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Original Article

Relationship Between the Hypertension Stage and Hemoglobin A1c in Patients With Type 2 Diabetes

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ABSTRACT

Background: It is now suggested that the hypertensive state in diabetic patients may be associated with the level of hemoglobin A1c (HbA1c). In line with this hypothesis, we aimed to compare the level of HbA1c in diabetic patients with and without hypertension to determine whether or not there is a correlation between HbA1c and the hypertension stage.

Methods: This cross-sectional survey was conducted in collaboration with the Physiology Research Center at Kerman University of Medical Sciences on 563 patients with type 2 diabetes. HbA1c was measured via the high-performance liquid chromatography (HPLC) technique. Hypertension was staged as normal, prehypertension, hypertension stage 1, or hypertension stage 2.

Results: We found no difference in the mean fasting blood glucose level and the mean HbA1c level between the different subgroups of hypertension stages; hence, the degree of hypertension was not associated with diabetes control status. The value of HbA1c was correlated with neither systolic blood pressure (P = 0.800) nor diastolic blood pressure (P = 0.215). We also failed to show any significant relationship between the intensity of physical activity and the HbA1c level (P = 0.517). Our multivariable linear regression model revealed that opium addiction was the only determinant significantly correlated with HbA1c (P = 0.038).

Conclusions: We showed no difference in the level of HbA1c between diabetic patients with and without hypertension. It appears that the degree of hypertension in such patients may not be associated with diabetes control status. ***(Iranian Heart Journal 2019; 20(3): 75-83)***

KEYWORDS: Glycated hemoglobin, Type 2 diabetes, Hypertension, Hypertension stage

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Despite the similarity in the clinical definition of hypertension in both diabetic and nondiabetic populations, this condition is a common comorbidity with a twofold prevalence in the former group. [1] In some community-based surveys, only half of the diabetic patients had a controlled state of both systolic and diastolic blood pressures. [2]

Moreover, both conditions are highly associated with serious clinical conditions such as cardiovascular diseases, cerebrovascular ischemic events, and metabolic disturbances. [3-5] Hence, it is not surprising that their coexistence is extremely prevalent. Most importantly, the coexistence between hypertension and diabetes mellitus can potentially increase the likelihood of coronary artery disease and, thus, may lead to considerable increased cardiovascular mortality and morbidity. In other words, due to the close association between both phenomena and microvascular complications, the increased risk for vascular-related adverse events can be more expected in patients with both diseases than each disorder per se. [6-7] Therefore, appropriate control of blood pressure in diabetic patients is an essential and vital issue.

Some hypertensive patients who are not obese display resistance to insulin, which characterizes type II diabetes. [7] This hypothesis arises from the fact that the severity of hyperglycemia contributes to the risk of cardiovascular disease via the development of hypertension. [8] In other words, the association between uncontrolled diabetes and endothelial dysfunction and vascular stiffness leads to increased cardiovascular risks and morbidity. [9] Several cohort studies have revealed that intensive control of diabetes could reduce the risk of incident hypertension by nearly 25%, [10-11] suggesting that strategies to improve glucose control might lower the hypertension risk among people with diabetes.

Glycated hemoglobin (HbA1c) is a form of hemoglobin which is directly related to the concentration of blood glucose for an average of 3 months and is globally accepted as the main indicator of glycemic control. As was mentioned before, since glucose control can be closely associated with hypertension, [12, 13] it can be suggested that the hypertension stage in diabetic patients may be related to the levels of HbA1c. On the basis of this hypothesis, we aimed to compare the level of HbA1c in diabetic patients with and without hypertension to investigate whether or not there is a close association between hypertension and the state of diabetes control.

METHODS

This cross-sectional survey was conducted in collaboration with the Physiology Research Center at Kerman University of Medical Sciences on 563 patients with type 2 diabetes. All baseline characteristics such as demographic features; anthropometric indices; medical history data including the level of physical activity, cigarette smoking, opium addiction, and the state of psychiatric disorders (depression/anxiety); values of systolic and diastolic blood pressure; and laboratory parameters were collected retrospectively by reviewing databases provided in the Physiology Research Center between 2009 and 2011. The exclusion criteria were comprised of diabetes according to the results of the fasting blood sugar (FBS) test or HbA1c levels > 6.5%, other vascular diseases, hemoglobin levels < 11 mg/dL, other systematic diseases including cancer, autoimmune diseases, active infection, splenectomy, and blood loss during recent months.

HbA1c levels, measured via the high-performance liquid chromatography (HPLC) technique, were collected from the aforementioned database. The state of diabetes mellitus control was categorized according to the level of HbA1c: values between 4.5% and 6.4% were defined as excellent control, values between 6.5% and 7% were considered good control, and levels between 7.1% and 8% and the ones exceeding 8% were defined as acceptable and poor control, respectively.

Depression and anxiety levels were collected from the registered database using questionnaires designed based on the Beck Depression and Anxiety Inventories. According to the registered scores and the Beck scoring categorization, the patients were divided into 4 groups regarding their depression and anxiety

status: no or minimal (0–13), mild (14–19), moderate (20–28), and severe (29–63).

Data on the patients' physical activity were collected from the aforementioned database, which included the type of physical activity, accompanied by the duration and weekly frequency of physical exercise. We categorized the patients as having moderate physical activity when they had at least 150 minutes of moderate intensity activity weekly. If they had at least 75 minutes of vigorous exercise, we defined them as having vigorous physical activity. The rest of the patients who had any kind of physical exercise were considered to have light physical activity.

Blood pressure was measured in 3 different visits during the follow-up of the patients, and the average was considered the value included in the study. Hypertension was defined as systolic blood pressure of at least 130 mm Hg or diastolic blood pressure of at least 80 mm Hg in persons with diabetes mellitus or in those with the self-reported use of medication for lowering blood pressure. [14] In this regard, hypertension state was staged as "normal" if systolic blood pressure was lower than 120 mm Hg or diastolic blood pressure was lower than 80 mm Hg; "prehypertension" if systolic blood pressure was between 120 and 139 mm Hg or diastolic pressure was between 80 and 89 mm Hg; "hypertension stage 1" if systolic blood pressure was between 140 and 159 mm Hg or diastolic pressure was between 90 and 99 mm Hg; and "hypertension stage 2" if systolic pressure was 160 mm Hg or higher or diastolic pressure was 100 mm Hg or higher. [15]

The results were presented as mean ± standard deviation (SD) for the quantitative variables and were summarized by absolute frequencies and percentages for the categorical variables. The normality of the data was analyzed using the Kolmogorov–Smirnov test. The categorical variables were compared using the χ^2 test or the Fisher exact test when more than 20% of cells with an expected count < 5 were observed. The quantitative variables were also compared using the ANOVA test or the Kruskal–Wallis H test. The association between the quantitative parameters was assessed using the Pearson or the Spearman correlation test. For the statistical analyses, the statistical software SPSS, version 16.0, for Windows (SPSS Inc, Chicago, IL) was used. A P value $\leq$ 0.05 was considered statistically significant.

RESULTS

As is shown in Table 1, comparisons of the baseline characteristics including gender distribution, depression and anxiety state, and also the lipid profile across the subgroups of hypertension stages showed no differences; however, higher stages of hypertension were significantly associated with a higher mean age as well as higher body mass index. In other words, the older and more obese patients suffered from higher degrees of raised blood pressure.

No difference was found in the mean fasting blood glucose level as well as the mean HbA1c level between the different subgroups of hypertension stages and, thus, the degree of hypertension was not related to blood glucose and diabetes control state. As is indicated in Table 2, most of the diabetic patients (regardless of the hypertension stage) had poorly controlled diabetes. As is revealed in the table, 48.13% of the normotensive, 48.62% of the pre-hypertensive, 47.47% of the hypertensive stage 1, and 47.67% of the hypertensive stage 2 cases had poor control of diabetes; nevertheless, there was no significant difference across the subgroups of hypertension state.

According to our correlation analysis, the value of HbA1c was correlated with neither systolic blood pressure (P = 0.800) nor diastolic blood pressure (P = 0.215). We also failed to show any significant relationship between the intensity of physical activity and the HbA1c level (P = 0.517). Our multivariable linear regression model demonstrated that opium

addiction was the only determinant significantly correlated with HbA1c (P = 0.038). These data are available in Table 3 and Table 4.

Table 1. Baseline characteristics among the different stages of hypertension

Item	Total (N = 563)	Normal BP (n = 97)	Pre-HTN (n = 218)	HTN Stage 1 (n = 158)	HTN Stage 2 (n = 86)	*P* value
Male	226 (40.14%)	40 (41.24%)	85 (38.99%)	67 (42.40%)	32 (37.20%)	0.666
Female	337 (59.86%)	57 (58.76%)	133 (61.01%)	91 (57.60%)	54 (62.79%)	0.564
Mean age	57.12 ± 11.03	52.27 ± 12.25	57.94 ± 11.05	57.69 ± 10.74	57.68 ± 10.41	<0.001
BMI	28.08 ± 10.96	26.38 ± 4.44	27.39 ± 4.51	28.39 ± 12.03	28.50 ± 12.12	<0.001
Smoking	65 (11.54%)	16 (16.49 %)	23 (10.55%)	15 (9.49%)	11 (12.79%)	0.118
Opium use	118 (20.96%)	21 (21.65%)	46 (21.10%)	33 (20.89%)	17 (19.77%)	0.629
Depression level						
No	136 (24.16%)	25 (25.77%)	50 (22.93%)	30 (18.99%)	29 (33.72%)	0.240
Mild	205 (36.41%)	34 (35.05%)	80 (36.70%)	57 (36.07%)	33 (38.37%)	
Moderate	169 (30.01%)	26 (26.80%)	69 (31.65%)	54 (34.18%)	19 (22.09%)	
Severe	51 (9.06%)	11 (11.34%)	19 (8.71%)	17 (10.76%)	4 (4.65%)	
Anxiety level						
No	151 (26.82%)	36 (37.11%)	53 (24.31%)	33 (20.89%)	26 (30.23%)	0.982
Mild	128 (22.73%)	20 (20.62%)	45 (20.64%)	39 (24.68%)	24 (27.91%)	
Moderate	146 (22.93%)	22 (22.68%)	70 (32.11%)	40 (25.32%)	14 (16.28%)	
Severe	137 (24.33%)	19 (19.59%)	50 (22.93%)	46 (29.11%)	21 (24.42%)	
Physical activity						
No	86 (15.28%)	17 (17.53%)	38 (17.43%)	24 (15.19%)	7 (8.14%)	0.253
Light	300 (53.28%)	42 (43.30%)	111 (50.92%)	99 (62.66%)	47 (54.65%)	
Moderate	169 (30.02%)	37 (38.14%)	66 (30.27%)	31 (19.62%)	32 (37.21%)	
Vigorous	8 (1.42%)	1 (1.03%)	3 (1.38%)	4 (2.53%)	0 (0%)	
FBS	174.78 ± 67.92	170.38 ± 67.82	172.71 ± 66.61	175.15 ± 67.86	175.46 ± 67.97	0.912
Cholesterol	202.13 ± 54.57	213.16 ± 54.62	204.63 ± 53.22	199.65 ± 71.77	199.21 ± 53.43	0.056
HDL	36 ± 9.30	37.17 ± 9.48	37.29 ± 9.29	36.96 ± 9.19	36.65 ± 9.26	0.626
LDL	127.01 ± 43.78	127.01 ± 49.56	130.45 ± 43.23	128.30 ± 41.31	125.74 ± 41.99	0.417
TG	199.15 ± 154.59	218.29 ± 125.69	191.71 ± 157.40	191.42 ± 156.05	193.10 ± 160.70	0.430
HbA1c	8.37 ± 1.81	8.35 ± 1.74	8.37 ± 1.81	8.32 ± 1.72	8.26 ± 1.60	0.303

HTN, Hypertension; BMI, Body mass index; FBS, Fasting blood sugar; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; TG, Triglyceride; HbA1c, Hemoglobin A1c

Table 2. Diabetes control state according to the different stages of hypertension

Item	Total (N = 563)	Normal BP (n = 97)	Pre-HTN (n = 218)	HTN Stage 1 (n = 158)	HTN Stage 2 (n = 86)	Missing BP Data (n = 4)	*P* value
Excellent	55 (9.77%)	13 (13.40%)	23 (10.55%)	12 (7.59%)	6 (6.98%)	1 (25%)	0.298
Good	102 (18.12%)	17 (17.53%)	43 (19.72%)	29 (18.36%)	12 (13.96%)	1 (25%)	
Acceptable	135 (23.98%)	20 (20.62%)	46 (21.11%)	42 (26.58%)	27 (31.39%)	0 (0%)	
Poor	271 (48.13%)	47 (48.45%)	106 (48.62%)	75 (47.47%)	41 (47.67%)	2 (50%)	

HTN, Hypertension; BP, Blood pressure

Table 3. Diabetes control state according to the various degrees of physical activity

Item	Total (N = 563)	No Physical Activity (n = 86)	Light Physical Activity (n = 300)	Moderate Physical Activity (n = 169)	Vigorous Physical Activity (n = 8)	*P* value
Excellent	55 (9.77%)	9 (10.46%)	27 (9.00%)	19 (11.24%)	0 (0%)	0.517
Good	102 (18.12%)	16 (18.61%)	49 (16.33%)	35 (20.72%)	2 (25%)	
Acceptable	135 (23.98%)	24 (27.91%)	80 (26.67%)	31 (18.34%)	0 (0%)	
Poor	271 (48.13%)	37 (43.02%)	144 (48.00%)	84 (49.70%)	6 (75%)	

Table 4. Correlations between the studied determinants and HBA1C

Item	Unstandardized Coefficients		Standardized Coefficients	*t*	*P* value
	B	Std. Error	Beta		
(Constant)	8.930	0.904		9.873	
Age	-0.003	0.008	-0.018	-.387	0.699
Body mass index	-0.031	0.017	-0.082	-1.830	0.068
Systolic BP	0.001	0.005	0.015	0.254	0.800
Diastolic BP	-0.013	0.010	-0.070	-1.242	0.215
Cigarette smoking	0.118	0.263	0.021	0.451	0.653
Opium addiction	0.224	0.108	0.097	2.082	0.038
Anxiety level	0.030	0.083	0.019	0.356	0.722
Depression level	0.043	0.147	0.015	0.293	0.770
Physical activity	0.126	0.199	0.090	-0.266	0.517
Dyslipidemia	0.249	0.288	0.038	0.866	0.387

HbA1c, Hemoglobin A1c; BP, Blood pressure

DISCUSSION

As was expected, we had a high overall prevalence of uncontrolled blood pressure in the diabetic population of our study. In fact, 82.7% of our diabetic patients had either pre-hypertension or hypertension and 43.3% of them had blood pressure levels ≥ 140/90 mm Hg, indicating poorly controlled hypertension. As has been clearly demonstrated, hypertension is an important risk factor in diabetic patients and also a major contributor to health care costs. This fact predicts higher rates of adverse complications related to the coexistence between diabetes and hypertension. [16]

In our study, we found that increased age and the body mass index were accompanied by higher degrees of blood pressure. This finding is concordant with the available literature, declaring that vascular and neurohumoral changes with increasing age and the body mass index are the major cause of subsequent hypertension. [17-21]

Many guidelines have emphasized the importance of hypertension control in diabetic patients to minimize diabetes-related complications. [22, 23] In fact, tightly controlled blood pressure can properly prevent renal and cardiovascular adverse events in diabetic patients. We found that the control and management of hypertension were largely far from the goal of the international guidelines.

Initially, we had hypothesized that diabetes control status, determined by the level of HbA1c, might be related to the hypertension stage. Nevertheless, we could not show any association between diabetes mellitus control state and the degree of hypertension in our study. In other words, the level of HbA1c was not significantly correlated with either systolic or diastolic blood pressures. Previous studies have demonstrated associations between hyperglycemia and endothelial dysfunction and

vascular stiffness, both of which are linked to increased hypertension.

On the other hand, there is a strong association between hypertension, diabetes, and insulin resistance. [24]

In a study by Bower et al, [25] higher HbA1c values at baseline were associated with increased risks of hypertension. The authors also showed that poor glycemic control was correlated with increased risks of hypertension among those with diagnosed diabetes, similar to our primary hypothesis but contrary to our final result.

Few prospective studies have examined the association between HbA1c and the subsequent hypertension risk. Although previous studies have reported a positive correlation between hyperglycemia and blood pressure levels, [26-29] some of these associations were weak or not statistically significant. [30] Therefore, there are mechanisms that explain the association between the level of HbA1c and blood pressure such as the role of adiposity or inflammatory mediators. [31] These theories still remain questionable based on our findings and, as such, need further assessment in physiological and molecular levels.

Interestingly, we found an inverse relationship between opium addiction and the level of HbA1c. This issue is still controversial in the literature inasmuch as there are studies maintaining that opium smoking will increase blood glucose, [32] whereas some others, like one investigation in 2008, claim that opium might decrease blood glucose temporarily, but it has no clear and long-lasting effect on blood glucose or HbA1c. [33] Byrkjeland et al [34] in 2011 revealed that the HbA1c level was lower in males with opium consumption, but there was no effect on the frequency of the chronic complications of diabetes. They also mentioned that despite their results, opium would not be a harmless treatment for diabetes. All these controversies need to be answered by more powerful studies with larger populations and longer-term follow-up durations.

Our study also failed to show any significant benefit for moderate or vigorous physical activity on the HbA1c level. Byrkjeland et al [34] found no significant effects of exercise training on the HbA1c level in patients with type 2 diabetes and coronary artery disease, although they noted HbA1c improvements in patients without vascular complications, implying that the degree of vascular disease may influence exercise responses. In 2010, Church et al [36] revealed that a combination of aerobic and resistance training might improve HbA1c levels, while this was not achieved by aerobic or resistance training alone. A recent survey in 2015 emphasized that exercising more frequently per week might be more beneficial than increasing the session's duration or intensity, especially in patients with multiple comorbidities and those with higher levels of HbA1c. [37] All such supporting and contradictory evidence signifies the need for further research.

Our study had several limitations. First, we had data on patients over a 2-year period, which is not enough for the occurrence of diabetes complications or the long-term effects of different determinants. We tried to overcome this limitation by including patients from different sites of Kerman province with different levels of health care availability. Another limitation was the lack of data regarding the patients' medications, which might have significantly affected their lab tests and the level of blood pressure. We also considered the patients' current cigarette smoking and opium addiction status, which might have caused bias because the effects of previous smoking and addiction are liable to remain significant for a long period of time.

In conclusion, we found no difference in the level of HbA1c between our diabetic patients with and without hypertension. It appears that the degree of hypertension in such patients may not be correlated with diabetes control state. According to the obtained contradictory results on the association between the level of HbA1c

and the hypertension risk in a diabetic population, this possible relationship should be further assessed considering different potential risk factors, confounders, and variable patients' habitual and molecular characteristics.

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There is no funding/support.

Conflict of Interest: None

Compliance With Ethical Standards
All procedures were in accordance with the ethical standards of the Ethics Committee of Kerman University of Medical Sciences. Informed consent or substitute was not needed since the patients' identification information was not registered in the recorded database used. The research was approved by the aforementioned committee on September 4th, 2017, with the approval number of IR.KMU.REC.1396.1532.

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