Research Article

Placental protein 13, galectin 14 and pentraxin 3 for prediction of pre-eclampsia in Egyptian patients

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ABSTRACT

Background: Pre-eclampsia (PE) is considered one of the most dangerous pregnancy complications, and the leading cause of maternal and perinatal mortality and morbidity. **Objective:** The aim of the current study was to evaluate two galectins (GAL) and some biochemical parameters in the diagnosis of PE. **Materials and Methods:** The study included a total of 96 women, including 66 pregnant women with PE, and 30 normotensive pregnant females. The biomarkers studied, at the 3 trimesters, included GAL13 and 14, pentraxin 3 (PTX3), C-reactive protein (CRP), liver function tests, and lipid profile. **Results:** Results indicated that a significant difference in GAL13 and 14 and PTX3 in preeclamptic women compared to normotensive pregnant ones. The level of CRP showed non-significant change in all patient's groups. Liver function tests, total cholesterol, low-density lipoprotein cholesterol, and triacylglycerols revealed a high significant increase in all patient's groups. Levels of high-density lipoprotein cholesterol were highly significant decreased in 2nd and 3rd-trimester patients. **Conclusion:** The specificity and sensitivity of GAL14 provided the highest diagnostic information of these biomarkers and are in close to GAL13 and PTX3; while, CRP yielded a significantly worse accuracy for diagnosing PE.

KEY WORDS: Preeclampsia**;** Galectins 13; Galectins 14; Pentraxin 3

INTRODUCTION

Pre-eclampsia (PE) is a disorder of pregnancy with a worldwide prevalence of about 5–8%.[1] The only known remedy is delivery of the placenta. PE is an important cause of premature delivery in developed countries, usually medically indicated for the benefit of the mother. This results in infant morbidity and substantial health-care expenditure.[2]

PE can be divided into two main types, early- and late-onset PE. This subtyping is based on the time of onset or recognition of the disease.[3] The late-onset PE comprises the majority (>80%) of preeclamptic. In the early onset type, the clinical signs appear before 33 gestational weeks, while in the late-onset type they occur at and after 34 weeks. The early-onset type that is responsible for most of the high maternal and fetal mortality and morbidity rates.[1]

The diagnosis of PE is clinical. As defined by the American College of Obstetrics and Gynecology, the diagnosis requires blood pressures >140/90 mm Hg on 2 occasions combined with urinary protein excretion >300 mg/d. Edema, a classic feature of the disease, is no longer considered a diagnostic feature due to lack of sensitivity or specificity. In 20% of cases, eclampsia may present without preceding proteinuria or hypertension, suggesting that the currently employed diagnostic markers are imperfect.[4]

In the absence of proteinuria, new-onset hypertension with new onset of any one of the following: Thrombocytopenia

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(platelet count <100 000/μl), renal insufficiency (serum creatinine concentration >1.1 m mg/dl or a doubling of the serum creatinine concentration in the absence of other renal disease), impaired liver function, pulmonary edema, or cerebral, or visual problems.[1]

Galectins (GAL) are multifunctional regulators of fundamental cellular processes. They are also involved in innate and adaptive immune responses and play a functional role in immune-endocrine crosstalk. Some GAL have attracted attention in the reproductive sciences because they are highly expressed at the maternal-fetal interface, their functional significance in eutherian pregnancies, and their dysregulated expression is observed in the "great obstetrical syndromes." These GAL; may serve as important proteins involved in maternal-fetal interactions. The study of these GAL may improve the prediction, diagnosis, and treatment of pregnancy complications.[5]

Twelve from the fifteen identified mammalian GAL are found in humans.[6] GAL 13 was originally identified as 16-kDa protein with lysophospholipase activity named placental protein 13 (PP13).[7] It is synthesized mainly by the placental syncytiotrophoblast, externalized to the cell surface and secreted in microvesicles associated with actin and annexin II.[8]

PP13 is selectively associated with T cell-, neutrophil-, and macrophage-rich decidual foci of necrosis,[9] suggesting that it might act to attract, activate and kill maternal immune cells facilitating trophoblast invasion and conversion of the maternal spiral arterioles. Recent studies suggest that expression of GAL13 is largely restricted to the human placenta, so it has an important role in the regulation of maternal vascular adaptations to pregnancy.[10]

GAL14 is known as PP13-like charcot leyden crystal protein 2. It contains 1 galectin domain and though it is highly expressed in the human placenta rather less is known about its function.[11] GAL-14 was reported to play a role in the immune response against gastrointestinal parasites serving as marker for worm burden, which was shown in sheep infected with *Haemonchus contortus*.[12]

This study aims to evaluate the potential role of circulating GAL13 and 14 and pentraxin 3 (PTX3) in the prediction of PE in EGYPTIAN patients. Besides the three parameters, the study also evaluated C-reactive protein (CRP), glucose, glycohemoglobin A1c (HbA1c), liver function tests, and lipid profile.

MATERIALS AND METHODS

Subjects

This randomized study was done on 30 healthy subjects (Control group GI) and 66 patients (divided equally into three groups G II: Women at the 1st trimester, G III: At the 2nd trimester and (G IV): At the 3rd trimester of gestation). The patients were from the Department of Gynecology and Obstetrics at Ain Shams University Educational Hospital (El Demerdash Hospital), Cairo, Egypt. A full medical history was taken with special attention to any associated medical problems. All subjects gave written informed consent to participate in the study, which was carried out in accordance with the Helsinki Declaration. The study was approved by the Ethics Committee at Ain-Shams University.

The exclusion criteria were: Chronic hypertension, pregestational diabetes mellitus, chronic renal disease, systemic lupus erythematosus, obesity (body mass index ≥30 kg/m^2), or a history of previous PE.

The preeclamptic patients were diagnosed based on International Society for the Study of Hypertension in Pregnancy. Patients had a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least two occasions 4 h apart developed after 20 weeks of gestation in previously normotensive women combined with proteinuria of ≥300 mg in 24 h, or two readings of at least 2+ on dipstick analysis of midstream or catheter urine specimens, if no 24 h collection was available.[13]

Biochemical Parameters

Venous blood samples were collected from patients and controls in the morning after an overnight fasting. Each blood sample was divided into two parts, whole blood (for glucose and glycosylated hemoglobin A1C) and serum (for the rest of the biochemical parameters).

GAL13 (PP13) was determined using a standard sandwich ELISA kit according to the method described by Bohn *et al*.,[14] Than *et al*.,[7] GAL14 using a standard sandwich ELISA kit, according to the method described by Young *et al*.,[15] PTX3 using a standard sandwich ELISA kit as described by *Inoue et al.*[16] Serum CRP was estimated according to the method of Roberts.[17]

Blood glucose was estimated by the method of Trinder,[18] blood HbA1c according to Trivelli,[19]

Liver functions tests included transaminases (alanine transaminase [ALT] and aspartate aminotransferase [AST]), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) were estimated according to Bergmeyer *et al.*,[20] King and Armstrong,[21] and Rosalki and Tarlow,[22] respectively. Bilirubin was estimated by the method of Walters and Gerarde.[23] Determination of total protein[24] was also done.

Statistical Analysis

Statistical analysis was carried out by the aid of a digital computer, using Excel, and IBM SPSS Statistics version 21 program.

RESULTS

GAL13 was highly significant increase in the 1st trimester and the 2nd trimester patients while in 3rd-trimester patients showed non-significant change. GAL14 was significantly increased in 1st trimester and 2nd trimester patients whereas, in 3rd trimester patients was highly significantly increased compared to the normal control group [Figure 1]. Highly significant increases in PTX 3 were observed in all patient's groups when compared with control group.

The level of CRP, glucose, and HbA1C showed non-significant changes in all patient's groups (Results not shown).

Activity of ALT and AST was significantly increased in the 2nd trimester patients while recorded non-significant changes in the 1st and 3rd-trimester patients when compared to control group. Results of ALP revealed non-significant changes in 1st-trimester patients while in the 2nd and 3rd trimester showed a significant increase compared to the control group [Table 1]. In the same table results of GGT in 3rd-trimester patients recorded significant increase whereas, in the 1st and 2nd-trimester patients showed non-significant change compared to control group.

Figure 2 shows results of bilirubin and total protein. A non-significant change with 7.84% in bilirubin was observed in the 1st trimester patients while in the 2nd and 3rd-trimester patients were highly significant increased by 64.71% and 74.22%, respectively, compared to the normal group. Total protein data revealed a non-significant decrease by 0.34% in 1st-trimester patients while in the 2nd and 3rd-trimester patients were highly significant decreased by 32.1% and 48.44%, respectively, when compared to control group.

Results of lipid profile of all the patients in Figure 3 showed that total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, and triacylglycerols (TAG) revealed high significant increase in the 1st trimester, 2nd and 3rd-trimester patients when compared with control group. Levels of HDLc were highly significant decreased in the 2nd and 3rd-trimester patients while in the 1st-trimester patients were non-significantly decrease.

PTX-3, GAL-13, and GAL-14 provided the highest diagnostic information of biomarkers with an AUC of 0.888, 0.802, and 0.942, respectively ($P < 0.001$), and cutoff values 1.45, 64.95, and 1.40 while, CRP exhibited inferior diagnostic performance with an AUC of 0.469 ($P > 0.05$) and cutoff value 3.5 as shown in Table 2 and Figure 4 in PE patients. Furthermore, the (%) sensitivity, specificity, positive predictive value, negative predictive value, and area under the curves (AUC) of PTX3, GAL13, GAL14, and CRP are presented in Table 3 and Figure 5.

DISCUSSION

Despite much improved clinical care and extensive investigation, PE still remains enigmatic, and no effective

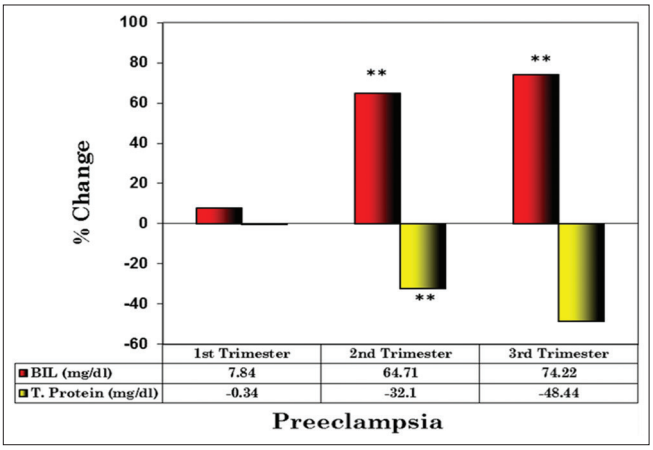

Figure 2: Percentage change in bilirubin and total protein between patient groups and control group

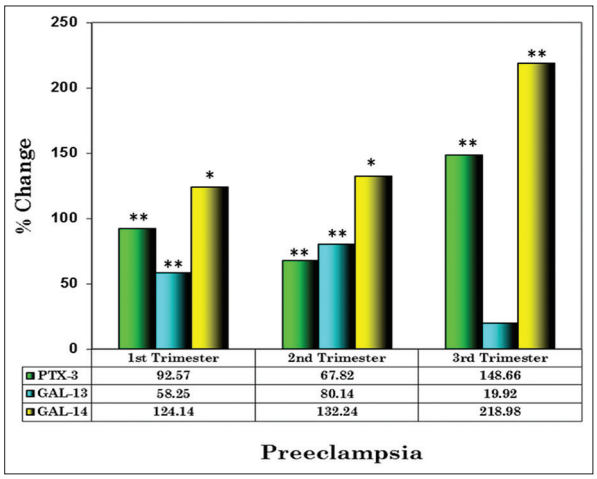

Figure 1: Percentage change of pentraxin 3 (ng/L), galectin-13 (GAL-13) (pg/L), and GAL-14 (ng/L) between patient groups and control group

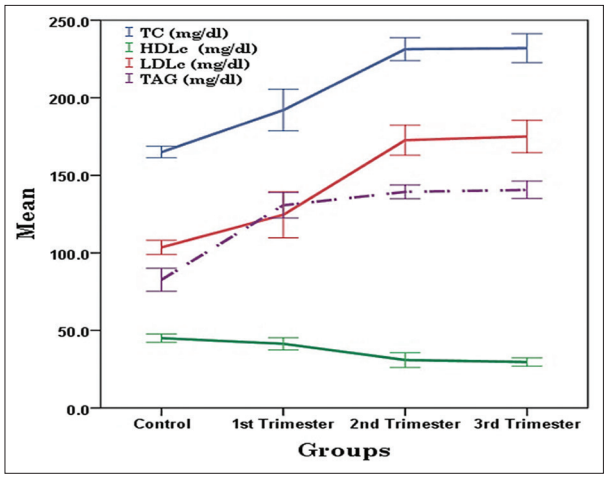

Figure 3: Mean plots ± standard error of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and TAG in control and patient groups

Table 1: Activities of liver enzymes in all groups

Group	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	GGT (IU/L)
Control	20.77±1.2	22.63±0.9	79.50±2.67	29.80±1.51
1st trimester	22.45±1.3	19.20±1.2	80.05±2.83	29.35±1.98
2nd trimester	32.55±5.9*	38.20±6.2**	106.85±4.97***	35.95±2.54
3rd trimester	22.85±3.9	29.62±3.6	91.5±4.22*	36.69±1.72*

Results are given as mean±SE, *P<0.05, **P<0.01, ***P<0.001. SE: Standard error, ALT: Alanine transaminase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase

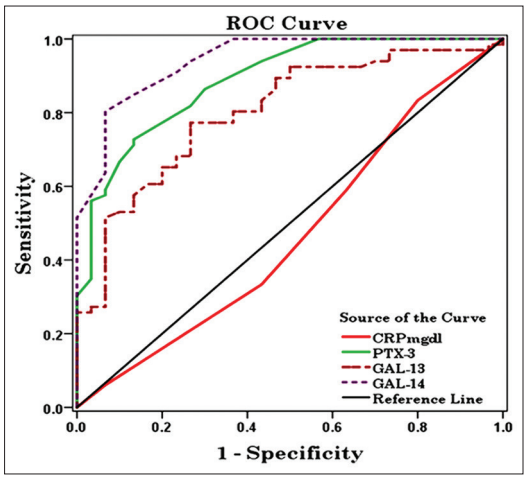

Figure 4: Receiver operating characteristic curves displaying the accuracy of C-reactive protein, pentraxin 3, Galectin-13 (GAL-13), and GAL-14 in preeclampsia patients

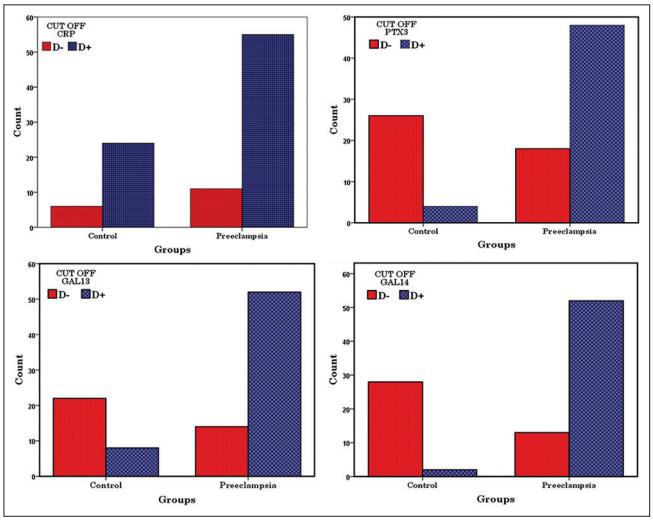

Figure 5: Cutoff values of galectin 13 and 14 show false positive and negative results

treatments are available. Delivery is the only treatment of controlling maternal symptoms associated with this disease.[1]

One of the proposed mechanisms leading to PE is the dysregulation of maternal-fetal immune tolerance. GAL are key regulator proteins of the immune response in vertebrates and maternal-fetal immune tolerance in eutherian mammals.[25]

Table 2: AUC and cutoff value of CRP, PTX-3, GAL-13, and GAL-14 in PE patients

Test result variable (s)	AUC	Asymptotic significant	Cut off value
CRP	0.469	0.624	3.5
PTX-3	0.888	0.000	1.45
GAL-13	0.802	0.000	64.95
GAL-14	0.942	0.000	1.40

CRP: C-reactive protein, PTX3: Pentraxin 3, GAL: Galectin, PE: Pre-eclampsia, AUC: Area under the curve

GAL13 mRNA expression profiles show that it is specifically expressed in the placenta compared with other tissues. This lack of PP13 is true for a very large selection of diversified human tissues from adult and fetal origin.[11]

The PP13 levels gradually increase in normal pregnancy. Abnormally low levels of PP13 were found in women who developed pre-eclampsia when compared to the controls during the 1st trimester.[26] The levels of PP13 were found to be high in pre-eclampsia, intrauterine growth restriction, and preterm delivery during 2nd and 3rd trimesters.[27]

As pre-eclampsia progresses the level of PP13 increases, most likely through the increased shedding of syncytiotrophoblast microparticles (STBM) that convey a high concentration of PP13 into maternal blood. The sharper the increase of PP13 from 1st to 3rd trimester, the more severe the anticipated pre-eclampsia symptoms.[28,29]

PP13 also demonstrates mild lysophospholipase-A activity that leads to the liberation of fatty acid constituents of the plasma membrane, particularly linoleic acid, which might contribute to normal implantation. Furthermore, PP13 increases liberation of prostaglandins, particularly prostacyclin, which are important for trophoblast-stimulated vascular remodeling in the maternal spiral arteries in early placental development.[30]

Our study indicates that the 1st–2nd-trimester increase in PP13 level correlates with the severity of the disease. The time of the increase corresponds to the onset of the release of STBM deported to the maternal blood, as described previously by Huppertz and Kingdom.[31]

Table 3: Cutoff values, (%) sensitivity, specificity, positive predictive value, negative predictive value, and area under the curves of PTX3, GAL13, GAL14, and CRP for diagnosing PE

Biomarker	PTX3		GAL13		GAL14		CRP	
	D+	D-	D+	D-	D+	D-	D+	D-
PE (*n*=66)	48	18	53	13	52	14	55	11
Control (*n*=30)	4	26	2	28	8	22	24	6
Cutoff point	1.45		64.95		1.4		3.5	
Sensitivity (%)	92.3		86.67		96.36		64.71	
Specificity (%)	59.1		61.11		68.29		30.38	
PPV (%)	72.73		78.79		80.30		83.33	
NPV (%)	86.67		73.33		93.33		20	
AUC (95% CI)	0.89 (0.82–0.96)		0.80 (0.71−0.89)		0.94 (0.90−0.99)		0.469 (0.34−0.6)	
P<	0.001		0.001		0.001		0.624	

D+: Positive disease, D-: Negative disease, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, 95% CI: 95% confidence interval, CRP: C-reactive protein, GAL: Galectin, PTX3: Pentraxin 3, PE: Pre-eclampsia

GAL-14 is specifically expressed by ovine eosinophils.[15] It contains 1 GAL domain and though it is highly expressed in the human placenta rather less is known about its function.[32]

Actually, few work was done on GAL 14 in case of preeclamptic. Than *et al*.[25] reported that the placental expression of LGALS13 and LGALS14 is impaired in preterm PE associated with small for gestational age (SGA) due to the dysregulated expression of key TFs controlling trophoblast functions, and the differential methylation of these genes is also associated with preterm PE irrespective of SGA.

PTX3 is an essential component of innate immunity and a member of the long PTX superfamily, which are soluble, multifunctional pattern recognition proteins induced by various inflammatory stimuli. PTX3 is produced locally in relevant cells such as endothelial cells, granulocytes, and macrophages at the site of inflammation.[33]

The increase in PTX3 is correlated with disease severity. PTX3 in PE has drawn increasing attention, as a potential inflammatory mediator.[34] The abnormal pro-inflammatory maternal status (interleukin 1 and tumor necrosis factor-alpha), pre-existing endothelial damage, and excess of oxidized LDL seen in the 1st trimester in preeclamptic, may all induce PTX3 elevation.[35]

Our results are in agreement with Cetin *et al*.[36] who found that the PTX3 level remained stable during normal pregnancy but the average values in each trimester were slightly higher than those in non-pregnant women and significantly higher in PE. Furthermore, previous studies[37,38] revealed that PTX3 levels were increased in maternal circulation during the 1st trimester in preeclamptic, suggesting that PTX3 may be an early predictive factor for PE. These findings also support an etiologic hypothesis for PE being an excessive maternal inflammatory response to pregnancy.

CRP found in the blood is considered as an acute-phase protein in which its level increases during inflammation, tissue damage, infection, and neoplasia.[39] Although maternal levels of CRP are elevated in overt PE, there is still a debate about its usefulness as a predictive marker for PE.[40] The results of our study showed that CRP provided a non-significant change in all patient's groups of PE when compared with control group.

These results are in agreement with previous studies,[41,42] who did not find a significant role of CRP in pregnancies complicated by PE as compared to normotensive pregnant women.

Our results concerning lipid profile are in agreement with Gohil *et al*.[43] who quoted that dyslipidemia in the form of significantly decreased HDL concentration and significantly increased TC, LDL, and Triglycerides concentration is conspicuously evident in subjects of PE as compared to non-pregnant, normotensive pregnant, and postpartum subjects. Furthermore, TAG and LDL levels were significantly higher in preeclamptic as compared to normal.[44]

Women with pre-eclampsia have higher levels of circulating serum triacylglycerols (TAG) which is an essential step in lipid-mediated endothelial dysfunction. The mechanisms driving the abnormal elevation of TAG leading to pre-eclampsia are unclear. During pregnancy, there is an increase in the hepatic lipase activity and a decrease in lipoprotein lipase activity. Hepatic lipase is responsible for the increased synthesis of the TAG at the hepatic level, and the decreased activity of lipoprotein lipase is responsible for the decreased catabolism at the adipose tissue level, whereas placental VLDL receptors are up-regulated. This results in re-routing of TAG-rich lipoproteins to the feto-placental unit.[43]

Different studies have proved that women with PE have higher levels of both circulating serum free fatty acids. Others have observed higher concentrations of TC,

phospholipids, and lipid peroxides in placental decidua basalis tissue derived from women with pre-eclampsia, the layer of the placenta that contains the spiral arteries and where the process of atherosis may heighten the risk of placental vascular disease. However; pre-eclampsia is multicausal disease, then TAG-related vasculopathy may be one plausible etiologic factor.[45]

In PE PE hypervascularization and vasoconstriction of liver leads to liver cell injury and alteration of cell membrane permeability and damage to the cells which allows intracellular enzyme to leak into the blood, leading to elevated liver enzymes such as ALT and AST.[46]

ALP is one of the important enzymes secreted by placenta. Placental alkaline phosphatase (PALP) is polymorphic and heat stable enzyme, and high levels of this enzyme are found in trophoblast of placenta. It is localized in apical and basal cells of syncytiotrophoblast plasma membrane. It is synthesized from placental syncytiotrophoblast from the 12th week of pregnancy and is released into the maternal blood.[47]

Shevade *et al.*[47] showed that abnormally high serum ALP levels represent placental damage and failing placental function**.** Placental ischemia, necrosis, damage of chorionic villi and infarction can increase the levels of PALP in maternal serum.

GGT is a microsomal glycoprotein enzyme that catalyzes the transfer of gamma-glutamyl group from a peptide to an acceptor peptide or an L-Amino acid. Endothelial cell dysfunction within the uteroplacental circulation leads to the systemic release of GGT.[48]

The increase in bilirubin was in agreement with Das *et al.*[49] who reported that serum bilirubin level was significantly higher in preeclamptic group than the control group. PE is associated with increased capillary permeability secondary to endothelial damage, and this seems to be partly responsible for the observed proteinuria and consequent significantly low serum total protein and albumin levels. These findings corroborate the earlier work of Bhatia *et al.*[50]

CONCLUSION

GAL14 and 13 could be used as good diagnostic markers for PE, where the specificity and sensitivity of GAL14 provided the highest diagnostic information of these biomarkers and are in close to GAL13 and PTX3. Concerning CRP results, it shows significantly worse accuracy for diagnosing PE.

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