Original Research Article

Glycemic Parameters in Relation to Pulse Pressure in Patients with Type 2 Diabetes Mellitus

Running Title: Glycemic Parameters and Pulse Pressure

ABSTRACT

Aims: Pulse pressure (PP) is determined by the complex relationship between stroke volume of the heart, aortic elasticity and peripheral vascular resistance. PP has been considered an independent risk factor for cardiovascular mortality of normotensive and hypertensive individuals. The aim of this study was to determine the prevalence of hypertension (HT) in patients with Type 2 diabetes mellitus (DM) and to evaluate the relationship between glycemic parameters and PP.

Methodology: A total of 422 patients with type 2 DM, mean age 58.0±13.2 years, were included in the study. Data on patient demographics, blood pressure and PP readings were recorded in each patient as were the glycemic parameters including fasting blood glucose (FBG), postprandial blood glucose (PPBG) and HbA1c. Glycemic parameters were also evaluated with respect to PP groups. The patients were divided into 4 groups according to the PP readings including group 1 (PP ≤45 mmHg), group 2 (PP:46-54 mmHg), group 3 (PP:55-64 mmHg) and group 4 (PP ≥65 mmHg).

Results: Hypertension was evident in 79.6% of patients. Mean PP was 55.3±12.5mmHg. While group 1 and 2 were similar in terms of glycemic parameters, FBG (p=0.026), PPBG (p=0.019) and HbA1c (%) (p=0.004) were significantly lower than group 3 and group 4 (p< .05).

Conclusions: Our findings revealed HT at a high frequency of 79.6% in patients with Type 2 DM. Significant higher values were found for FBG, PPBG and HbA1c in high PP patients. These results may be associated with increased cardiovascular risk in patients with poor glycemic control with Type 2 DM and high PP.

Keywords: Type 2 diabetes mellitus; hypertension; Pulse pressure; Glycemic control

1. INTRODUCTION

Diabetes Mellitus (DM) is a global health problem. People with DM have an increased risk of developing a number of serious life-threatening health problems resulting in higher medical care costs, reduced quality of life and increased mortality. It was estimated that in 2017 there are 451 million (age 18-99 years) people with DM worldwide [1]. The 5.0 million estimated DM-attributable deaths estimated to have occurred in 2015 is higher than the combined number of annual deaths from HIV/AIDS (1.2 million), tuberculosis (1.5 million) and malaria (0.4 million) [2].

Despite well-documented correlation of glycemic regulation with the all-cause mortality and availability of hypoglycemic agents and insulin that offer a wide range of treatment for glycemic regulation, failure to achieve adequate glycemic control based on suggested HbA1c targets has been considerable debate [3]. As demonstrated in a past meta-analysis of 218 randomized

controlled trials comprising 78 945 patients, target HbA1c levels (7%) was achieved in 25.9% to 63.2% of the patients depending on the modalities of treatment [4].

Defined as the difference between the systolic blood pressure (SBP) and the diastolic blood pressure (DBP), pulse pressure (PP) was considered to increase as a consequence of arterial stiffening starting from the fourth decade of life [5], while associated with a decrease in DBP and a gradual rise in SBP over 60 years of age [6].

PP is determined by the complex relationship between stroke volume of the heart, aortic elasticity and peripheral vascular resistance [7] and has been considered an independent risk factor for the all-cause and cardiovascular mortality of normotensive and hypertensive individuals [8]. Besides, data from *The Survival And Ventricular Enlargement (SAVE) study* revealed a positive correlation between the PP measured during 3-16 days following a myocardial infarction and the presence of diabetes [9].

Although hypertension (HT) was consistently reported to more prevalent among diabetic than nondiabetic population and shown to be a significant risk factor for diabetic complications [10,11], it has not yet been fully elucidated whether PP is a better indicator of diabetic complications than SBP. To our knowledge the relation of glycemic parameters directly to PP has never been explored in patients with type 2 DM.

The present multi-center retrospective study, therefore, was designed to evaluate HT prevalence and the relation of glycemic parameters to PP in patients with type 2 DM.

2. MATERIAL AND METHODS

2.1. Study population

A total of 422 patients (female n=290, 68.7%) with type 2 DM, mean age 58 ±13.2 years, were included in the multi-center retrospective study. Patients aged <20 years or >80 years, patients with malignancy, type 1 DM, chronic liver disease, pregnant patients, cardiac patients with New York Heart Association (NYHA) stage ≥III and patients with renal failure of glomerular filtration rate (GFR) <60% were excluded from the study. The patients were divided into 4 groups according to the PP readings including group 1 (PP ≤45 mmHg), group 2 (PP 46-54 mmHg), group 3 (PP 55-64 mmHg) and group 4 (PP≥ 65 mmHg).

The permission was obtained from our institutional ethics committee for the use of patient data for publication purposes.

2.2. Study parameters

Data on patient demographics (such as age, gender) the presence of HT, antihypertensive medications in use, SBP, DBP and PP readings were recorded in each patient as were the glycemic parameters including fasting blood glucose (FBG), postprandial blood glucose (PPBG) and HbA1c. Glycemic parameters were also evaluated with respect to PP groups.

2.3. Blood pressure measurement

Blood pressure measurements were performed using Omron M6 (HEM-7001-E; Omron, Kyoto, Japan) device. Patients on antihypertensive medication with a diagnosis of hypertension and those with blood pressure readings > 140/90 mmHg were considered hypertensive. PP values were calculated according to the “PP = SBP - DBP” formula.

2.4. Glycemic parameters

HbA1c levels were measured with boronate affinity high performance liquid chromatography method using Trinity Biotech Premier HB9210 device. For FBG and PPBG levels enzymatic UV test (hexokinase method) was used.

2.5. Statistical analysis

All statistical analyses were performed using SPSS version 17.0 (SPSS Inc. Chicago, IL, USA). Descriptive statistics for the continuous variables were expressed within a 95% confidence interval. Chi-square test was used for the comparison of qualitative data and Kruskal Wallis test for the comparison of glycemic parameters between groups. The Mann Whitney U test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. Data were expressed as “mean (standard deviation; SD)”, minimum-maximum and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1. Demographic and clinical characteristics of patients

Hypertension was evident in 79.6% of patients, while 85.7% of hypertensive patients were on antihypertensive medication. Mean (SD) SBP, DBP and glycemic parameters in the overall study population are shown in Table 1.

Table 1. Demographic and clinical characteristics of patients

Total patients	n	422
Female gender	n (%)	290 (68.7)
Age (years)	mean (min-max)	58 (41-76)
Hypertension	n (%)	336 (79.6)
Antihypertensive medication use	n (%)	288 (85.7)
Systolic blood pressure (mmHg)	mean (SD)	135.9 (19.3)
Diastolic blood pressure (mmHg)	mean (SD)	80.7 (11.1)
Pulse pressure (PP) (mmHg)	mean (SD)	55.3 (12.5)
Group 1: PP ≤ 45 mmHg	n (%)	102 (24.2)
Group 2: PP 46-54 mmHg	n (%)	124 (29.4)
Group 3: PP 55-64 mmHg	n (%)	128 (30.3)
Group 4: PP ≥ 65 mmHg	n (%)	68 (16.1)
Fasting blood glucose (mmol/L)	mean (SD)	9.0 (3.5)
Postprandial blood glucose(mmol/L)	mean (SD)	13.0 (3.2)
HbA1c (%)	mean (SD)	7.6 (1.7)

PP: pulse pressure

Mean PP was 55.3±12.5 mmHg and 24.2% of patients (n=102) were determined to have PP of less than 45 mmHg categorized in Group 1, 29.4% (n=124) were in Group 2 (PP between 46-54 mmHg), 30.3% (n=128) were in Group 3 (PP between 55-64 mmHg) and 16.1% (n=68) were in Group 4 (PP more than 65 mmHg) (Table 1).

3.2. Glycemic parameters with respect pulse pressure groups

Gender distribution was similar within the groups (p=0.35). In Group 1, the FBG (mmol/L), PPBG (mmol/L) and HbA1c (%) levels were determined as 8.6±3.9, 11.9±4.3, 7.2±1.4, respectively. In Group 2, the FBG (mmol/L), PPBG (mmol/L) and HbA1c (%) levels were determined as 8.8±3.7,

11.8±4.0, 7.0±1.2, respectively. In Group 3, the FBG (mmol/L), PPBG (mmol/L) and HbA1c (%) levels were determined as 9.2±4.1, 13.7±3.7, 7.9±1.6, respectively. In Group 4, the FBG (mmol/L), PPBG (mmol/L) and HbA1c (%) levels were determined as 9.4±3.2, 14.4±3.8, 8.4±2.1, respectively. While group 1 and 2 were similar in terms of glycemic parameters, FBG, PPBG and HbA1c were significantly lower than group 3 and group 4 ($p < .05$). Group 1 and 2 compared with group 3 and 4; The *p* values for FBG, PPBG and HbA1C were .026, .019 and .004, respectively (Table 2).

Table 2. Glycemic parameters with respect pulse pressure (PP) groups

	Pulse pressure			
	Group 1	Group 2	Group 3	Group 4
FBG (mmol/L), mean (SD)[1]	8.6 (3.9)	8.8 (3.7)	9.2 (4.1)	9.4 (3.2)
PPBG (mmol/L), mean (SD)[1]	11.9 (4.3)	11.8 (4.0)	13.7 (3.7)	14.4 (3.8)
HbA1c (%), mean (SD)[1]	7.2 (1.4)	7.0 (1.2)	7.9 (1.6)	8.4 (2.1)
Female, n (%)[2]	68 (66.7)	86 (69.3)	92 (71.9)	44 (64.7)

Group 1: PP ≤ 45 mmHg; Group 2: PP 46-54 mmHg; Group 3: PP 55-64 mmHg; Group 4: PP ≥ 65 mmHg. Group 1 and 2 compared with group 3 and 4; The *p* values for FBG, PPBG and HbA1C were .026, .019 and .004, respectively.
FBG: Fasting blood glucose; PPBG: Postprandial plasma glucose.
[1]Mann-Whitney U test with Bonferroni correction, [2] Chi-square test

Our findings in a retrospective cohort of patient with type 2 DM revealed the evidence of HT in 79.6% of patients along with significantly higher values for FBG, PPBG and HbA1c in patients with higher PP.

Elevation in PP was reported to be an independent risk factor for the all-cause and cardiovascular mortality of normotensive and hypertensive individuals [11]. According to Framingham data PP was identified to be the most important determinant of coronary artery disease in patients aged ≥50 years, when the association between the risk of coronary artery disease and SBP, DBP and PP was taken into account [12]. *INternational VErapamil-trandolapril STudy* (INVEST) also showed that PP is a strong predictor of cardiovasculer events in hypertensive elderly patients [13].

Given that aortic stiffness is an independent risk factor for coronary heart disease in patients with essential HT, being an indirect indicator of aortic stiffness, PP has been considered an important risk parameter for coronary heart disease and elevated levels were reported to be correlated also with left ventricular hypertrophy [14]. Harbaoui B at al. [15] showed that PP measured at admission is a strong, independent prognostic marker predicting mortality after acut coronary syndrome. Notably, based on the identification of higher PP in diabetes than nondiabetes in the previous reports [16] it has been suggested that diabetes may accelerate aortic and large arterial stiffness [17,18].

In this regard based the significantly higher values for FBG, PPBG and HbA1c in diabetic patients with higher PP, especially when PP values were ≥ 65 mmHg, our findings seem to indicate the negative impact of elevated PP on glycemic control in patients with type 2 diabetes mellitus, in addition to its well-documented relation to increased risk for coronary heart disease in patients with essential HT [19].

The United Kingdom Prospective Diabetes Study (UKPDS) showed that for every 1% decrease in HbA1c levels the incidence of myocardial infarction decreases by 14%, DM-related mortality by 21%, microvascular complications by 37% and amputations resulting from peripheral vascular disease by 43% [2]. Given that that glycemic regulation targets cannot be reached for about 60% of patients despite obvious importance of glycemic control, correlates of glycemic control in diabetic patients should be thoroughly investigated in terms of possible contributing factors. In our study, statistically significant differences were detected when the PP groups were compared for FBG, PPBG and HbA1c levels. This implies that increased PP may be a parameter that impairs glycemic regulation.

Considering the prevalence of HT in Type 2 DM, further analysis of 3648 patients newly diagnosed with type 2 DM who had been examined in the UKPDS study revealed HT in 39% of them according to data from *Hypertension in Diabetes Study* [20]. Likewise, Klein et al. [10] reported that HT affects 70% of diabetics, and it was two times more common among diabetic than non-diabetic population. *The Third National Health and Nutrition Evaluation Survey* (NHANES III) conducted in the United States revealed that 71% of the diabetics also suffer from HT [11]. Accordingly, identification of HT in 336 of 422 (79.6%) in our study population is in agreement with data on prevalence of HT on among patients with type 2 DM reported in past studies and confirms that DM and HT, which are major cardiovascular risk factors, often occur concomitantly and interact both in etiopathogenesis and in complications [21,22].

As a matter of fact, while there are numerous studies showing that HT is a risk factor for patients with DM, it is not still fully elucidated if PP is a better indicator of diabetic complications than SBP [11]. In the literature review that we conducted we could not find any studies directly comparing glycemic parameters and PP in diabetic patients. By which mechanism PP effects glycemic regulation seems a topic that needs to be thoroughly investigated. It is conceivable that antihypertensive drugs, which don't increase the pulse pressure, may provide additional benefits in the treatment of diabetic patients. As a result when deciding on the antihypertensive treatment of diabetic patients, the effects of the drugs on PP should be an important factor to be considered.

Zhang L at al. [23] showed that PP is related to risk of DM in prospective cohort study of 12 272 participants, especially in elderly women. There are studies showing a positive relationship between PP and diabetic microvascular complications in the literature. However, we did not find any study showing the relationship between PP and glycemic regulation.

Certain limitations to this study should be considered. Due to retrospective design of the present study, establishing the temporality between cause and effect as well as generalizing our findings to overall diabetic population seems difficult. Secondly, accuracy of data on blood pressure and glycemic parameters seems questionable given that they were based on single-measurement readings of blood pressure, FBG and PPBG or HbA1c. Lack of data on duration of diabetes, diabetes related complications and type of antihypertensive agents prescribed in treated hypertensive subjects is another limitation which otherwise would extend the knowledge achieved in the current study. Nevertheless, despite these certain limitations, given the paucity of the solid information available on this area, our findings represent a valuable contribution to the literature.

4. CONCLUSION

Our findings in the retrospective cohort revealed HT at a high frequency of 79.6% in patients with Type 2 DM. Significant higher values were found for FBG, PPBG and HbA1c in high PP patients. These results may be associated with increased cardiovascular risk in patients with poor glycemic control with Type 2 DM and high PP. Conduction of future larger scale prospective studies will allow better understanding of the association between glycemic control and PP in patients with type 2 DM.

CONSENT (WHERE EVER APPLICABLE)

Authors may use the following wordings for this section: "All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal".

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number 2016/44) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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