on oral hypertensive medication patients and assessment of medication adherence to JNC-8 guidelines in North Indian tertiary care hospital: A cross-sectional study. Open Hypertens J 2018;10:3-9.
5. Asia S, Aguiree F, Brown A, Cho N, Dahlquist G, Aguiree, Brown, Cho, Dahlquist, Dodd, Dunning and Whiting. IDF Diabetes Atlas. 6th ed. 2013. p.1-160.
6. International Diabetes Federation. IDF Diabetes Atlas. 6th ed. India: International Diabetes Federation; 2013. p. 1-2.
7. Kushawaha SK, Sharma A, Ralta A, Sharma R, Raj D. Pharmacovigilance study:

Drugs used in the treatment of tuberculosis at civil hospital Rohru (Shimla), Himachal Pradesh. Int J Adv Case Rep 2014;1:37-41.

8. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: Prevalence, numerical estimates, and projections. Diabetes Care 1998;21:1414-31.
9. Dwivedi M, Sharma A, Arora S. A review on medication errors. J Pharm Technol Res Manag 2015;3:89-96.
10. Deary IJ, Batty GD. Cognitive epidemiology. J Epidemiol Community Health 2007;61:378-84.
11. Sharma P, Sharma A, Gaur A, Chhabra M, Kaur R. A cross sectional study on diabetes mellitus Type 2 at a tertiary care hospital. Adv Res Gastroenterol Hepatol 2017;8:001-6.
12. Lezak M. Neuropsychological Assessment. 2nd ed. New York: Oxford University Press; 1983.
13. Sharma A, Baldi A, Sharma DK. Drug utilization study at tertiary care hospitals in punjab. Adv Res Gastroenterol Hepatol 2017;7:101-5.
14. Diana SW. Understanding Aging: The Psychology of Adult Development. The Neuropsychology of Aging. Malden: Blackwell Publishing; 1997.
15. Kravitz E, Schmeidler J, Beeri MS. Type 2 Diabetes and Cognitive Compromise. Potential Roles of Diabetes-Related Therapies. Endocrinol Metab Clin North Am 2013;42:489-501.
16. Singh R, Singh S, Sharma A, Arya R. Impact of anxiety on stuttering: Neurobehavioral aspects. J Pharm Biol Sci 2018;6:55-66.
17. Mariani E, Monastero R, Mecocci P. Mild cognitive impairment: A systematic review. J Alzheimers Dis 2007;12:23-35.
18. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus : A systematic review. Lancet Neuro 2006;5:64-74.
19. Strachan MW, Deary IJ, Ewing FM FB. Is Type II diabetes associated with an increased risk of cognitive dysfunction? Diabetes Care 1997;20:438-45.
20. Crosby-Nwaobi R, Sivaprasad S, Forbes A. A systematic review of the association of diabetic retinopathy and cognitive impairment in people with Type 2 diabetes. Diabetes Res Clin Pract 2012;96:101-10.
21. Sharma A. Socio-demographic characteristics and drug related problems of patients presenting to the emergency department: General linear model and factorial analysis. J Pharm Care Heal Syst 2018;5:1-6.
22. Amit S, Ashish B, Kumar SD. Socio-demographic characteristic and drug utilization evaluation of hypertensive patients in Punjab. Eur J Clin Pharm 2018;20:238-49.
23. Biessels GJ, Strachan MW, Visseren FL, Kappelle LJ, Whitmer RA. Dementia and cognitive decline in Type 2 diabetes and prediabetic stages: Towards targeted interventions. Lancet Diabetes Endocrinol 2014;2:246-55.
24. Manik C, Amit S, Sourabh K, Raj K. Socio-demographic study of hepatitis C patients visiting tertiary care hospital. Pharma Aspire 2015;9:108-12.
25. Sharma A, Vinay P. Importance of poison information centre and role of a pharmacist in management of poisoning. Int J Pharm Teach Pract 2014;5:905-9.
26. Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC. Increased risk of Type 2 diabetes in Alzheimer disease. Diabetes 2004;53:474-81.
27. Amit S, Durgadas A, Rathore Singh Mahendra. Treatment and Management of Poisoning. 1st ed. Mauritius: Omni Scripyum Publishing Group, Lap Lembert Academic Publishing; 2018.
28. Feinkohl I, Keller M, Robertson CM, Morling JR, Williamson RM, Nee LD, *et al.* Clinical and subclinical macrovascular disease as predictors of cognitive decline in older patients with Type 2 diabetes: The Edinburgh Type 2 diabetes study. Diabetes Care 2013;36:2779-86.
29. Kwa VIH, Van der Sande JJ, Stam J, Tijmes N, Vrooland JL. Retinal arterial changes correlate with cerebral small-vessel disease. Neurology 2002;59:1536-40.
30. Patton N, Aslam T, MacGillivray J, Pattie A, Deary I, Dhillon B. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease. J Anat 2005;206:318-48.
31. Kadoi Y, Saito S, Fujita N, Goto F. Risk factors for cognitive dysfunction after coronary artery bypass graft surgery in patients with Type 2 diabetes. J Thorac Cardiovasc Surg 2005;129:576-83.
32. Sharma A, Pandit V, Kushawaha SK, Sharma DR. Intensive care management of poisoning. Int J Adv Case Rep 2014;1:13-6.
33. Sharma A, Kaur T, Vishal B, Rathore MS, Chhabra M, Gaur A. Drug utilization study on oral hypertensive medication patients and assessment of medication adherence to JNC-8 guidelines in North Indian tertiary care hospital: A cross-sectional study. Res Rev 2018;10:5-12.
34. Ding J, Strachan MW, Reynolds RM, Frier BM, Deary IJ, Fowkes FG, *et al.* Diabetic retinopathy and cognitive decline in older the edinburgh Type 2 diabetes study. Diabetes 2010;59:2883-9.
35. Patton N, Pattie A, MacGillivray T, Aslam T, Dhillon B, Gow A, *et al.* The association between retinal vascular network geometry and cognitive ability in an elderly population. Investig Ophthalmol Vis Sci 2007;48:1995-2000.
36. Ravona-Springer R, Luo X, Schmeidler J, Wysocki M, Lesser G, Rapp M, *et al.* Diabetes is associated with increased rate of cognitive decline in questionably demented elderly. Dement Geriatr Cogn Disord 2010;29:68-74.
37. Dandona L, Dandona R, Naduvilath TJ, McCarty CA, Rao GN. Population based assessment of diabetic retinopathy in an urban population in Southern India. Br J Ophthalmol 1999;83:937-40.
38. Gadkari S, Maskati Q, Nayak B. Prevalence of diabetic retinopathy in India: The all India ophthalmological society diabetic retinopathy eye screening study 2014. Indian J Ophthalmol 2016;64:38.
39. Raman R, Rani PK, Rachepalle SR, Gnanamoorthy P, Uthra S, Kumaramanickavel G, *et al.* Prevalence of diabetic retinopathy in India. Sankara nethralaya diabetic retinopathy epidemiology and molecular genetics study report 2. Ophthalmology 2009;116:311-8.
40. Tarlok S, Amit S, Shina P, Sourabh K, Shalini D. Introduction to poisoning; A systematic review. Int J Pharm Teach Pract 2015;6:2609-19.
41. Sharma A, Kushawaha SK, Anghore D, Pandit V, Sharma DR. HIV/AIDS overview recent advancement made by WHO. Int J Pharm Teach Pract 2015;6:1582-90.
42. Manschot SM, Brands AM, van der Grond J, Kessels RP, Algra A, Kappelle LJ, *et al.* Brain magnetic resonance imaging correlates of impaired cognition in patients with Type 2 diabetes. Diabetes 2006;55:1106-13.
43. van Harten B, Oosterman J, Muslimovic D, van Loon BJ, Scheltens P, Weinstein HC. Cognitive impairment and MRI correlates in the elderly patients with Type 2 diabetes mellitus. Age Ageing 2007;36:164-70.
44. Okereke OI, Kang JH, Cook NR, Gaziano JM, Manson JA, Buring JE, *et al.* Type 2 diabetes mellitus and cognitive decline in two large cohorts of community-dwelling older adults. J Am Geriatr Soc 2008;56:1028-36.
45. Sharma A, Dogra N. Therapeutic drug monitoring of gentamicin: A prospective study. Int J Curr Pharm Clin Res 2014;4:139-44.
46. Sharma A, Baldi A, Sharma DK, Singh R, Anghore D. Fluoroquinolone (Levofloxacin) induced tendinopathy with partial tearing of the achilles tendon a case report. J Clin Case Stud 2017;2:2-5.
47. Amit S, Hemraj, Kumar R, Kosey S, Negi N. Side effects of chemotherapy and cancer treatment in tertiary care teaching hospital. Res Pharm Health Sci 2016;2:62-78.
48. Sharma A, Ghuman G. Hypertension in pregnancy an overview. World J Pharm Sci 2016;4:420-30.
49. Bansal S, Singh S, Sharma A. Role of reactive oxygen species (ROS) and cytokines in vascular dementia: A review. Int J Pharm Teach Pract 2015;6:2620-9.
50. Elias PK, Elias MF, D'Agostino RB, Cupples LA, Wilson PW, Silbershatz H, *et al.* NIDDM and blood pressure as risk factors for poor cognitive performance: The Framingham study. Diabetes Care 1997;20:1388-95.
51. Saczynski JS, Jónsdóttir MK, Garcia ME, Jonsson PV, Peila R, Eiriksdottir G, *et al.* Cognitive impairment: An increasingly important complication of Type 2 diabetes. Am J Epidemiol 2008;168:1132-9.
52. Cosway R, Strachan MW, Dougall A, Frier BM, Deary IJ. Cognitive function and information processing in Type 2 diabetes. Diabet Med 2001;18:803-10.
53. Sharma A, Baldi A, Sharma DK. Drug induced generalized skin eruption in a diabetes mellitus patient receiving a metformin plus simvastatin in a tertiary care teaching hospital in Punjab. Curr Res Diabetes Obes J 2017;4:4-6.