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Authors

Nelson, Noelle E
Hluhanich, Rebecca M
Wilson, Machelle
et al.

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Pharmacist Intervention Lowers HgbA1c in Diabetic Patients Regardless of HIV Status

Noelle E. Nelson, PharmD, MSPH,
University of California, Davis Health, 2315 Stockton Blvd, Sacramento, CA 95817

Machelle Wilson, PhD,
University of California, Davis Health, 2315 Stockton Blvd, Sacramento, CA 95817

Jeffrey Fine, MS,
University of California, Davis Health, 2315 Stockton Blvd, Sacramento, CA 95817

Rebecca M. Hluhanich, PharmD
University of California, Davis Health, 2315 Stockton Blvd, Sacramento, CA 95817

Abstract

Aim: Compare glycemic control in human immunodeficiency (HIV)-positive patients on antiretroviral therapy to HIV-negative patients following pharmacist interventions.

Methods/Results: This retrospective observational cohort study conducted at a Federally Qualified Health Center included adults with type II diabetes mellitus who attended at least two clinical pharmacy appointments between January 1, 2018 and July 31, 2019. Exclusion criteria included missing pre- or post-hemoglobin A1c (HgbA1c) values, type 1 diabetes, pregnancy, breastfeeding, deceased, or untreated HIV. The primary endpoint was change in HgbA1c from baseline to month 3. Secondary endpoints were change in HgbA1c at 6, 9, and 12 months, and time to goal. Additional endpoints included changes in number of anti-diabetic agents, blood pressure, body mass index, hypoglycemic events, percent of patients on a sodium-glucose co-transporter-2 (SGLT-2) inhibitor or glucagon-like peptide (GLP-1) agonist. This study was exempt from the University of California, Davis Institutional Review Board as a continuous quality improvement study.

Seventy-eight patients were included, 17 of whom were HIV-positive. At 3 months, HgbA1c was reduced by −1.7% and −1.2% (p =0.31) for HIV-positive and –negative patients, respectively. In the pooled cohort, HgbA1c was reduced from baseline at all time points, and 24% of patients achieved HgbA1c below 7.0%. The number of antidiabetic medications remained unchanged or was decreased in 60% of patients.

Corresponding Author: Nnelson@ucdavis.edu, rhluhanich@ucdavis.edu.

Authorship Statement

All listed authors comply with the journal's Authorship policy. None of the material has been published previously, is under consideration, or has been accepted for publication elsewhere. All persons listed as authors have read and given approval for the submission of the manuscript.

Ethics Statement

This study was exempt from University of California, Davis Health Center IRB as a quality improvement study.

Conflict of Interest Statement

None to disclose

Conclusion: The study demonstrated clinically important HgbA1c reductions without increasing the medication burden in most patients. There was no significant difference in glycemic management between HIV-positive and HIV-negative patients.

Keywords

diabetes mellitus; type 2; Human Immunodeficiency Virus; pharmacists; blood glucose; ambulatory care; Antiretroviral Therapy; Highly Active; clinical pharmacists

Introduction:

Human immunodeficiency virus (HIV) is a chronic inflammatory condition that alters insulin response in the body, increasing the risk for the development of type II diabetes mellitus (T2DM).[1] In the HIV-positive population, the prevalence of T2DM has been estimated to affect between 2–14% of patients.[2] Additionally, HIV-positive patients have been found to have a prevalence of T2DM 5.5% higher than non-HIV-positive persons (14% vs. 8.5%, respectively).[2] Several hypotheses have been proposed to explain the molecular mechanisms by which insulin resistance develops in patients with HIV. Mechanisms include the effects of combination antiretroviral therapies (cART) and the inflammatory pathophysiology of HIV disease in the development of insulin resistance.

In 2005, the Multicenter AIDS Cohort Study found that the incidence of T2DM was 1.4 per 100 person-years for HIV-negative men compared to 1.7 in HIV-positive men and 4.7 in HIV-positive men receiving cART.[3] This finding was substantiated in a 2017 meta-analysis, which found the odds of having T2DM were four times higher in HIV-positive, cART-exposed patients compared to those HIV-positive patients who were treatment naïve.[4]

In addition to cART being associated with an increased risk of T2DM, the chronic inflammatory nature of HIV may lead to metabolic dysfunction, thus increasing the risk for the development of insulin resistance. A review article by Hruz discussed the hypothesis that metabolic dysfunction in HIV-positive patients is related to decreased ability for adipose tissue to store triglycerides, causing increased lipid accumulation in liver and skeletal muscle, thereby inhibiting these organ's ability to respond to insulin.[1] Another hypothesized mechanism of insulin resistance in HIV-positive patients is the result of impaired glucose transport into adipose tissues, skeletal muscle, and the liver.[1] This impaired glucose uptake leads to increased hepatic glucose production and a worsening of glycemic control. Thus, infection with HIV and its subsequent treatment with cART places this patient population at an increased risk for T2DM.

Despite the higher prevalence of T2DM co-morbidity in patients with HIV, little research has been done into the ability to meet glycemic targets in HIV-positive patients versus HIV-negative patients. More studies are needed to address whether the management of T2DM in patients with co-morbid HIV is more complex in terms of reaching guideline-directed glycemic target endpoints compared to the management of T2DM in patients without HIV. The purpose of this study was to evaluate the difference in glycemic control between HIV-positive and HIV-negative patients when managed by a clinical pharmacist in a federally qualified health center (FQHC).

Methods:

Trial Design

This was a retrospective observational cohort quality improvement study of adults enrolled in a FQHC in Sacramento, California who were referred to a clinical pharmacist for diabetes management. Once referred by their primary care physicians, clinical pharmacists assisted with the management of the patient's diabetes with a focus on tailoring the patient's pharmacotherapy and lifestyle modifications. Patients routinely met with the clinical pharmacist either in-clinic or telephonically for 30 to 60-minute appointments dedicated to diabetes, hypertension, and hyperlipidemia. Clinical pharmacists at this clinic practice under a collaborate practice agreement which allows for initiation, titration, and discontinuation of medication therapies, ordering labs, and placing referrals to a registered dietician, if appropriate. Clinical pharmacists also provide education in a manner that is consistent with the current American Diabetes Association (ADA) guidelines. Areas of education routinely provided to all patients include disease state education, diet and lifestyle modifications, medication counseling, review of the signs and symptoms of hypo- and hyperglycemia, and hypoglycemia prevention and management. Through collaboration with pharmacy technicians, clinical pharmacists also provide medication access support to all patients. The study included patients with a clinical diagnosis of T2DM who attended at least two diabetes-focused appointments with a clinical pharmacist between January 1, 2018 and July 31, 2019. Data were collected through November 30, 2019 to allow at least one hemoglobin A1c (HgbA1c) measurement to be collected after patients completed their first appointment. Patients were excluded if they did not have a HgbA1c measured prior to their first appointment with the clinical pharmacist or any HgbA1c measured two to 13 months after their first meeting with a clinical pharmacist. Additionally, patients were excluded if they had type 1 diabetes, were pregnant or breastfeeding, were deceased at the time of enrollment, or had a diagnosis of HIV, but were not on cART.

This study was exempt from the University of California, Davis Institutional Review Board as a continuous quality improvement study as defined by the United States Department of Health and Human Services. All patient records and pertinent information were de-identified prior to the analysis.

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Outcomes

The primary outcome was defined as the change in HgbA1c at baseline to HgbA1c measured 3 months after the patient's first appointment with a clinical pharmacist, with a range of plus or minus one month. Secondary outcomes included the change in HgbA1c at baseline to HgbA1c at months 6, 9, and 12 after the patient's first visit with a clinical pharmacist, again with a range of plus or minus one month, as well as the percent of patients reaching goal HgbA1c per 2019 ADA guidelines, and time, in months, to reach

this goal.[5] Change from baseline in the HbgA1c in the pooled cohort was also analyzed at all timepoints. Additional endpoints collected included changes in the following variables pre- and post-intervention: number of anti-diabetic agents; blood pressure; body mass index (BMI); percent with reported hypoglycemia; and percent on a sodium-glucose transport protein 2 (SGLT-2) inhibitor or a glucagon-like peptide (GLP-1) agonist. HgbA1c goal according to ADA guidelines was defined as a HgbA1c less than 7% for all patients. Patients met criteria for hypoglycemia if at any visit they endorsed having signs and symptoms of low blood sugar, or if they had a home glucometer reading of less than or equal to 70 mg/dL.

Statistical Analysis

The sample size calculation for this study was based on a 1.0% difference in mean HgbA1c values between groups and a standard deviation of 1.3, which has been used in clinical trials to assess HgbA1c lowering efficacy of pharmacologic therapy. Enrollment of 36 patients per group was calculated to provide 80% power and a two-sided alpha of 0.05 for the primary endpoint. All continuous variables were compared using a student's t-test assuming unequal variances and a two-tailed alpha of 0.05. All categorical variables were analyzed using descriptive statistics and Fisher's exact with a two-tailed alpha of 0.05. Multivariable general linear models were performed to test for differences in A1c levels at four different time points by HIV status, controlling for baseline A1c, BMI, sex, and ethnicity. A p-value of 0.05 was considered statistically significant. All analyses were performed in SAS® software version 9.4 for Windows®. The small sample size and degree of missingness did not allow for repeated measures regression.

Results:

From January 1, 2018 to July 31, 2019 a total of 228 patients were referred for appointments with a clinical pharmacist, 224 of which were referrals for diabetes management. Of those patients, only 78 met inclusion criteria, 17 of whom were HIV positive. Reasons for exclusion are as follows: never made appointment (n=49), outside of inclusion window (n=45), only had one appointment (n=23), lacked initial HgbA1c (n=11), lacked post-intervention HgbA1c (n=4), deceased (n=2), and age (n=1). Baseline demographics are presented in Table 1. The average age was 52 years for both groups. The majority of patients in the HIV-positive cohort self-identified as African American and male while the majority of HIV-negative patients self-identified as Hispanic and female. Baseline HgbA1c were relatively similar between groups, however, baseline BMIs were higher in the HIV-negative group.

On average, patients attended eight 30 to 60-minute diabetes-focused visits with a clinical pharmacist over the course of a 12-month follow-up period. For the primary endpoint, 13 patients in the HIV-positive group and 46 patients in the HIV-negative group had HgbA1c values measured at month 3. There was no difference in the change in HgbA1c compared to baseline between patients in the HIV-positive and –negative cohorts with a HgbA1c measurement at month 3 (−1.7 ± 1.2% vs. −1.2 ± 2.3%, respectively; p=0.31) (Table 2).

HgbA1c was reduced in the majority of HIV-positive and -negative patients at months 3, 6, 9, and 12 (Table 3). After controlling for baseline differences in HgbA1c, sex, ethnicity, and

BMI, HIV-positive patients did not have statistically significant changes in average HgA1c at any of the four follow-up time points compared to the HIV-negative group (p_{month3}=0.10, p_{month6}=0.89, p_{month9}=0.24, and $p_{month12}$=0.48). It took an average of 5.7 months for 19 total patients to reach an HgbA1c goal of less than 7%. It took an average of 4.4 months for 47 patients to reach HgbA1c values of less than or equal to 8%.

In the pooled cohort, HgbA1c values were reduced from baseline at month 3 by 1.3%, month 6 by 1.6%, month 9 by 1.0%, and month 12 by 1.1% (Figure 1). In the pooled cohort, 24% of patients achieved HgbA1c levels less than 7.0%, and 47% achieved HgbA1c levels less than or equal to 8.0%, which is the Medicare and Medicaid goal HgbA1c for FQHC metrics.[6]

Overall, pharmacist intervention resulted in 22% of patients being started on an SGLT-2 inhibitor or GLP-1 agonist, a reduction in hypoglycemic episodes by 9%, and systolic and diastolic blood pressures reduction by 4.3 mmHg and 5.1 mmHg, respectively. The number of antidiabetic medications remained unchanged (51%) or was decreased (9%) in most patients. Of the eight patients who had an increase in the number of antidiabetic agents by two or three agents, the average baseline HgbA1c was 11.4% and HgbA1c was reduced to an average of 10.2% following pharmacist intervention. The two patients who had three agents added compared to baseline both had baseline HgbA1c's greater than 10% and were not on any antidiabetic agents prior to pharmacist intervention.

By the end of the study period, all 29 patients who did not have a referral to a registered dietician from their primary care provider prior to pharmacist intervention were referred. Additionally, all patients were provided with education on diabetes disease state, diet, and exercise.

Discussion:

In this study, clinically significant reductions in HgbA1c were observed in both the HIV-positive and HIV-negative cohorts following pharmacist's interventions, which included pharmacotherapy modifications, counseling on lifestyle modifications, and disease state education. However, the study was underpowered to detect a difference in glycemic control between the groups. Although the study was not powered to find a statistical difference, the clinical significance of the observed effects of pharmacist intervention cannot be overlooked. The 2000 United Kingdom Prospective Diabetes Study (UKPDS) found that for every percent reduction in HgbA1c, there was a 21% corresponding reduction in the risk for events related to diabetes, a 21% reduction in risk of death from diabetes, a 14% reduction in risk for myocardial infarction, and a 37% reduction in risk for microvascular complications.[7]

Nearly half of patients in the pooled cohort reached the FQHC goal HgbA1c of 8% or less. Given the social and medical complexity and financial disadvantage of patients seen at our clinic, the impact of pharmacist intervention to promptly reduce HgbA1c and with durability over the following 12 months is clinically significant. Additionally, 24% of patients were able to surpass FQHC glycemic standards and achieved HgbA1c target of less than 7%, consistent with national guidelines.

Pharmacist intervention also resulted in the initiation of antidiabetic agents with cardiovascular and renal benefits (GLP-1s and SGLT-2s) in an additional 22% of patients. These agents have been shown in clinical trials to reduce the risk for cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for heart failure in patients with T2DM, and will likely have clinical benefit beyond what was measured in the current study.[8–13] In addition, pharmacist intervention resulted in reductions in systolic and diastolic blood pressures and an overall maintenance of BMI, which both have the potential to reduce cardiovascular risk. Finally, pharmacist intervention resulted in improved safety outcomes for patients as evidenced by the reduction in reports of hypoglycemia.

Most patients were maintained on the same number of antidiabetic agents (51%) or had a reduction of agents (9%) compared to baseline. In this study, pharmacists demonstrated their ability to improve glycemic control through careful medication selection without needing to increase the medication burden for 60 percent of patients. This is especially important for patients with limited resources in which medication copays can be burdensome and complex medication regimens can be overwhelming, especially in the setting of low health literacy.

One weakness of the present study was that it was underpowered in the HIV-positive group to find a statistical difference in the primary endpoint. A second weakness was that our study used HgbA1c as a surrogate marker for glycemic control, which may not be the most accurate measure in HIV-positive patients. In their prospective cross-sectional study, Kim et al. found that HgbA1c underestimates glycemia in HIV-infected patients, and the underestimation was most pronounced in patients on nucleoside reverse transcript inhibitors (NRTI).[14] Thus, HgbA1c measurement may have underestimated hyperglycemia in 15 of 17 patients in our HIV-positive cohort who were on NRTI therapies during the study duration. Finally, the retrospective nature of this study did not allow for control over potential confounding factors that could have resulted in changes in HgbA1c such as weight loss, nutrition changes, or other lifestyle modifications. However, it is important to note that part of the standardized pharmacist workflow in this FQHC is to provide education on diet, nutrition, and exercise, while optimizing medications that promote weight loss and minimize weight gain.

One strength of our study was its inclusion of patients with significantly elevated baseline HgbA1c values receiving care at a FQHC by a clinical pharmacist. Another strength of the present study was that it included diabetic patients with HIV and assessed their ability to reach glycemic targets compared to a cohort of diabetic patients without HIV. The current ADA guidelines do not make special recommendations for how to manage diabetes in patients with concomitant HIV, and thus is it important to look at management strategies for these patients to determine how to safely and effectively address glycemic control in this population.[5]

Although our study was underpowered to see a difference in the ability to reach glycemic targets in HIV versus non-HIV infected patients in this cohort, we did appreciate clinically significant HgbA1c reductions from baseline, without increasing the medication burden and while reducing the incidence of hypoglycemia for most patients. Future studies are needed

to prospectively examine the impact of a standardized pharmacist workflow on glycemic outcomes for patients with and without HIV.

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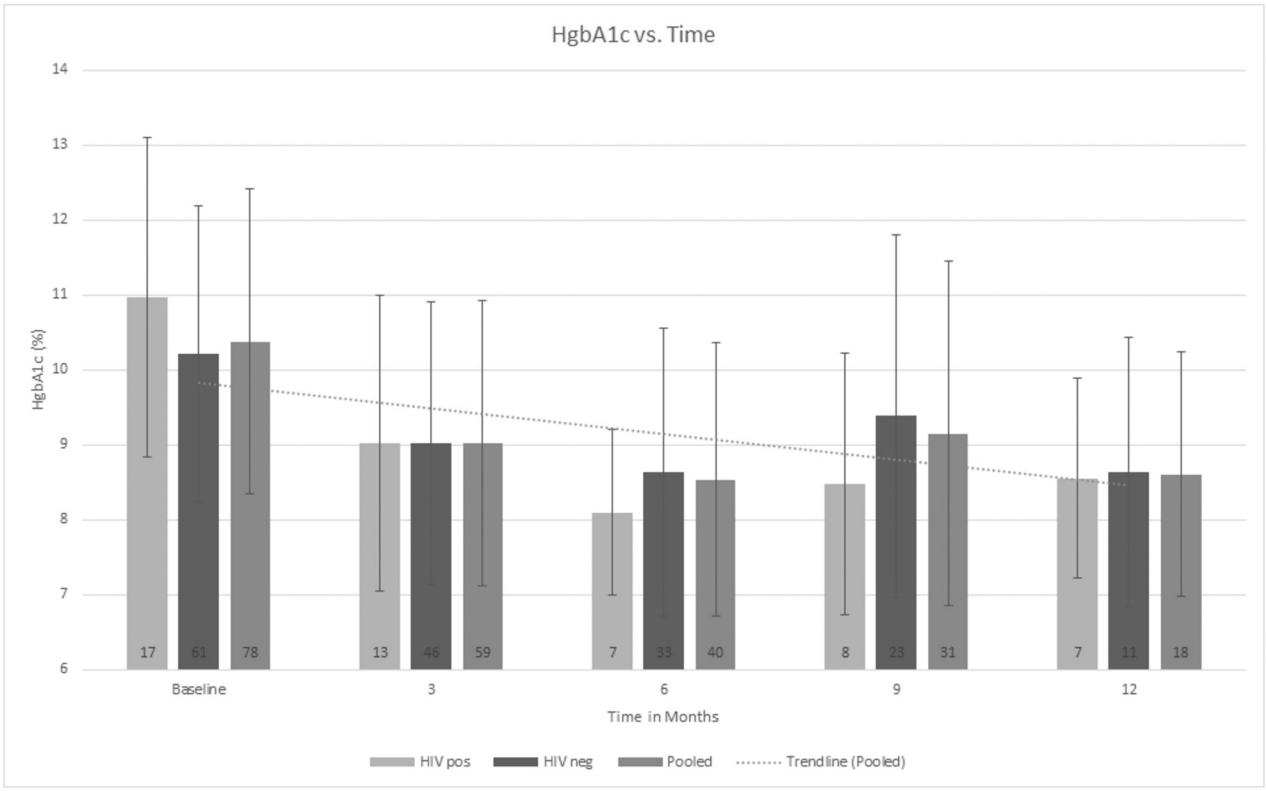

Figure 1: HgbA1c vs. Time

Numbers in the bottom of each bar denotes number of patients with measured HgbA1c at that time point. Abbreviations: HIV neg: HIV negative; HIV pos: HIV positive

Table 1.

Baseline Characteristics

Demographic Data	HIV Positive (n=17)	HIV Negative (n=61)	P-value
Age (years ± SD)	52.5 ± 8.4	52.6 ± 10.0	0.98
Male, n (%)	13 (76%)	24 (39%)	0.005*
Ethnicity, n (%)			
White	3 (18%)	17 (28%)	0.019*
African American	10 (59%)	10 (16%)	
Hispanic	4 (24%)	27 (44%)	
Other	0	7 (12%)	
Baseline HgbA1c (% ± SD)	11.0 ± 2.1	10.2 ± 2.0	0.216
Baseline BMI (kg/m^2 ± SD)	30.2 ± 5.2	34.1 ± 9.7	0.036*
Established ASCVD, n (%)	5 (29%)	10 (16%)	0.297
Active Smoker, n (%)	8 (47%)	20 (33%)	0.392
CKD Stage 3–4, n (%)	0	9 (15%)	0.193
CKD on dialysis, n (%)	1 (6%)	1 (2%)	0.391
On hormone therapy, n (%)	2 (12%)	2 (3%)	0.205
Baseline SBP (mmHg ± SD)	135 ± 14.0	137 ± 20.9	0.685
Baseline DBP (mmHg ± SD)	85 ± 7.6	81 ± 12.8	0.074
Antidiabetic agents, (number ± SD)	1.7 ± 1.0	2.8 ± 1.0	0.074

*denotes $p < 0.05$; SD: standard deviation; HgbA1c: hemoglobin A1c; BMI: body mass index; ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease, SBP: systolic blood pressure; DBP: diastolic blood pressure

Table 2:

Primary Endpoint

	HIV Positive (n=17)	HIV Negative (n=61)	P-value for difference	Pooled Cohort (N=78)
Average baseline HgbA1c (% ± SD)	11.0 ± 2.1	10.2 ± 2.0	0.22	10.4 ± 2.0
Average HgbA1c (% ± SD) at month 3	9.0 ± 2.1 n=13	9.0 ± 1.9 n= 46	> 0.99	9.0 ± 1.9 n=59
Average change in HgbA1c at month 3 (% ± SD)	−1.9 (95% CI −2.4 to −1.0) n=13	−1.2 (95% CI −1.9 to −0.5) n=46	0.31	−1.4 (95% CI −1.9 to −0.8) n=59

SD: standard deviation; HgbA1c: hemoglobin A1c

Table 3:

Additional Endpoints

Endpoint	HIV Positive (n=17)	HIV Negative (n=61)	Pooled Cohort (N=78)
Average number of visits with clinical pharmacist	7.7	7.4	7.7
Number of patients with HgbA1c reduction at month:			
3	12 (92%)	33 (72%)	45 (76%)
6	8 (100%)	24 (75%)	32 (80%)
9	7 (88%)	15 (65%)	22 (71%)
12	6 (86%)	8 (73%)	14 (78%)
Average change in HgbA1c at month:			
6 (% ± SD)	−2.8 ± 2.2, (n=8)	−1.4 ± 2.4, (n=32)	−1.6 ± 2.4, (n=40)
9 (% ± SD)	−3.2 ± 2.9, (n=8)	−0.2 ± 2.7, (n=23)	−1.0 ± 3.0, (n=31)
12 (% ± SD)	−2.1 ± 2.1, (n=7)	−0.4 ± 2.3, (n=11)	−1.1 ± 2.3, (n=18)
Patients reaching HgbA1c less than 7%	5 (29%)	14 (23%)	19 (24%)
Time to reaching HgbA1c less than 7% (months ± SD)	4.6 ± 3.8	6.6 ± 2.9	5.7 ± 3.5
Patients reaching HgbA1c less than or equal to 8%	10 (59%)	27 (44%)	37 (47%)
Time to reaching HgbA1c less than or equal to 8% (months ± SD)	6.0 ± 3.7	3.8 ± 3.7	4.4 ± 3.5
Change in percent on SGLT-2 inhibitor or GLP-1 agonist	+35%	+18%	+22%
Change in percent of hypoglycemic events	+6%	−13%	−9%
Average change in SBP pre and post (mmHg)	−2.9 ± 12.7	−4.6 ± 21.6	−4.3 ± 19.9
Average change in DBP pre and post (mmHg)	−4.1 ± 10.1	−5.4 ± 14.3	−5.1 ± 13.4
Average change in BMI pre and post (mg/m^2)	+0.9 ± 1.9	−0.1 ± 2.1	+0.1 ± 2.1
Change in Number of antidiabetic agents	--	-	−1: 7 (9%) 0: 40 (51%) +1: 23 (30%) +2: 6 (8%) +3: 2 (4%)

SD: standard deviation; HgbA1c: hemoglobin A1c; SGLT-2; Sodium glucose co-transporter; GLP-1: glucagon-like peptide; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index