CLINICAL AND GENETIC PREDICTORS OF BLOOD PRESSURE CONTROL IN PATIENTS WITH CONCOMITANT TYPE 2 DIABETES MELLITUS AND ARTERIAL HYPERTENSION

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Annotation. Concomitant type 2 diabetes mellitus (T2DM) and arterial hypertension (AH) is one of the most challenging combinations in internal medicine. International guidelines classify these patients as very high cardiovascular risk and recommend stringent blood pressure targets, generally below 130/80 mmHg. Nevertheless, real-world data consistently show that fewer than one in four patients with T2DM+AH achieves recommended control. The reasons for this therapeutic gap are multifactorial, encompassing treatment adherence, lifestyle, physician inertia, comorbidity burden and, increasingly recognized, genetic variability in the physiological systems that regulate blood pressure.

INTRODUCTION

The renin–angiotensin–aldosterone system (RAAS) is the principal pharmacological target in this population, and the efficacy of RAAS blockade is well established. Yet response to RAAS-modulating drugs varies considerably between individuals. Genetic polymorphisms that influence the activity of the RAAS cascade — such as the angiotensinogen gene M235T variant (rs699) and the angiotensin II type-1 receptor gene A1166C variant (rs5186) — have been proposed as determinants of both hypertension susceptibility and treatment response. The 235T allele of AGT is associated with higher angiotensinogen levels, while the 1166C allele of AGTR1 may alter receptor expression and signaling. Individually, each variant confers a modest effect; in combination, they may substantially modify the clinical phenotype.

Most studies of RAAS pharmacogenetics have been conducted in European or East Asian cohorts. Data from Central Asia, including Uzbekistan, are scarce despite a high and rising burden of T2DM+AH in the region. Identifying clinical and genetic predictors of poor blood pressure control in Uzbek patients would support risk stratification and could ultimately guide individualized therapy — for instance, earlier or more intensive RAAS blockade in carriers of risk alleles.

LITERATURE REVIEW

Blood pressure control in diabetes has been examined in large trials and registries. The ADVANCE and ACCORD studies established that intensive blood pressure lowering reduces cardiovascular events in diabetic patients, while UKPDS demonstrated the long-term benefit of tight control beginning early in the disease course. However, post-hoc analyses of these trials revealed substantial inter-individual variability in achieved blood pressure, only partly explained by baseline characteristics, adherence or drug class — pointing to a genetic contribution.

Pharmacogenetic studies of RAAS variants have produced a complex picture. For AGT M235T, several reports suggested that 235T carriers respond better to angiotensin-converting enzyme inhibitors, with greater blood pressure reduction, whereas other studies found no interaction. For AGTR1 A1166C, some investigators reported enhanced response to angiotensin receptor blockers in 1166C carriers. Meta-analyses have generally concluded that effects are real but small, and that their clinical utility depends on the genetic background of the population studied and on the clinical phenotype examined — susceptibility, severity or treatment response.

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Importantly, most pharmacogenetic work has focused on treatment response rather than on the clinically prior question of which patients fail to reach blood pressure targets despite therapy. Few studies have combined both major RAAS variants in a single analysis of control status. Asian data indicate that combined risk-allele carriage is associated with earlier onset and more severe hypertension; however, to our knowledge, no study has quantified the effect of dual RAAS risk-allele carriage on blood pressure control in Central Asian patients with T2DM+AH. The present study was designed to address this gap.

MATERIALS AND METHODS

Study population. This cross-sectional study enrolled 120 patients with concomitant T2DM and AH receiving regular outpatient care in Samarkand region, Uzbekistan, between 2024 and 2026. T2DM was diagnosed according to WHO/IDF criteria, and AH according to current ESH/ESC office blood pressure thresholds or documented antihypertensive therapy. Patients were classified as controlled (office SBP <140 and DBP <90 mmHg) or uncontrolled (SBP ≥140 and/or DBP ≥90 mmHg). Exclusion criteria were type 1 diabetes, gestational diabetes, secondary hypertension, severe renal impairment (eGFR <30 ml/min/1.73 m²), acute cardiovascular events in the preceding three months, and absence of informed consent.

Clinical and laboratory assessment. Standardized office blood pressure measurement was performed twice after five minutes of rest; the mean was used. Anthropometry included height, weight, BMI and waist circumference; abdominal obesity was defined as waist circumference >102 cm in men and >88 cm in women. Fasting glucose, HbA1c, lipid profile, creatinine and urinary albumin-to-creatinine ratio were measured by routine methods. Target-organ damage was assessed by electrocardiographic LVH criteria (Sokolov–Lyon, Cornell) and urinary albumin excretion. Physical activity, smoking status and antihypertensive regimen were recorded; adherence was assessed by pill count and self-report.

Genotyping. Genomic DNA was extracted from peripheral leukocytes. AGT M235T (rs699) and AGTR1 A1166C (rs5186) were genotyped by PCR–RFLP: the 429-bp AGT amplicon was digested with Tth111I (235M → 329+100 bp; 235T uncut), and the 376-bp AGTR1 amplicon with Tsp45I (AA → 376 bp; AC → 376+284+92 bp; CC → 284+92 bp). Ten percent of samples were re-genotyped with 100% concordance.

Statistical analysis. Continuous variables are presented as mean ± SD and compared by Student's t-test or Mann–Whitney U test; categorical variables by chi-square test. Logistic regression identified independent predictors of uncontrolled hypertension, adjusting for age, sex, BMI, diabetes duration and antihypertensive regimen. Multiplicative interaction between the two genetic variants was tested by including a product term in the model. Two-sided $p<0.05$ was considered significant. Analyses were performed in SPSS 26.0.

RESULTS

Study population characteristics. The cohort comprised 120 patients (61 men, 59 women) with a mean age of 57.8±7.4 years and mean diabetes duration of 8.2±4.1 years. Mean BMI was 29.5±3.6 kg/m² and mean HbA1c was 7.9±1.3%. Antihypertensive regimens included RAAS blockers in 78.3% of patients, calcium channel blockers in 52.5%, diuretics in 43.3% and beta-blockers in 30.8%; most patients (64.2%) received two or more agents.

Blood pressure control status. Controlled hypertension was achieved in 41.7% (50/120) of patients; 58.3% (70/120) remained uncontrolled. Compared with the controlled group, uncontrolled patients were

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older (59.6±6.8 vs 55.3±7.6 years, p<0.01), had longer diabetes duration (9.1±4.0 vs 6.9±3.9 years, p<0.01), higher HbA1c (8.4±1.2 vs 7.2±1.1%, p<0.001), higher BMI (30.2±3.4 vs 28.5±3.7 kg/m², p<0.05) and more frequent abdominal obesity (65.7% vs 46.0%, p<0.05). There was no significant difference in antihypertensive regimen intensity between groups.

Genetic findings. The frequency of AGT 235T allele carriers (MT+TT) was 58.6% in uncontrolled versus 40.0% in controlled patients (p<0.05); AGTR1 1166C allele carriers (AC+CC) were 55.7% versus 34.0% (p<0.05). Combined carriers of both risk alleles (T and C) represented 31.4% of uncontrolled patients versus 12.0% of controlled patients (p<0.01). Both genotype distributions were in Hardy–Weinberg equilibrium.

Logistic regression analysis (adjusted for age, sex, BMI, diabetes duration and regimen) identified the following independent predictors of uncontrolled hypertension: HbA1c >8% (OR 2.31; 95% CI 1.12–4.78), abdominal obesity (OR 1.96; 95% CI 1.03–3.73), AGTR1 1166C allele carriage (OR 2.07; 95% CI 1.08–3.97) and AGT 235T allele carriage (OR 1.84; 95% CI 1.02–3.34). Combined carriage of both risk alleles increased the odds of uncontrolled hypertension 3.2-fold (OR 3.19; 95% CI 1.40–7.31).

Secondary outcomes. Among uncontrolled patients, target-organ damage was more frequent: LVH by ECG criteria 40.0% versus 22.0% (p<0.05) and microalbuminuria 45.7% versus 24.0% (p<0.01). In the subgroup carrying both risk alleles, the mean number of antihypertensive agents (2.3±0.8) and the prevalence of LVH (47.4%) were the highest in the cohort.

Correlation analysis showed that HbA1c correlated with office SBP (r=0.34, p<0.01) and that the number of risk alleles (0, 1, or 2 loci) correlated with uncontrolled status (r=0.31, p<0.01).

DISCUSSION

In this cohort of Uzbek patients with T2DM+AH, three clinical variables — poor glycemic control, abdominal obesity and longer diabetes duration — and two RAAS genetic variants independently predicted uncontrolled hypertension. The clinical findings are consistent with the established literature: hyperglycemia promotes vascular stiffness and sodium retention, visceral adiposity amplifies RAAS activation through adipose-derived angiotensinogen, and prolonged exposure to both insults accumulates target-organ damage that further blunts pressure control.

The genetic findings are the novel contribution of this study. Both AGT 235T and AGTR1 1166C allele carriages were independent predictors of poor control, and their combined effect was more than additive, with a 3.2-fold increase in odds. This synergy is biologically plausible: the 235T allele raises substrate supply for the RAAS cascade, while the 1166C allele may enhance receptor-mediated signaling of angiotensin II. In the metabolically adverse environment of T2DM, this dual genetic load appears to overwhelm standard antihypertensive regimens, as reflected by the higher pill burden and LVH prevalence in dual carriers.

Our results extend previous Asian reports of single-variant associations by demonstrating a dose–response relationship between the number of RAAS risk alleles and control failure. They also resonate with the concept of precision cardiovascular medicine: patients carrying both risk alleles might benefit from earlier initiation of combination therapy with RAAS blockade as the backbone, possibly combined with mineralocorticoid receptor antagonism or sodium-glucose cotransporter-2 inhibition, and from structured home blood pressure monitoring to verify control.

Several limitations must be noted. The cross-sectional design precludes causal inference, and office blood pressure — rather than ambulatory monitoring — was used to define control, which may misclassify white-coat and masked hypertension. The sample size limits the power of subgroup and

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interaction analyses, and plasma renin/angiotensinogen levels were not measured. Replication in a larger, prospective cohort with ambulatory blood pressure monitoring and detailed pharmacological phenotyping is the logical next step.

CONCLUSION

1. Uncontrolled hypertension was observed in 58.3% of Uzbek patients with concomitant T2DM and AH despite active therapy.

2. Independent predictors of poor control included HbA1c >8% (OR 2.31), abdominal obesity (OR 1.96), AGTR1 1166C allele carriage (OR 2.07) and AGT 235T allele carriage (OR 1.84).

3. Combined carriage of both RAAS risk alleles increased the odds of uncontrolled hypertension more than threefold (OR 3.19; 95% CI 1.40–7.31), indicating a clinically relevant gene–gene interaction.

4. A combined clinical–genetic assessment, integrating glycemic control, adiposity measures and RAAS-variant genotyping, is a rational basis for personalized cardiovascular risk stratification and intensified antihypertensive strategies in this high-risk population.

DISCUSSION (continued)

From a public health perspective, these findings are relevant to the organization of hypertension care in Uzbekistan. Integrating HbA1c monitoring and waist circumference measurement — both inexpensive and widely available — with targeted genetic testing in selected high-risk patients could improve resource allocation. Patients identified as dual risk-allele carriers could be enrolled in intensified management pathways with home blood pressure telemonitoring and earlier specialist review.

Finally, the interaction between glycemic control and genetic risk observed in our cohort suggests that diabetes management and hypertension management should be pursued as a unified strategy in this population. Optimizing HbA1c may partially offset the genetic disadvantage, whereas neglecting either component compounds the risk of both target-organ damage and loss of blood pressure control.

REFERENCES

1. IDF Diabetes Atlas. 10th ed. Brussels: International Diabetes Federation; 2025.
2. Williams B., Mancia G., Spiering W. et al. ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2024.
3. Patel A., MacMahon S., Chalmers J. et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (ADVANCE). Lancet. 2007;370:829–840.
4. Cushman W.C., Evans G.W., Byington R.P. et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus (ACCORD). N Engl J Med. 2010;362:1575–1585.
5. Turnbull F., Neal B., Algert C. et al. Effects of different blood pressure-lowering regimens on major cardiovascular events: results of prospectively designed overviews of randomized trials. Lancet. 2003;362:1527–1535.
6. Staessen J.A., Wang J., Bianchi G., Birkenhäger W.H. Essential hypertension. Lancet. 2003;361:1629–1641.
7. Arnett D.K., Davis B.R., Ford C.E. et al. Pharmacogenetic association of the angiotensinogen M235T variant with blood pressure response to antihypertensive treatment. J Hypertens. 2005;23:1771–1778.
8. Kurland L., Melhus H., Karlsson J. et al. AGTR1 gene polymorphism and cardiovascular response to antihypertensive therapy. J Hypertens. 2004;22:2211–2218.

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9. Shi G., Li M. et al. Combined association of AGT M235T and AGTR1 A1166C polymorphisms with hypertension in a Chinese population. Clin Chim Acta. 2023;540:117–123.
10. O'zbekiston Respublikasi Sog'liqni saqlash vazirligi. Qandli diabetning diagnostikasi va davolash bo'yicha milliy protokol. Toshkent; 2024.
11. Ellamonov S.N. 2 tip qandli diabet bilan og'rigan bemorlarda arterial gipertenziyaning avj olishining klinik-genetik omillari. Dissertatsiya materiallari. Samarqand; 2026.

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