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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

# SERUM ANJİYOPOİETİN BENZERİ PROTEİN 8 DÜZEYLERİ İLE HİPERTANSİYON EVRELERİ ARASINDAKİ İLİŞKİ

# THE RELATIONSHIP BETWEEN SERUM ANGIOPOIETIN-LIKE PROTEIN 8 LEVELS AND HYPERTENSION STAGES

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**ÖZET**

**AMAÇ:** Hipertansiyon ciddi komplikasyonlara yol açabilen ciddi bir durumdur. Günümüzde, hipertansiyon tanısı koymak ve hastalığı evrelemek için klinik uygulamada kullanılan standart bir biyobelirteç yoktur. Bu çalışmanın amacı, anjiyopoietin benzeri protein 8'in (sANGPTL8) serum düzeylerinin hipertansiyon hastalarında ve hipertansiyonun ileri evrelerinde değişip değişmediğini araştırmaktır.

**GEREÇ VE YÖNTEM:** Çalışmamız, prospektif gözlemsel bir çalışmadır. Kardiyoloji polikliniğimizde, 42 hipertansif ve 41 hipertansif olmayan sağlıklı hastada, sANGPTL8 düzeylerini ölçmek için bir ELISA kiti kullandık ve gruplar arasındaki istatistiksel farklılıkları değerlendirdik. Two-tailed p< 0.05 değerini istatistiksel olarak anlamlı kabul ettik.

**BULGULAR:** Evre 2 hipertansiyon grubundaki ortalama sANGPTL8 düzeyleri, evre 1 ve hipertansif olmayan gruba göre istatistiksel olarak anlamlı derecede yüksek olarak tespit edildi (sırasıyla, 813 pg/ml, 524.89 pg/ml ve 518.07 pg/ml) (p= 0.001).

**SONUÇ:** Çalışmamız, evre 2 hipertansif hastalarda ortalama sANGPTL8 düzeylerinin, evre 1 hipertansif ve normotansif bireylerden daha yüksek olduğunu göstermiştir (p= 0.001). ANGPTL8 ile birlikte kullanılabilecek ek biyobelirteçler ve ANGPTL8 üzerine yapılacak daha fazla araştırma, bu adipokinin ileri evre hipertansiyon tanısında etkili bir biyobelirteç olarak kullanılmasını sağlayabilir.

**ANAHTAR KELİMELER:** Hipertansiyon, Anjiyopoietin benzeri protein 8, Kan basıncı, Son organ hasarı.

**ABSTRACT**

**OBJECTIVE:** Hypertension is a serious condition that can lead to serious complications. Currently, there is no standard biomarker used in clinical practice to diagnose hypertension and stage the disease. The aim of this study was to investigate whether serum levels of angiopoietin-like protein 8 (sANGPTL8) change in hypertensive patients and advanced stages of hypertension.

**MATERIAL AND METHODS:** Our study is a prospective observational study. We used an ELISA kit to measure sANGPTL8 levels in 42 hypertensive patients and 41 healthy non-hypertensive patients at our cardiology clinic and evaluated statistical differences between the groups. A two-tailed p< 0.05 was considered statistically significant.

**RESULTS:** The mean sANGPTL8 levels in the stage 2 hypertension group are statistically significantly higher than in the stage 1 and non-hypertensive group (813 pg/ml vs 524.89 pg/ml and 518.07 pg/ml respectively) (p= 0.001).

**CONCLUSIONS:** According to our study, mean sANGPTL8 levels were higher in stage 2 hypertensive patients compared to stage 1 hypertensive and normotensive individuals (p=0.001). Additional biomarkers that can be used in combination with ANGPTL8 and further research on ANGPTL8 may enable this adipokine to be used as an effective biomarker in diagnosing advanced hypertension.

**KEYWORDS:** Hypertension, Angiopoietin-Like Protein 8, Blood Pressure, End-organ damage.

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## INTRODUCTION

Hypertension is a major risk factor for cardiovascular disease, contributing significantly to morbidity and mortality worldwide. High systolic blood pressure is a primary cause of death and disability, according to the 2017 Burden of Disease Study (1). The relationship between blood pressure and increased cardiovascular disease risk is gradual and continuous from 115/75, considered the normotensive range (2).

In April 2013, Yi and colleagues discovered a hormone called ANGPTL8, which they named "betatrophin" due to its significant role in promoting pancreatic b-cell proliferation (3). ANGPLT8 is mainly synthesized in the liver and adipose tissues. It is a circulating adipokine that affects glucose and lipid metabolism (4).ANGPTL8 has been identified as a critical marker regulating serum glucose and lipid metabolism, controlling cardio-metabolic disease risk (5, 6). The ANGPTL8 gene expression is regulated by the inflammatory state, and its levels are decreased by tumor necrosis factor-a (TNF-a) under inflammation (7). Circulating ANGPTL8 is related to inflammatory disease, metabolic parameters, and oxidative stress (8).

Studies over the past 15 years have determined that inflammation plays a vital role in developing essential hypertension (9 - 12). A recent study consisting of 14 prospective cohort studies, 2 retrospective cohort studies, 5 nested case-control studies, and a systematic overview has shown that individuals with high levels of inflammation markers in their bloodstream are at a heightened risk of developing hypertension (13).

Our team posited that advanced hypertensive patients may have elevated sANGPTL8 levels, given the known involvement of inflammatory processes in the development of hypertension. Our hypothesis further suggested that there is a positive correlation between ANGPTL8 levels and the stage of hypertension. There is no previous study comparing sANGPTL8 levels in hypertension stages. In light of the knowledge that the probability of fatal end-organ damage increases as the hypertension stage progresses, early diagnosis, treatment and staging of hypertension are crucial. The purpose of this study is to investigate the potential of serum levels of sANGPTL8 to serve as a diagnostic marker for hypertension and its progression to advanced stages.

## MATERIALS AND METHODS

### The Study Population

Our study is a prospective observational study. We enrolled hypertensive patients and healthy individuals who applied to our cardiology outpatient clinic between June and July 2017. We divided hypertensive individuals into stage 1 and stage 2 hypertension patients. We excluded stage 3 hypertensive patients (2 patients), which we first included in the study because we determined that they would not gain statistical significance in comparison due to their small number. We excluded hypertensive patients with secondary hypertension, antihypertensive medication, diabetes, heart failure, coronary artery disease, peripheral artery disease, cerebrovascular disease, chronic renal failure, obesity, cancer, inflammatory and infectious diseases, and pregnancy.

### Laboratory Measurements

The diagnosis of hypertension was confirmed with a 24-hour ambulatory blood pressure measuring device (Contec brand, ABPM50 model, made in China). We described hypertension stages according to the 2018 European Guidelines On The Management of Hypertension as stage 1; systolic blood pressure (SBP) 140-159 mmHg or diastolic blood pressure (DBP) 90-99 mmHg, and stage 2, SBP 160-179 mmHg or DBP 100-109 mmHg (14). The body mass index is calculated as weight in kilograms divided by the square of the height in meters, expressed as $kg/m^2$. To measure waist and hip circumference, a tape measure is used. The waist-hip ratio is then calculated by dividing the waist circumference in centimeters by the hip circumference in centimeters. sANGPTL8 levels were obtained venously after 8-10 hours of fasting and placed in vacuum blood collection tubes containing gel and clot activator. Serum was obtained by rotating these tubes at 1600 rpm for 10 minutes in a centrifuge device. Collected samples were stored in the refrigerator at -20 degrees Celsius. sANGPTL8 levels were measured

with the commercially available enzyme-linked immunosorbent assay kit (Catalogue no. E11644h; Wuhan EIAab Science, Wuhan, China).

### Ethical Committee

Our study was approved by the Malatya Clinical Research Ethics Committee with protocol number 2017/24 and the research was conducted under the Declaration of Helsinki. Written and signed consent was obtained from each participant.

### Statistical Analysis

The data were analyzed using SPSS software (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY, USA, IBM Corp.). We expressed categorical variables as frequencies and percentages and continuous variables as mean and standard deviation for normally distributed data or median values and interquartile ranges for non-normally distributed data. We conducted the Kolmogorov-Smirnov test to determine if the variables followed a normal distribution. Taking George et al.'s study as a reference, it was determined that the variables were normally distributed since their skewness and kurtosis values were within ±2 (15). Parametric tests were applied: Independent-Samples T test for variables with two subgroups and One-way ANOVA test for variables with more than two subgroups. Two-tailed p-values < 0.05 were considered statistically significant. Upon detection of non-homogeneity of variances, Tamhane's T2 post hoc test performed a pairwise comparison between groups. The categorical variables were analyzed using the appropriate chi-square test and expressed as percentages (%) and absolute numbers. In contrast, we expressed continuous variables as means and standard deviations or medians for normally distributed data. Since the variables were normally distributed, the correlation between the continuous variables was evaluated using the Pearson correlation test. The relationship between sANGPTL8 levels and the hypertension stages was analyzed through a linear regression model. The effect size in the three-group variables was measured using the formula $(\eta^2 = \frac{SS_{ef}}{SS_t})$ (16,17). Receiver Operating Characteristic (ROC) curve analysis was used to predict stage 2 hypertension using sANGPTL8 levels.

## RESULTS

We conducted a prospective observational study with 83 participants, 41 healthy and 42 hypertensive. The mean age of the study population is 39.73 with ±14.09 standard deviation. The study population consisted of 37 males and 46 females. There were no statistically significant differences between hypertension subgroups regarding age, gender, and waist-hip ratio classes. A statistically significant difference was determined between the three groups regarding sANGPTL8 levels and body mass index values (p=0.001, and p=0.002 respectively) **(Table 1)**.

**Table 1:** Demographic and clinical data of the study population

| Characteristics | Normotensive (n=41) | Stage 1 HT (n=19) | Stage 2 HT (n=23) | *p* |
|---|---|---|---|---|
| Age (years) | 33.49 ± 10.28 | 44.47 ± 13.13 | 46.96 ± 16.12 | .3 |
| Male n (%) | 18 (43.9) | 9 (47.4) | 10 (43.5) | .1 |
| WHR (0.8- 1.0) n (%) | 31 (47) | 16 (24.2) | 19 (28.8) | .7 |
| BMI (kg/m²) | 24.60 ± 4.65 | 28.01 ± 2.51 | 27.57 ± 4.12 | **.002*** |
| SBP (mmHg) | - | 146.84 ± 6.71 | 163.04 ± 7.8 | **.002*** |
| DBP (mmHg) | - | 90.53 ± 8.48 | 98.3 ± 6.53 | **.002*** |
| MAP (mmHg) | - | 109.32 ± 4.89 | 119.83 ± 4.82 | **.003*** |
| sANGPTL 8 levels (pg/ml) | 518.07 ± 211.76 | 524.89 ± 184.61 | 813 ± 351.11 | **.001*** |

*Age and BMS values are presented as mean ± standard deviation. All other data expressed as mean ± standard deviation or n (%). Differences between groups were analyzed by the χ² test or One- Way Anova Test. Abbreviations: BMI= Body mass index. sANGPTL8= Serum angiopoietin-like protein 8. WHR= Waist-hip ratio. SBP= Systolic blood pressure. DBP= Diastolic blood pressure. MAP= Mean arterial pressure. *p < .01*

The mean sANGPTL8 level of stage 2 hypertensive individuals (813 ± 351.11 pg/ml) was higher than the normotensive (518.07 ± 211.76 pg/ml) and stage 1 hypertensive individuals (524.89 ± 184.61 pg/ml) **(Figure 1)**.

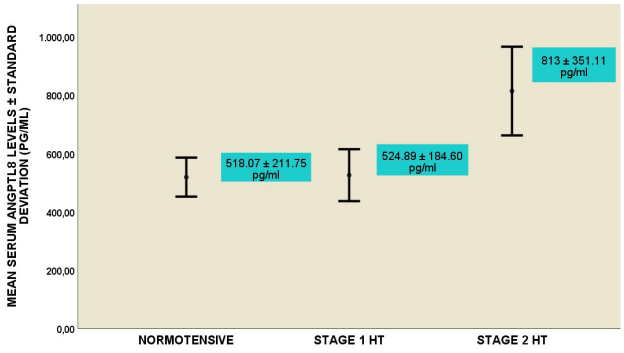


**Figure 1:** Serum ANGPTL8 levels (pg/ml) at different stages of hypertension. Data expressed as mean ± standard deviation. The One way ANOVA test was performed. p< .01. ANGPTL8: Angiopoietin-like protein 8. HT: Hypertension

Based on post-hoc tests, it has been determined that patients with stage 2 hypertension exhibit notably elevated sANGPTL8 levels compared to those with stage 1 hypertension and those who are normotensive (with p-values of 0.005 and 0.003, respectively). Conversely, no significant disparity was detected between those with stage 1 hypertension and normotensive individuals (p= 0.99) **(Table 2)**.

**Table 2:** Comparison of hypertension stages according to sANGPTL 8 levels

| Hypertension Stage | n | Mean | Std. Dev. | F | *p* | Sig. dif. | $\eta^2$ (Eta$^2$) |
|---|---|---|---|---|---|---|---|
| Normotensive | 41 | 518.07 | 211.75 | 11.140 | **.001** | 3>1 | .22 |
| Stage 1 HT | 19 | 524.89 | 184.60 | | | 3>2 | |
| Stage 2 HT | 23 | 813 | 351.11 | | | | |

**p< .01 One Way Anova Test. $\eta^2$ (Eta$^2$)= .22 means that the effect size is large. Abbreviations: HT= Hypertension. sANGPTL8= Serum angiopoietin-like protein 8. Std Dev.= Standard deviation. Sig. dif. : Significant difference 1= Normotensive Group. 2= Stage 1 Hypertensive Group. 3= Stage 2 Hypertensive Group.*

When age, systolic, diastolic, body mass index, and sANGPTL8 levels were evaluated using one-tailed Pearson correlation analysis, a statistically significant, low-level positive relationship was found between sANGPTL8 levels and systolic blood pressure (r= 0.286, p= 0.03) **(Table 3)**.

**Table 3:** Pearson's correlation test to determine the relationship between sANGPTL 8 levels and age, systolic and diastolic blood pressures and BMI

| Variables | N | *r* | *p* |
|---|---|---|---|
| Age (years) | 83 | .062 | .289 |
| BMI (kg/m$^2$) | 83 | .159 | .076 |
| SBP (mmHg) | 42 | .286 | **.033*** |
| DBP (mmHg) | 42 | .128 | .209 |

*Abbreviations: BMI= Body mass index. sANGPTL8= Serum angiopoietin-like protein 8. SBP= Systolic blood pressure. DBP= Diastolic blood pressure. *p< .01, r= Pearson correlation.*

However, no statistically significant correlation was found between diastolic blood pressures and sANGPTL8 levels (p= 0.2). Linear regression analysis was performed to predict sANGPTL 8 levels. The levels of sANGPTL8 were significantly predicted by systolic blood pressure and BMI (F=2.866, p=0.35, and 0.37 respectively). Systolic blood pressure and BMI accounted for approximately 18% of the variation in sANGPTL8 levels. When the body mass index and systolic blood pressure increase by one unit each, the levels of sANGPTL8 increase by 29,656 and 9,432 units respectively **(Table 4)**.

**Table 4:** Linear regression analysis to predict sANGPTL 8 levels

| Variables | R | $R^2$ | F | *p* | B | t | *p* |
|---|---|---|---|---|---|---|---|
| Age (years) | .430 | .184 | 2.866 | **.049** | .325 | .101 | .920 |
| BMI (kg/m$^2$) | | | | | 29.656 | 2.157 | **.037** |
| SBP (mmHg) | | | | | 9,432 | 2.181 | **.035** |

*Abbreviations: BMI= Body mass index. SBP= Systolic blood pressure. sANGPTL8= Serum angiopoietin-like protein 8. *p< .05*

We measured the η2 (Eta2) value as .22 for three groups. The study's effect size is large according to Cohen's guidelines Table 2 (18). In the ROC curve analysis, the sANGPTL8 cut-off point for predicting stage 2 hypertension was 530.5 pg/ml. Sensitivity and specificity by this cut-off point for sANGPTL8 in predicting stage 2 hypertension are 69.6% and 70%, respectively **(Table 5)**. The AUC (Area under the ROC curve) for ANGPTL8 was 0.769 **(Figure 2)**.

**Table 5:** Sensitivity And Specificity By The Optimized Cut-off Points For Serum ANGPTL8 Levels In Predicting Hypertension

| Risk Factor | AUC (95%) | Cutt off | *p* | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|
| serum ANGPTL8 | 0.769 (0.653-0.886) | 530.5 pg/ml | **.001*** | 69.6 | 70 |

*Abbreviations: ANGPTL8= Angiopoietin-like protein 8. AUC= Area Under the ROC (*Receiver Operating Characteristic*) Curve. *p< .01*

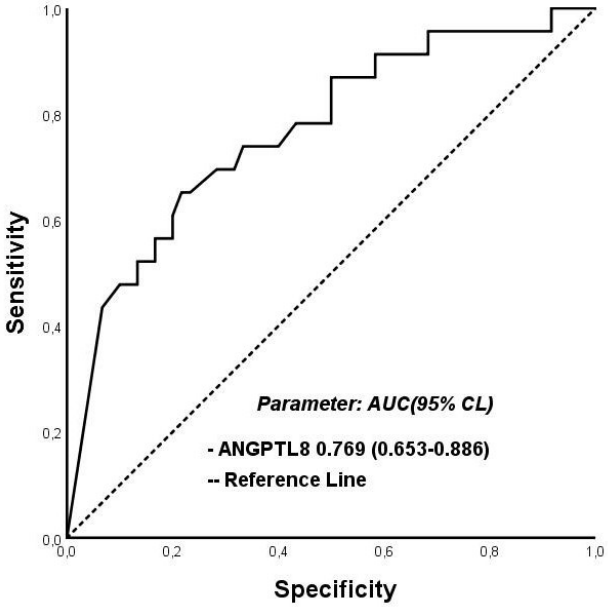


**Figure 2:** ROC curve analysis of Angiopoietin-like protein 8 in predicting hypertension. CI: Confidence interval. AUC: Area Under the ROC Curve. ANGPTL8: Angiopoietin-like protein 8.

## DISCUSSION

Our research has delved into the correlation between sANGPTL8 level and hypertension stage. Notably, our study is the first to have explored this association. Previous studies have indicated that sANGPTL8 levels tend to be higher in individuals with hypertension. Our team's study has revealed a notable difference in sANGPTL8 levels between hypertensive patients classified as stage 1 versus those classified as stage 2 and normotensive individuals. Specifically, the sANGPTL8 levels of patients with stage 2 hypertension were found to be significantly higher than those with stage 1 hypertension and normotensive individuals (**Figure 3)**.

Previous studies consistently demonstrate that high systolic blood pressure is a leading risk factor for morbidity and mortality (1). It is known that the duration of the disease and the blood pressure elevation are linked to life-threatening complications like congestive heart failure, end-stage renal disease, and stroke (19). Therefore, early hypertension diagnosis, staging, and treatment are crucial.

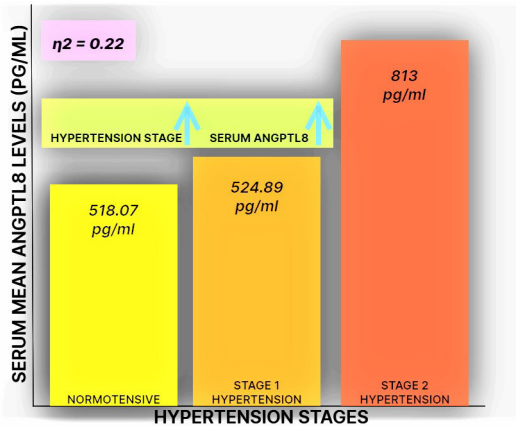


**Figure 3:** As the stage of hypertension advances, the levels of ANGPTL 8 serum increase. η2 (Eta2): effect size symbol. ANGPTL8: Angiopoietin-like protein 8.

In 2013, a hormone by the name of ANGPTL8 was identified by Yi and a team of colleagues (3). This hormone regulates glucose and lipid metabolism and is involved in metabolic diseases such as obesity and diabetes (20 - 22). Circulating ANGPTL8 is related to inflammatory disease. Zhang Y et al. showed that ANGPTL8 has an intracellular location associated with regulating inflammation (8). As a result of a study, it was determined that plasma ANGPTL8 levels were high in patients with severe infection. Furthermore, a strong correlation between circulating ANGPTL8 and lipopolysaccharide-induced acute inflammatory response was reported in animal models (23). However, the role of ANGPTL8 in the inflammation and inflammation-related signalling pathway is unknown.

Many studies showed that inflammation plays a vital role in developing essential hypertension, and high circulating inflammation markers were significantly related to the risk of developing hypertension (9 - 13). There are various ways in which inflammation and blood pressure can be linked. One possible mechanism is that high blood pressure can trigger the development of atherosclerosis by altering the biomechanical stimuli exerted by pulsating blood flow, such as increased hydrostatic pressure or cyclic strain, which can affect the genes and function of endothelial cells (24).

Our study indicated a positive correlation between systolic blood pressure and sANGPTL8 levels, but there was no correlation between diastolic blood pressure and sANGPTL8 levels. Maurer L et al. (25) also found similar correlation results between ANGPTL8 and blood pressure in their study. In a recent study, Chae et al. (26) noted that increased blood pressure may stimulate inflammation, a possible mechanism underlying hypertension. They found a positive correlation between increased blood pressure and inflammatory markers measured in their study. They also reported that serum levels of the inflammatory marker Intercellular adhesion molecule-1 (sICAM-1) positively correlated with systolic blood pressure but no diastolic blood pressure. It is unknown why some inflammatory marker's serum levels correlate with systolic blood pressure but not diastolic blood pressure. More comprehensive studies are needed in the future to elucidate this situation.

Many studies have reported that sANGPTL8, which is increased in inflammatory conditions, is also increased in hypertensive patients (25, 27, 28). Based on the knowledge that inflammatory processes are involved in the development of hypertension, we aimed to determine the relationship between sANGPTL8 levels and the presence and stage of hypertension. According to the results of our study, sANGPTL8 levels increased in stage 2 hypertensive patients. The results of our study are partially different from those of Abu-Farha et al. (27) and Hu, Lin et al. (28). As a result of these two studies, sANGPTL8 levels were found to be higher in hypertensive patients than in normotensive individuals. However, these two studies did not evaluate the relationship between hypertension stages and sANGPTL8 levels. In a recent animal experiment, Jiao et al. (29) found that ANGPTL8 expression was increased in hypertensive mice, rats and patients. They also found that VSMC (Vascular smooth muscle cell) -specific deletion of ANGPTL8 attenuated AngII-induced hypertension and hypertensive cardiovascular remodelling. Based on the findings of our study, sANGPTL8 levels exhibit an increase with a rise in systolic blood pressure but not with an increase in diastolic blood pressure. Additionally, these levels tend to increase in patients with stage 2 hypertension but not necessarily in all hypertensive patients. ROC analysis suggests that ANGPTL8 adipokinin is not a potent biomarker for predicting stage 2 hypertension (sensitivity 69.6%, specificity 70%). However, additional

biomarkers that can be used with ANGPTL8 and further research on ANGPTL8 may enable ANGPTL8 to be used as an effective biomarker in the diagnosis of advanced hypertension. Our research has several limitations. We conducted our study at a single center with a relatively small sample size due to the high cost of the sANGPTL8 ELISA kit, which was constrained by our budget. The group of stage 3 hypertensive patients was excluded from the evaluation due to the small number of such patients initially included in the study. Another area for improvement of the study is its design, which did not allow us to establish the causality and role that sANGPTL8 may play in hypertension development. The study's division into normotensive and hypertensive subgroups instead of observing patients with similar clinical characteristics suggests a high standard deviation of sANGPTL8 levels between the two groups. Furthermore, although we controlled for potential confounders that elevate sANGPTL8 levels, such as diabetes, hypercholesterolemia, and obesity, it is always possible that unrecognized confounding variables exist.

In conclusion, ANGPTL8 along with other biomarkers, could potentially be used as an effective tool to diagnose advanced hypertension. In selected hypertensive patients who do not have underlying conditions that may cause an increase in sANGPTL8 levels, such as diabetes, coronary artery disease, chronic inflammatory disease, or acute infection, those with elevated sANGPTL8 levels may be at a higher risk of advanced hypertension. Also, with future studies comparing sANGPTL8 levels measured before and after antihypertensive treatment in patients with hypertension, it will be possible to determine whether this adipokine is an appropriate biomarker to measure the success of antihypertensive treatment and blood pressure regulation in routine clinical use.

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