



## Could AGEs be markers of pre-eclampsia? Study of concentration of advanced protein glycation products in pregnant women with physiological pregnancy and pregnancy complicated with pre-eclampsia

Czy AGEs mogą być markerami stanu przedrzucawkowego?  
Badanie stężenia zaawansowanych produktów glikacji białek  
u kobiet ciężarnych z ciążą fizjologiczną i ciążą powikłaną  
stanem przedrzucawkowym

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### ABSTRACT

**INTRODUCTION:** The role of advanced glycation end products (AGEs) in the pathomechanism of arterial hypertension has been demonstrated, but little information is available on the influence of AGEs on the course of pre-eclampsia (PE). The aim of the study was to assess the concentration profile of advanced protein glycation products in pregnant women diagnosed with PE.

**MATERIAL AND METHODS:** The concentrations of AGEs, carboxymethyllysine (CML), carboxyethyllysine (CEL) and methylglyoxal (MG) in the sera of female respondents were determined using the enzyme immunoassay method.

**RESULTS:** The levels of AGE and CML were lower in the group of women with PE compared to the group of non-pregnant women ( $p = 0.0411$  and  $p = 0.0072$ ). A lower CML concentration was found in healthy pregnant women as compared to healthy non-pregnant women ( $p = 0.00068$ ). Positive correlations were found between AGE and CML levels in women with PE ( $R = 0.339$ ,  $p = 0.032$ ) and between CML and CEL in healthy non-pregnant women ( $R = 0.447$ ,  $p = 0.012$ ).

**CONCLUSIONS:** We suggest that there is a decrease in the intensity of non-enzymatic protein glycation during pregnancy. Moreover, our study indicates that isolated PE may be associated with a different pathomechanism than chronic hypertension, and therefore AGEs cannot be at present considered a marker of PE.

#### KEY WORDS

AGEs, pregnancy, pre-eclampsia, non-enzymatic glycosylation, advanced glycation end products

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## STRESZCZENIE

**WSTĘP:** Rola końcowych produktów zaawansowanej glikacji (*advanced glycation end products* – AGEs) w patomechanizmie nadciśnienia tętniczego została udowodniona, jednak niewiele jest informacji na temat wpływu AGEs na przebieg stanu przedzrzucawkowego (*pre-eclampsia* – PE). Celem pracy była ocena profilu stężeń zaawansowanych produktów glikacji białek u kobiet ciężarnych z rozpoznaniem PE.

**MATERIAŁ I METODY:** Oznaczenia stężeń AGEs, karboksymetylilizyny (*carboxymethyllysine* – CML), karboksyetylilizyny (*carboxyethyllysine* – CEL) i metyloglioksalu (*methylglyoxal* – MG) w surowicy badanych kobiet wykonano metodą immunoenzymatyczną.

**WYNIKI:** Stężenia AGE i CML były niższe w grupie kobiet z PE w porównaniu z grupą kobiet nieciążarnych ( $p = 0,0411$  i  $p = 0,0072$ ). Stwierdzono niższe stężenie CML u zdrowych ciężarnych w porównaniu ze zdrowymi nieciążarnymi ( $p = 0,00068$ ). Stwierdzono dodatnie korelacje pomiędzy stężeniem AGE i CML u kobiet z PE ( $R = 0,339$ ,  $p = 0,032$ ) oraz pomiędzy CML i CEL u zdrowych kobiet nieciążarnych ( $R = 0,447$ ,  $p = 0,012$ ).

**WNIOSKI:** Sugerujemy, że w czasie ciąży dochodzi do zmniejszenia intensywności nieenzymatycznej glikacji białek. Ponadto nasze badanie wskazuje, że izolowane PE może być związane z innym patomechanizmem niż przewlekłe nadciśnienie tętnicze i dlatego AGEs nie mogą być obecnie uważane za marker PE.

## SŁOWA KLUCZOWE

AGEs, ciąża, stan przedzrzucawkowy, nieenzymatyczna glikozylacja, zaawansowane produkty glikacji białek

## INTRODUCTION

Protein glycation is a non-enzymatic process involving the attachment of hexoses (mainly glucose) to free amino groups of proteins in the so-called Maillard reaction [1,2]. This process occurs under the influence of reducing sugars. As a result of glycation, a heterogeneous group of compounds is formed, collectively referred to as advanced glycation end products (AGEs). AGE precursors include glyoxal, methylglyoxal (MG) and 3-deoxyglucosone, but MG is the most powerful of them [3]. They accumulate in cells and cause changes at the molecular and cellular level, leading to the formation of free radicals. Therefore, the end products of advanced protein glycation and their receptors are involved in the pathogenesis of a number of diseases. AGEs are bound by many proteins, of which only some (RAGE, MSR, AGE-R1/R2/R3) are defined as receptors. They were found, among others, on the surface of endothelial cells, smooth muscles, adipocytes, monocytes and hepatocytes [2,4]. Combining them with AGEs leads to the intensification of oxidative stress by the increased production of cytokines and growth factors. The effect of these processes may be the stimulation of angiogenesis, disorders of the coagulation process, changes in the tension of the vascular walls and the induction of a specific immune response (both humoral and cellular) to the neoepitopes of the organism's own proteins. High concentrations of AGEs and the increased expression of AGE receptors were observed in the course of diabetes mellitus, atherosclerosis, renal failure and liver cirrhosis. For neoplastic diseases, this relationship has been described, among others, in cancer of the pancreas, colon, kidney and acute lymphocytic leukemia [5,6].

Pre-eclampsia (PE) is a serious complication of pregnancy associated with arterial hypertension and

proteinuria developing in the second half of pregnancy. The etiology of PE remains unknown, but the role of the circulating factors of placental origin is mentioned as they cause vascular endothelial dysfunction, thus inducing the main clinical features of PE in the mother, including arterial hypertension and proteinuria [7]. The role of AGEs in the pathomechanism of arterial hypertension has been demonstrated [8], but little information is available on influence of AGEs on the course of PE. Hence, the question of how the process of non-enzymatic protein glycation takes place in pregnancies complicated with PE, and whether AGE concentrations can serve as biomarkers of this pathology of pregnancy need to be answered.

The aim of the study was to assess the concentration profile of advanced protein glycation products in pregnant women diagnosed with PE in comparison to non-pregnant women and those with a physiological pregnancy. Understanding the changes occurring within the scope determined for the purpose of the study is an important element of obstetric knowledge, allowing better understanding of the pathomechanism of PE. In future, this knowledge may be used in clinical practice to diagnose or predict the occurrence of this dangerous pathology.

## MATERIAL AND METHODS

111 female patients participated in the study. They were divided into 3 groups. The first study group consisted of patients diagnosed with PE ( $n = 40$ ). The diagnosis of PE was in accordance with international guidelines and definitions [9]. The second group included pregnant women with a physiological pregnancy ( $n = 40$ ). The exclusion criteria included a previous history of arterial hypertension, diabetes, heart disease, liver disease and kidney disease, as well as other pregnancy and obstetric complications. The gestation



week at the time of sample collection is given in Table I. The control group consisted of healthy volunteers of a comparable age ( $n = 31$ ). Consent was obtained from all the study participants following a full explanation of the nature of the procedure. The study was approved by the Bioethics Committee of the Medical University of Silesia, Katowice, Poland.

The concentrations of selected parameters of advanced protein glycation were determined: AGE, CML, CEL and MG in the sera of pregnant women with PE, healthy pregnant women and healthy non-pregnant women using the enzyme immunoassay method (ELISA) with commercially available kits. The determinations were carried out in one series according to the manufacturer's instructions.

#### Determination of advanced protein glycation products (AGEs)

The OxiSelect™ Advanced Glycation End Product (AGE) ELISA Kit by CELL BIOLABS (USA), catalog number STA-817, was employed to determine the concentrations of advanced protein glycation products in the studied blood sera.

#### Determination of carboxymethyllysine (CML)

The OxiSelect™ N<sup>ε</sup>- (carboxymethyl) lysine (CML) Competitive ELISA Kit by CELL BIOLABS (USA), catalog number STA-816, was utilised to determine the concentrations of carboxymethyllysine in investigated sera.

#### Determination of carboxyethyllysine (CEL)

OxiSelect™ N<sup>ε</sup>- (carboxyethyl) lysine (CEL) Competitive ELISA Kit by CELL BIOLABS (USA) with catalog number STA-813 was used to determine the carboxyethyl lysine concentrations in the examined sera.

#### Determination of methylglyoxal (MG)

The OxiSelect™ Methylglyoxal (MG) Competitive ELISA Kit by CELL BIOLABS (USA), catalog number STA-811, was employed to determine the concentration of methylglyoxal in the tested samples. Absorbance readings were made by means of a PowerWave XS reader (BioTek, USA) at a wavelength of 450 nm (reference 630 nm), and processing of the results – using the KCJunior computer program (BioTek, USA). The within-run error for all the kits used was less than 10%.

The obtained results were presented using the basic parameters of descriptive statistics such as the mean value and standard deviation. Compliance of the distribution of variables with the normal distribution

was verified using the Shapiro-Wilk test. The non-parametric Kolmogorov-Smirnov and the Mann-Whitney U tests were employed for comparisons between the groups. The Kruskal-Wallis rank ANOVA test was utilised to study the within-group variability. The existence of a correlation between the parameters was sought by means of Spearman's rank correlation test. The significance level of  $p < 0.05$  was adopted as statistically significant. The computer program STATISTICA for Windows 13.3 (Tibco Software Inc.) was used for the calculations.

## RESULTS

The clinical characteristics of the studied pregnant women are presented in Table I. The pregnant women, both with PE and healthy, did not differ in terms of age or week of pregnancy at which the study was conducted, nor in parity, but they showed differences in body mass index (BMI), pregnancy duration, weight and the birth status of the newborn assessed on the basis of the pH of the fetal blood taken directly after birth from the umbilical cord.

**Table I.** Clinical characteristics of studied pregnant women  
**Tabela I.** Charakterystyka kliniczna badanych kobiet ciężarnych

Characteristic	PE (n = 40)	Healthy pregnant (n = 40)
Age	29.1 ± 3.9	27.4 ± 4.1
Week of pregnancy at time of sample collection	33.6 ± 3.9	34.4 ± 1.4
Week of pregnancy at time of labor	34.7 ± 3.4	39.5 ± 0.8*
Parity	1.9 ± 0.8	2.35 ± 1.1
BMI [kg/m <sup>2</sup> ]	34.4 ± 5.9	33.2 ± 5.6*
Body weight of neonate [g]	1880 ± 1025	2760 ± 740*
pH of fetal blood	7.23 ± 0.25	7.34 ± 0.3*

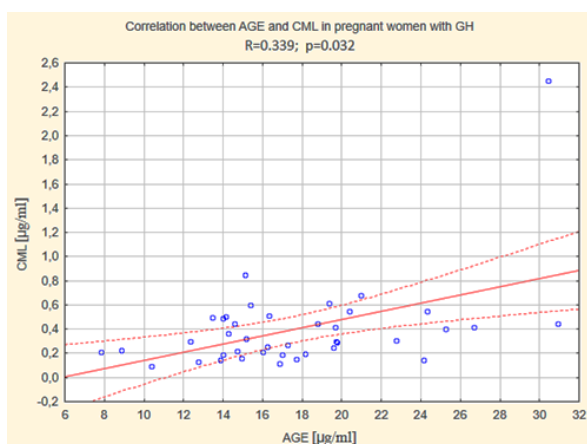
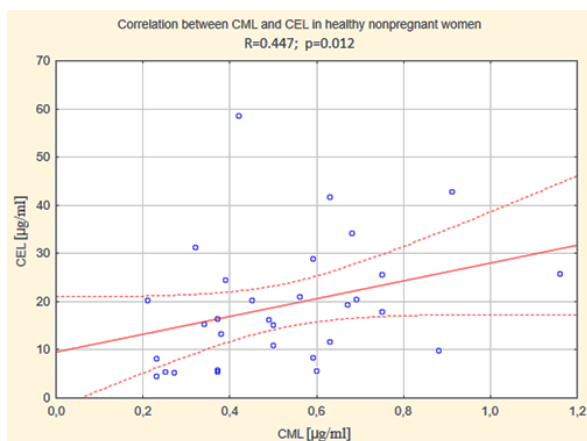
PE – pre-eclampsia; BMI – body mass index; \* $p < 0.05$

As shown in Table II, the levels of AGE and CML were lower in the group of women with PE compared to the group of non-pregnant women ( $p = 0.0411$  and  $p = 0.0072$ , respectively). In addition, a statistically significantly lower CML concentration was found in the healthy pregnant women as compared to the healthy non-pregnant women ( $p = 0.00068$ ). There were no differences in the CEL or MG levels between the groups. Positive correlations were found between AGE and CML levels in the women with PE ( $R = 0.339$ ,  $p = 0.032$ ) and between CML and CEL in the healthy non-pregnant women ( $R = 0.447$ ,  $p = 0.012$ ) (Figures 1 and 2).

**Table II.** Values of studied parameters [ $\mu\text{g/ml}$ ] in individual groups of women (mean  $\pm$  standard deviation, and range)**Tabela II.** Wartości badanych parametrów [ $\mu\text{g/ml}$ ] w poszczególnych grupach kobiet (średnia, odchylenie standardowe i zakres)

Studied parameter	PE	Healthy pregnancy	Non-pregnant women
AGE [ $\mu\text{g/ml}$ ]	17.6 $\pm$ 5.2* (7.8–30.9)	19.4 $\pm$ 6.5 (12.0–48.0)	21.9 $\pm$ 7.2 (10.5–35.8)
CML [ $\mu\text{g/ml}$ ]	0.4 $\pm$ 0.4* (0.1–1.4)	0.3 $\pm$ 0.2* (0.0–0.7)	0.6 $\pm$ 0.2 (0.2–2.1)
CEL [ $\mu\text{g/ml}$ ]	16.7 $\pm$ 10.1 (5.2–50.9)	15.9 $\pm$ 12.3 (1.3–75.3)	19.1 $\pm$ 12.7 (4.6–58.7)
MG [ $\mu\text{g/ml}$ ]	0.8 $\pm$ 0.4 (0.1–1.8)	1.1 $\pm$ 0.9 (0.4–4.1)	0.8 $\pm$ 0.47 (0.14–2.4)

PE – pre-eclampsia; AGE – advanced glycation end product; CML – carboxymethyllysine; CEL – carboxyethyllysine; MG – methylglyoxal; \*  $p < 0.05$  compared to non-pregnant

**Fig. 1.** Linear correlation between AGE and CML levels in women with PE.**Ryc. 1.** Korelacja liniowa między poziomami AGE i CML u kobiet ze stanem przedrzucawkowym.**Fig. 2.** Linear correlation between CML and CEL in healthy non-pregnant women.**Ryc. 2.** Korelacja liniowa pomiędzy CML i CEL u zdrowych kobiet nieciążących.

## DISCUSSION

Arterial hypertension is a major risk factor for cardiovascular diseases. It is strongly associated with the risk of cardiovascular events, kidney diseases and mortality. PE complicates 2–12% of pregnancies and is associated with significant maternal and neonatal mortality [10]. The disease triggering factors and pathogenesis mechanisms remain elusive. Recent reports have hypothesized that PE is a result of a transient inflammatory reaction during pregnancy, caused among others by inappropriate or excessive complement activation in the placenta [11,12], leading to its dysfunction. Placental dysfunction due to ischemia and oxygen deficiency causes damage to vascular endothelial cells (VEC) and the activation of neutrophils and monocytes. IL-6, TNF- $\alpha$ , calprotectin, inflammation-related proteins and endotoxins derived from neutrophils and macrophages, as well as many other chemical compounds are involved in the pathogenesis of this disease [12,13,14]. Many risk factors for PE have been identified, but the exact etiology of this disorder has not been explained yet [15]. Considering the above, the role of the cell surface pattern recognition receptor for advanced glycation end products (RAGE) seems to be of significant importance in the etiology of PE [16].

Little is known about the levels of circulating AGEs in pregnancy. One study found elevated serum AGE levels in women with PE [17], while another suggested that gestational diabetes was associated with increased serum AGE levels [18]. Single studies indicate the potential applicability of protein glycation end products in predicting premature rupture of the amniotic fluid sac and preterm labor [19]. In our study, the AGE levels were measured to ascertain if there were any significant changes in their concentrations in the course of PE. Most studies report that in women with hypertensive complications in pregnancy, AGE levels increase as a consequence of an increase in the expression of adipokines, cytokines and ligands of the receptor for advanced glycation end products (RAGE) [10,13,20, 21,22,23,24]. In our study, no differences in the concentrations of AGEs tested were found between the pregnant women with PE and healthy women. These results are partially consistent with the report by Feng et al. [13], who reported that the increase in RAGE in pregnancies complicated with hypertension positively correlated with a severity of hypertensive disorders in pregnancy. In their research the increase was found only in groups of women with severe hypertension and, similar to our study, was not observed in cases with a lower severity of the disease. It can therefore be hypothesized that a gradual increase in RAGE with increasing hypertension in pregnant women is due to



the release of inflammatory mediators by a hypoxic placenta. Those mediators promote the infiltration of inflammatory cells. A local inflammatory reaction is then exacerbated and VECs become damaged, leading to the further progression of PE. Feng et al. [13] believe that the assessment of RAGE may be a valuable clinical clue in predicting hypertension-related disorders in pregnant women. The above studies confirm a different etiology of PE than of gestational hypertension.

The study by Sankaralingam et al. [24] showed that the expression of the low-density lipoprotein 1 receptor (LOX-1) was induced by MG, which may affect the course of PE. It has also been shown that the serum MG level in individuals with hypertension was significantly higher than in the control group [25]. MG is perceived as a potential new biomarker to identify patients at high risk of developing late diabetic complications and at risk of accidental cardiovascular events, especially in people with type 1 diabetes [26,27]. In our research, no relationship between the MG level and PE was found. CML is one of the best known and most widespread AGEs. Moreover, in women with PE, an increase in the AGE concentration results in an increase in CML expression, as evidenced by the correlation found in this study (Figure 1). However, our results indicate that neither AGE nor CML contribute to the pathogenesis of hypertensive pregnancy complications, as confirmed by other researchers [28]. The study by Alexander et al. [7], who prove that the plasma CML concentration is higher in women with gestational diabetes and PE compared to the control group stands in opposition to these results. CML in large amounts are generated during the thermal processing of food (mainly during frying) and are found in processed foods; they are also present in smaller amounts in the raw food of animal and vegetable origin [2,29]. Probably it is dietary AGEs that are involved in the pathogenesis of common complications related to pregnancy, which is confirmed by scientific reports [29].

The literature also raises the role of the soluble receptor for advanced protein glycation products (sRAGE – soluble RAGE). sRAGE is a newly discovered biomarker for diabetes, vascular and inflammatory diseases and cancer [18]. Research has shown that its concentration in the serum of pregnant women is significantly lower than in non-pregnant patients. However, in the case of PE, the sRAGE concentration increases compared to healthy pregnant patients [30]. This may be related to the fact that in healthy pregnant

women glycemia is lower than in the rest of the population [31]. RAGE activation causes cell dysfunction at the molecular level, leading to an increased expression of pro-inflammatory genes. On the other hand, sRAGE captures AGEs just like RAGE, but due to the fact that it does not have a transmembrane and signaling domain, it does not activate metabolic pathways in cells, and therefore its high concentration may have a protective effect on the organism against high serum AGE levels [32]. A study of the AGE-RAGE-sRAGE axis in pregnant and hypertensive pregnant populations may shed more light on these clinical problems in terms of protein glycation.

Protein glycation affects many other physiological processes, and its association with gestational hypertension and PE suggests that AGE levels will be increased in placental pathologies such as IUGR or ablation, or will be part of a wide range of causes of implantation-related infertility. Nevertheless, these hypotheses remain unconfirmed and may initiate the direction of further research on the process of protein glycation in the aspect of pregnancy. Further research is being carried out in our center, whose results will be presented after its completion.

In conclusion, we did not demonstrate any relationship between the AGEs studied and the pathomechanism of PE. The main limitation of this experiment was the small size of groups and the inability to separate AGEs arising as a result of the pathophysiology of pregnancy complications from dietary AGEs. It seems that the higher AGE concentrations reported in numerous publications are a consequence rather than a cause of pregnancy complications related to hypertension. We suggest that there is a decrease in the intensity of non-enzymatic protein glycation during pregnancy and the formation of non-dietary AGEs. One of the reasons for this may be a reduction in the glucose level in pregnancy in the general population [33]. Moreover, our study indicates that isolated PE may be associated with a different pathomechanism than chronic hypertension and PE associated with diseases such as diabetes, and therefore AGEs cannot be at present considered a marker of PE.

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**Author's contribution**

Study design – P. Bodzek, I. Janosz  
Data collection – P. Bodzek, I. Janosz  
Data interpretation – P. Bodzek, I. Janosz  
Statistical analysis – A. Damasiewicz-Bodzek  
Manuscript preparation – P. Bodzek, A. Olejek  
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