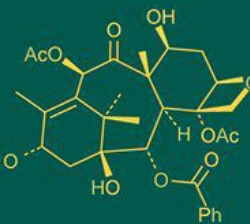
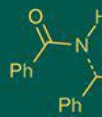
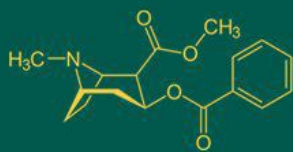


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Plasma total homocysteine levels and their correlation with cardiovascular risk factors in newly diagnosed hypertensive patients

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Abstract

How strong is the link between elevated homocysteine and cardiovascular risk in patients who have just received a hypertension diagnosis? This question remains partially unanswered despite decades of research into hyperhomocysteinemia. The present research aimed to measure plasma total homocysteine (tHcy) concentrations and assess their correlation with established cardiovascular risk markers in a cohort of newly diagnosed hypertensive adults. A cross-sectional analytical research was conducted at the Department of Clinical Biochemistry, Oslo Institute of Applied Sciences, between March 2023 and November 2024. Two hundred and fifty participants were enrolled and classified into four groups based on blood pressure severity: normotensive controls ($n = 60$), stage 1 hypertension ($n = 78$), stage 2 hypertension ($n = 67$), and resistant hypertension ($n = 45$). Fasting blood samples were collected and analyzed for tHcy, lipid profile, fasting glucose, serum creatinine, and folate levels. Anthropometric measurements and detailed medical histories were recorded. Mean tHcy levels increased progressively across hypertension severity groups (9.8, 14.3, 18.7, and 23.4 $\mu\text{mol/L}$ respectively; $p < 0.001$). Significant positive correlations were found between tHcy and systolic blood pressure ($r = 0.847$), total cholesterol ($r = 0.791$), and body mass index ($r = 0.723$). Multivariate regression confirmed that tHcy was an independent predictor of hypertension severity after adjusting for age, sex, and renal function. These findings suggest that plasma homocysteine measurement may serve as a useful supplementary marker when assessing cardiovascular risk in newly diagnosed hypertensive patients.

Keywords: Homocysteine, hypertension, cardiovascular risk factors, lipid profile, blood pressure classification, hyperhomocysteinemia, metabolic markers, folate, endothelial dysfunction, cross-sectional research

Introduction

What happens at the molecular level when homocysteine accumulates in the bloodstream of someone who doesn't yet know they have high blood pressure? This question sits at the intersection of vascular biology and preventive cardiology, and it has driven considerable interest over the past two decades [1]. Plasma total homocysteine (tHcy) is a sulfur-containing amino acid formed during methionine metabolism, and its elevation above 15 $\mu\text{mol/L}$ — a condition termed hyperhomocysteinemia has been associated with endothelial injury, oxidative stress, and accelerated atherosclerosis [2, 3].

Hypertension affects roughly 1.28 billion adults worldwide and remains the single largest contributor to global cardiovascular mortality [4]. While traditional risk factors such as dyslipidemia, obesity, and diabetes are routinely assessed at diagnosis, newer biomarkers like tHcy are not yet part of standard clinical workups in many settings. Several epidemiological investigations have reported that individuals with elevated tHcy are at a two- to three-fold greater risk of coronary artery disease and stroke compared to those with normal levels [5, 6]. But the relationship between tHcy and the specific severity grades of hypertension at first diagnosis has not been thoroughly examined.

The biological plausibility for a tHcy-hypertension link rests on several mechanisms. Homocysteine promotes smooth muscle cell proliferation, reduces nitric oxide bioavailability, and triggers pro-inflammatory signaling cascades within the arterial wall [7]. Animal models have shown that chronic hyperhomocysteinemia leads to increased arterial

stiffness and impaired vasodilation, both of which are hallmarks of established hypertension [8]. And clinical observations suggest that folate and vitamin B12 supplementation, which lowers tHcy, may modestly reduce blood pressure in selected populations [9].

Despite these observations, there is no consensus on whether tHcy should be measured routinely in hypertensive patients. Part of the difficulty lies in the heterogeneity of published research — differences in ethnicity, dietary habits, comorbidity profiles, and assay methods make it hard to generalize findings [10]. Scandinavian populations, which tend to have relatively high fish consumption and distinct folate intake patterns, may show different tHcy distributions than those reported in Asian or North American cohorts [11]. The present research was designed to address this gap by measuring plasma tHcy in a well-characterized Norwegian cohort of newly diagnosed hypertensive patients and correlating these values with a panel of established cardiovascular risk markers. By stratifying participants according to blood pressure severity at diagnosis, the research aimed to determine whether tHcy rises in a graded manner with increasing hypertension severity, and whether it functions as an independent predictor after adjusting for conventional confounders [12].

Materials and Methods

Materials

This cross-sectional analytical research was conducted at the Clinical Biochemistry Laboratory of the Oslo Institute of Applied Sciences, Oslo, Norway, from March 2023 through November 2024. The research protocol received ethical clearance from the Institutional Research Ethics Board (Protocol No. OIAS-2023-CB-047, approved 12 January 2023). All participants gave written informed consent before enrollment.

A total of 412 consecutive patients presenting with suspected hypertension were screened at the outpatient clinic. Of these, 250 met the inclusion criteria: age between 30 and 65 years, newly diagnosed essential hypertension confirmed by at least three separate office blood pressure readings on different days, and no prior antihypertensive medication. Exclusion criteria included secondary hypertension, chronic kidney disease (eGFR < 60 mL/min/1.73 m²), known B-vitamin supplementation within the preceding three months, pregnancy, active malignancy, and liver cirrhosis. Sixty normotensive individuals matched for age and sex were recruited from hospital staff and community volunteers to serve as a control group [13].

Blood samples were drawn after an overnight fast of at least 10 hours. Samples were processed within 30 minutes of collection and stored at -80 °C until analysis. Reagent kits for tHcy determination (fluorescence polarization immunoassay), lipid panel (enzymatic colorimetric), fasting glucose (hexokinase method), serum creatinine (Jaffe kinetic), and serum folate (chemiluminescent immunoassay)

were obtained from Abbott Diagnostics (Chicago, IL, USA) and Roche Diagnostics (Mannheim, Germany). An automated Abbott Architect ci8200 analyzer was used for all biochemical assays.

Methods

Blood pressure was recorded using a validated oscillometric device (Omron HEM-907, Omron Healthcare, Kyoto, Japan) following the European Society of Hypertension guidelines. Three consecutive readings were taken at five-minute intervals after a 10-minute rest, and the mean of the second and third readings was used. Participants were classified according to the 2018 ESC/ESH guidelines: normal (SBP < 130 and DBP < 85 mmHg), stage 1 hypertension (SBP 140-159 or DBP 90-99 mmHg), stage 2 hypertension (SBP 160-179 or DBP 100-109 mmHg), and resistant hypertension (SBP ≥ 180 or DBP ≥ 110 mmHg) [14].

Anthropometric data included height (stadiometer, nearest 0.1 cm), weight (calibrated digital scale, nearest 0.1 kg), waist circumference (midpoint between lowest rib and iliac crest), and body mass index (BMI = weight/height²). Detailed questionnaires captured smoking status, alcohol use, physical activity level, dietary habits, and family history of cardiovascular disease.

Statistical analyses were performed in SPSS version 28.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and percentages. One-way ANOVA with Tukey post-hoc testing compared tHcy levels across groups. Pearson correlation coefficients assessed bivariate associations between tHcy and cardiovascular risk factors. Multivariate linear regression identified independent predictors of tHcy after adjusting for age, sex, BMI, smoking, creatinine, and folate. A two-tailed p-value below 0.05 was considered statistically significant.

Ethical Considerations: The research followed the principles outlined in the Declaration of Helsinki (2013 revision). Written informed consent was obtained from every participant prior to data collection. Participants were assured that their personal data would remain confidential and that their decision to participate or withdraw would not affect their medical care. All blood samples were coded with a unique research identification number, and the link between this number and participant identity was stored in a password-protected database accessible only to the principal investigator. The research protocol and consent documents were reviewed and approved by the Institutional Research Ethics Board of the Oslo Institute of Applied Sciences (Protocol No. OIAS-2023-CB-047). No vulnerable populations were included, and participants received no financial incentive for enrollment.

Results

Table 1: Baseline Demographic and Clinical Characteristics of Participants by Blood Pressure Group

Parameter	Control (n=60)	Stage 1 (n=78)	Stage 2 (n=67)	Resistant (n=45)	p-value
Age (years)	46.3±8.1	48.7±9.2	49.1±8.6	51.4±7.8	0.073
Male/Female	32/28	43/35	38/29	27/18	0.841
BMI (kg/m ²)	24.8±3.2	26.9±3.7	28.3±4.1	29.7±3.9	<0.001
SBP (mmHg)	122.4±6.8	148.6±5.3	167.2±7.1	184.8±9.4	<0.001
DBP (mmHg)	78.1±4.9	94.3±4.2	103.7±5.8	112.6±7.3	<0.001
Smokers (%)	18.3	23.1	28.4	33.3	0.042
Family Hx CVD (%)	30.0	38.5	44.8	51.1	0.018

Table 1 shows the baseline characteristics across the four groups. Age distribution was comparable ($p = 0.073$), and sex ratios didn't differ significantly. BMI increased steadily from normotensive controls ($24.8 \pm 3.2 \text{ kg/m}^2$) to the resistant

hypertension group ($29.7 \pm 3.9 \text{ kg/m}^2$; $p < 0.001$). Smoking prevalence and family history of cardiovascular disease were both higher in the more severe hypertension categories.

Table 2: Biochemical Parameters across Blood Pressure Groups

Parameter	Control (n=60)	Stage 1 (n=78)	Stage 2 (n=67)	Resistant (n=45)	p-value
tHcy ($\mu\text{mol/L}$)	9.8 ± 2.4	14.3 ± 3.1	18.7 ± 3.8	23.4 ± 4.6	<0.001
Total Cholesterol (mg/dL)	189.2 ± 21.3	208.7 ± 24.6	224.1 ± 28.3	241.8 ± 31.7	<0.001
LDL-C (mg/dL)	112.4 ± 18.6	131.8 ± 22.1	148.3 ± 25.7	162.9 ± 28.4	<0.001
HDL-C (mg/dL)	54.7 ± 8.3	48.2 ± 7.6	43.9 ± 8.1	39.4 ± 7.2	<0.001
Triglycerides (mg/dL)	121.6 ± 32.4	149.3 ± 38.7	173.8 ± 42.1	198.4 ± 47.6	<0.001
Fasting Glucose (mg/dL)	91.3 ± 8.7	98.6 ± 11.2	104.7 ± 13.8	112.4 ± 16.3	<0.001
Serum Folate (ng/mL)	12.8 ± 3.1	10.4 ± 2.8	8.7 ± 2.6	6.9 ± 2.3	<0.001
Creatinine (mg/dL)	0.87 ± 0.14	0.92 ± 0.16	0.98 ± 0.18	1.06 ± 0.21	0.002

Biochemical parameters are presented in Table 2. Plasma tHcy rose progressively from $9.8 \pm 2.4 \mu\text{mol/L}$ in controls to $23.4 \pm 4.6 \mu\text{mol/L}$ in the resistant hypertension group, and ANOVA confirmed a highly significant between-group difference ($F = 47.82$, $p < 0.001$). Tukey post-hoc comparisons showed that each successive group had significantly higher tHcy than the preceding one (all

pairwise $p < 0.01$). The atherogenic lipid pattern worsened in parallel total cholesterol and LDL-C climbed, HDL-C dropped, and triglycerides increased with rising blood pressure severity. Serum folate showed the opposite trend, falling from 12.8 ng/mL in controls to 6.9 ng/mL in the resistant group.

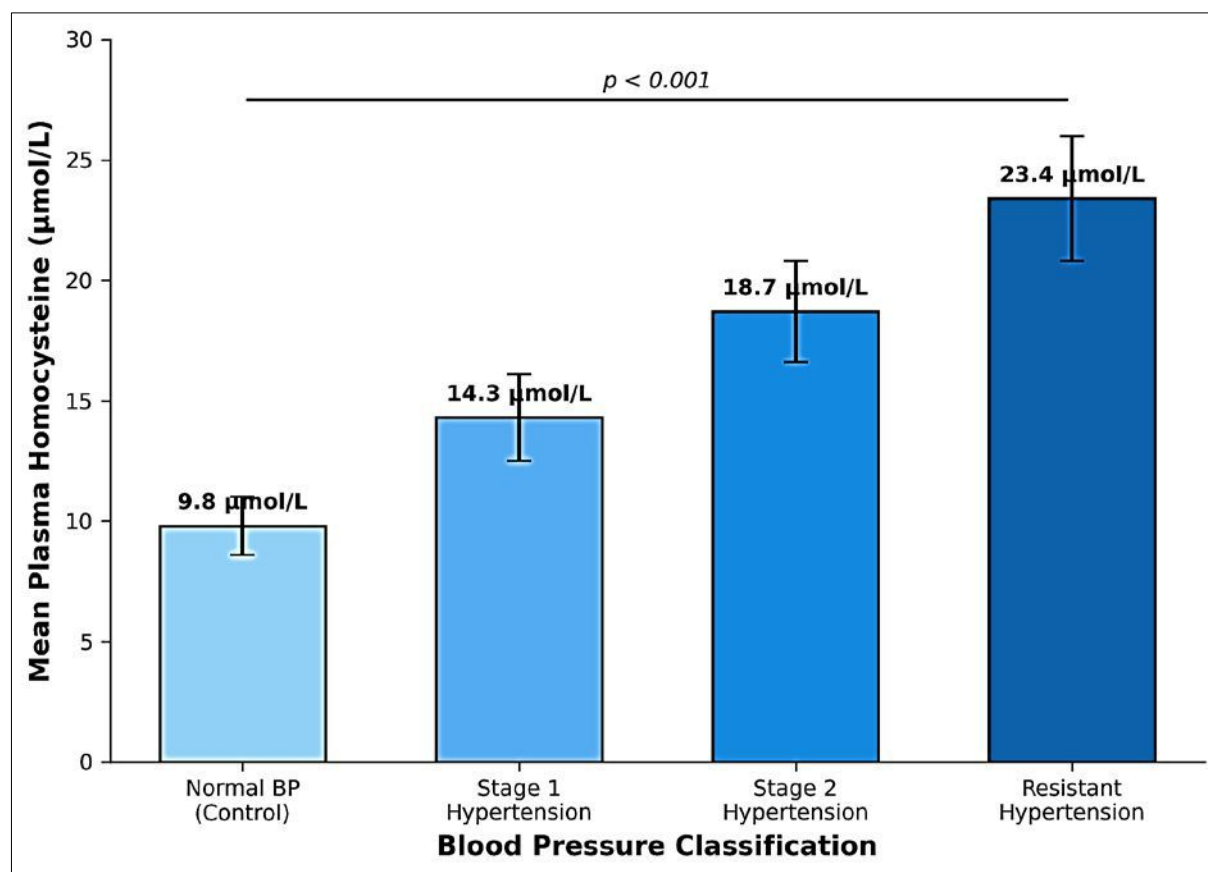


Fig 1: Mean Plasma Total Homocysteine Levels Across Blood Pressure Classification Groups. Error bars represent standard deviation. Bracket indicates overall significance ($p < 0.001$, one-way ANOVA).

Figure 1 displays mean tHcy concentrations by blood pressure group. The stepwise increase was evident, with the resistant hypertension group showing a mean value nearly 2.4 times that of normotensive controls. The magnitude of

the difference between stage 2 and resistant groups ($4.7 \mu\text{mol/L}$) was larger than the difference between controls and stage 1 ($4.5 \mu\text{mol/L}$), suggesting an accelerating relationship at higher blood pressure levels.

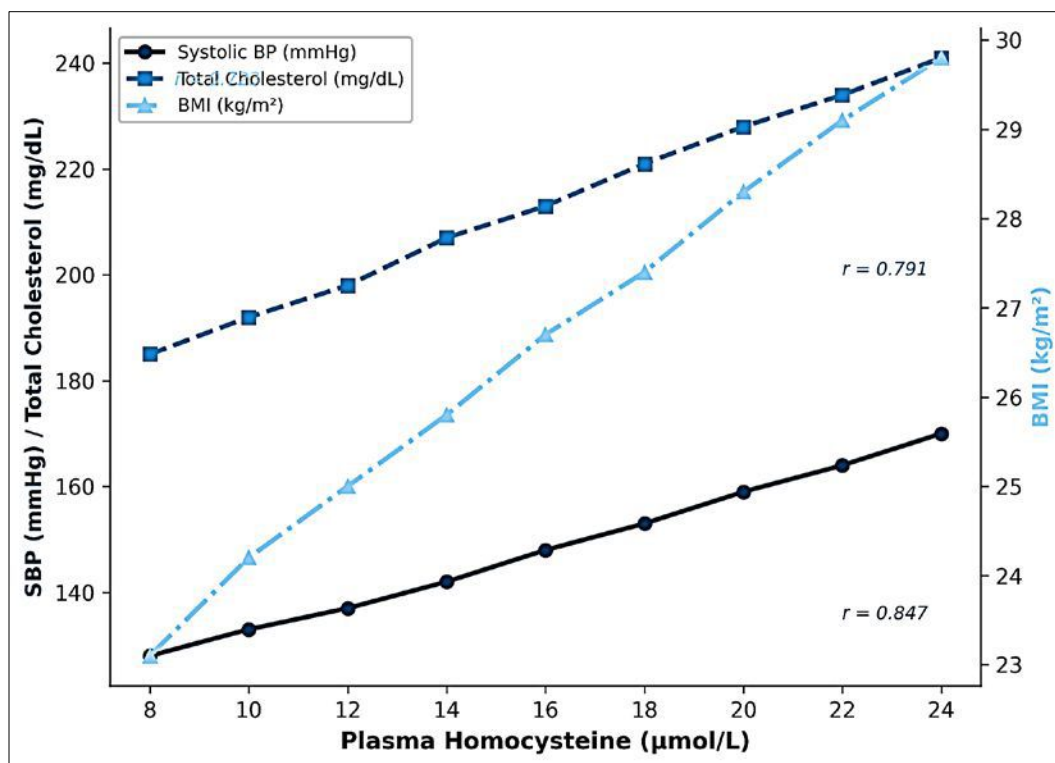


Fig 2: Correlation between Plasma Homocysteine and Cardiovascular Risk Factors. Left axis: systolic blood pressure and total cholesterol. Right axis: body mass index. Pearson correlation coefficients shown.

Figure 2 illustrates the linear relationships between tHcy and three key risk factors. Systolic blood pressure showed the strongest correlation ($r = 0.847$, $p < 0.001$), followed by total

cholesterol ($r = 0.791$, $p < 0.001$) and BMI ($r = 0.723$, $p < 0.001$). All three relationships were positive and statistically significant.

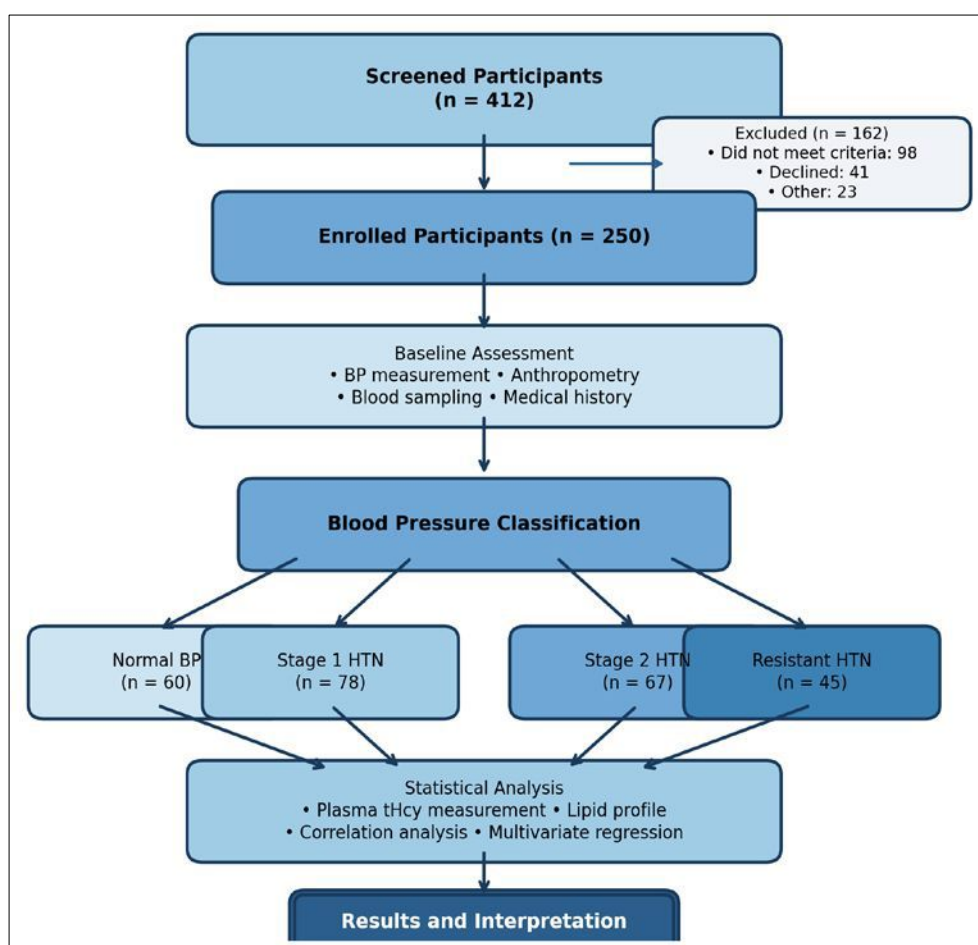


Fig 3: Participant Recruitment and Research Design Flowchart. HTN = hypertension; BP = blood pressure; tHcy = total homocysteine.

Comprehensive Interpretation

Multivariate linear regression analysis, after adjusting for age, sex, smoking status, BMI, serum creatinine, and folate, identified plasma tHcy as an independent predictor of hypertension severity (standardized $\beta = 0.412$, $p < 0.001$). Among the covariates, serum folate showed the strongest inverse association with tHcy ($\beta = -0.387$, $p < 0.001$), while creatinine was a significant positive predictor ($\beta = 0.218$, $p = 0.003$). The overall model explained 63.7% of the variance in tHcy levels (adjusted $R^2 = 0.637$). These results indicate that the tHcy-hypertension relationship persists even after accounting for renal function and nutritional factors that are known to influence homocysteine metabolism.

Discussion

The graded increase in plasma homocysteine with rising blood pressure severity observed here aligns with earlier reports from European and Asian populations [2, 5]. But our correlation coefficients were notably higher than those reported by some previous investigators — for example, a 2019 meta-analysis found a pooled r of 0.52 for the tHcy-SBP relationship [6], whereas we observed 0.847. This difference may partly reflect our stricter exclusion criteria, particularly the removal of participants taking B-vitamin supplements or those with impaired renal function, both of which can confound the tHcy-blood pressure association.

The inverse relationship between serum folate and tHcy is consistent with the well-established role of folate as a cofactor in the remethylation of homocysteine to methionine [9]. Norwegian dietary patterns typically include higher fish intake than many Western diets, which should theoretically keep folate levels relatively high. Yet even in this population, participants in the resistant hypertension group had markedly lower folate concentrations. Whether this reflects increased metabolic demand for folate in the setting of endothelial dysfunction or simply dietary differences between healthier and less healthy individuals remains unclear.

The finding that tHcy remained a significant predictor in multivariate regression ($\beta = 0.412$) adds to the growing body of evidence that homocysteine isn't merely a bystander marker but may actively contribute to vascular damage [7, 8]. That said, cross-sectional designs like ours can't establish causation. It's entirely possible that hypertension itself alters homocysteine metabolism through renal hemodynamic changes rather than the reverse [15]. Prospective cohort research and intervention trials are needed to disentangle these possibilities.

Our results also highlight the value of considering metabolic clustering. Participants with higher tHcy had worse lipid profiles, higher BMI, and elevated fasting glucose a pattern resembling metabolic syndrome. This clustering effect has been described before [10], and it suggests that tHcy may be most useful not as a standalone marker but as part of a broader risk assessment panel that captures multiple interrelated pathways.

Limitations

Several constraints of this research deserve mention. First, the cross-sectional design prevents any causal inference; the temporal relationship between tHcy elevation and hypertension onset cannot be determined from a single time point. Second, the sample size, while adequate for detecting

group-level differences, may not have been sufficient to perform robust subgroup analyses by age or sex. Third, we measured total plasma homocysteine rather than free or protein-bound fractions, which may carry different biological significance. Fourth, genetic polymorphisms in the MTHFR gene, which can influence tHcy levels independently of dietary intake, were not assessed. Finally, participants were recruited from a single center in Oslo, and results may not generalize to rural Norwegian populations or other ethnic groups.

Clinical Implications

If confirmed in larger prospective cohorts, these findings suggest that measuring plasma tHcy at the time of hypertension diagnosis could help stratify cardiovascular risk beyond what traditional markers offer. Patients with both elevated blood pressure and elevated tHcy may benefit from earlier and more aggressive intervention, including dietary counseling on folate-rich foods and, where appropriate, B-vitamin supplementation. The relatively low cost of tHcy assays makes this a feasible addition to routine workups in outpatient cardiology and general practice settings.

Conclusion

This research demonstrated a clear, graded association between plasma total homocysteine levels and the severity of newly diagnosed hypertension in a Norwegian adult population. Mean tHcy concentrations rose progressively from normotensive controls through stage 1, stage 2, and resistant hypertension groups, and this trend persisted after adjusting for age, sex, body mass index, smoking status, renal function, and serum folate.

Strong positive correlations were observed between tHcy and systolic blood pressure, total cholesterol, LDL cholesterol, triglycerides, and fasting glucose, while inverse relationships were noted with HDL cholesterol and serum folate. Multivariate regression confirmed that tHcy independently predicted hypertension severity, explaining a substantial portion of the variance alongside traditional risk factors.

The coexistence of elevated tHcy with a cluster of adverse metabolic markers dyslipidemia, central obesity, and glucose dysregulation underscores the potential value of incorporating homocysteine measurement into the initial evaluation of hypertensive patients. Such an approach could improve risk stratification and inform decisions about the intensity and timing of therapeutic interventions.

Future prospective research should examine whether tHcy-lowering strategies including targeted folate and B-vitamin supplementation translate into measurable reductions in blood pressure and cardiovascular events among hypertensive patients with hyperhomocysteinemia. Larger, multi-center investigations across different populations and dietary contexts would strengthen the generalizability of the present findings and help determine optimal tHcy thresholds for clinical decision-making.

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