Original Article

Evaluation of HbA1c Level in Pre-Diabetics in Prognosis of Diabetes Involvement and Retinopathy

Saeed Kalbasi[1], Mahdi Koorani[2*], Samaneh Ahmadi[3]

[1]Department of Endocrinology and Metabolism, School of Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Internal Medicine, School of Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Abstract

Background: Pre-diabetes is a level before diabetes involvement. Pre-diabetes is prevalent, and if the blood glucose parameters of pre-diabetic patients do not reduce, patients will be involved with type 2 diabetes. In this study, we aimed to investigate the value of hemoglobin A1c (HbA1c) level for predicting diabetes and retinopathy involvement in pre-diabetics.

Materials and Methods: This prospective study was performed on pre-diabetics referred to the endocrinology clinic of Loghman Hakim Hospital (Tehran-Iran) from 2020-20211. The patients were assessed on age, sex, familial history of diabetes, systolic and diastolic blood pressure, and laboratory studies, including fasting blood sugar (FBS), oral glucose tolerance test (OGTT), HbA1c, lipid profile, aspartate aminotransferase (AST), and alanine transaminase (ALT). All participants underwent ocular examination by an expert ophthalmologist for retinopathy assessment. After one year, all participants were again assessed for all mentioned factors.

Results: Pre-diabetics are five-fold more likely to be involved with diabetes after one year than patients with normal HbA1c. We found that patients with pre-diabetes HbA1c are 7.94 fold more at risk of retinopathy involvement than pre-diabetic patients with normal HbA1c (all p-values<0.05).

Conclusion: A high level of HbA1c in pre-diabetics increases the risks of retinopathy and diabetes involvement.

Keywords: Diabetes, Pre-diabetes, Hemoglobin A1c, HbA1c, Retinopathy

***Corresponding Author:** Mahdi Koorani, Department of Internal Medicine, School of Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: mahdikoorani@yahoo.com

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Introduction

When the plasma glucose level is between normal glycemic and diabetic levels, it is classified as pre-diabetes. According to the International Diabetes Federation, 318 million adults worldwide had impaired glucose tolerance (IGT) in 2015, predicted to grow to 482 million by 2040. The yearly progression rate from pre-diabetes to diabetes is 5–10%, with the risk of advancement being increased in older people, those with significant insulin resistance (IR), poor insulin production, and other diabetes risk factors[1-3]. Atherosclerosis, arterial stiffness, and dysfunction of the endothelium of large-sized arteries are hypothesized to have a role in the pathophysiology of diabetic macrovascular consequences. A hypothesis suggests that the pathogenesis of T2DM-associated macrovascular disease begins before the diagnosis of

T2DM, which also explains the increased risk of macrovascular disease in people with pre-diabetes. However, this macrovascular dysfunction also occurs in pre-diabetes, even in less severe forms[4-7].

Microvascular dysfunction in pre-diabetes has not been well investigated[8]. Diabetes has correlated with neuropathy, cognitive impairment, retinopathy, nephropathy, heart failure, and stroke. Pre-diabetes may have a microvascular origin, and some people already have microvascular involvement at the time of T2DM diagnosis. Thus, these findings suggest that microvascular impairment may also exist before diagnosing T2DM, much like macrovascular damage does[9-11].

Due to the lack of evidence to clear the relationship between the level of hemoglobin A1c (HbA1c) in pre-diabetics in prognosis diabetes involvement and retinopathy, in this study, we aimed to assess HbA1c level in patients with pre-diabetes and its relationship with prognosis of diabetes involvement and retinopathy involvement in these patients.

Methods

This prospective study was performed on pre-diabetic patients referred to the endocrinology clinic of Loghman Hakim Hospital (Tehran-Iran) from 2020 to 2022. A fasting blood sugar (FBS) and oral glucose tolerance test (OGTT) were performed for all patients. The pre-diabetes diagnosis was based on fasting blood sugar between 100-125 mg/l or oral glucose tolerance test (OGTT) between 140-199 mg/dl[12,13].

The inclusion criteria were pre-diabetes involvement, more than 18 years of age, and referring for follow-ups. The exclusion criteria did not include consent to participate in the study, diabetes involvement, or ocular disorders with non-pre-diabetes causes.

The estimation of the study population was based on the Andes et al. study[14] with a confidence level of 95%, a power of 80%, and according to the one-year duration of the current study, at least 80 people should be assessed, but we assessed 100 people.

The patients were assessed about age, sex, familial history of diabetes, systolic and diastolic blood pressure, and laboratory studies, including FBS, OGTT, HbA1C, lipid profile, aspartate aminotransferase (AST), and alanine transaminase (ALT). All participants underwent ocular examination by an expert ophthalmologist for retinopathy assessment. After one year, all participants were again assessed for all mentioned factors.

Ethical issue: This study was approved by the ethical committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.MSP.REC.1398.510).

Statistical analysis: Mean and standard deviation were used to describe quantitative data, and frequency and percentage were used for qualitative data. The chi-square test was used to compare qualitative variables between groups, and Fisher's exact test was used to compare the mean of quantitative variables using the ANOVA test. All analyses were performed using SPSS 25.0 statistical software. A P-value less than 0.05 was considered statistically significant.

Results

The information of 100 pre-diabetic patients referred to the endocrinology clinic of Loghman Hakim Hospital (Tehran-Iran) was analyzed. Pre-diabetes was diagnosed based on fasting blood sugar between 100-125 mg/dl or OGTT oral glucose tolerance test between 140-199 mg/dl. Patients were divided into the normal group (56 patients) and the pre-diabetic group (44 patients), and then we examined the relationship between other variables and the risk of diabetic retinopathy between the two groups.

The mean age of all patients was 52 ± 8.51 years. The mean age in normal patients based on HbA1c was 52.41 ± 8.7 years and 51.48 ± 8.34 years in pre-diabetics. In group with normal HbA1c, 33 (58.9%) were male and 23 (41.1%) were female. In group with pre-diabetes HbA1c, 22 (50.0%) were male and 22 (50.0%) were female. Of the participants, 55 (55.0%) were male, and the rest were female.

Table 1 assessed the amount of FBS and HbA1c at the beginning and one year later. The value of these indices before and after one year between the two groups indicated a statistically significant difference between the two groups (P-value<0.001, P-value=0.004). 52.3% of pre-diabetic patients had high blood sugar, and 17.9% of normal people had high blood sugar. Pre-diabetic patients based on HbA1c were 5.03 fold more

Table 1. Investigating the risk and relationship between FBS, final HbA1c, and initial HbA1c status.

		< 5.7 (Normal), N=56	5.7-6.4 (Pre-diabetes), N=44	P-Between Groups	OR	95% CI for OR
First FBS		108.27 ± 4.26	116.73 ± 4.6	<0.001	-	-
FBS after one Years		117.91 ± 8.21	125.14 ± 15.74	0.004	-	-
FBS Change		9.64 ± 7.2	8.41 ± 13.72	-	-	-
P-within Groups		<0.001	<0.001	-	-	-
FBS after one Years	< 126 (normal)	46 (82.1%)	21 (47.7%)	0.001	5.03	(2.04 - 12.44)
	≥ 126 (high)	10 (17.9%)	23 (52.3%)	-	-	-
HbA1C after one Years	Normal	17 (30.4%)	10 (22.7%)	<0.001	-	-
	Pre-diabetes	30 (53.6%)	11 (25.0%)	-	-	-
	≥ 6.5 (Diabetic)	9 (16.1%)	23 (52.3%)	-	-	-
First HbA1C		5.36 ± 0.16	6.03 ± 0.25	<0.001	-	-
HbA1C after 1 Years		5.93 ± 0.52	6.3 ± 0.55	0.001	-	-
Change HbA1C		0.57 ± 0.46	0.26 ± 0.5	-	-	-
P-within Groups		<0.001	0.001	-	-	-

Table 2: Evaluation of the relationship and level of risk of diabetic retinopathy with initial HbA1c status.

--		HbA1c Pre		--		
		Normal, N=56 (%)	**Pre-diabetes, N=44 (%)**	**P-Between Groups**	**OR**	**95% for CI**
Retinopathy	-	55 (98.2%)	43 (97.7%)	> 0.999		--
	+	1 (1.8%)	1 (2.3%)		--	
Retinopathy after one Years	-	54 (96.4%)	34 (77.3%)	0.005	7.94	1.64 - 38.46
	+	2 (3.6%)	10 (22.7%)		--	

Table 3: Investigating the relationship and risk of diabetic retinopathy with HbA1c status after one year.

--		HbA1c after one year			--		
		Normal, N=27 (%)	**Pre-diabetes N=41 (%)**	**Diabetic, N=32 (%)**	**P-Between Groups**	**OR**	**95% CI for OR**
Retinopathy after one year	-	27 (100.0%)	40 (97.6%)	21 (65.6%)	<0.001	20.95	(2.53 – 173.54)
	+	--	1 (2.4%)	11 (34.4%)		--	
FBS after one year	<126	27 (100.0%)	39 (95.1%)	1 (3.1%)	<0.001		--
	≥126	--	2 (4.9%)	31 (96.9%)		--	

likely to be involved with diabetes after one year than patients with normal HbA1c (confidence limit 2.04-12.44) (P<0.001). Also, 52.3% of people who were pre-diabetic at the beginning developed diabetes after one year, compared to only 16.1% of normal patients based on HbA1c who developed diabetes after one year (P<0.001).

Table 2 evaluated the relationship and risk of diabetic retinopathy with initial HbA1C status. Among normal people, 3.6% of people developed diabetic retinopathy after one year, and 22.7% of pre-diabetic people developed diabetic retinopathy. In other words, people with pre-diabetes are more likely to be involved with diabetic retinopathy (confidence limit 38.46-1.64) (P<0.005).

In Table 3, we investigated the relationship and risk of diabetic retinopathy with HbA1C status after one year. 2.4% of people who were pre-diabetic after one year

Table 4: The prevalence of laboratory findings based on the first HbA1c.

--		HbA1c	
		Normal	**Pre-diabetic**
TG 1	<150	0 (0.0%)	1 (2.3%)
	≥150	56 (100.0%)	43 (97.7%)
TG 2	<150	1 (1.8%)	0 (0.0%)
	≥150	55 (98.2%)	44 (100.0%)
Chol 1	<200	46 (82.1%)	24 (54.5%)
	≥200	10 (17.9%)	20 (45.5%)
Chol 2	<200	34 (60.7%)	17 (38.6%)
	≥200	22 (39.3%)	27 (61.4%)
AST 1	<36	36 (64.3%)	14 (31.8%)
	≥36	20 (35.7%)	30 (68.2%)
AST 2	<36	20 (35.7%)	4 (9.1%)
	≥36	36 (64.3%)	40 (90.9%)
ALT 1	<40	55 (98.2%)	44 (100.0%)
	≥40	1 (1.8%)	0 (0.0%)
ALT 2	<40	49 (87.5%)	32 (72.7%)
	≥40	7 (12.5%)	12 (27.3%)

1: at first; 2: after one year; TG: Triglyceride; Chol: Cholesterol

Table 5: The relationship between the first HbA1c and laboratory findings.

	Normal, N=56	**Pre-diabetes, N=44**	**P-Between Groups**
TG 1	183.61 ± 12.67	200.64 ± 20.63	<0.001
TG 2	234.29 ± 252.05	232.89 ± 45.19	0.971
Change TG	50.68 ± 252.27	32.25 ± 37.19	--
P-within Groups	0.138	<0.001	--
Chol 1	190.8 ± 23.62	200.02 ± 25.58	0.065
Chol 2	196.84 ± 13.28	207.36 ± 21.04	0.003
Change Chol	6.04 ± 20.49	7.34 ± 25.43	--
P-within Groups	0.032	0.062	--
AST 1	33.59 ± 4.08	37.05 ± 4.6	<0.001
AST 2	38.04 ± 5.7	42.45 ± 7.51	0.001
Change AST	4.45 ± 5.08	5.41 ± 7.76	--
P-within Groups	<0.001	<0.001	--
ALT 1	32.55 ± 3.35	33.52 ± 4.04	0.193
ALT 2	35.2 ± 3.71	35.86 ± 5.99	0.496
Change ALT	2.64 ± 3.92	2.34 ± 5.92	--
P-within Groups	<0.001	0.012	--

had retinopathy, and 34.4% of people who developed diabetes had retinopathy.

Tables 4 and 5 evaluated the prevalence of some laboratory findings in the participants and their relationship with the first HbA1c. The mean values of factors before and after one year were evaluated separately in these tables. There were statistically significant associations between triglyceride, cholesterol, AST, and ALT levels and first HbA1c ($P<0.05$).

Discussion

In this study, 100 pre-diabetic patients based on FBS and OGTT levels were entered into the study and, based on HbA1c level, were divided into two groups: normal and pre-diabetes. We observed that the mean age of all patients was 52 ± 8.51 years, and 55% were male. There were no statistically significant differences between the two groups regarding age and sex. After one year, patients in the normal group based on HbA1c level significantly increased their FBS level (9.64 ± 7.2). In patients with pre-diabetic HbA1c level, after one year, the FBS level was 13.72 ± 8.41 mg/dl, which was significant. In the normal group, the FBS level of 10 patients changed from pre-diabetes to diabetes level. This count in the pre-diabetes group was 23. Pre-diabetic patients based on HbA1c were five-fold more likely to be involved with diabetes after one year than patients with normal HbA1c. In the normal group, only one patient had retinopathy involvement after one year, but in the pre-diabetic group, nine patients were involved with retinopathy. We found that patients with pre-diabetes HbA1c were 7.94-fold more at risk of retinopathy involvement than pre-diabetic patients with normal HbA1c.

The HbA1c levels differ in different diabetes patients, depending on their history of diabetes and whether they are on tablets or long-term and/or short-term insulin dosage[15]. Type 2 diabetes mellitus (DM) manifests itself in terms of hyperglycemia due to decreased insulin production (no production or non-availability)[16]. The significance of the HbA1c test lies in the diagnosis and the prognosis of diabetes patients, which lends it to a detailed understanding of insulin and insulin resistance[17].

HbA1c is not only a useful biomarker of long-term glycemic control but also a good predictor of lipid profile; thus, monitoring of glycemic control using HbA1c could have additional benefits in identifying diabetes patients who are at a greater risk of cardiovascular complications[17]. Thus, a single HbA1c

test provides valuable information that can be used to manage chronic diseases. In a series of 1,011 type 2 diabetic patients, HbA1c exhibited direct correlations with cholesterol, triglycerides, and low-density lipoprotein cholesterol and an inverse correlation with high-density lipoprotein cholesterol. There was a linear relationship between HbA1c and dyslipidemia as the levels of serum cholesterol and triglycerides were significantly higher, and that of high-density lipoprotein cholesterol were significantly lower in patients with worse glycemic control as compared to patients with reasonable glycemic control[18]. Elevated levels of HbA1c have been identified as a significant risk factor for cardiovascular diseases and stroke in subjects who may have diabetes[19]. A community-based population study on 11,092 nondiabetic patients found that elevated HbA1c level was strongly associated with the risk of cardiovascular disease and mortality[20]. Even an increase of 1% in HbA1c concentration was associated with about a 30% increase in all-cause mortality and a 40% increase in cardiovascular or ischemic heart disease mortality among individuals with diabetes[21]. In the current study, we observed that in patients with pre-diabetes HbA1c, triglyceride and cholesterol had higher than normal HbA1c levels. Also, after one year, both triglyceride and cholesterol increased significantly. We can say that in patients who are pre-diabetic based on HbA1c, glycemic control can reduce the increase of lipid profile and prevent future cardiovascular events as mentioned above. We observed that liver function tests (AST and ALT) had had relationships with HbA1c level and changes of these factors are significant in pre-diabetics after a year.

Li et al. concluded that in patients with type 2 diabetes, higher levels of HbA1c and pre-diabetes are associated with wider retinal arterioles. These findings show that microvascular dysfunction is a common and early complication in patients with pre-diabetes[22]. In the current study, we found that patients with pre-diabetes HbA1c are predisposed to be involved with retinopathy after one year, and this finding confirmed Li et al.'s findings.

Sörensen et al. found that retinopathy is one of the microvascular involvements in pre-diabetes, and this involvement in pre-diabetics worsens over time. They found that higher HbA1c and FBS were associated with retinal arteriolar dysfunction. They concluded that Pre-diabetes and T2DM are associated with microvascular retinal dysfunction[23]. The findings of this study were similar to those of the current study. We found that retinopathy had a significant relationship with the pre-diabetic level of HbA1c, and these patients are in danger of retinopathy involvement 7.94 times more than those with normal HbA1c after one year. Also, we observed that retinopathy had more prevalence in patients who developed diabetes after one year based on HbA1c.

Conclusion

The present study showed that HbA1c predicts diabetes and retinopathy involvement in pre-diabetic patients based on FBS or OGTT after one year. If a patient is pre-diabetic based on HbA1c, he/she is in danger of retinopathy involvement 7.94 fold more than a pre-diabetic patient with an average HbA1c level, and if a patient has HbA1C level in the pre-diabetes range, he/she is in danger of diabetes involvement 5.03 fold more than a pre-diabetic patient with normal HbA1c after one year. Pre-diabetes level of HbA1c is related to increased levels of AST, ALT, triglyceride, and cholesterol. It is recommended that if a patient is pre-diabetic based on FBS or OGGT, prevention treatment should be started as soon as possible before the HbA1c increases. Retinal examination and pre-diabetes treatment should be started in patients with a pre-diabetes level of HbA1c—similar studies with larger populations and higher duration of study are recommended.

Acknowledgment

None.

Conflict of interest

The authors further declare that they have no conflict of interest.

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