ORIGINAL ARTICLE

CONTENTS

# Association of calcitonin gene-related peptide levels with cardiovascular disease in hypertensive male patients

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## ABSTRACT

**Aim:** The current study aimed to investigate the association between CGRP, lipid profile, and atherogenic indices in hypertensive male patients with respect to cardiovascular risk.

**Materials and Methods:** Fifty-four male HTN patients and 45 healthy controls (ages 51–69) were enrolled. The subjects were divided into two subgroups according to LAP: Group 1 was HTN patients with LAP (≤50), and Group 2 was HTN patients with LAP >50. Serum CGRP (pg/mL) was measured via ELISA; lipid profiles and atherogenic indices were assessed spectrophotometrically.

**Results:** The mean values of WHR, VAI, LAP, SBP, DBP, atherogenic indices, and lipid profile in the HTN patients showed a statistically significant increase compared to the control, except CGRP and HDL-C, which revealed a significant decrease ($P < 0.001$). Also, the G2 displayed a decrease in CGRP compared to the G1. After adjusting for main hazard factors, the relation between CGRP and CVD remained significant in the multivariate analysis. The curve of ROC based on CGRP levels to indicate the existence of CVD in HTN patients was 0.80. Additionally, the AUC of CGRP was 0.82 in patients with a LAP greater than 50, compared to those with a LAP less than 50.

**Conclusions:** These findings indicate that reduced CGRP levels are significantly associated with higher CVD risk in hypertensive men, suggesting that CGRP may be explored as a potential biomarker for cardiovascular risk assessment in future longitudinal studies.

**KEY WORDS:** AIP, vasodilator, LAP, VAI, BF%, HTN

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## INTRODUCTION

Cardiovascular disease (CVD) encompasses a wide spectrum of disorders concerning the blood vessels and heart, such as coronary artery disease, heart failure, and stroke [1]. It remains the leading cause of mortality worldwide, with marked regional variations in prevalence and mortality rates. Unhealthy lifestyle factors, such as poor dietary habits, physical inactivity, and psychological stress, are strongly associated with these diseases [2]. The World Health Organization estimates that, lifestyle modification could prevent more than 75% of CVD-related deaths [3]. Hypertension (HTN) is a main risk contributing to the progression of CVD, leading to severe complications such as left ventricular hypertrophy (LVH), heart failure, and arrhythmias caused by impaired diastolic filling [4].

Understanding this link is essential for designing effective prevention and management strategies. Recent research has highlighted the complex role of neuropeptides in cardiovascular regulation. A new, secure, and useful index to represent excessive cerebral lipid accumulation is being proposed by Lipid Accumulation Product (LAP), which depends on a combination of two straightforward and cost-effective measurements: waist circumference (WC) and triglyceride concentration. This index was later referred to as the LAP. In women, LAP is closely associated with different metabolic and cardiovascular risk factors. Previous investigations performed in various populations of both male and female have revealed that LAP displays a high predictive value of other indicators such as BMI, WHR, WHtR, and visceral adiposity index (VAI), in diagnosing metabolic syndrome [5].

The multifunctional peptide Calcitonin gene-related peptide (CGRP) plays a pivotal role in a wide range of physiological processes. It exists in two primary isoforms, α-CGRP and β-CGRP, in sensory neurons; they are widely expressed and are also present in neuroendocrine cells and motor neurons [6]. The effects of CGRP are mediated through G protein-coupled receptors (GPCRs) that are in complex with receptor activity-mod-

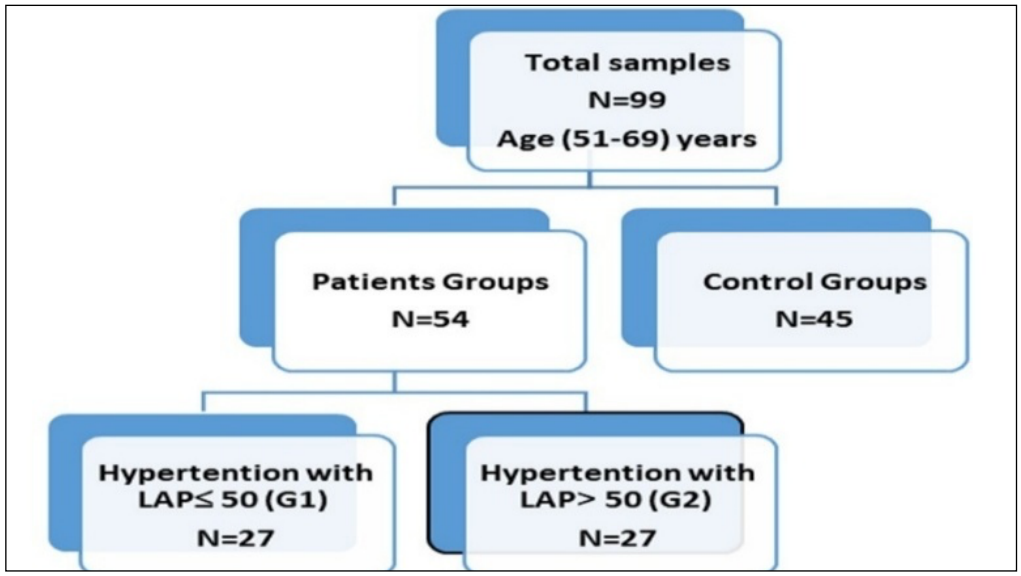


**Fig. 1** Study design flowchart of participant groups
*Source: compiled by the authors of this study*

ifying proteins (RAMPs). The receptor of CGRP and receptor of Amylin 1 (AMY1) are the most prominent, while additional receptor subtypes have been identified in rodents. Functionally, CGRP regulates multiple organ systems, including the central and peripheral nervous systems, where it mediates pain signaling and vascular tone; the cardiovascular system, as a potent vasodilator and cardioprotective agent; the respiratory and gastrointestinal systems; the hematopoietic and immune systems; and metabolic regulation in adipose and muscle tissues.

The CGRP peptide is implicated in various pathological conditions, most notably migraine, in which it contributes to peripheral vasodilation and nociceptive signaling. Therapeutically, targeting the CGRP pathway through monoclonal antibodies against CGRP or its receptor represents a benchmark bench-to-bedside success. Ongoing research into CGRP biology offers opportunities for the development of novel pharmacological interventions or combinatorial strategies targeting this pathway in diseases beyond migraine [7].

Despite extensive experimental evidence, the clinical relevance of CGRP in hypertension and its potential role as an associated biomarker for cardiovascular complications remains poorly understood. This knowledge gap highlights the need for a comprehensive investigation of CGRP in conjunction with other metabolic and vascular indices to improve risk stratification in hypertensive patients.

## MATERIALS AND METHODS

Seven milliliters of venous blood were drawn from each subject after 12 hours of fasting. The blood was collected in a gel tube, allowed to clot for 10 minutes at 37 °C, and then centrifuged at 1200 × g for 15 minutes. The serum was aliquoted into labeled Eppendorf tubes and then frozen at -80 °C until analysis. A study was carried out at Al-Sadder Hospital. Fifty-four male patients with hypertension were enrolled and subdivided based on the Lipid Accumulation Product (LAP) into two groups: G1 (LAP ≤ 50) and G2 (LAP > 50). LAP values were categorized according to the thresholds reported by Milla et al. (2023) [8], based on their analysis of adults at high cardiovascular risk. This approach allowed the identification of participants with elevated LAP levels relative to population-based cardiovascular risk. It should be noted that population-specific thresholds may vary, and future studies should validate the optimal cut-off in local populations.

All participants were non-smokers, newly diagnosed hypertensive males who had not received any antihypertensive or lipid-lowering medications. Dietary habits and physical activity were carefully controlled, as all participants followed comparable lifestyle patterns. Forty-five age-matched healthy males served as the control group. Participant ages ranged from 51 to 69 years (Fig. 1). Sample collection was carried out from November 2024 to the end of March 2025. Individuals with chronic kidney disease, cardiovascular disease, diabetes mellitus, cancer, and liver disease were excluded.

Cholesterol, high-density lipoprotein (HDL-C), and triglycerides (TG) were determined using colometric methods (Biolabo, France). CGRP levels were measured using a commercially available ELISA kit (Elabscience Biotechnology Co., Ltd, EKHU-0679). The assay sensitivity was < 1 pg/mL, with intra-assay and inter-assay coefficients of variation of < 10% and < 15%, respectively, indicating acceptable reproducibility and reliability

**Table 1.** Comparison of Anthropometric measurements and biomarkers of the studied groups

| Variables | Control n=45 | G1 n=27 | G2 n=27 | LSD | F | df | P value |
|---|---|---|---|---|---|---|---|
| Age (Years) | 61.0 ± 4.1 | 60.6 ± 5.1 | 63.01± 3.5 | 2.357403 | 2.685 | 2 | 0.073 |
| Duration of Disease (Years) | - | 4.74 ± 1.9 | 5.81 ± 1.7 | - | - | - | - |
| Weight (g) | 76.28 ± 6.47 | 75.74± 4.39 | 78.00± 4.86 | 3.001 | 1.253 | 2 | 0.290 |
| BMI (kg/m$^2$) | 25.82± 2.10 | 25.81 ± 1.70 | 26.56± 1.51 | 1.000 | 1.587 | 2 | 0.210 |
| WHR | 0.91 ± 0.01 | 0.93 ± 0.01 | 0.92 ± 0.01 | 0.000 | 17.171 | 2 | < 0.001 |
| BF% | 39.51± 2.62 | 39.53± 2.55 | 41.06± 2.26 | 1.356 | 3.691 | 2 | 0.29 |
| VAI | 1.382 ± 0.16 | 3.21 ± 0.64 | 3.80 ± 0.68 | 0.271 | 229.401 | 2 | < 0.001 |
| LAP | 34.21 ± 8.24 | 31.73 ± 5.84 | 58.71 ± 7.98 | 4.103 | 110.957 | 2 | < 0.001 |
| SBP (mmHg) | 120.06± 1.54 | 138.77 ± 4.5 | 137.34 ± 6.7 | 2.356 | 209.522 | 2 | < 0.001 |
| DBP (mmHg) | 80.87 ± 1.72 | 91.00 ± 3.49 | 91.48 ± 2.42 | 1.352 | 210.884 | 2 | < 0.001 |
| TG (mg/dl) | 134.1 ± 5.62 | 177.0 ± 7.54 | 178.5 ± 7.38 | 3.611 | 23369.2 | 2 | < 0.001 |
| TC (mg/dl) | 145.33 ± 7.21 | 156.03 ± 6.0 | 157.64 ± 4.7 | 3.412 | 1642.6 | 2 | < 0.001 |
| HDL (mg/dl) | 54.22 ± 3.94 | 28.81 ± 5.13 | 28.37 ± 4.62 | 2.420 | 8062.9 | 2 | < 0.001 |
| LDL (mg/dl) | 63.98 ± 7.79 | 91.82 ± 6.79 | 93.55 ± 5.88 | 3.810 | 10130.5 | 2 | < 0.001 |
| VLDL (mg/dl) | 26.97 ± 1.21 | 35.40 ± 1.50 | 35.71 ± 1.47 | 0.742 | 904.8 | 2 | < 0.001 |
| AC | 1.68 ± 0.19 | 4.57 ± 0.97 | 4.74 ± 1.00 | 0.400 | 108.948 | 2 | < 0.001 |
| AIP | 0.394 ± 0.02 | 0.794 ± 0.08 | 0.806 ± 0.07 | 0.034 | 2.020 | 2 | < 0.001 |
| CRI-I | 2.68 ± 0.19 | 5.57 ± 0.97 | 5.74 ± 1.00 | 0.400 | 198.258 | 2 | < 0.001 |
| CRI-II | 1.18 ± 0.18 | 3.30 ± 0.74 | 3.43 ± 0.77 | 0.308 | 58.742 | 2 | < 0.001 |
| CGRP (pg/ml ) | 33.60 ± 5.06 | 30.62 ± 6.91 | 23.48 ± 5.07 | 3.042 | 871.1 | 2 | < 0.001 |

*Source: compiled by the authors of this study*

of the measurements. Low-density lipoprotein (LDL-C) and very low-density lipoprotein (VLDL-C) were estimated using $LDL_C = T.C - HDL_C - VLDL\_C$ [9], $VLDL_C = \left(\frac{TG}{5}\right)$ [10] respectively.

The atherogenic index of plasma (AIP) was calculated as:

$$AIP = LOG\left(\frac{TG}{HDL_C}\right)$$ [11].

The atherogenic coefficient (AC) was determined using:

$$AC = (TC - HDL_C)/HDL\_C$$ [12].

Castelli's Risk Indexes (CRI I and CRI II), also referred to as cardiac risk indexes, were calculated using:

$$CRI_I = TC/HDL\_C,\ CRI_{II} = LDL_{\_C}/HDL\_C$$ [13]

$$VAI = \left(\frac{waist(cm)}{39.68} + (1.88 * BMI)\right) * \text{TG}\left(\frac{mmol}{L}\right)/1.03*1.31/\text{HDL}$$ [14]

$$LAP = (waist(cm) - 65) * TG\left(\frac{mmol}{L}\right)$$ [8].

Dividing the weight by height squared in meters is used to calculate body mass index (BMI) [15]. Waist-to-hip ratio (WHR) was determined [16]. Body fat percentage **,** where Gender = '1' for men and '0' for women [17].

For all statistical studies, SPSS software 27 was used. The Kolmogorov–Smirnov test was used to evaluate variable distribution. The mean and standard deviation (SD) were used to represent variables. Differences between continuous variables were examined using one-way analysis of variance (ANOVA) with a significance threshold of $p < 0.05$. Pearson's correlation coefficient was used to evaluate linear correlations between variables.

## ETHICAL APPROVAL

Permission to conduct the study was given by the University of Kufa's Institutional Review Board (IRB) and the Sadr Teaching Hospital Committee of Ethics (IRB reference number 7547 R/2023). The IRB adheres to the International Guidelines for the Protection of Human Subjects of Research as mandated by the Declaration of Helsinki 2024. Prior to enrolment, each subject provided written, informed consent to take part in the trial.

# RESULTS

The anthropometry and biomarker findings for the HTN and control groups are displayed in Table 1. There was non-significant difference in weight, BMI, age, and body

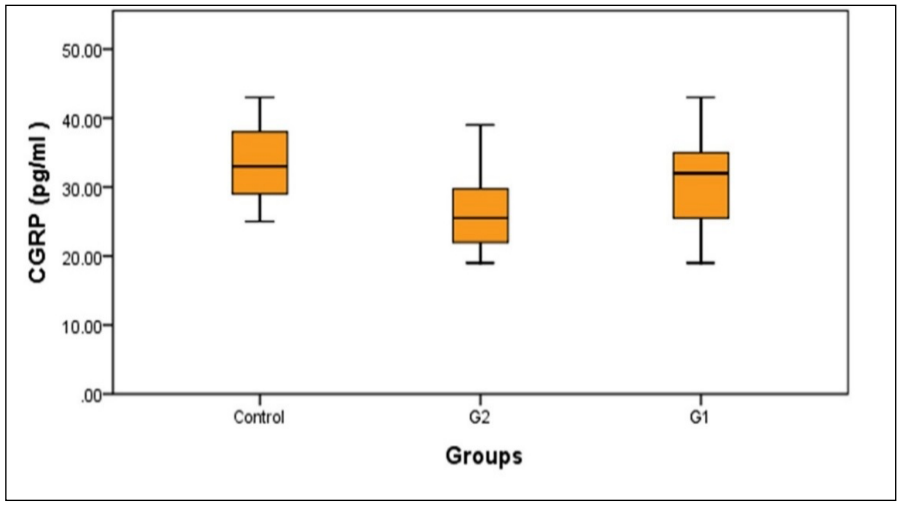


**Fig. 2.** Comparison of serum CGRP between HTN (G1, G2) and the control group
*Source: compiled by the authors of this study*

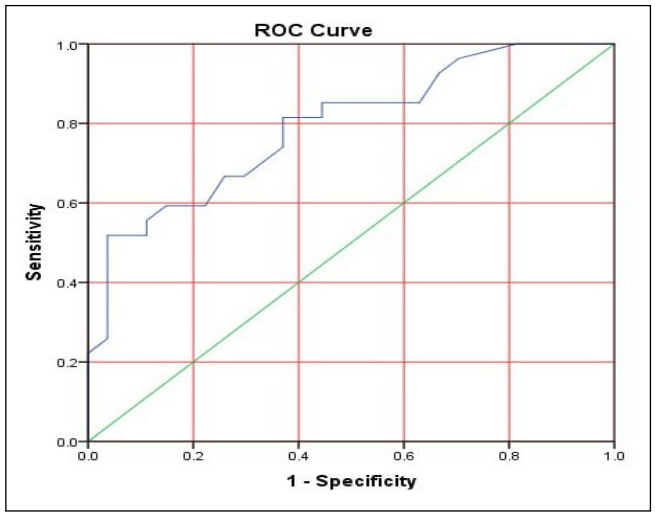


**Fig. 3.** ROC curve of CGRP in differentiating between control and HTN patient groups
*Source: compiled by the authors of this study*

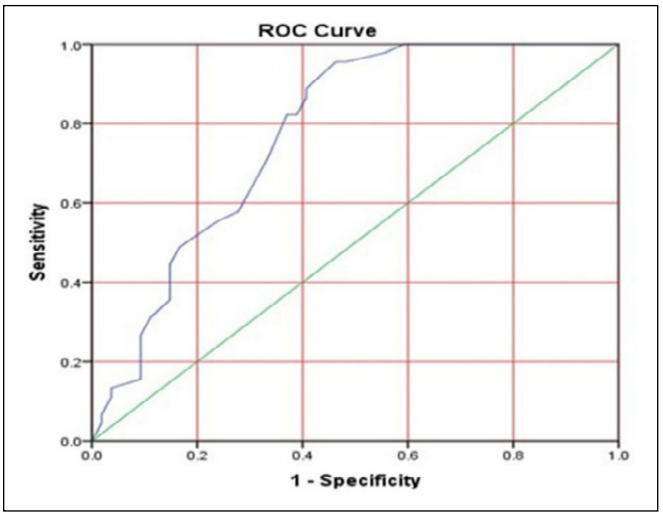


**Fig. 4.** Receiver operating characteristic curves of CGRP for differentiating between two groups of hypertensive (HTN) patients
*Source: compiled by the authors of this study*

fat percentage (BF%); whereas it found differences among the groups regarding WHR, VAI, LAP, SBP, DBP, TG, TC, HDL, LDL, VLDL, AC, AIP, CRI, and CGRP (P< 0.001). In addition to a significant difference in age, BF%, VAI, LAP, and CGRP between G1 and G2 (P< 0.001). Fig. 2 illustrates.

Figure 2 shows that an increase in CGRP concentrations occurred in the control group compared to both hypertensive groups (G1 and G2). Among the hypertensive groups, G2 exhibited the lowest CGRP levels, while G1 showed intermediate levels. This demonstrates a marked reduction of CGRP in hypertensive patients, particularly in G2 (HTN patients with LAP >50).

The correlations between the CGRP levels and the anthropometric and clinical data are presented in Table 2. The search revealed a negative relation between CGRP and LAP (r = -0.453, p = 0.001), TC (r = -0.382, p = 0.004), duration (r = -0.332, p = 0.014), and DIA (r = -0.276, p = 0.044).

Table 3 shows The incidence of CVD using a multivariable stepwise logistic regression considering the common risk variables and CGRP

The sensitivity and specificity of the detected CGRP in identifying patients with HTN from healthy people were assessed using a receiver operating characteristic (ROC), and the results were displayed in Table 4 and Figure 3

Using a receiver operating characteristic (ROC) analysis, the sensitivity and specificity of CGRP in two groups of HTN were shown in Table 5 and Fig. 4.

## DISCUSSION

Patients with hypertension decrease the risk of cardiovascular diseases because of their dyslipidemia and an inflammatory state [18]. Various studies have shown how the lipid profile affects CVD development, impacted by higher concentrations of TG and TC. Because LDL-C accumulates in the artery's intima-media, it may promote thrombocytopoiesis, which is another way that elevated LDL-C might lead to atherosclerosis. On the other hand, people with higher HDL-C levels might be less likely to develop CVD [19]. The constriction and abstraction of cardiac arteries, which are

**Table 2.** Correlation of bivariate between serum CGRP and parameters in HTN patients

| Parameters | CGRP | |
|---|---|---|
| | r | p-value |
| Age | - 0.076 | 0.583 |
| Duration | - 0.332* | 0.014 |
| Weight | 0.006 | 0.968 |
| BMI | - 0.092 | 0.508 |
| WHR | - 0.027 | 0.848 |
| BF | - 0.13 | 0.350 |
| VAI | - 0.032 | 0.018 |
| LAP | - 0.453** | 0.001 |
| SYS | 0.195 | 0.158 |
| DIA | -0.276* | 0.044 |
| TC (mg/dl) | - 0.382** | 0.004 |
| LDL (mg/dl) | - 0.148 | 0.286 |
| HDL (mg/dl) | - 0.215 | 0.119 |
| VLDL (mg/dl) | - 0.066 | 0.634 |
| TG (mg/ ml) | - 0.066 | 0.634 |
| AIP | 0.171 | 0.216 |
| AC | 0.104 | 0.454 |
| CRI-I | 0.104 | 0.454 |
| CRI-II | 0.089 | 0.522 |

* Significant correlation ($p < 0.05$), ** significant correlation ($p < 0.01$)
*Source: compiled by the authors of this study*

**Table 3.** The incidence of CVD using a multivariable stepwise logistic regression considering the common risk variables and CGRP

| Parameters | B | Wald | df | P-value | Exp(B) | 95% CI for EXP(B) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| LAP | 0.046 | 4.339 | 1 | 0.037 | 1.048 | 1.003 | 1.094 |
| CGRP | -0.131 | 10.110 | 1 | 0.001 | 0.877 | 0.809 | 0.951 |

*Source: compiled by the authors of this study*

**Table 4** Area under the curve (AUC) and ROC of determined CGRP for the diagnose HTN patients

| Parameter | Cut-off | Sensitivity % | Specificity % | Youdin's J statistic | AUC (95 % CI) | P |
|---|---|---|---|---|---|---|
| **CGRP** | < 28.75 | 0.822 | 0.630 | 0.452 | 0.82(0.684-0.867) | <0.0001 |

*Source: compiled by the authors of this study*

**Table 5.** ROC and AUC of determined CGRP for HTN patients (G1 and G2)

| Parameter | Cut-off | Sensitivity % | Specificity % | Youdin's J statistic | AUC (95 % CI) | P |
|---|---|---|---|---|---|---|
| **CGRP** | < 31.5 | 0.52 | 0.96 | 0.48 | 0.80(0.674-0.911) | <0.0001 |

*Source: compiled by the authors of this study*

strongly connected with the risk of CVD [20], the logarithm of (TG/HDL) ratio, often referred to as AIP, which are identified as a risk for the emergence of myocardial infarction, stroke, and CVD [21], Studies show that AC values are higher significant in patients with CAD, indicating its potential as a risk marke [22]. CRI I and II demonstrated significant relationships with CVD mortality, emphasizing their role in long-term risk assessment [23]. VAI serves as an indirect marker of adipose tissue dysfunction, which is closely linked to cardiometabolic risks, particularly in type 2 diabetes patients. Research indicates that dietary interventions, such as Gum Arabic supplementation, can significantly reduce VAI and improve blood pressure, thereby potentially mitigating CVD risk [24]. A recent study found that higher LAP levels were strongly correlated to higher mortality from CVD and all causes. Participants in the highest LAP quartile had a

55% higher risk of CVD mortality compared to those in the lowest quartile [25]. In the Isfahan Cohort Study, LAP was correlated with metabolic variables and showed a significant association with CVD incidence, although it was not independently predictive of CVD mortality in multivariate analysis [26].

According to the present study, results in Table 1 showed a significant increase in all lipid markers, consistent with previous reports, as well as an increase in WHR. Importantly, CGRP levels were significantly lower in HTN patients with LAP > 50 compared to those with LAP ≤ 50 (Table 1, Fig. 2), a novel finding since no prior research has investigated the link between CGRP and CVD in the context of hypertension based on LAP. CGRP has a complex role in cardiovascular disease, with evidence suggesting both protective and neutral effects [27, 28]. Given its vasodilatory and cardioprotective properties [29, 30], our results highlight that lower CGRP levels may reflect greater disease severity. Correlation analysis in Table 2 revealed significant negative correlations of CGRP, particularly with disease duration, suggesting that CGRP levels may decline over time in patients, which is crucial for understanding its temporal dynamics in disease contexts. Moreover, the negative correlation of CGRP with diastolic blood pressure indicates a potential role in cardiovascular regulation and blood pressure management. Additionally, its negative correlation with total cholesterol and LAP highlights its involvement in lipid metabolism, underscoring the multifaceted role of CGRP in the pathophysiology of cardiovascular disease [6]. These findings emphasize the importance of CGRP as both a biomarker and a therapeutic target in cardiovascular research. Furthermore, results from Table 3 indicate that CGRP had a stronger and more statistically significant effect than LAP, suggesting a potential protective role. Nonetheless, LAP remains an important risk factor. Together, these markers may provide complementary insights: LAP as a risk indicator and CGRP as a protective factor.

Finally, ROC findings demonstrated that CGRP has diagnostic value in identifying hypertensive patients (Table 4, Fig. 3) and showed potential in diagnosing CVD in this population based on the LAP marker, as indicated by ROC curve analysis (Table 5, Fig. 4). Serum CGRP levels may be associated with cardiovascular risk in hypertensive patients with LAP >50 and could be explored as a potential biomarker in future longitudinal studies.

A limitation of the current work is the need for longitudinal data to confirm these findings and to establish whether reduced CGRP levels can reliably serve as a biomarker for CVD in hypertensive patients.

## CONCLUSIONS

Reduced CGRP levels are associated with higher cardiovascular risk in hypertensive men with LAP >50. CGRP may serve as a potential biomarker for cardiovascular risk assessment; however, longitudinal studies are required to confirm its predictive value.

## LIMITATIONS

This study has several inherent limitations. The sample size was relatively small (n = 54) and included only male participants, which may reduce the generalizability of the findings. The restriction to males was intentional to minimize sex-related biological variability and to obtain a more homogeneous study population. Future studies including both sexes are recommended to evaluate possible sex-specific differences. Although CRP and other inflammatory markers were not measured, cardiovascular risk assessment was based on detailed lipid profile parameters and atherogenic indices, including the recently proposed lipid accumulation product (LAP), which has been reported in recent studies to have a strong association with cardiovascular diseases [26].

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