Association of HbA1C with Symptoms Related to Diabetes Mellitus Type 2 in Undiagnosed Population of Lahore

Javed R[1]., Zulfiqar S[2]., Mohsin S.N[3]., Rafique A[4]. and Naz S[5].

[1,2,3] *Sheikh Zayed Medical Complex, Lahore-Pakistan.*
[4]*Mohtarma Benazir Bhutto Medical College, Mirpur* [5]*Lahore College for Women University, Lahore-Pakistan.*

ABSTRACT

Background and Objective: *Patients having diabetes mellitus type 2 (DM-2) are increasing all over the world. Early detection could decrease the risk of morbidities in general population. Glycated haemoglobin-A (HbA1C) is not only a reliable screening test for diabetes but also provides an insight in long-term complications related with this disease. Therefore this study was designedto determine the association of HbA1C with clinical symptoms of DM-2 in general, undiagnosed population of Lahore.*

Methods: *A cross sectional survey was conducted for 15 months enrolling 2500 participants from community of Lahore, Punjab. A well-structured questionnaire recorded familial histories and clinical symptoms (if any present) related with DM-2. HbA1C levels were detected by standard methods. Data was analyzed using SPSS version 20.*

Results: *HbA1C level > 7% was observed in 1651 (66%) patients who were previously unaware of their diabetic condition. There was a highest positive association of HbA1C status with polyuria [Odds ratio: 2.60 (2.14–3.17)]. No significant association was observed from adjusted odds ratios with hypertension, cardiovascular disease and numbness. When odds ratios were adjusted for all factors, blurred vision, body mass index and age showed a negative association with HbA1C status.*

Conclusion: *Approximately two third of patients tested positive for diabetes were previously unaware of their status. Earlier detection of prediabetes offers an opportunity to take stringent measures for deferring its progression to diabetes.*

KEYWORDS: *Glycated Hemoglobin A (HbA1C), Diabetes Mellitus, Type 2, Undiagnosed.*

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder that causes high blood sugar level resulting from defects in insulin secretion, insulin action, or both.[1] It is produced when pancreas does not produce enough insulin or when cells of the body get resistant to the insulin.[3] Insulin is a peptide hormone, produced by beta cells in the pancreas and regulates carbohydrate and fat metabolism in the body.[2]

Diabetes mellitus is mainly of three types: In type 1 DM (previously referred as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes") body fails to produce insulin.[4,5] Type 2 DM previously known as non-insulin-dependent diabetes mellitus (NIDDM) or "adult-onset diabetes" results when body cells become resistant to the insulin and fails to use insulin properly.Gestational diabetes is the third main type which occurs only in pregnant females without previous diagnosis of diabetes.[6]

In asymptomatic subjects, performing the blood sugar level test on one time is not sufficient to diagnose the disease. It should be further confirmed by performing at least one more test on a subsequent day. The World Health Organization (WHO) now recommends that glycated hemoglobin (HbA1C) can be a better diagnostic test for detecting plasma glucose concentration.[7] Glycated hemoglobin-A (HbA1C) is measured primarily to determine the average blood glucose level over extended period of time. It is formed when high amount of glucose builds up in blood, it starts binding to red blood cells in a non-enzymatic glycation pathway. Healthy human body produces normal amount of glycated hemoglobin but the fraction of glycated hemoglobin starts to increase when blood glucose level is high.[7] This serves as a marker for measuring average blood glucose levels for the past three months.

Studies from different parts of world have shown that a significant number of undiagnosed population are having HbA1C level equal and above 6.9%.[8,9] Recent substantiation has shown pre-diagnostic era of diabetes mellitus can be as long as 9-12 years before the onset of disease showing apparent symptoms like polyuria, polydipsia, weight changes, blurred vision,

Corresponding Author: Dr. Shafqat Mukhtar, Associate Professor
Department of Gynae/Obs., Shaikh Zayed Medical Complex, Lahore-Pakistan.
Email: shafqatzulfiqar63@gmail.com

numbness in hands or feet and increased thirst.[10,11] Clinical symptoms of diabetes in relation to HbA1C sometimes become more appropriate in symptomatic patients rather than symptomatic diabetes patients. Many of the diabetes symptoms such as polyuria, blurred vision, numbness and polyhedral thirst are not only associated with this disease but also present in isolation. In asymptomatic patients, HbA1C test seems a suitable option for confirming in relation with clinical symptoms (if any) of the person.[12,13]

The present study was aimed to determine any association of HbA1C with clinical symptom(s) related with diabetes mellitus type 2 (DM-2) in general undiagnosed population of Lahore for better identification of this disease at earliest.

METHODS

It was a multi-centered cross sectional survey and was carried out at ten different towns of Lahore. Three centers of Pakistan National Health Research Council (NHRC), Sheikh Zayed Medical Complex and Fatima Jinnah Medical College have participated in the study for the duration of 15 months. Considering confidence level (95%), margin of error (1%), and expected frequency of diabetes of 7% as reported[14] previously for an undiagnosed healthy adult population, the calculated sample size was 2500.

Two-stage random sampling method was used for this study. For this, town-wise union councils (UCs) boundaries of Lahore including DHA were taken into consideration. In stage one, 5UCs from each of the nine towns were selected at random, whereas five phases from DHA were selected in first stage random sampling. It is important to mention here that in each phase of DHA any sub-urban areas adjacent to that phase were also considered the part of that phase. In stage 2, one household from each UC was selected randomly for start and continued till 25 respondents from 25 households were enrolled. Non diabetic participants of both genders having age above 45 years were enrolled for the study. While pregnant women, individuals having rheumatoid arthritis, chronic kidney disease, taking steroids orany drug for treating psychological issues or had major abdominal surgery or any clinical condition that might alter HbA1C levels were excluded from this study. A standardized proforma was used as data collection tool. Each participating center was required to collect samples from five allocated towns and each center collected equal number of sample to reach calculated sample size.

The study got ethical approval from Institutional Review Board, Shaikh Zayed Medical Complex Lahore (IRB Reference #1445). An informed consent was taken from Incharge of each UC followed by an individual consent that was taken from each participant after explaining them the purpose and benefit of the study. All the data (socio demographic as well as clinical history), from each participant was recorded on a specially designed proforma. Three milliliters blood from each participant was drawn and immediately shifted to EDTA tubes. The samples were stored at 4-8 degree Celsius(^{o}C) until analysis of HbA1C which was done within 24 hours of sample collection. The equipment used for this purpose was GP HbA1C FIA8000 analyzer (GP Getein Biotech Incorporation, China) based on a quantitative immunoassay method. The cutoff used for HbA1Cwas ≥ 6.5%. HbA1C analysis of all samples was done at NHRC for maintaining same standard throughout the study.

STATISTICAL ANALAYSIS

Data was entered and analyzed using SPSS (version 20). Age was described by using mean ± SD and categorized as below and above 50 years. Gender, income class, familial, clinical histories, body mass index (BMI) status and symptoms of diabetes were described by using frequency and percentages. Odds ratios with 95% confidence interval were used to see association of each factor with HbA1C status independently. Multiple binary logistic regressions were used and presented with adjusted Odds ratios and 95% confidence intervals to see the association of each factor with HbA1C status in presence of other factors.

RESULTS

In this study the subjects enrolled had mean age of 47.6 ± 12.3 years, with 60.7% females. HbA1C levels greater than 7% was observed in 1651 (66%) patients who were previously unaware of their diabetic condition. This level showed a trend of a decrease with increase in age (Table- 1). Most of them (57.1%) had an income between 10,000 40,000 Pakistani rupees. It was observed that 20.28% participants in middle age group (41-50 years) had HbA1C levels > 7% and total 33.96% were having HbA1C levels > 7% out of 2500

Table -1: *HbA1C Levels of participants distributed by age.*

Age Distribution (years)	HbA1C Level of Patients (%)	
	≤ 7	> 7
41 – 50	962	507
51 – 60	412	221
61 – 70	157	62
71 – 80	106	47
> 80	14	12

participants (Table-2). In present study, family history of diabetes was found in 32.2% while clinical history of hypertension and cardiovascular disease was seen in

Table -2: *Characteristics of Population Screened for Type-2 Diabetes.*

Gender		Females	Males	Total
Average Age (Mean ± SD		**50.2 ± 12.7**	**46.0 ± 11.8**	**47.6 ± 12.3**
	Nil	50	20	70
	<10,000	448	323	771
Family	10000 - 40,000	860	569	1429
Income per month (Rs.)	40000-100,000	89	65	154
	>100 K	0	5	5
	Housewife	71	0	71
	Mother	372	200	572
	Father	149	92	241
	Paternal grand mother	50	15	65
Family history	Paternal grand father	42	15	57
	Maternal grand mother	65	20	85
	Maternal grand father	33	3	36
Hypertension (clinical history)		565	243	808
Cardiovascular disease (clinical history)		79	87	166
Symptoms	Polyuria	376	152	528
	Numbness	645	250	895
	Blurred vision	680	341	1021
	Polyhedral thirst	419	156	575
Hb A1c ≤ 7.0		990	661	1651
HbA1C> 7.0		528	321	849

32.3% and 6.6% respectively.

There were an average of 30.67% cases who had at least one of the symptoms of diabetes recorded (polyuria, numbness, blurred vision and polyhedral thirst) (Table- 3). When association was studied with each of the factors independently, except gender, all of the included factors were observed to have positive association with HbA1C status with odds ratio more than 1.0. Lowest of the significant odds ratio was 1.35 (1.14 – 1.60) for blurred vision and highest was 2.60 (2.14 – 3.17) for polyuria. When all of these variables were included in multiple binary logistic regression model, it was found out that gender, hypertension, cardiovascular disease and numbness had insignificant association as can be observed from adjusted odds ratios. When odds ratios were adjusted for all factors, blurred vision, BMI and age showed a negative association with HbA1C status. Polyhedral thirst and numbness were positively correlated with clinical hypertension (Table-3). The logistic regression exposes some of the factors like BMI more than 30, history of blurred vision, age more than 50 years and independently predicts the presence of DM-2 development.

Table- 3: *Association of Factors with HbA1C Status.*

		HbA1C						Odds Ratio	Adj Odd Ratio
		> 7.0		≤ 7.0		Total			
		N	%	n	%	N	%	95 % CI	95 % CI
Gender	Female	528	62.1	990	59.9	1518	60.7	1.09	1.00
	Male	321	37.9	661	40.1	982	39.3	(0.92 – 1.29)	(0.82 – 1.21)
Family history for diabetes	Yes	374	44.0	433	26.2	807	32.2	2.17	1.93
	No	475	66.7	1218	73.8	1693	67.8	(1.82 – 2.58)	(1.60 – 2.33)
Hypertension (clinical history)	Yes	320	37.7	488	29.6	808	32.3	1.47	0.96
	No	529	62.3	1163	70.4	1692	67.7	(1.23 – 1.75)	(0.79 – 1.18)
Cardiovascular disease (clinical history)	Yes	73	8.6	93	5.6	166	6.6	1.60	1.16
	No	776	91.4	1558	94.5	2334	93.4	(1.16 – 2.21)	(0.82 – 1.66)
Polyuria	Yes	279	32.8	264	15.9	543	21.7	2.60	1.80
	No	570	67.2	1387	84.1	1957	78.3	(2.14 – 3.17)	(1.42 – 2.29)
Numbness	Yes	384	45.8	518	31.5	902	36.3	1.84	1.21
	No	454	54.2	1127	68.5	1581	63.7	(1.55 – 2.18)	(0.96 – 1.53)
Blurred vision	Yes	391	46.1	643	38.9	1034	41.3	1.35	0.77
	No	458	53.9	1008	61.1	1466	58.7	(1.14 – 1.60)	(0.62 – 0.96)
Polyhedral thirst	Yes	293	34.5	294	17.8	587	23.4	2.46	1.49
	No	556	65.5	1357	82.2	1913	76.6	(2.04 – 2.98)	(1.17 – 1.91)
BMI	>30.0	276	34.5	432	26.1	708	28.3	1.38	0.82
	≤ 30.0	573	65.5	1219	73.9	1792	71.7	(1.15 – 1.66)	(0.74 – 0.92)
Age	> 50	326	38.4	470	28.4	796	31.8	1.57	0.76
	≤ 50	523	61.6	1181	71.6	1704	68.2	(1.32 – 1.88)	(0.69 – 0.84)

Odds ratio are measured for association of each factor independently
Adjusted odds ratio are measured for each factor by adjusting to the remaining factors given in this table
If "1" is part of interval the odds ratio is insignificant and significant other wise
The first row in each factor is considered risk positive

DISCUSSION

There has been an outstanding upsurge in metabolic illnesses such as diabetes mellitus type-2 particularly in the last few years. The latest estimates of WHO reveal that upto (9%) population from all over the world had diabetes out of which more than (90%)

presented with DM-2. This huge statistics reveals that by year 2030, DM-2 will turn out to be the 7th major cause of mortality all around the world.[15]

WHO corroborates that two out of three diabetic individuals belong to the low socio-economic class and living in urban areas.[15,16] American Diabetic Association revealed a high chance of getting DM-2 with the increase in age.[16] Similar results are reported in present study.There are increased chances of developing DM-2 and the associated risk factors among those having family history of diabetes.

In present study, family history for diabetes, history of hypertension and cardiovascular disease was found in (32.2%), (32.3%) and (6.6%) participants respectively. Studies conducted on US and South Indian populations found almost (65%) and (21.5%) participants with family history of type 2 diabetes.[17,18] It has been reported that family history could be taken as an important marker for predicting DM-2.[17] It is common in individuals with diabetes mellitus type 2 followed by polyhedral thirst, polyuria and numbness.[19] Hyperglycemia aggravates the likelihoods of hypertension and cardiovascular diseases.[20] While a study conducted in Italy revealed DM-2 as a core reason of cardiovascular diseases that can lead to increased mortality as well.[21]

Similar studies conducted in different population found HbA1C levels equaling prediabetes and diabetes in 33% to 48% of undiagnosed subjects which is quite lower than the findings of the present study.[22-24]

CONCLUSION
It is concluded that in undiagnosed patients, polyuria has a positive while BMI and age has a negative association with HbA1C. There is a high prevalence of this disease in our country as compared to rest of the world. Earlier detection of prediabetes offers an opportunity to take stringent measures for halting its progression to diabetes through a periodic screening program especially in individuals having family history of diabetes.

LIMITATIONS OF STUDY
This study was limited to finding association of HbA1C with clinical symptoms and could not follow up patients due to community survey and approach difficulties. A follow up survey can provide comparing results for better statistical findings.

ACKNOWLEDGEMENT

AUTHOR'S CONTRIBUTION
RJ: Concept and design of study, acquisition and analysis of data, drafting the manuscript, final approval of manuscript.
SM: Revising the manuscript for intellectual content.
SNM: Data collection, drafting the manuscript.
AR: Analysis and interpretation of data.
SN: Critical revision of manuscript, analysis and interpretation of data, final approval of manuscript.

CONFLICT OF INTEREST
None to declare.

GRANT SUPPORT AND FINANCIAL DISCLOSURE

REFERENCES
1. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus. Geneva: World Health Organization; 2014.
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diab Care, 2009; 32, Suppl. 1 (Suppl. 1): S62–7.
3. Gardner DG, Shoback D. Greenspan's basic & clinical endocrinology. 10th ed. New York: McGraw-Hill Medical, 2011.
4. WHO. Diabetes Fact sheet N 312. 2014. Available online at:https://www.who.int/news-room/fact-sheets/detail/diabetes. [Last accessed: June 10, 2019].
5. Rayburn WF. Diagnosis and classification of diabetes mellitus: highlights from the American Diabetes Association. J Reprod Med. 1997; 42 (9): 585-6.
6. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, et al. National Academy of Clinical Biochemistry; Evidence-Based Laboratory Medicine Committee of the American Association for Clinical Chemistry. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diab Care. 2011; 34 (6): e61-99.
7. WHO.Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. 2014. Available online at: https://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/. [Last accessed: July, 2019].
8. Lu ZX, Walker KZ, O'Dea K, Sikaris KA. A1C for screening and diagnosis of type 2 diabetes in routine clinical practice. Diab Care. 2010; 33(4): 817–9.
9. Dunstan DW, Zimmet PZ, Welborn TA, De Courten MP, Cameron AJ, Sicree RA, et al. The rising prevalence of diabetes and impaired glucose tolerance: the Australian Diabetes, Obesity and Lifestyle Study. Diab Care. 2002; 25(3): 829–34.
10. Narayan KMV, Chan J, and Mohan V. Early Identification of type 2 diabetes. Diab Care. 2011; 34 (1): 244-6.

11. Engelgau MM, Narayan V, Herman WH. Screening for type 2 diabetes. Diab Care, 2000; 23 (10): 1563-80.

12. Sherwani SI, Khan HA, Ekhzaimy A, Masood A. Significance of HbA1Ctest in diagnosis and prognosis of diabetic patients. Biomark Insights. 2016; 11(2): 95–104.

13. Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, et al. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig.2010; 1 (5): 212-28.

14. Deshpande, Anjali D. Epidemiology of diabetes and diabetes-related complications. Phys Ther. 2008; 88 (11): 1254-64.

15. Whiting David R. IDF Diabetes Atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pr.2011; 94 (3): 311-21.

16. American Diabetic Association. Statistics about diabetics 2006. Available online at: https://www.diabetes.org/resources/statistics/statistics-about-diabetes. [Last accessed: June, 2019].

17. Hariri S, Yoon PW, Qureshi N, Valdez R, Scheuner MT, Khoury MJ, et al. Family history of type 2 diabetes: a population-based screening tool for prevention? Genet Med .2006; 8 (2): 102-8.

18. Das M, Pal S, Ghosh A. Family history of type 2 diabetes and prevalence of metabolic syndrome in adult Asian Indians. J Cardiovasc Dis Res. 2012; 3 (2): 104–8.

19. Cox ME, Edelman D. Tests for screening and diagnosis of type 2 diabetes. Clin Diab. 2009; 27 (4): 132-8.

20. Laakso M. Cardiovascular disease in type 2 diabetes from population to man to mechanisms: the Kelly West Award Lecture 2008. Diab Care. 2010; 33 (2): 442-9.

21. Mohan G, Kaur R, Heli. Sex differences in cardiovascular risk factors among people with type two diabetes. Int J Adv Med. 2018; 5 (2): 384-9.

22. Ming T, Hor A, Ravi S, Hor A, Ravi S, Feng X, et al. Diabetes case finding in the emergency department, using HbA1c: an opportunity to improve diabetes detection, prevention, and care. BMJ Open Diab Res Care. 2016; 4(3): e000191-99.

23. Florkowski C. HbA1c as a diagnostic test for diabetes mellitus – reviewing the evidence. Clin Biochem Rev. 2013; 34 (2): 75-83.

24. Silverman RA, Thakker U, Ellman T, Wong I, Smith K, Ito K, et al. Hemoglobin A1C as a screen for previously undiagnosed prediabetes and diabetes in an acute-care setting. Diab Care. 2011; 34 (9): 1908-12.