

Optimal Glycemic Control, Pre-eclampsia, and Gestational Hypertension in Women With Type 1 Diabetes in the Diabetes and Pre-eclampsia Intervention Trial

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OBJECTIVE—To assess the relationship between glycemic control, pre-eclampsia, and gestational hypertension in women with type 1 diabetes.

RESEARCH DESIGN AND METHODS—Pregnancy outcome (pre-eclampsia or gestational hypertension) was assessed prospectively in 749 women from the randomized controlled Diabetes and Pre-eclampsia Intervention Trial (DAPIT). HbA_{1c} (A1C) values were available up to 6 months before pregnancy ($n = 542$), at the first antenatal visit (median 9 weeks) ($n = 721$), at 26 weeks' gestation ($n = 592$), and at 34 weeks' gestation ($n = 519$) and were categorized as optimal ($<6.1\%$: referent), good (6.1–6.9%), moderate (7.0–7.9%), and poor ($\geq 8.0\%$) glycemic control, respectively.

RESULTS—Pre-eclampsia and gestational hypertension developed in 17 and 11% of pregnancies, respectively. Women who developed pre-eclampsia had significantly higher A1C values before and during pregnancy compared with women who did not develop pre-eclampsia ($P < 0.05$, respectively). In early pregnancy, A1C $\geq 8.0\%$ was associated with a significantly increased risk of pre-eclampsia (odds ratio 3.68 [95% CI 1.17–11.6]) compared with optimal control. At 26 weeks' gestation, A1C values $\geq 6.1\%$ (good: 2.09 [1.03–4.21]; moderate: 3.20 [1.47–7.00]; and poor: 3.81 [1.30–11.1]) and at 34 weeks' gestation A1C values $\geq 7.0\%$ (moderate: 3.27 [1.31–8.20] and poor: 8.01 [2.04–31.5]) significantly increased the risk of pre-eclampsia compared with optimal control. The adjusted odds ratios for pre-eclampsia for each 1% decrement in A1C before pregnancy, at the first antenatal visit, at 26 weeks' gestation, and at 34 weeks' gestation were 0.88 (0.75–1.03), 0.75 (0.64–0.88), 0.57 (0.42–0.78), and 0.47 (0.31–0.70), respectively. Glycemic control was not significantly associated with gestational hypertension.

CONCLUSIONS—Women who developed pre-eclampsia had significantly higher A1C values before and during pregnancy. These data suggest that optimal glycemic control both early and throughout pregnancy may reduce the risk of pre-eclampsia in women with type 1 diabetes.

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The rates of pre-eclampsia are two to four times higher for women with type 1 diabetes than the background maternity population and are known to increase with the complexity of diabetes (1–3). Pre-eclampsia is a multisystem disorder of pregnancy, characterized by gestational hypertension and new-onset proteinuria occurring in the second half of pregnancy (4,5). Pre-eclampsia can lead to serious maternal complications, such as eclampsia and HELLP (hemolysis elevated liver enzymes and low platelets) syndrome, and is a leading cause of maternal death (6). Moreover, because delivery is the only effective intervention, pre-eclampsia is responsible for up to 15% of preterm births, with a consequent increase in infant mortality and morbidity (7).

An association between glycemic control during pregnancy and pre-eclampsia has been reported previously (8–11), but the data are few, with most of the studies being small or failing to control for confounding variables (8–10). In addition, the relative importance of glycemic control during early and late pregnancy for hypertensive complications of pregnancy remains unclear. Although some studies have reported an association between poor glycemic control early in pregnancy and the risk of pre-eclampsia (10,11), other studies found that mid- to late-trimester values were more important (8,9). Data relating glycemic control to gestational hypertension also are few and conflicting (10–12), with an association being reported in one study (12) but not in others (10,11). Finally, there is currently a dearth of evidence in relation to prepregnancy A1C and pre-eclampsia.

Current international guidelines, informed primarily by evidence relating to the risk of fetal malformations (13) and miscarriage, differ with regard to A1C targets before conception. The U.K. National Institute for Clinical Excellence recommends that if it is safely achievable,

women with diabetes who are planning to become pregnant should aim to maintain their A1C below 6.1% (14). On the other hand, the Scottish Intercollegiate Guidelines Network recommends a minimum A1C for most women of <7%, although lower A1C targets may be appropriate if maternal hypoglycemia still can be minimized (15). The American Diabetes Association recommends that A1C levels should be as close to normal as possible (<7%) in an individual patient before conception is attempted (16). To date, there is limited evidence showing that these targets are achievable or actually equate with normoglycemia (17), and the impact of glycemic control, as defined by international guidelines (<6.1 or <7%) in early pregnancy, on the risk of pre-eclampsia is not known. Although the need to optimize blood glucose control periconceptionally is now well established, A1C values fall with pregnancy duration (18), leading some expert bodies to recommend that A1C should not be routinely used for assessing glycemic control beyond the first trimester (14).

The aim of this study was to assess the association between glycemic control before and during pregnancy and the risk of pre-eclampsia and gestational hypertension in women with type 1 diabetes, controlled for relevant confounding variables.

RESEARCH DESIGN AND METHODS

The study population comprised 762 women with type 1 diabetes recruited from 25 joint antenatal-metabolic clinics across Northern Ireland, Scotland, and northwest England between April 2003 and June 2008 into the Diabetes and Pre-eclampsia Intervention Trial (DAPIT) (19). DAPIT was a multicenter, randomized, placebo-controlled intervention trial of vitamin C and E supplementation to prevent pre-eclampsia in pregnant women with type 1 diabetes. Women were enrolled between 8 and 22 weeks' gestation. Eligibility criteria included type 1 diabetes preceding pregnancy, a singleton pregnancy, and being aged ≥ 16 years (19). Women with chronic hypertension were included in the trial.

As previously described (19), pre-eclampsia was defined as gestational hypertension with proteinuria for previously normotensive women, according to the International Society for the Study of Hypertension in Pregnancy guidelines (4) and according to National High Blood

Pressure Education Program Working Group's guidelines for women with pre-existing hypertension and/or proteinuria (5). Each case of hypertensive pregnancy was confirmed by three senior clinicians, acting independently. Pre-eclampsia and gestational hypertension could be assessed for 749 (98%) women whose pregnancies progressed to at least 20 weeks' gestational age.

Prepregnancy and first antenatal visit glycosylated hemoglobin (A1C) values (measured locally using Diabetes Control and Complications Trial-aligned methods as part of routine care) were abstracted by trained researchers from the women's hospital records and recorded on study-specific case report forms. Prepregnancy A1C values were those measured up to 6 months prior to pregnancy, as recorded in the booking history by the attending physician or on recall from the patient. The first antenatal visit A1C values were measured at a median of 9 weeks' gestation (95% by the end of week 15) at the joint antenatal-metabolic clinic. Study-specific peripheral venous blood samples for A1C were collected at 26 (± 2) and 34 (± 2) weeks' gestation and stored immediately at -70°C until analysis. Samples were batch analyzed centrally in the Nutrition and Metabolism Laboratories, Centre for Public Health, Queen's University Belfast, at the end of the trial. A1C (Diazyme Laboratories, Poway, CA) was measured by spectrophotometry using an automated ILab600 biochemical analyzer. As a National Glycohemoglobin Standardisation Programme- and International Federation for Clinical Chemistry-certified method, the values reported were aligned with the Diabetes Control and Complications Trial system, with intra- and interassay coefficients of variation values <2%. A1C results were arbitrarily categorized as optimal (<6.1%: the referent value), good (6.1–6.9%), moderate (7.0–7.9%), and poor ($\geq 8.0\%$) glycemic control. The West Midlands Multicentre Research Ethics Committee provided ethical approval (MREC 02/7/016).

Statistical analysis

Group comparisons were performed using independent-samples *t* tests and χ^2 tests. Logistic regression was used to estimate the odds of pre-eclampsia and gestational hypertension in women with poor, moderate, and good control relative to women with optimal control both before and after adjustment for potentially confounding variables, including

treatment group, center, BMI, diabetes duration, parity, current smoking, age, aspirin consumption, microalbuminuria before pregnancy, low serum α -tocopherol, and low plasma ascorbate at randomization (or plasma ascorbate level in the 26- and 34-week analyses). Similar analyses were conducted using uncategorized A1C results and were used to derive estimates of the odds of pre-eclampsia and gestational hypertension for each 1% decrement in A1C. All statistical analyses were performed using SPSS software, version 17 (SPSS, Chicago, IL).

RESULTS—Pre-eclampsia and gestational hypertension developed in 17 and 11% of 749 pregnancies, respectively (19). Seventy-two percent of women ($n = 542$) reported an A1C result measured in the 6 months prior to pregnancy. A1C results were available for 96, 79, and 69% of participants at the first antenatal visit, at 26 weeks' gestation, and at 34 weeks' gestation, respectively. Maternal characteristics and glycemic control of women with and without pre-eclampsia and of women with and without gestational hypertension (excluding women with pre-eclampsia) are shown in Table 1. The clinical characteristics of the two groups were similar, with the exception that significantly more women with pre-eclampsia were primiparous compared with women without pre-eclampsia ($P < 0.001$); primiparity did not differ significantly between those with and without gestational hypertension. Although not significant, more women without pre-eclampsia were current smokers. Women with pre-eclampsia had significantly poorer glycemic control both before and during pregnancy compared with women without pre-eclampsia, whereas glycemic control did not differ between women with or without gestational hypertension (Table 1). In women who developed pre-eclampsia, there was no significant difference in glycemic control between women with and without essential hypertension before pregnancy or between women with and without pre-existing proteinuria (data not shown).

The frequency of subjects by category of glycemic control before pregnancy, at the first antenatal visit, at 26 weeks' gestation, and at 34 weeks' gestation is shown in Table 2. Only 7% of women had optimal glycemic control (A1C <6.1%) at their first antenatal visit, increasing to 23 and 25% at 26 and 34 weeks' gestation, respectively. At 34 weeks' gestation,

Table 1—Maternal characteristics and glycemic control in women with and without pre-eclampsia and gestational hypertension

	Pre-eclampsia	No pre-eclampsia	P	Gestational hypertension	No gestational hypertension or pre-eclampsia	P
<i>n</i> _{max}	127	622		83	539	
Age (years)	28.9 (5.5)	29.7 (5.6)	0.16	29.3 (5.6)	29.7 (5.6)	0.52
Diabetes duration (years)	15.4 (7.1)	14.4 (8.4)	0.14	14.2 (8.4)	14.4 (8.3)	0.86
Primiparous, <i>n</i> (%)	85 (67)	286 (46)	<0.001	44 (53)	242 (45)	0.17
Smoker, <i>n</i> (%)	18 (14)	129 (21)	0.09	17 (20)	112 (21)	0.95
Glycemic control, A1C (%)						
Prepregnancy*	8.5 (1.5)	8.0 (1.8)	0.03	8.1 (1.8)	8.0 (1.8)	0.78
First antenatal visit*	8.2 (1.4)	7.8 (1.4)	0.002	7.9 (1.4)	7.8 (1.4)	0.53
26 weeks' gestation†	6.9 (0.9)	6.6 (0.8)	0.001	6.7 (0.9)	6.6 (0.8)	0.82
34 weeks' gestation†	6.8 (0.8)	6.5 (0.7)	0.002	6.5 (0.7)	6.5 (0.6)	0.85

Data are means (SD), unless otherwise indicated. *Local laboratory. †Central laboratory.

22% of women had an A1C $\geq 7.0\%$ and 4% had a value of $\geq 8.0\%$.

Data on the risk of pre-eclampsia and gestational hypertension in relation to glycemic control throughout pregnancy are shown in Table 2. Glycemic control was not significantly associated with gestational hypertension either before or during pregnancy. There was a progressive increase in the odds of pre-eclampsia with worsening glycemic control before pregnancy relative to the referent A1C $< 6.1\%$; although none of the individual odds ratios reached statistical significance, this may have reflected the small number of subjects in the reference category (Table 2). In early pregnancy (median 9 weeks' gestation), there was a trend for increasing pre-eclampsia with worsening glycemic control, and poor glycemic control (A1C $\geq 8.0\%$) was associated with a significantly increased risk of pre-eclampsia (odds ratio 3.68 [95% CI 1.17–11.6]) compared with optimal control. At both 26 and 34 weeks' gestation, there was a progressive and significant increase in the odds of pre-eclampsia for suboptimal control (A1C $\geq 6.1\%$) compared with the referent value (A1C $< 6.1\%$), with odds ratios ranging from 2.09 to 3.81 and 1.78 to 8.01, respectively. For each 1% decrement in A1C at the first antenatal visit, at 26 weeks' gestation, and at 34 weeks' gestation, the risk of pre-eclampsia was significantly reduced (0.75 [0.64–0.88], 0.57 [0.42–0.78], and 0.47 [0.31–0.70], respectively), with a nonsignificant reduction in risk for the preconception A1C of 0.88 (0.75–1.03) (Table 3). A test for interaction between parity (primiparous or multiparous) and A1C in the logistic model did not show evidence that the

change in pre-eclampsia risk per 1% decrement in A1C differed between primiparous and multiparous women. The effect of a 1% decrement in A1C during pregnancy was examined in two separate logistic models containing measurements: 1) at the first antenatal visit and 26 weeks' gestation and 2) at the first antenatal visit and at 34 weeks' gestation, fitted simultaneously to predict the risk of pre-eclampsia. Although the numbers of patients with complete data were reduced, in both models A1C at the first antenatal visit remained a significant independent predictor of pre-eclampsia. Controlled for A1C at the first antenatal visit, A1C levels at 34 weeks' gestation remained significantly predictive of pre-eclampsia with only slightly attenuated odds ratios for a 1% decrement (Table 4), but A1C levels at 26 weeks' gestation were no longer significant ($P = 0.07$).

CONCLUSIONS—The overall incidence of pre-eclampsia and gestational hypertension reported in this population of women with type 1 diabetes was 17 and 11%, respectively, in agreement with previous reports (1–3). The data indicate that poor glycemic control during pregnancy is associated with the development of pre-eclampsia but not with gestational hypertension. Furthermore, we have shown, for the first time, an association between A1C values before pregnancy and the development of pre-eclampsia. These results are of clinical importance and suggest that optimal glycemic control (A1C $< 6.1\%$) during early pregnancy and later in pregnancy may reduce the risk of pre-eclampsia in women with type 1 diabetes.

Our results are consistent with other data in showing a clear association between

glycemic control in early pregnancy and pre-eclampsia (10,11). Conflicting findings may possibly be explained by other studies being generally smaller (8,9) and by the timing of the first antenatal visit A1C measurement; A1C values in the study reported here and in that of Hanson et al. (10) were measured at a mean of 9 weeks' gestation, whereas Temple et al. (8) reported their first-visit A1C levels at 7 weeks' gestation. However, Hiilesmaa et al. (11) also found a positive association between pre-eclampsia and A1C levels at 7 weeks' gestation. Our data relating glycemic control in mid- to late-pregnancy with pre-eclampsia concur with some reports (8,9,20), although others (8) found no association between A1C values and pre-eclampsia in the third trimester.

We have shown that higher A1C values during pregnancy are independently predictive of pre-eclampsia. International recommendations for optimal A1C values during pregnancy are inconsistent. Our data show that a reduction of 1% in A1C at any time during pregnancy is associated with a significantly reduced risk of pre-eclampsia, pointing to a benefit of even a modest reduction in A1C at any time for the individual patient. Our data also suggests that optimal A1C ($< 6.1\%$) in late pregnancy may be of particular importance in risk prediction; for each 1% decrement in A1C the lowest odds ratios for pre-eclampsia were observed in the third trimester. Contrary to other recommendations (14,15), and consistent with American Diabetes Association guidelines (16), our findings support the use of A1C both to monitor glycemic control and also to assess pre-eclampsia risk throughout pregnancy.

Table 2—Optimal vs. suboptimal glycemic control (good, moderate, and poor) and risk of pre-eclampsia and gestational hypertension

Time point	Pre-eclampsia		Gestational hypertension*	
	n (%)	Adjusted odds ratio (95% CI)†	n (%)	Adjusted odds ratio (95% CI)†
Prepregnancy‡				
A1C				
Optimal (reference)	47 (9)	1.00	44 (10)	1.00
Good	89 (16)	1.68 (0.40–7.07)	80 (18)	0.60 (0.21–1.67)
Moderate	152 (28)	2.44 (0.66–9.05)	128 (28)	0.45 (0.17–1.20)
Poor	254 (47)	3.46 (0.95–12.6)	203 (45)	0.60 (0.24–1.47)
	542		455	
First antenatal visit‡				
A1C				
Optimal (reference)	49 (7)	1.00	45 (7)	1.00
Good	147 (20)	1.13 (0.33–3.92)	134 (22)	1.58 (0.48–5.16)
Moderate	221 (31)	2.55 (0.81–8.04)	181 (30)	1.83 (0.58–5.75)
Poor	304 (42)	3.68 (1.17–11.6)	241 (40)	1.39 (0.44–4.40)
	721		601	
26 weeks' gestation§				
A1C				
Optimal (reference)	137 (23)	1.00	123 (25)	1.00
Good	275 (46)	2.09 (1.03–4.21)	229 (47)	0.85 (0.43–1.66)
Moderate	140 (24)	3.20 (1.47–7.00)	107 (22)	0.78 (0.35–1.76)
Poor	40 (7)	3.81 (1.30–11.1)	31 (6)	0.66 (0.19–2.26)
	592		490	
34 weeks' gestation§				
A1C				
Optimal (reference)	131 (25)	1.00	118 (27)	1.00
Good	276 (53)	1.78 (0.83–3.81)	239 (54)	0.73 (0.37–1.44)
Moderate	92 (18)	3.27 (1.31–8.20)	74 (17)	0.97 (0.41–2.27)
Poor	20 (4)	8.01 (2.04–31.5)	14 (3)	0.64 (0.12–3.54)
	519		445	

Results were categorized as optimal (A1C <6.1%), good (A1C 6.1–6.9%), moderate (A1C 7.0–7.9%), and poor (A1C ≥8.0%) glycemic control. *Gestational hypertension analysis excludes subjects with pre-eclampsia. †Adjusted for treatment group, center, BMI, diabetes duration, parity, current smoking, age, microalbuminuria before pregnancy, aspirin consumption, low serum α -tocopherol, and low plasma ascorbate at randomization (or plasma ascorbate level in the 26- and 34-week analyses). ‡Local laboratory. §Central laboratory.

However, in the interpretation of A1C, cognizance needs to be taken of the reduction in A1C levels during pregnancy observed in nondiabetic women of similar

age (18), which may help explain why in our study, optimal A1C (<6.1%) in late pregnancy was associated with the lowest risk of pre-eclampsia.

Table 3—Glycemic control (per 1% decrement in A1C) and risk of pre-eclampsia and gestational hypertension

Time point	Pre-eclampsia		Gestational hypertension*	
	n	Adjusted odds ratio (95% CI)†	n	Adjusted odds ratio (95% CI)†
Prepregnancy‡	542	0.88 (0.75–1.03)	455	1.01 (0.85–1.19)
First antenatal visit‡	721	0.75 (0.64–0.88)	601	0.99 (0.82–1.19)
26 weeks' gestation§	592	0.57 (0.42–0.78)	490	1.04 (0.73–1.48)
34 weeks' gestation§	519	0.47 (0.31–0.70)	445	1.02 (0.66–1.56)

*Gestational hypertension analysis excludes subjects with pre-eclampsia. †Adjusted for treatment group, center, BMI, diabetes duration, parity, current smoking, age, microalbuminuria before pregnancy, aspirin consumption, low serum α -tocopherol, and low plasma ascorbate at randomization (or plasma ascorbate level in the 26- and 34-week analyses). ‡Local laboratory. §Central laboratory.

The DAPIT population is the largest contemporary prospective dataset of women with type 1 diabetes in the U.K. (19). This cohort consists of a carefully characterized population of women with type 1 diabetes, in whom comprehensive data about pregnancy progress and pregnancy outcomes has been collected. Furthermore, a major strength of this study is the extent to which the International Society for the Study of Hypertension in Pregnancy pre-eclampsia definition criteria have been applied, with each case of hypertensive pregnancy undergoing rigorous review and the diagnosis of pre-eclampsia confirmed by three senior clinicians, thus minimizing potential confounding by chronic hypertension or pre-existing nephropathy. Another strength of this study is the availability of serial A1C values during pregnancy and rigorous control for relevant confounding variables. Furthermore, although prepregnancy A1C values were collected by recall, to the best of our knowledge this is the first study to date to report such data in relation to the risk of pre-eclampsia and adds to the current knowledge on the relevance of prepregnancy planning to pregnancy outcome.

Nevertheless, our study has a number of limitations. First, not all blood samples were centralized for A1C analyses. Although samples for A1C determination at 26 and 34 weeks' gestation were collected by trained study personnel, according to a strict protocol, and batch analyzed centrally using Diabetes Control and Complications Trial-aligned methodology, A1C values for up to 6 months before pregnancy and at the first antenatal visit were measured in local laboratories where different A1C assays (Diabetes Control and Complications Trial aligned) may have been used. In addition, prepregnancy A1C values were collected from a review of patient notes and patient interviews, which is highly dependent on patient recall. However, frequently this is the best and only prepregnancy clinical information available, and although subject to recall bias, it is conceivable that patients may have recalled more favorable values than the true value, thus tending to diminish the association between A1C and pre-eclampsia. Finally, women in this study were those who consented to participate in DAPIT and thus may not be totally representative of the entire population of women with type 1 diabetes. It should be noted that the DAPIT intervention (vitamins C and E) did not

Table 4—Glycemic control (per 1% decrement in A1C) during pregnancy with measurements at the first antenatal visit and 26 weeks' gestation and the first antenatal visit and 34 weeks' gestation fitted simultaneously in separate logistic models to predict the risk of pre-eclampsia

Time point	First antenatal visit and 26 weeks' gestation		First antenatal visit and 34 weeks' gestation	
	Pre-eclampsia (n = 571)		Pre-eclampsia (n = 499)	
	Adjusted odds ratio (95% CI)*	P	Adjusted odds ratio (95% CI)*	P
First antenatal visit†	0.79 (0.64–0.98)	0.03	0.76 (0.59–0.97)	0.03
26 weeks' gestation‡	0.72 (0.50–1.02)	0.07	—	—
34 weeks' gestation‡			0.58 (0.37–0.91)	0.02

*Adjusted for treatment group, center, BMI, diabetes duration, parity, current smoking, age, microalbuminuria before pregnancy, aspirin consumption, low serum α -tocopherol, and plasma ascorbate at randomization (or plasma ascorbate level in the 26- and 34-week analyses). †Local laboratory. ‡Central laboratory.

significantly reduce the incidence of pre-eclampsia, and both treatment groups were therefore included in a single analysis, albeit with adjustment for treatment group, low plasma ascorbate, and serum α -tocopherol at randomization (or plasma ascorbate level in the 26- and 34-week analyses) in the logistic regression model.

In line with most other studies, we found no impact of glycemic control on gestational hypertension (10,11), which might lend support to the previously proposed divergent etiologies for pre-eclampsia and gestational hypertension (21,22). Although the pathophysiology of both conditions remains unclear (22), these data add to increasing evidence linking glycemic control with pre-eclampsia in women with type 1 diabetes (8–11) and indeed in women with only minor degrees of hyperglycemia during pregnancy (23,24). As a concept, the role of oxidative stress in the development of pre-eclampsia remains persuasive, but the lack of randomized trial evidence demonstrating any reduction in incidence with specific antioxidant therapy rather points to a multifactorial etiology in which poor glycemic control (possibly compounded by vitamin depletion) (19) remains among the most readily identifiable and treatable risk factors.

The results of this study highlight the importance of assessing glycemic control throughout pregnancy to reduce the incidence of pre-eclampsia. The 26 and 34 weeks' gestation A1C values were most predictive of pre-eclampsia, with only minor attenuation after controlling for A1C at the first antenatal visit. On the other hand, after controlling for A1C

values later in pregnancy, A1C at the first antenatal visit remained an independent predictor of pre-eclampsia, lending additional support to the importance of periconceptual glycemic control for maternal fetal outcome. Although women who went on to develop pre-eclampsia reported higher A1C values in the 6 months prior to pregnancy, additional prospective research is needed to evaluate the impact of glycemic control before pregnancy on pregnancy outcomes such as pre-eclampsia.

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V.A.H. researched data and wrote, reviewed, and edited the manuscript. I.S.Y., C.C.P., D.W.M.P., J.D.W., M.J.A.M., and D.R.M. researched data, contributed to discussion, and reviewed and edited the manuscript.

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