VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2023, vol. 94, no. 8, 633–637

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2022.0095

# Serum MOTS-c levels remain unchanged in patients with preeclampsia

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## ABSTRACT

**Objectives:** Mitochondrial open-reading-frame of the twelve S rRNA-c (MOTS-c) is a mitochondrial derived peptide which has beneficial effects on muscle metabolism, insulin sensitivity, weight regulation, and bone mineral density. This study aims to investigate whether serum levels of MOTS-c are altered in patients with preeclampsia.

**Material and methods:** This is cross sectional a case-control study of 30 patients with uncomplicated pregnancy, 30 patients with mild preeclampsia and 30 patients with severe preeclampsia that were admitted to the study center between June 2020 and January 2021.

**Results:** When compared to the healthy controls and patients with mild preeclampsia, maternal smoking was significantly more frequent, systolic and diastolic blood pressures were significantly higher and platelet count was significantly lower in patients with severe preeclampsia ($p = 0.045$, $p = 0.0001$, $p = 0.0001$ and $p = 0.024$ respectively). Serum MOTS-c concentrations were statistically similar in healthy controls, mild and severe preeclampsia patients (159.1 ± 28.7 ng/mL vs 129.6 ± 54.7 ng/mL vs 146.4 ± 48.3, $p = 0.166$). When compared to the healthy controls, systolic and diastolic blood pressures were significantly higher and platelet count was significantly lower in patients with late onset preeclampsia ($p = 0.0001$, $p = 0.0001$ and $p = 0.022$ respectively). Healthy controls and patients with early and late onset preeclampsia were statistically similar with respect to MOTS-c levels (159.1 ± 28.7 ng/mL vs 126.7 ± 56.9 vs 153.7 ± 39.8, $p = 0.102$).

**Conclusions:** This study failed to detect any significant relationship between MOTS-c and preeclampsia. Large scale research is needed to clarify if MOTS-c is a novel biomarker for preeclampsia and therapeutic target for preeclampsia patients.

**Key words:** endothelium; mitochondria; preeclampsia

Ginekologia Polska 2023; 94, 8: 633–637

## INTRODUCTION

Mitochondrial open-reading-frame of the twelve S rRNA-c (MOTS-c) is a mitochondrial derived peptide which is made up of 16 amino acids [1]. The other mitochondrial derived peptides are humanin and small humanin-like peptides [2].

Humanin protects endothelial cells form oxidative stress and helps to maintain endothelial functions [3, 4]. It has been shown that humanin levels in peripheral circulation are related with the preservation of coronary endothelial functions in patients with non-obstructive coronary artery disease [5]. Similarly, small humanin-like peptides exert protective effects on cells *in vitro* [1]. It has been also reported that these peptides have both neuroprotective and anti-diabetic effects [6]. As for MOTS-c, its beneficial effects on muscle metabolism, insulin sensitivity, weight regulation, and bone mineral density have been demonstrated [7, 8]. However, data related with the effects of MOTS-c on coronary endothelial function is scarce.

Preeclampsia is defined as new onset hypertension with proteinuria during pregnancy. It affects 5% of pregnancies and sometimes progresses into more severe forms of the disease, identified as HELLP or eclampsia [9, 10]. Preeclampsia is associated with intrauterine growth restriction, chronic immune activation and multi-organ endothelial dysfunction [10].

Since MOTS-c is a mitochondrial signaling peptide which is encoded by mitochondrial DNA that regulates physiology,

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Received: 6.05.2022 Accepted: 10.08.2022 Early publication date: 7.10.2022

it would be prudent to expect that MOTS-c might influence endothelial functions [11]. A body of evidence for this suggestion is the detection of lower serum concentrations of MOTS-c in patients with coronary endothelial dysfunction and the improvement of endothelial functions by the administration of MOTS-c in rodents [12].

Therefore, it has been hypothesized that MOTS-c might act as a novel marker for endothelial dysfunction in preeclampsia patients. This study aims to investigate whether serum concentrations of MOTS-c are altered in patients with mild preeclampsia and preeclampsia with severe features.

## MATERIAL AND METHODS

This is a case-control study of 30 patients with uncomplicated pregnancy, 30 patients with mild preeclampsia and 30 patients who had preeclampsia with severe features. All patients were consecutively admitted to the department of obstetrics at a tertiary level university hospital between June 2020 and January 2021. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and, thus, it was approved by the Ethical Committee of the study center (#2020/11) Every participant was informed about the study and written consent was obtained from each participant.

The pregnant women aged younger than 18 years and older than 40 years, the pregnant women with previously diagnosed cardiovascular diseases such as hypertension and coronary artery disease, the pregnant women with diabetes mellitus and other endocrinopathies and the pregnant women with vascular diseases were excluded. Data related with maternal age, gravidity, parity, maternal smoking, and preeclampsia in previous pregnancy were recorded. In addition, data about gestational age and oligohydramnios were inscribed. Body mass index (BMI) was calculated when body weight (kg) was divided by the square of body height (m).

Preeclampsia is identified as the new-onset hypertension which is reflected by systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg on two occasions at least four hours apart after 20 weeks of gestation

The presence of at least one of the following criteria indicated preeclampsia with severe features: Systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg on two occasions at least four hours apart while the patient is on bed rest, new onset cerebral or visual symptoms, such as photopsia, scotomata, cortical blindness, retinal vasospasm, severe headache, elevated serum transaminases (> 2 times the upper limit of the normal range) or severe persistent right upper quadrant or epigastric pain, thrombocytopenia (< 100000 platelets/mL), renal dysfunction (serum creatinine > 1.1 mg/dL) and pulmonary edema.

Early onset preeclampsia is diagnosed < 34 weeks of gestation while late onset preeclampsia is specified ≥ 34 weeks of gestation.

Three samples of 20 mL venous blood were drawn by standard phlebotomy from all of the participants. The first sample was used to evaluate platelet count by means of an automated commercial counter (Coulter counter, Max Instruments Laboratory). The second sample was analyzed to measure serum concentrations of alanine transferase (ALT), aspartate transferase (AST) and creatinine by spectrophotometry (AU5400, Beckman Coulter). The third sample was allocated for the measurement of plasma MOTS-c level by an in-house sandwich ELISA assay, as reported previously [7].

A prospective power analysis was carried out to determine that a cohort size of 105 women (35 women with uncomplicated pregnancy, 35 women with mild preeclampsia and 35 women with severe preeclampsia) had 90% power to detect a difference at the 0.05 significance level [12].

### Statistical analysis

Collected data were analyzed by Statistical Package for Social Sciences version 23.0 (SPSS IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation while categorical variables were denoted as numbers or percentages where appropriate. Kolmogorov-Smirnov test was used to test the normality of data distribution. One-way analysis of variance was utilized to compare the groups with respect to continuous variables with normal distribution and Kruskal-Wallis H test was used to compare the groups in aspect of continuous variables without normal distribution. Chi-square test was used to compare the groups with respect to categorical variables. Pearson test was utilized to detect the correlations among variables with normal distribution whereas Spearman test was used to detect the correlations among the variables without normal distribution. Two-tailed p values < 0.05 were accepted as statistically significant.

## RESULTS

Table 1 summarizes the demographic and clinical characteristics of the women with uncomplicated pregnancy, patients with mild preeclampsia and patients who had preeclampsia with severe features. When compared to the women with uncomplicated pregnancy and patients with mild preeclampsia, maternal smoking was significantly more frequent in patients who had preeclampsia with severe features ($p = 0.045$). As expected, systolic and diastolic blood pressures were significantly higher and platelet count was significantly lower in patients who had preeclampsia with severe features than the women with uncomplicated pregnancy and patients with mild preeclampsia ($p = 0.0001$, $p = 0.0001$ and $p = 0.024$ respectively). Serum MOTS-c levels were statistically similar in women with uncomplicated pregnancy, patients with

**Table 1.** Demographic and clinical characteristics of the participants with uncomplicated pregnancy, mild and severe preeclampsia

| | Uncomplicated Pregnancy (n = 30) | Mild Preeclampsia (n = 30) | Preeclampsia With severe features (n = 30) | p value |
|---|---|---|---|---|
| Maternal age [years] | 29.0 ± 5.2 | 29.5 ± 6.7 | 31.2 ± 5.4 | 0.324[a] |
| Body mass index [kg/m$^2$] | 28.2 ± 1.7 | 28.2 ± 2.0 | 28.8 ± 1.1 | 0.294[b] |
| Gravidity | 2.8 ± 1.4 | 3.0 ± 2.0 | 3.1 ± 2.1 | 0.955[b] |
| Parity | 1.4 ± 1.2 | 2.1 ± 0.3 | 1.2 ± 0.2 | 0.700[b] |
| Maternal smoking | 0 (0.0%) | 0 (0.0%) | 3 (10.0%) | 0.045*[d] |
| Preeclampsia in previous pregnancy | 0 (0.0%) | 1 (3.3%) | 3 (10.0%) | 0.295[d] |
| Gestational age [weeks] | 31.5 ± 2.1 | 32.3 ± 3.3 | 32.4 ± 3.2 | 0.238[b] |
| Oligohydramnios | 0 (0.0%) | 5 (16.7%) | 3 (10.0%) | 0.074[d] |
| Systolic blood pressure [mmHg] | 116.2 ± 13.1 | 145.6 ± 11.1 | 160.6 ± 16 | 0.0001*[b] |
| Diastolic blood pressure [mmHg] | 67.2 ± 11.3 | 83.1 ± 10.2 | 92.1 ± 9.0 | 0.0001*[b] |
| Platelet [×10$^3$/mm$^3$] | 252.5 ± 78.4 | 226.7 ± 81.3 | 179.6 ± 75.4 | 0.024*[c] |
| Creatinine [mg/dL] | 0.53 ± 0.18 | 0.55 ± 0.14 | 0.59 ± 0.22 | 0.877[c] |
| Alanine transferase [IU/L] | 15.6 ± 7.2 | 12.4 ± 8.1 | 34.9 ± 6.5 | 0.192[c] |
| Aspartate transferase [IU/L] | 24.8 ± 6.3 | 22.6 ± 10.0 | 59.9 ± 11.8 | 0.053[c] |
| MOTS-c [ng/mL] | 159.1 ± 28.7 | 129.6 ± 54.7 | 146.4 ± 48.3 | 0.166[b] |

[a]ANOVA; [b]Kruskal-Wallis H test; [c]Independent samples test; [d]Chi-square test; *p < 0.05 was accepted as statistically significant

**Table 2.** Demographic and clinical characteristics of participants with uncomplicated pregnancy, early and late onset preeclampsia

| | Uncomplicated pregnancy (n = 30) | Early onset preeclampsia (n = 36) | Late onset preeclampsia (n = 24) | p value |
|---|---|---|---|---|
| Maternal age [years] | 29.0 ± 5.2 | 29.2 ± 7.1 | 32.1 ± 5.5 | 0.316[a] |
| Body mass index [kg/m$^2$] | 28.2 ± 1.7 | 28.0 ± 1.8 | 29.5 ± 1.1 | 0.244[b] |
| Gravidity | 2.8 ± 1.4 | 3.0 ± 2.0 | 3.1 ± 2.1 | 0.905[b] |
| Parity | 1.4 ± 1.2 | 2.1 ± 0.3 | 1.2 ± 0.2 | 0.638[b] |
| Maternal smoking | 0 (0.0%) | 2 (8.3%) | 1 (0.0%) | 0.441[d] |
| Preeclampsia in previous history | 0 (0.0%) | 3 (8.3%) | 0 (0.0%) | 0.098[d] |
| Gestational age [weeks] | 31.5 ± 2.1 | 30.4 ± 3.2 | 35.3 ± 2.8 | 0.038*[b] |
| Systolic blood pressure [mmHg] | 116.2 ± 13.1 | 142.6 ± 8.7 | 168.2 ± 12.3 | 0.0001*[b] |
| Diastolic blood pressure [mmHg] | 67.2 ± 11.3 | 80.3 ± 8.2 | 99.1 ± 7.0 | 0.0001*[b] |
| Platelet [×10$^3$/mm$^3$] | 252.5 ± 78.4 | 223.2 ± 61.3 | 185.6 ± 55.4 | 0.022*[c] |
| Creatinine [mg/dL] | 0.53 ± 0.18 | 0.52 ± 0.11 | 0.65 ± 0.17 | 0.846[c] |
| Alanine transferase [IU/L] | 15.6 ± 7.2 | 9.4 ± 1.1 | 41.9 ± 6.5 | 0.212[c] |
| Aspartate transferase [IU/L] | 24.8 ± 6.3 | 18.4 ± 7.2 | 53.9 ± 8.4 | 0.033*[c] |
| MOTS-c [ng/mL] | 159.1 ± 28.7 | 126.7 ± 56.9 | 153.7 ± 39.8 | 0.102[b] |

[a]ANOVA; [b]Kruskal-Wallis H test; [c]Independent samples test; [d]Chi-square test; *p < 0.05 was accepted as statistically significant

mild preeclampsia and patients who had preeclampsia with severe features (p = 0.166).

Table 2 demonstrates the demographic and clinical characteristics of the women with uncomplicated pregnancy and the patients with early and late onset preeclampsia. When compared to the women with uncomplicated pregnancy, systolic and diastolic blood pressures were significantly higher and platelet count was significantly lower in patients with late onset preeclampsia (p = 0.0001, p = 0.0001 and p = 0.022 respectively). The patients with late onset preeclampsia also had significantly higher serum AST levels than women with uncomplicated pregnancy and patients with early onset preeclampsia (p = 0.033). Healthy controls and patients with early and late onset preeclampsia were statistically similar with respect to MOTS-c levels (p = 0.102).

There were no statistically significant correlations between MOTS-c concentrations and variables including ma-

**Table 3.** Correlations of variables

| | MOTS-c | |
|---|---|---|
| | **Correlation coefficient** | **p value** |
| Maternal age | –0.148 | 0.165[a] |
| Body mass index | 0.064 | 0.548[b] |
| Gravidity | –0.131 | 0.221[b] |
| Parity | –0.188 | 0.077[b] |
| Gestational age | 0.101 | 0.346[b] |
| Systolic blood pressure | –0.054 | 0.615[b] |
| Diastolic blood pressure | –0.081 | 0.446[b] |
| Platelet [$\times 10^3/mm^3$] | 0.032 | 0.806[a] |
| Creatinine | 0.208 | 0.110[b] |
| Alanine transferase | –0.241 | 0.063[b] |
| Aspartate transferase | –0.102 | 0.437[b] |

[a]Pearson correlation test; [b]Spearman correlation test

ternal age, BMI, gravidity, parity, gestational age, systolic and diastolic blood pressure, platelet count and serum transferase levels (Tab. 3.).

## DISCUSSION

Preeclampsia is a life-threatening disease of pregnancy which is characterized by hypertension and proteinuria becoming evident after 20 weeks. The mechanisms underlying its pathogenesis have not been clarified exactly and preeclampsia has been considered as a multifactorial disease [9, 10].

The mechanisms related with the pathogenesis of preeclampsia include impaired placentation, incomplete spiral artery remodeling, and endothelial damage, which are further aggravated by immune factors, mitochondrial stress and disequilibrium of pro- and anti-angiogenic molecules [13]. Endothelial damage in maternal and placental vasculature is generally defined by the increase in superoxide production and reduction in nitric oxide activity which eventually end up with inflammation, apoptosis and vasoconstriction [9, 10]. It has been well established that endothelial damage might persist after delivery [9].

The AMP activated protein kinase (AMPK) is a serine/threonine kinase which regulates the energy homeostasis in cells by modulating energy supply, accelerating autophagy and suppressing apoptosis. Moreover, AMPK induces vasodilatation by activating endothelial nitric oxide synthase in endothelial cells [14, 15]. It has been reported that the dysregulation of AMPK might contribute to the emergence of cardiovascular diseases, inflammatory diseases and malignancies [16]. Accordingly, AMPK is essential for placentation, nutrient transportation, maternal and fetal energy homeostasis, and protection of the fetal membranes during pregnancy [16, 17].

Nuclear factor-kappaB (NF-κB) is a common nuclear transcription factor which takes part in inflammation, oxidative stress, immune response and apoptosis by regulating cytokines, adhesion molecules and the expression of enzymes and growth factors. It has been highlighted that NF-κB pathway can promote uteroplacental dysfunction, endothelial stress and development of preeclampsia [18, 19].

Mitochondria are the cellular organelles which generate energy, regulate apoptosis and neutralize oxidative stress. These organelles also function as signaling units which help to sustain communication between cells [1]. Additionally, mitochondria convey information by means of retrograde signaling molecules such as reactive oxygen species, cytochrome c and mitochondrial derived peptides such as MOTS-c [1, 2].

It has been designated that MOTS-c activates AMPK so that it might contribute to the improvement in endothelial functions [7, 8]. The activation of AMPK can upregulate the phosphatidylinositol-3 kinase/protein kinase B/endothelial nitric oxide synthase pathway and, thus, trigger the production of nitric oxide in endothelial cells [20, 21]. Since endothelial dysfunction is featured by the tendency towards inflammation, thromboembolism and vasoconstriction, nitric oxide can play a significant role in vasorelaxation and subsequent improvement in endothelial functions [22].

Previous studies have also determined that MOTS-c blocks the expression of pro-inflammatory cytokine (tumor necrosis factor-α, interleukin-6, interleukin-1β) by inhibiting the mitogen activated protein kinase (MAPK) signaling pathway [23]. Thus, it can be presumed that MOTS-c prevents endothelial dysfunction by inhibiting the MAPK/NF-κB pathway [24]. A prior study has also indicated that MOTS-c maintains the endothelium-dependent vasodilatation in thoracic aorta [25].

The study of Qin et al. [12] reported significantly lower plasma MOTS-c levels in patients with endothelial dysfunction when compared to patients with normal endothelial function. Plasma MOTS-c concentrations were also found to correlate with microvascular and epicardial coronary endothelial functions. In the same study, it was demonstrated that MOTS-c was able to reverse acetylcholine-mediated vasodilatation in aortic tissues of normal rats. On the other hand, MOTS-c significantly improved acetylcholine-mediated vasodilatation in aortic tissues of rats with renal artery stenosis. Therefore, the authors concluded that MOTS-c had no direct impact on vasculature but the administration of MOTS-c enhanced the responsiveness of vasculature to acetylcholine [12].

## CONCLUSIONS

As for the present study, serum MOTS-c concentrations were statistically similar in healthy pregnant women, pregnant women with mild preeclampsia and pregnant women who had preeclampsia with severe features. Serum MOTS-c levels were also found to be statistically similar in healthy pregnant women, pregnant women with early and late onset preeclampsia. This study also failed to detect any statistically significant correlations between MOTS-c concentrations and variables including systolic and diastolic blood pressure, platelet count and serum transferase levels. Yet, these findings should be interpreted carefully as their power is limited by relatively small cohort size, lack of longitudinal data and variability in demographic and clinical characteristics of the participants. Large scale research is needed to clarify if MOTS-c is a novel biomarker for preeclampsia and therapeutic target for preeclampsia patients.

## Article information and declarations

### *Conflict of interest*

There is no conflict of interest.

### *Funding*

No funding was received for the study.

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