The role of endothelial dysfunction and inflammation in young-onset hypertension

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ABSTRACT

Young-onset hypertension is defined as hypertension seen in patients under 40 years of age. The relationship between hypertension and inflammation has been identified. In hypertensive patients, YKL-40 has been shown to be increased by endothelial dysfunction as a local secreted mediator. Vaspin, an adipokine, is derived from adipose tissue and irreversibly inhibits serine proteases. It has been reported that vaspin may act as an anti-inflammatory agent and increases endothelial-dependent relaxation, also has a positive effect on nitric oxide bioavailability, which is important in the etiology of endothelial dysfunction. In clinical practice, some indirect and practical methods may help to evaluate endothelial functions, including flow-mediated dilatation (FMD), which is considered to be the most practical and effective method. The present study was performed to determine the circulating YKL-40 and vaspin levels in young-onset hypertensive patients and healthy subjects and to reveal their relationships with vascular function evaluated by FMD. We enrolled 24 patients diagnosed with young-onset hypertension and 22 volunteers without hypertension. The plasma levels of YKL-40 and vaspin were determined using an enzyme-linked immunosorbent assay and quantitative enzyme-linked immunoassay, respectively. FMD was measured using a Doppler ultrasound device. Compared with those in normotensive controls, the plasma levels of YKL-40 were significantly higher, and FMD values were significantly lower in patients with young-onset hypertension (P<0.05). The plasma levels of YKL-40 were also negatively correlated with FMD. However, no statistically significant difference was noted in the levels of vaspin between the two groups (P=0.531). In this study, decreased FMD and increased levels of YKL-40 were associated with endothelial dysfunction and inflammation in patients with young-onset hypertension, suggesting the role of these factors in the etiology of hypertension.

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Introduction

Hypertension is the most common cardiovascular risk factor that contributes to morbidity and mortality worldwide, and approximately 90% of cases are classified as essential hypertension because the exact cause of their disease is unknown.1,2 Young-onset hypertension is defined as hypertension seen in patients under 40 years of age and has been shown to present with target organ damage similar to that observed in later stages of hypertension.3,4 The development of hypertension is a complex mechanism involving many factors. The relationship between hypertension and inflammation has been identified, but it remains unclear whether inflammation is the cause or consequence of hypertension.5 Increased inflammatory status in hypertensive patients occurs not only due to the increased excessive pressure load and subsequent activation of systemic pathways but also as a result of locally secreted mediators.6

In hypertensive patients, YKL-40 has proven to be increased by endothelial dysfunction as a local se-
creted mediator, and it is considered to be an indicator of subclinical diseases related to vascular endothelial
damage. In endothelial dysfunction, increased YKL-
40 levels seem to be related to cell migration and or-
ganization and tissue reconstruction as a response to
endothelial damage. Vaspin, an adipokine, is de-
derived from adipose tissue and irreversibly inhibits ser-
ine proteases. However, little is known about the
effects of vaspin on the pathogenesis of hyperten-
sion. A variety of evidence has shown that vaspin
suppresses inflammatory cytokine release and may act
as an anti-inflammatory agent.

In clinical practice, there is no direct method to
measure endothelial functions; however, some indirect
and practical methods may help to evaluate these func-
tions, including flow-mediated dilatation (FMD),
which is considered as the most practical and effective
method. This is a noninvasive ultrasonographic
evaluation based on endothelium-dependent arterial
vasodilatation.

The present study was performed to determine the
circulating YKL-40 and vaspin levels in young-onset
hypertensive patients and healthy subjects and to re-
veal their relationships with vascular function evalu-
ated by FMD.

Materials and Methods

Between December 2018 and September 2019, 24
patients with a diagnosis of young-onset hypertension,
al aged over 18 and under 40 years, and 22 volunteers
without hypertension were included in the study. Pa-

tients with rheumatic disease, hyperlipidemia, and acute
or chronic infection and those receiving medications
that could influence vascular function were excluded
from the study in addition to smokers. Both groups
were matched for age and gender. White blood cell lev-

els, C-reactive protein levels, and sedimentation rates
of all participants were within normal limits. All partici-
pants gave their informed consent, and the ethics com-
mittee of the Medical Faculty of Afyonkarahisar
University of Health Sciences approved the study.

The plasma levels of YKL-40 (gp-39) were deter-





For the FMD measurements, participants were ex-
amed following fasting and avoiding smoking and con-
sumption of caffeine for at least 12 h. An Apio MX
duplex Doppler ultrasound device (Toshiba, Japan, 2010)
and a 7.5 MHz probe were used to measure brachial FMD. In the supine position, the basal
measurements of the right brachial artery were longi-
tudinally recorded in the end-diastole, approximately
5 cm proximally to the antecubital fossa, and the cuff
was placed in the proximal portion of the brachial ar-
tery. The Doppler probe was inflated until no blood
flow from the brachial artery was detected and held at
this pressure for 5 min. The cuff was then deflated,
and the arterial diameter was measured 45 to 60 s after
the cuff was released. FMD, showing the brachial ar-
tery vasodilator response to reactive hyperemia, was
calculated as the maximum percentage change in the
internal diameter of the brachial artery after basal and
reactive hyperemia: 

\[
\text{FMD} (\%) = \left( \frac{\text{maximum diameter} - \text{diameter at rest}}{\text{diameter at rest}} \right) \times 100
\]

Statistical analysis

Statistical analysis was performed using the Sta-
tistical Package for the Social Sciences (SPSS Inc.,
version 21.0 Chicago, IL, USA). The normally distrib-
uted data were expressed as mean ± standard deviation
(SD) and non-normally distributed data as median
(25%-75%) values. The comparison between cate-
gorical and continuous variables was performed using
the chi-square and Mann-Whitney U tests, respecti-



Results

Of the 24 patients with young-onset hypertension
who participated in the study, 15 were male, and nine
were female, with a mean age of 31.7 (range: 19-40)
years. The control group comprised 22 individuals, 12
males, and ten females, with a mean age of 30.2 (range:
18-39) years. The body mass index and the mean levels
of low-density lipoprotein and triglyceride of the two
groups are shown in Table 1. There were no significant
differences between the patient and control groups in
any of the variables examined (Table 1).

The mean level of YKL-40 significantly differed
between the patient (926.64±384.18; range: 163.5-
1905.1 pg/mL) and control groups (749.50±622.68;
range: 42.71-1893.67 pg/mL; P<0.05). The mean level
of vaspin in the patient group (123.70±98.55 pg/mL; range: 39.7-236 pg/mL) was not significantly different from that in the control group (106.36±75.49 pg/mL; range: 18.8-231.88 pg/mL; P=0.531) (Table 2).

The mean FMD in the patient group (6.72±3.52; range: 2.5-16) was significantly lower than that in the control group (106.36±75.49 pg/mL; range: 39.7-236 pg/mL) was not significantly different from that in the control group (11.89±3.04; range: 7.9-21.8; P<0.05) (Table 2). The levels of YKL-40 were negatively correlated with FMD (r= -0.679, P<0.05).

**Discussion**

This study demonstrated for the first time that plasma YKL-40 concentration was high in patients with young-onset hypertension compared with normotensive subjects, and the higher plasma YKL-40 levels were associated with the deterioration of vascular function determined by FMD. These results provide evidence for the potential role of YKL-40 in the pathogenesis of young-onset hypertension and hypertension-related vascular injury.

The pathogenesis of essential hypertension is unknown due to the presence of multiple etiologies and the complexity of this disease. Experimental and clinical evidence indicates the critical role of oxidative stress and inflammation in the development of hypertension. There is an independent link between systemic inflammation and increased risk of hypertension. The inflammatory response in the vascular wall and oxidative stress plays an important role in the early stages of the development of hypertension. Oxidative stress caused by oxygen free radicals leads to the development of hypertension through endothelial dysfunction, vascular wall remodeling, and vascular inflammation. In the early stages of hypertension, patients are exposed to endothelial dysfunction in the microvascular system without clinically detectable target organ damage. Continuous increase in systemic pressure causes the premature aging of the microvascular system and frequent regeneration of endothelial cells, reducing the ability of endothelin to secrete factors, which leads to an imbalance in favor of vasoconstriction.

The vascular endothelium plays a role in the production and secretion of various molecules that are involved in the adhesion of leukocytes to the vascular endothelium and the regulation of vascular permeability and vascular tone, and therefore injuries caused by hypertension lead to the development of vascular endothelial dysfunction. Although hypertension includes both endothelial dysfunction and inflammation in its pathophysiology, the degeneration of the vascular structure characterized by endothelial dysfunction may be both the cause and the result of hypertension. It is also known that endothelial dysfunction is associated with inflammation and contributes to hypertension. The plasma concentrations of proinflammatory cytokines have been reported to be higher in hypertensive patients.

YKL-40 is a proinflammatory protein that has been proven to play a role in the pathogenesis of endothelial dysfunction. YKL-40 (human cartilage glycoprotein 39) is mainly secreted from macrophages.

**Table 1. The demographic features of the patients with young-onset hypertension and normotensive controls.**

|                | Patients (n=24) (Mean±SD) | Controls (n=22) (Mean ± SD) | P value |
|----------------|---------------------------|-----------------------------|---------|
| Age (mean)     | 31.7±8.7                  | 30.2±5.8                    | 0.592   |
| Sex (male)     | 15 (62%)                  | 12 (55%)                    | 0.442   |
| Body mass index (kg/m²) | 27.3±3.31                | 26.9±3.14                   | 0.114   |
| Low-density lipoprotein (mg/dL) | 103.8±21.4              | 102.2±20.6                  | 0.128   |
| Triglyceride (mg/dL) | 193.2±25.6               | 188.5±22.3                  | 0.168   |

SD, standard deviation.

**Table 2. The mean levels of YKL-40, vaspin, and flow-mediated dilatation of the patients with young-onset hypertension and normotensive controls.**

|                | Patients (Mean ± SD) | Controls (Mean ± SD) | P value |
|----------------|----------------------|----------------------|---------|
| YKL-40 (pg/mL) | 926.64±384.18        | 749.50±622.68        | <0.05   |
| Vaspin (pg/mL) | 123.70±98.55         | 106.36±75.49         | 0.531   |
| FMD (%)        | 6.72±3.52            | 11.89±3.04           | <0.05   |

SD, standard deviation; FMD, flow-mediated dilatation.
neutrophils, and vascular smooth muscle cells, and is significantly involved in remodeling of the extracellular matrix and in the maturation, adhesion, and migration of macrophages. The increased level of YKL-40 has been reported to be associated with low-grade inflammatory conditions. In addition, the relationship between the YKL-40 level and blood pressure has been previously demonstrated.

Vaspin, an adipokine inhibiting serine proteases, has been shown to have a protective effect on endothelial cells through increasing endothelial repair by endothelial progenitor cells and inhibiting the apoptosis of vascular endothelial cells. The previously shown effects of vaspin inhibiting tumor necrosis factor-mediated inflammatory responses and platelet-mediated growth factor migration through smooth antioxidant mechanisms in smooth muscle cells suggest that it may act as an anti-inflammatory agent. It has been reported that vaspin induces acetylcholine through the inhibition of acetylcholine esterase, it increases endothelial-dependent relaxation, and has a positive effect on nitric oxide (NO) bioavailability, which is important in the etiology of endothelial dysfunction. Vaspin has also been shown to inhibit the elevation of blood pressure by inhibiting peripheral arterial hypertrophy, possibly due to its effect on antioxidant and anti-inflammatory mechanisms. These results indicate that vaspin has preventive roles in the pathogenesis of hypertension.

In the literature, there is only one study on vaspin levels in young-onset hypertension patients, and it reports an increase in blood vaspin values in young-onset hypertension patients compared to normal controls. It was suggested that high vaspin levels might be a compensatory mechanism against hypertension. In our study, no significant difference was found between the patient and control groups in terms of vaspin values. Unlike our findings, the only other study available in the literature attributed the high level of vaspin produced from adipose tissue to the presence of obese patients in the sample.

The FMD of the brachial artery has emerged as an important method for demonstrating endothelium-dependent vasodilatation via NO in response to reactive hyperemia in order to assess vascular endothelial function. In this study, we found that FMD was decreased in patients with young-onset hypertension compared to the control group. Our findings confirm previous evidence that FMD is reduced in patients with essential hypertension, but this is also seen in young patients, suggesting that endothelial dysfunction begins to occur before adaptive changes to the vascular wall in response to high blood pressure. In our study, the YKL-40 level was found to be significantly higher in patients with young-onset hypertension. In addition, a negative correlation was observed between YKL-40 and FMD. Increased levels of YKL-40 and decreased FMD values suggest that increased inflammation and endothelial dysfunction may play a role in the etiology of young-onset hypertension.

**Limitations of the study**

The first limitation was that it was a case-control study that did not involve any investigation into causality. Thus, it was not possible to clarify whether lower FMD and higher YKL-40 levels were the cause or result of hypertension. Secondly, the sample size of the study was relatively small, and larger prospective studies are needed to reveal the clinical significance of inflammation and endothelial dysfunction in hypertensive patients.

**Conclusions**

Decreased FMD and increased levels of YKL-40 were associated with endothelial dysfunction and inflammation in patients with young-onset hypertension, suggesting the role of these factors in the etiology of hypertension. To the best of our knowledge, this is the first study in literature to show elevated serum YKL-40 levels, a potential biomarker of inflammation and vascular dysfunction in patients with young-onset hypertension.

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