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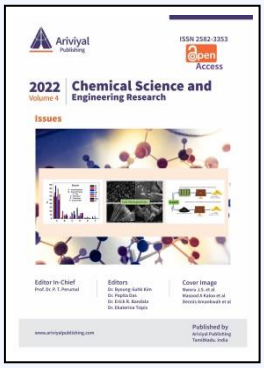

Evaluation of Plasma Cadmium Levels in Pregnancy and Outcome Implications, Kinshasa, DR Congo

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Abstract: Although the most majority of Cd in whole blood is bound to red blood cells, the remaining Cd in the plasma represents the toxicologically active fraction for exchange with target tissues, including the developing fetus and the relevant index of health risks of Cd exposure. In whole blood, the evidence has been shown that prenatal exposure to Cd is associated with neurological dysfunctions, stillbirths, hypertension, spontaneous abortions, preterm birth, and reduced birth weight and birth size. The aim of this work was to evaluate plasma Cd levels in pregnancy and their birth outcomes implications. Plasma-Cd levels were measured by AA500FG-with graphite furnace in 396 pregnant women with 56 fetal-maternal clusters. For analysis, plasma samples were diluted quantitatively (1+10) with a matrix modifier solution containing 0.5% Triton X-100 (PA Sigma-Aldrich), 0.06% magnesium nitrate (98% PA Sigma-Aldrich) and 1% ammonium phosphate (1 mg/mL PO_4^{3-}, Sigma-Aldrich). Levels of plasma Cd were observed in multiparous women with a family history of preeclampsia and diabetes mellitus (t-test, p=0.040, 0.0321 and 0.012, respectively). Plasma Cd levels were also significantly higher in in 20-36 weeks of amenorrhea period as compared to other periods [means (±SD), 0.284 µg/L (± 0.142) in 20-36 weeks, 0.195 µg/L (± 0.137) in 10-19 weeks and 0.097 µg/L (± 2.091) at delivery (≥37 weeks), ANOVA, p < 35 0.001] and newborns showed lower plasma Cd levels than their mothers [means (±SD), 0.012 µg/L (± 0.081) versus 0.226 µg/L (± 0.147), t-test, p < 0.001]. No significant associations were observed between maternal plasma Cd and birth weight (g), birth height (cm), ponderal index (g/cm^3), Apgar score, head circumference at birth (cm) or gestational age at birth (weeks). Globally, maternal plasma Cd levels show no significant linear negative correlation to all of these outcomes (birth weight, birth height, ponderal index Apgar score, gestational age at birth, head circumference at delivery). However, multiparous women with a family history of preeclampsia and diabetes mellitus had significantly higher plasma Cd levels in this study. Furthermore, plasma Cd levels reported in Kinshasa constitute a major public health concern for pregnant women. Risk assessment of Cd exposure should take place in Kinshasa providing useful information and necessary 47 interventions for pregnant women to limit exposure to toxic metals.

Keywords: Plasma cadmium; Birth outcomes; Maternal outcomes; Prenatal exposure; Kinshasa

1. Introduction

Cadmium (Cd) is one of the most common toxic metals in the world to which population are exposed. Dietary intake and tobacco smoking are the primary sources of Cd exposure in the general non-smoking population and smokers, respectively.[1-3] Although the placenta protects the fetus by restricting Cd, pregnant women and their fetuses are especially susceptible to the health effects of Cd exposure, including carcinogenic and genotoxic effects.[1,4-5-8] In whole blood, the evidence has been shown that prenatal exposure to low levels of Cd is associated with elevated risk of low birth weight and fetal growth restriction.[9-11]

In DRC, Tuakuila et al.[12] reported high levels of Cd in blood and urine samples of children in Kinshasa. Furthermore, increased urinary excretion of toxic metals, including Cd, was observed in preeclampsia by Elongi-Moyene et al.[13] In line with these results, Kabamba et al.[14] showed that exposure levels to heavy metals, including Cd are connected to negative effects such as, preeclampsia, birth defects, children's temperament difficulties and holoprosencephaly.

Although plasma Cd represents a more relevant index of exposure to, distribution of, and health risks associated with Cd than does blood Cd,[7,15] most researches on associations between maternal Cd levels and adverse birth outcomes have been reported in whole blood because blood Cd sampling is recognized as a relatively easy procedure. In this work, the plasma Cd levels in pregnancy and their birth outcomes will be evaluated in Kinshasa. A conclusion will be given by providing recommendations to create a local Cd screening committee during pregnancy and lactating.

Table 1. Sociodemographic characteristics of the study subjects (2019 - 2020, Kinshasa, n = 396)

Sociodemographic characteristics		
Maternal Characteristics - 396(100)		**n(%)**
Age (years)	<18	36(9)
	18-29	163 (41)
	≥30	177 (45)
Education	Lower school or none	20 (5)
	Middle school	286 (72)
	High school or university degree	90 (23)
Marital Status	Married or living as married	315 (80)
	Unmarried	81 (20)
Family Income (Month)	None	86 (22)
	<100 $ USD	100 (25)
	100$ - 500$	196 (49)
	≥ 500$	14 (4)
Smoking during pregnancy	Yes	0
	No	396 (100)
Alcohol use during pregnancy	Yes	40 (10)
	No	356 (90)
Parity	0 (primiparous)	184 (46)
	≥1 (multiparous)	212 (54)
BMI	≤18.5 (underweight)	5
	18.5 – 24 (normal)	149 (38)
	25 -29 (overweight)	141 (36)
	≥30 (Obese)	97 (26)
Diabetes mellitus	Yes	69 (17)
	No	327 (83)
Family history of preeclampsia	Yes	142 (36)
	No	254 (64)
Newborn characteristics - 56(100)		**n(%)**
Sex	Female	35(63)
	Male	31 (47)
Birth weight (g)	<2500 (underweight)	3(5)
	2500 – 4000 (normal)	49 (88)
	> 4000 (overweight)	4(7)
Ponderal Index (g/cm^3)[40]	≤ 2.49 (Low ponderal index)	56 (100)
	2.50–3.16 (Normal Ponderal index)	0
	≥ 3.17 (high ponderal index)	0
Gestational age (weeks)	<37 (pre-term)	6(11)
	37 – 41 (normal)	45 (80)
	>42 (post-term)	5(9)
Delivery method (n)	Vaginal	56 (100)
	Caesarean section	0
Apgar score	5 min <7	1(2)
	5 min ≥7	55 (98)

2. Methods

2.1. Study population and Data collection

Pregnant women were recruited at the maternity hospitals [Hôpital Général de Référence de Kinshasa (Gombe), Maternité Delvaux (Binza), Centre de Santé Saint-Christophe (Binza) ; Centre de Santé et Maternité Saint-Raymond (Matete), Maternité Esengo (Kisenso), Maternité Lisanga (Lemba); Centre de Santé et Maternité Bomoyi (Tshangu)]. Enrollment was implemented between June 2019 and June 2020 during the pregnancy visit. Eligible women (400) received a detailed explanation of study procedures before consenting to participate [living in Kinshasa ≥ 6 months, amenorrhea period ≥ 10 weeks, not planning to move out of the city before delivery, etc.]. Positive responses were obtained from more than 95% (396 pregnant women) of those approached. The research protocol was approved by the Bio-ethics Committee of the School of Public Health at the University of Kinshasa.

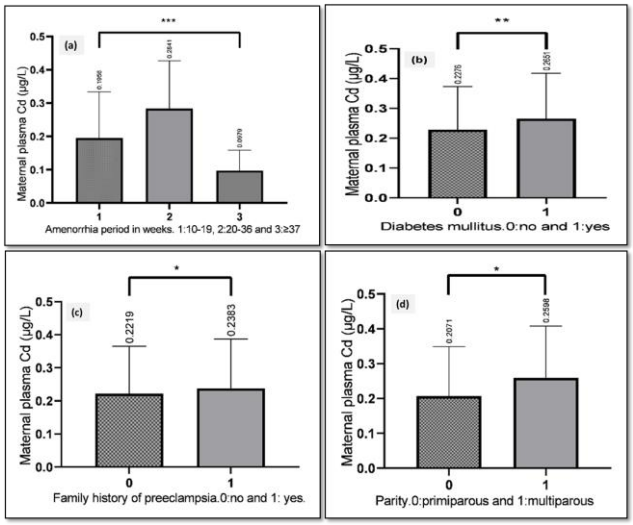

Fig. 1. Comparison between plasma Cd levels and maternal outcomes (t-test or ANOVA). Maternal plasma Cd levels (µg/L) against (a) Amenorrhea period in weeks, (b) Diabetes mellitus, (c) Family history of preeclampsia and (d) Parity.

2.2. Data collection

During the pregnancy visit women provided venous blood samples in 10 87 mL metal free tubes containing lithium heparin as described elsewhere.[16] At delivery, both maternal venous blood and umbilical cord blood samples were collected. All blood was immediately centrifuged (10 minutes, 3000 g) and the plasma fraction was transferred into 2.5 mL pre-cleaned glass vials (Supelco) and stored at -80°C for the Cd analysis. The plasma samples were transported to the Analytical chemistry and Environmental toxicology laboratory of the University of Kinshasa. Pregnancy and delivery information collected in the questionnaires were clinics, socio-demographics, Anthropometrics, current and previous pregnancies, current and previous preeclampsia or diabetes mellitus, smoking during pregnancy, and lifestyle.

2.3. Analytical methods

The samples were brought to room temperature and vortexed after thawing. Cd was measured by atomic absorption (PG-Instruments combined Flame and Furnace -AA500FG- with graphite furnace, Germany).[17-20] Plasma samples (100 µL) were diluted quantitatively (1+10) with a matrix modifier solution containing 0.5% Triton X-100 (PA Sigma-Aldrich), 0.06% magnesium nitrate (98% PA Sigma-Aldrich) and 1% ammonium phosphate (1 mg/mL PO_4^{3-}, Sigma-Aldrich). Determinations were calibrated with Cd solutions prepared from Cd standard solution suitable for atomic spectrometry [1000 ppm Cd, 1 mg/mL Cd – Sigma-Aldric]. Because the Plasma Cd levels were low, triplicate samples were analyzed, repeated for each sample with a coefficient of variation less than 15%, and the detection of limit (LOD) was 0.01 µg/L. Analytical validity was confirmed using commercial standard serum (Seronorm L1 and L2) at the beginning of the run and the end of each run of 20 samples, as previously described.[20,21]

Table 2. Association between maternal - child parameters and plasma Cd levels.

Variables	AM ±SD	Percentiles				Min - Max
		P25	P50	P75	P95	
Mothers						
Cd (µg/L)	0.226 ± 0.147	0.111	0.223	0.324	0.479	0.01 – 0.655
Age (years)	26.57 ± 4.70	23.00	26.00	29.50	35.00	16.00- 45.00
Weight (kg)	68 ± 12	59	66	75	91	40 - 116
Height (m)	1.60 ± 0.07	1.60	1.60	1.70	1.7	1.00 - 1.80
Amenorrhea period	26.0 ± 8.5	19	26	32	39	10 - 42
BMI (kg/m^2)	27 ± 5	23	26	30	35	16 - 45
Systolic blood pressure (mm Hg)	107 ± 15	100	110	110	113	69 - 221
Diastolic blood pressure (mm Hg)	66 ± 10	60	60	70	80	55 - 126
Newborns						
Cd (µg/L)	0.012 ± 0.081	0.010	0.013	0.177	0.252	0.01 – 0.313
Birth weight (g)	3190 ± 530	2820	3200	3543	4215	1500 - 4340
Birth height (cm)	49.0 ± 3.8	46	48	50	56	38 - 59
Ponderal Index (g /cm^3)	1.393 ± 0.284	1.173	1.400	1.580	1.985	0.679 - 2.008
Gestational age at birth (weeks)	38.38 ± 1.53	33.00	38.50	39.00	40.45	33.00 - 42.00
Head circumference at birth (cm)	34 ± 2	33	34	36	37	29 - 38
Apgar Score	9 ± 1	9	10	10	10	5 - 10

AM: Arithmetic means, SD: Standard deviation, Percentiles (P25, P50, P75, P95), Min: Minimum and Max: Maximum.

2.4. Statistical analysis

Statistical data analysis was completed using Prism GraphPad 9.41 (GraphPad Soft - ware, San Diego, CA, USA). The normality of residuals was evaluated using Kolmogorov–Smirnov test for continuous variables. For the descriptive statistics, results are presented as percentage for categorical variables and as means (± standard deviation), percentiles (P25, P50, P75, P95) and minimum-maximum for continuous variables. Differences between groups were analyzed with analysis of variance (ANOVA), t-test, and trend test after log transformation of skewed variables. Differences in proportions were analyzed with chi-square test. A multiple linear regression was used to estimate the association between log-transformed continuous plasma Cd and other continuous or categorial variables. Two-sided p <0.05 was considered statistically significant. Cd levels below the LOD were assigned a value of LOD/2 for statistical calculations.[22,23]

3. Results

Of the 396 women included in this study, 177 (45%) had 30 years of age or more, 306 (77%) had lower or middle school degree, 81 (20%) were unmarried, 186 (47%) earned less than 100$ USD monthly, 212 (54%) were multiparous, 69 (17%) had diabetes mellitus, 142 (36%) had history of preeclampsia and 243 (62%) were underweight, overweight or obese women. 40 (10%) consumed alcohol during pregnancy. None of them smoked during pregnancy (Table 1). Among the 56 births occurred, 11 (20%) were pre-term or post-term, 35 (63%) were female, 1 (2%) was under 7 Apgar score in 5 minutes, 7 (12%) were underweight or overweight newborns (Table 1).

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Table 2 lists the means (±SD), percentiles (P25, P50, P75 and P95) and minimum as well as maximum of the continuous variables: maternal parameters including, plasma Cd (µg/L), age (years), weight (kg), height (m), amenorrhea period (weeks), BMI (kg/m^2), SBP (mm Hg), DBP (mm Hg), and newborn parameters containing foetal plasma Cd, birth weight (g), birth height (cm), ponderal index (g/cm^3), gestational age at birth (weeks), head circumference at birth (cm) and Apgar score. The plasma Cd means (±SD) were respectively 0.226 µg/L (± 0.147) in maternal and 0.012 µg/L ± (0.081) in newborns.

Regarding differences between groups, levels of plasma Cd were observed in multiparous women with a family history of preeclampsia and diabetes mellitus (t-test, p=0.040, 0.0321 and 0.012, respectively). Plasma Cd levels were also significantly higher in in 20-36 weeks of amenorrhea period as compared to other periods [means (±SD), 0.284 µg/L (± 0.142) in 20-36 weeks, 0.195 µg/L (± 0.137) in 10-19 weeks and 0.097 µg/L (± 2.091) at delivery (≥37 weeks), ANOVA, p < 0.0001] and newborns showed lower plasma Cd levels than their mothers [means (±SD), 0.012 µg/L (± 0.081) versus 0.226 µg/L (± 0.147), t-test, p < 0.001] (Fig. 1). No significant associations were observed between maternal plasma Cd and birth weight (g), birth height (cm), ponderal index (g/cm^3), Apgar score, head circumference at birth (cm) or gestational age at birth (weeks) (Fig. 2).

4. Discussion

The most majority of Cd in whole blood is bound to red blood cells.[7,15] And the remaining Cd in the plasma which is bound with proteins such as albumin and globulin (15, 24). Because of very lower Cd levels found in fetal blood or plasma, the Cd relationship between maternal and fetal blood or plasma levels is less evident.[24] However, although transplacental Cd exposure is limited, Cd levels in fetal plasma increase with maternal exposure[25] and imply more circulating Cd is free to cross the placenta increasing risk of Cd

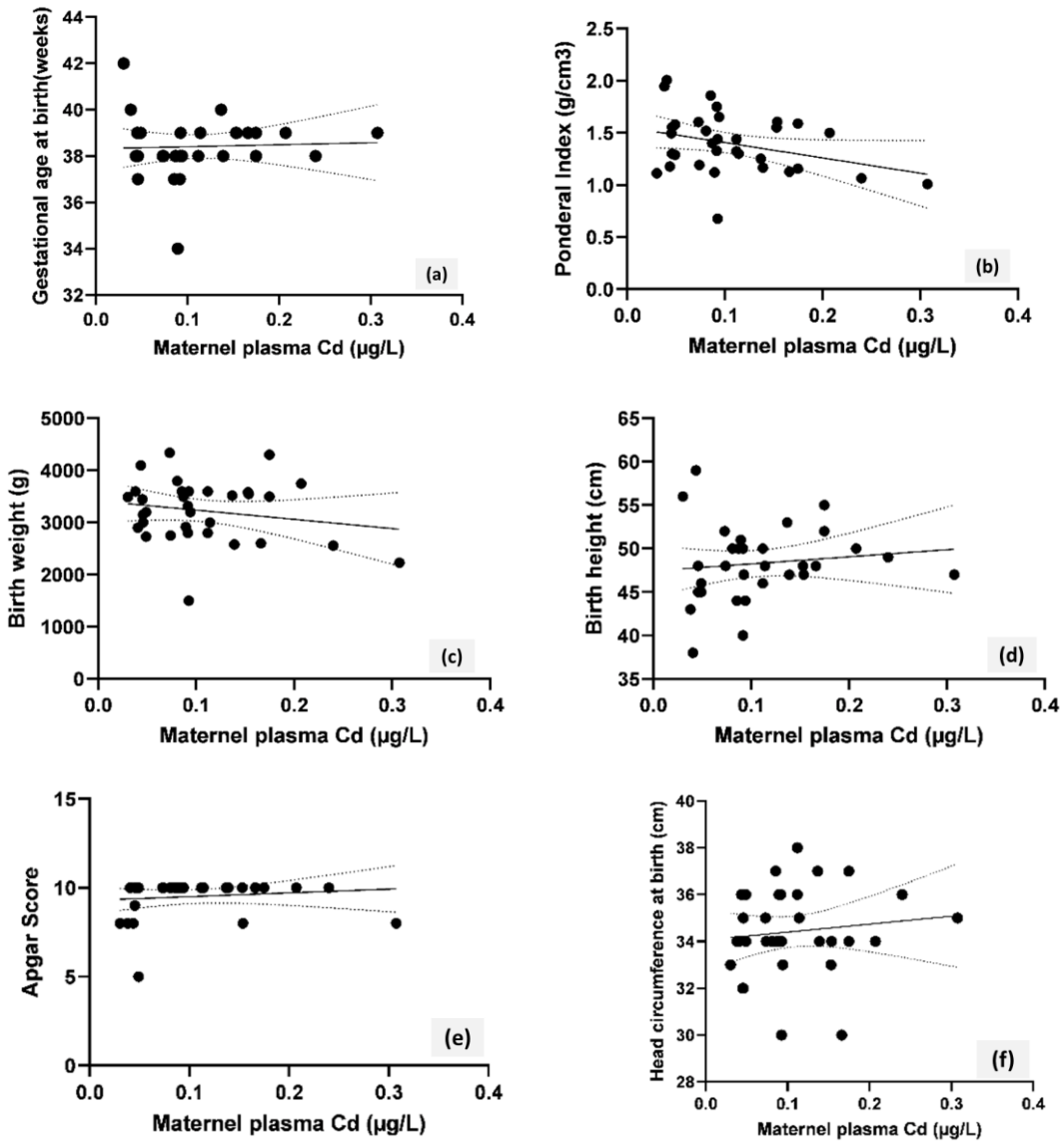

Fig. 2. Scatter Plot of Maternal plasma Cd levels (µg/L) against birth outcomes. Maternal plasma Cd levels (µg/L) against (a) Gestational age at birth (weeks), (b) Ponderal Index (g/cm^3), (c) Birth weight, (d) Birth height (cm), (e) Apgar Score, and (f) Head circumference at birth (cm).

Table 3. Multiple regression analysis model

Parameter (dependent variable)	Partial R^2 (Independent variables)				Total R^2
	BMI	multiparous	Family history of preeclampsia	Amenorrhea period	
Log (maternal plasma Cd levels)	0.02018	0.02425	0.02019	0.02418	0.0888

R^2: explained variance.

exposition and toxicity in fetus.[26,27] Nevertheless, laborious methods, specialized equipment and ultraclean techniques are required for measuring Cd plasma accurately.[18,28,29] Consequently, the interest in using Cd plasma measures during pregnancy is less or modest.

The overall mean and range values of plasma Cd levels [AM (P25-P75) and n: 0.226 µg/L 169 (0.111 – 0.324), n = 396] in this study were slightly higher or similar to those reported in China by Lin et al.[30]: median (P25-P75): 0.14 µg/L (0.09-0.21) in 2005 and 0.09 µg/L (0.05-0.13) in 2012. The traditional use of fired clay for the treatment of gastritis by pregnant women and food habits appear to constitute the main sources of exposure in the city of Kinshasa.[31]

Blood Cd levels have been linked with hypertension (13,32,33). English et al.[34] reported principal risk factors for preeclampsia (≥ 140 mm Hg systolic pressure and/or ≥ 190 mm Hg diastolic pressure after week 20 as promulgated by ACOG et al.,[35] including multiple pregnancy, nulliparity, family history of preeclampsia and obesity. Moreover, in a previous studies higher Cd levels were associated with greater preeclampsia risk.[32,36] In light of the above results, multiparous women with a family history of preeclampsia and diabetes mellitus had significantly higher plasma Cd levels in this study. However, most of these women had a normal systolic blood pressure with the 95th percentile of 113 mm Hg for systolic pressure and 90 mm Hg for diastolic pressure. Consequently, pressure has not been found to correlate with maternal plasma Cd levels as reported

elsewhere.[37] Otherwise, no significant difference was observed in plasma Cd levels as compared to certain characteristics such as marital status, family income, education and alcohol use during pregnancy. These results were consistent with certain studies.[36]

In pregnancy, elevated blood Cd levels have been associated with several adverse outcomes, including gestational hypertension, fetal growth restriction, short gestation, low birth height and low birth weight.[1,2,8,10,32,36,38] This study reported low levels of plasma Cd were observed at delivery as compared to other amenorrhea periods ($p<0.001$) and Cd levels in fetal plasma were lower than those reported in maternal plasma ($p<0.001$). This is consistent with previous data in the literature confirming that placenta is a barrier, but not complete, against Cd transferring only traces of this element (< 10%) to neonatal blood (Table 3).[39]

Although the evidence of associations between elevated Cd levels and several adverse outcomes reported in whole blood,[3,9,11,15] the findings of this work indicate there was no significant linear negative correlation between maternal plasma Cd and all of these outcomes (birth weight, birth height, Apgar score, head circumference at delivery, ponderal index, gestational age at birth). The Possible reasons for this might be that the relatively small number of birth cohort studied and research on associations between plasma Cd and adverse outcomes is still sparse in literature. Nevertheless, despite this gap in knowledge, it is clear that the plasma Cd levels measured in this study constitute a major public health concern for pregnant women and newborns.[14,42] Risk assessment of Cd exposure should take place at the earliest contact with pregnant and lactating women as recommended by committee opinion of the American College of Obstetricians and Gynaecologists that healthcare professionals provide useful information and necessary interventions for pregnant women to limit exposure to toxic metals.[35]

A major limitation should be considered in evaluating present results. With regard to study population, data collection and analytical methods, the relatively small number of birth cohort studied. The sample collection methods used here were not robust but by chance, which were practically inevitable under present survey conditions and susceptible to errors associated with sample collection. Analytical problems at the low levels of Cd found in plasma are major reasons that plasma Cd should be measured routinely with much lower detection limits and with better accuracy by ICP-MS without advanced clean room facilities.[20,28] Moreover, potential contamination by environmental tobacco smoking as well as analysis of plasma Fe and free haemoglobin was not assessed.[22,23,28,40]

5. Conclusions and Recommendations

Although no significant linear negative correlation between maternal plasma Cd and all of these outcomes (birth weight, birth height, Apgar score, head circumference at delivery, ponderal index and gestational age at birth) has been found in this study, possibly due to small number of birth cohort studied and scarce relevant data on associations between plasma-Cd and adverse outcomes, multiparous women with a family history of preeclampsia and diabetes mellitus had significantly higher plasma Cd levels. Furthermore, plasma Cd levels reported in Kinshasa constitute a major public health concern for pregnant women and newborns. Risk assessment of Cd exposure should take place in Kinshasa providing useful information and necessary interventions for pregnant women to limit exposure to toxic metals.

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Conflicts of Interest

The authors declare no conflict of interest.

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