Heterogeneity of pregnancy outcomes and risk of LGA neonates in Caucasian females according to IADPSG criteria for gestational diabetes mellitus

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Abstract

Objective. – The International Association of Diabetes and Pregnancy Study Group (IADPSG) guidelines for gestational diabetes mellitus (GDM) diagnosis determines that fasting, 1-h and 2-h glucose values may contribute independently to adverse outcomes. However, given the different physiological bases of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), differences in pregnancy outcomes are to be expected. This study aimed to determine whether classification of GDM women according to glucose homoeostasis results in heterogeneity in maternal and/or fetal outcomes.

Material and methods. – Of the 75 pregnant women included after a 75-g 2-h OGTT performed between weeks 24–32 of gestation as per WHO criteria, 55 were classified as GDM (16 with IFG and 39 with IGT) according to IADSPG criteria. Their anthropometric and metabolic characteristics were compared with those of non-GDM women with IFG or IGT. Maternal and neonatal outcomes were prospectively recorded for each group.

Results. – GDM women with IFG, including isolated IFG and combined IFG + IGT, were significantly heavier, had higher leptin values and were more frequently multiparous than GDM women with isolated IGT. HOMA-IR was significantly higher when fasting glucose was impaired. There were no significant differences in maternal outcomes according to metabolic status. In addition, large for gestational age (LGA) neonates were significantly seen more often in the IFG group. Fasting glucose was significantly associated with LGA independently of BMI and 2-h OGTT glucose. The > 5.1 mmol/L cut-off value for fasting glucose was highly predictive of delivery of LGA infants.

Conclusion. – IFG in GDM women was associated with increases in BMI, fat mass and hepatic insulin resistance. Delivery of LGA neonates was more frequent when fasting glycaemia was increased during the third trimester of pregnancy, and was independent of BMI and 2-h OGTT glucose values.

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Keywords: Diabetes; Gestational impaired fasting glucose; Impaired glucose tolerance; LGA

Résumé

Hétérogénéité du pronostic maternel et fœtal au cours du diabète gestationnel en fonction des critères du Groupe international d’étude diabète et grossesse (IADPSG).

Objectif. – Les recommandations du Groupe international d’étude diabète et grossesse (IADPSG) indiquent que le diabète gestationnel peut se définir par une seule anomalie de la glycémie soit à jeun soit à une ou deux heures après une charge orale de 75 g de glucose. Nous avons cherché à déterminer dans quelle mesure cette classification induisait une hétérogénéité du pronostic maternel et/ou fœtal en fonction du type d’anomalie métabolique sous-jacente.

Patientes et méthodes. – Soixante-quinze femmes enceintes ont été incluses après une HGPO de 75 de glucose entre 24 et 32 semaines d’aménorrhée. Parmi elles, 55 avaient les critères du diabète gestationnel (DG) en fonction des critères du IADPSG dont 16 avec une anomalie de la glycémie à jeun (IFG) et 39 avec une intolérance au glucose (IGT) soit isolée soit combinée avec une hyperglycémie à jeun. Les données anthropométriques et métaboliques ont été comparées entre les groupes et les données maternelles et fetales analysées.
Résultats. – Les femmes du groupe IFG avaient un poids, des concentrations plasmatiques de leptine plus élevés et étaient plus fréquemment multipares que les femmes du groupe IGT. Les indices HOMA-IR étaient plus importants dans le groupe IFG. Nous n’avons pas observé de différences dans le pronostic maternel entre les groupes. En revanche, la proportion d’enfants nés avec un poids au-delà des normes pour l’âge gestationnel était plus élevée dans le groupe IFG. La glycémie à jeun était significativement associée à l’augmentation du poids fœtal de façon indépendante de l’IMC et de la glycémie deux heures après l’HGPO. Une valeur de glycémie à jeun supérieure à 5,1 mmol/L était fortement prédictive d’une anomalie pondérale fœtale.

Conclusions. – Une augmentation de la glycémie à jeun au cours de la grossesse est associée avec un IMC plus élevé, une masse grasse plus importante et une insulinorésistance hépatique. Le risque d’augmentation du poids de l’enfant à la naissance est plus fréquent lors d’une élévation de la glycémie au-delà de 5,1 mmol/L au troisième trimestre de grossesse, et cela de façon indépendante de l’IMC et des valeurs de glycémie à deux heures lors de l’HGPO.

Mots clés : Diabète ; Grosseur ; Glycémie à jeun ; Intolérance au glucose ; Développement fœtal

1. Introduction

Gestational diabetes mellitus (GDM) represents a healthcare burden that is expected to rise as the frequency of obesity increases worldwide [1,2]. This means that GDM is the subject of considerable clinical interest. The International Association of Diabetes and Pregnancy Study Group (IADPSG) has recently revisited the criteria for diagnosis [3] established more than 40 years ago [4]. Beyond the utility for detecting women at high risk of developing diabetes in later life, current strategies of GDM screening [5] were defined to improve pregnancy outcomes and reduce fetal complications. GDM and maternal obesity are independently associated with adverse effects [1]. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study demonstrated a positive linear relationship between glucose values and adverse perinatal outcomes, and argued for new screening values that would better identify pregnancies at risk of perinatal complications [6,7]. One characteristic of the new IADPSG criteria is that only one single value above defined fasting or post-load glucose thresholds is now sufficient for a diagnosis of GDM.

However, the metabolic roots underlying impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) with elevated 1- or 2-h oral glucose tolerance test (OGTT) plasma glucose levels are different. Isolated IFG is a common feature of insulin resistance [8], while subjects with isolated IGT exhibit more severe deficits in beta-cell function with defects in early- and late-phases of insulin secretion [9]. Given the different physiological bases of IFG and IGT, differences in pregnancy outcomes and fetal complications are to be expected. Delivery of infants large for gestational age (LGA) in terms of body weight is the most common complication of GDM, and is linearly related to maternal plasma glucose levels [6]. Birth weight above the 90th percentile for gestational age is associated with serious birth complications, including neonatal hyperinsulinaemia and adiposity resulting from insulin resistance during fetal life [10], and later health risks with a greater prevalence of the metabolic syndrome in childhood [11]. In a recent meta-analysis of several interventional trials [12], it was reported that the detection and treatment of mild GDM was associated with reductions in birth weight. Thus, an important rationale for GDM screening is to identify women at higher risk of LGA neonates to allow intensive targeted interventions. It was also hypothesized that women screened according to the IADPSG criteria for GDM were heterogeneous from a metabolic point of view, thereby resulting in different possible outcomes. The present study was performed to determine whether the type of glucose abnormalities in GDM presages maternal and fetal outcomes.

2. Material and methods

2.1. Participants

All pregnant women at a single institution were eligible to participate unless they had one or more of the following exclusion criteria: age < 18 years; type 1 or type 2 diabetes mellitus before pregnancy; gestational age > 32 weeks; and multiple pregnancies. The study cohort was initially selected to determine the predictive value of proinflammatory cytokines during GDM, as diagnosed by World Health Organization (WHO) criteria, for maternal and fetal outcomes. The local Institutional Review Board approved the protocol, and all participants provided their written informed consent.

All of the selected pregnant women underwent a standard OGTT with a 75-g dose of glucose at 24–32 weeks of gestation between July 2009 and January 2010. Of the 88 women referred to the Department of Endocrinology and Diabetes (Fig. 1), 75 were included in the final analysis and 13 were excluded because of multiparity (n = 7), prepregnancy type 2 diabetes (n = 3) and steroid therapy (n = 3). Maternal height, weight and blood pressure levels were obtained during a visit to the clinic a few days or weeks after the OGTT. Body mass index (BMI) was defined as weight divided by height squared (kg/m²). Blood glucose values were all analyzed at the same laboratory, and the diagnosis of GDM was re-established according to the new IADPSG guidelines [4].

Of the 75 women initially included, 55 met the new IADPSG criteria, including 39 with a fasting plasma glucose (FPG) level ≤ 5.1 mmol/L, but a 2-h OGTT glucose > 8.5 mmol/L (isolated IGT group), and 16 with FPG levels > 5.1 mmol/L (IFG group) that was either isolated (n = 5) or combined with IGT (n = 11). Twenty women initially classified as GDM according to WHO criteria (FPG < 5.1 mmol/L and 2-h OGTT glucose values between 7.8 and 8.5 mmol/L) were reclassified as normal and served as controls for the study. All women, including those
in the control group, were given advice on dietary and lifestyle modifications, and instructed on how to self-monitor their blood glucose management. If fasting and 2-h postprandial glucose targets were not achieved by lifestyle measures alone within 10 days, insulin therapy was initiated. Age, smoking status, drug medication, personal medical history (history of GDM or new-born macrosomia), family history of diabetes and antepartum weight were obtained using a standardized questionnaire.

2.2. Maternal and neonatal outcomes

These outcomes were prospectively recorded by obstetricians. Gestational age and expected date of delivery were estimated by means of ultrasonography performed during the first trimester. Hypertensive disorders (gestational hypertension and preeclampsia), hydramnios, mode of delivery (normal vaginal delivery or caesarean section), instrumental action for extraction and postpartum haemorrhage were also recorded. In addition, premature delivery (defined as delivery before 37 weeks of gestation), LGA (defined as weight > 90th percentile for gestational age), neonatal hypoglycaemia, neonatal jaundice and respiratory distress were recorded as well as Apgar scores at 1, 5 and 10 min.

2.3. Biochemical analyses

Maternal fasting serum samples were collected after an overnight fast. Glucose concentration was determined by the glucose oxidase enzymatic method. Insulin was determined by immunoassay (BI-INS-IRMA kit, IBA, Cisbio Bioassays, Gif-sur-Yvette, France), with a coefficient of variation (CV) of 5.3%, 4.1% and 5% at 7.2, 25.9 and 54.4 mIU/L, respectively. HbA1c levels were measured by high-performance liquid chromatography (HPLC) and serum leptin was determined by the Human Leptin Elisa kit, Clinical Range (BioVendor, Candler, NC, USA). Insulin sensitivity was determined by homoeostasis model assessment for insulin resistance [HOMA-IR = fasting glucose (mmol/L) × fasting insulin (mIU/L)/22.5] and insulin secretion was determined by HOMA-β [20 × fasting insulin (mU/mL)/fasting glucose (mmol/L) − 3.5].

2.4. Statistical analysis

Descriptive statistics included means ± SD for continuous variables, and numbers and percentages for categorical variables. The normality of each parameter was checked with the Shapiro-Wilk test. To examine the associations of GDM and glucose homoeostasis according to IADPSG criteria, participants were divided into three exclusive groups: women with IGT; women with IFG; and the normal control women. Comparisons were performed using one-way analysis of variance (Anova) for continuous variables, and Chi² analysis for categorical variables. Odd ratios (ORs) were obtained for all combinations. Adjusted ORs were also determined for FPG according to 2-h OGTT glucose levels and body weight gain. Univariate and multiple logistic regressions were used to explore the crude and adjusted effects of FPG and 2-h plasma glucose levels on the prevalence of maternal and fetal outcomes. A P value < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were constructed, and areas under the curves (AUCs) were calculated to demonstrate the performance of the different variables in predicting LGA neonates with various discrimination thresholds. All analyses were performed with the statistical software programmes MedCalc 5.00.017 (MedCalc Software, Mariakerke, Belgium) and STATVIEW 5 (Abacus Corporation, Baltimore, MD, USA).

3. Results

3.1. Demographic and anthropometric characteristics

The demographics of the study population are shown in Table 1. Women in the GDM group (n = 55) had comparable age, personal history of GDM, history of type 2 diabetes in first-degree relatives and smoking status to those of the control group (n = 20). Women in the IFG group (isolated IFG or combined with IGT) had a higher prevalence of multiparity compared with the IGT group (P < 0.05). In addition, women in the IFG group had significantly higher antepartum weights than either the IGT group (BMI 30.1 ± 5.3 vs. 23.6 ± 4.3 kg/m², respectively; P < 0.001) or the controls (25.1 ± 5.1 kg/m²; P < 0.001). In addition, BMI at the clinical visit (31 ± 3 weeks of gestation) was higher in the IFG group than in the IGT group (34.6 ± 4.5 vs. 26.9 ± 4.4 kg/m², respectively; P < 0.001) and controls (28.6 ± 5 kg/m²; P < 0.001). Leptin, a surrogate marker of body fat mass, was significantly lower in the IGT group in comparison to the IFG and control groups (23.4 ± 3.3, 45 ± 5.3 and 31.7 ± 5.1 ng/mL, respectively; P < 0.01).

3.2. Glucose homoeostasis

As expected, women in the IFG group exhibited higher fasting glucose values than either the control women or those in the IGT group (P = 0.001). The 2-h OGTT glucose values were
also higher (P = 0.001) in both the IGT and IFG groups in comparison to the controls. HbA1c levels were significantly higher in the IFG group (5.52 ± 0.4%) than in the IGT and control groups (5.18 ± 0.4% and 5.19 ± 0.38%, respectively; P < 0.05). Fasting insulin levels, a surrogate marker of hepatic insulin resistance, were significantly higher (P < 0.001) in the IFG women (9.7 ± 4.8 mU/L) than in the controls (6.6 ± 3.8 mU/L) and IGT women (4.7 ± 2.4 mU/L). There was also a trend towards lower fasting insulin levels in the IGT group vs. controls that did not reach the level of significance. Levels of C-peptide were significantly higher in the IFG group compared with the two other groups, and were lower in the IGT group vs. the two other groups. Insulin resistance as measured by HOMA-IR was significantly higher in the IFG group compared with both the control and IGT groups (P < 0.001). Thus, GDM women with IFG can be considered more insulin-resistant than both GDM women with IGT and pregnant women without GDM. Insulin secretion as measured by HOMA-β tended to be lower in the IGT group vs. the controls and IFG group (97.1 ± 12.8 vs. 147.4 ± 17.5 and 132.1 ± 14.3, respectively), but failed to reach significance. All women in the control group remained free of therapeutic interventions in contrast to 18 women (34.5%) in the GDM group who required insulin therapy. No difference in the number of insulin-requiring women was noted between the IGT and IFG groups.

### 3.3. Adverse maternal and fetal outcomes

Rates of adverse maternal outcomes are presented in Table 2. No difference was observed for the prevalence of caesarean section, postpartum haemorrhage, instrumental action for extraction, gestational hypertension or hydramnios. As shown in Table 2, neonatal outcomes were also comparable across all three groups for neonatal hypoglycaemia, jaundice and premature delivery. There was no increased risk associated with GDM for SGA. In contrast, percentiles of birth weight and percentages of LGA neonates were higher in the IFG group compared with the IGT and control groups (P < 0.001), with an unadjusted OR of 10.62 [range: 3.02–37.34]. As preventing LGA neonates is one of the major objectives of GDM treatment, the whole study population (n = 75) was investigated for predictive factors associated with delivery of LGA neonates. Univaried logistic regression using LGA neonates as the dependent variable showed that the risk of LGA was significantly associated with higher values of BMI (P = 0.02), HbA1c (P = 0.027), FPG (P = 0.0003), 2-h glucose (P = 0.045), fasting insulin (P = 0.038) and HOMA-IR (P = 0.012). On controlling for antepartum BMI, maternal age and fasting insulin, multiple logistic regression analysis showed that the risk of delivering an LGA neonate remained correlated with FPG regardless of 2-h glucose levels and body weight gain during pregnancy (OR: 1.12; 95% CI: 1.03–1.21).

FPG and the 2-h OGTT glucose value at 24–32 weeks of pregnancy were also tested for their ability to predict LGA neonates. ROC analysis of the whole study population. ROC AUC for FPG was 0.783 (95% CI: 0.672–0.870) and ROC AUC for 2-h OGTT glucose was 0.549 (95% CI: 0.430–0.664). The difference between the two AUCs was statistically significant (P = 0.017). In our cohort, FPG > 5.1 mmol/L, which corresponds to the IADPSG threshold for a diagnosis of GDM, had a sensitivity of 50%, a specificity of 95% and a positive likelihood ratio of 9.75 to predict the delivery of LGA neonates.

### 4. Discussion

Pregnant women with IADPSG criteria for GDM are heterogeneous in their underlying metabolic alterations and thus have potentially different fetal outcomes. Indeed, it was observed that
Maternal and neonatal outcomes.

IGT: isolated impaired glucose tolerance; IFG: impaired fasting glucose; LGA: large for gestational age; SGA: small for gestational age.

Maternal outcomes

Our GDM women with IFG were heavier and fatter, and had greater fasting insulin levels and hepatic insulin resistance compared with GDM women with normal fasting glucose. Our study also demonstrated that GDM women with IFG were at higher risk of delivering LGA neonates than were GDM women with normal fasting glucose, independently of body corpulence.

The new IADPSG algorithm for GDM diagnosis improves both maternal and fetal outcomes due to abnormal glucose homoeostasis and is internationally recognized. However, the IADPSG recommends that all pregnant women at risk of GDM undergo OGTT at between 24–28 weeks of gestation, and this may be a heavy burden for national healthcare systems especially in underdeveloped countries. In the HAPO study, which inspired the IADPSG criteria, a positive linear relationship between glucose output, whereas the latter is associated with muscle insulin resistance and/or a relative deficit in glucose-induced insulin secretion [9]. By separating our study population, it was observed that women with IFG were heavier than either GDM women with IGT or women without GDM both at baseline and during the third trimester of gestation. The increased BMI was due to excess fat mass, as leptin levels were higher in the IFG group compared with the other two groups. Obesity is a well-known risk factor for insulin resistance, type 2 diabetes and GDM [15,16], and maternal obesity and GDM are independently associated with perinatal adverse effects [7,17].

It is noteworthy that, in the analyses conducted by the HAPO study group, confounders such as antepartum BMI and gestational weight gain were not taken into account. As a consequence of greater fat mass, the IFG group exhibited higher fasting insulin and C-peptide levels and, subsequently, an increased HOMA-IR. Thus, in our present study, it can be hypothesized that GDM women with IFG had higher hepatic insulin resistance than either non-GDM women or GDM women with isolated IGT.

Although our study population was too small to address the issue, it is also of interest to note the trend in our GDM women with isolated IGT towards lower fasting insulin, C-peptide and HOMA-IR values. In addition, differences between the IGT and control groups may have been minimal in our sample screened by WHO criteria. When calculating HOMA-β, a surrogate index of insulin secretion, GDM women with IGT demonstrated lower beta-cell function in comparison to non-GDM women and GDM women with isolated IGT.

Table 2
Maternal and neonatal outcomes.

<table>
<thead>
<tr>
<th>Maternal outcomes</th>
<th>Controls</th>
<th>IGT</th>
<th>IFG</th>
<th>Chi² test</th>
<th>Unadjusted OR [95% CI]a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caesarean section</td>
<td>20%</td>
<td>18%</td>
<td>31%</td>
<td>0.55</td>
<td>1.98 [0.57–6.88]</td>
</tr>
<tr>
<td>Postpartum haemorrhage</td>
<td>20%</td>
<td>15%</td>
<td>12.5%</td>
<td>0.82</td>
<td>0.70 [0.13–3.57]</td>
</tr>
<tr>
<td>Instrumental action for extraction</td>
<td>30%</td>
<td>25.6%</td>
<td>25%</td>
<td>0.9</td>
<td>1.19 [0.32–4.38]</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>0%</td>
<td>7.7%</td>
<td>6.2%</td>
<td>0.46</td>
<td>1.24 [0.12–12.8]</td>
</tr>
<tr>
<td>Hydramnios</td>
<td>10%</td>
<td>2.5%</td>
<td>18.7%</td>
<td>0.12</td>
<td>4.30 [0.77–23.82]</td>
</tr>
<tr>
<td>Neonatal outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentile of birth weight</td>
<td>59.4%</td>
<td>48.9%</td>
<td>81.4%</td>
<td>0.001</td>
<td>IFG vs. controls, IFG vs. IGT</td>
</tr>
<tr>
<td>Apgar score at 1 min</td>
<td>9.8 ± 0.7</td>
<td>9.3 ± 1.3</td>
<td>9.0 ± 2.3</td>
<td>0.26</td>
<td>3.91 [1.01–15.17]</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>5%</td>
<td>2.5%</td>
<td>0%</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>10%</td>
<td>10.2%</td>
<td>12.5%</td>
<td>0.96</td>
<td>1.26 [0.23–6.94]</td>
</tr>
<tr>
<td>Premature delivery</td>
<td>0%</td>
<td>2.5%</td>
<td>12.5%</td>
<td>0.13</td>
<td>8.28 [0.70–97.9]</td>
</tr>
<tr>
<td>LGA</td>
<td>25%</td>
<td>7.7%</td>
<td>62.5%</td>
<td>&lt; 0.001</td>
<td>IFG vs. controls, IFG vs. IGT</td>
</tr>
<tr>
<td>SGA</td>
<td>5%</td>
<td>10.2%</td>
<td>0%</td>
<td>0.4</td>
<td></td>
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<td></td>
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</table>

a IFG group vs. other study (IGT and control) groups.

It is not a good marker of glucose-induced insulin secretion and additional markers of insulin secretion, such as the frequently sampled intravenous glucose tolerance test index [19], should be applied to allow any conclusions to be made. It is also worth noting that our results are in line with the large body of literature on the pathophysiologica differences between IFG and IGT subjects demonstrating increased insulin resistance as measured by HOMA in subjects with IFG [8], whereas those with IGT...
exhibited more severe deficits during early- and late-phase insulin secretion [9]. Despite the small size of our cohort and a study design not dedicated to assessing glucose homeostasis abnormalities, our study has successfully demonstrated that the use of one abnormal value for the diagnosis of GDM as per IADPSG criteria led to the identification of a heterogeneous population in terms of glucose homeostasis.

Differences in pregnancy outcomes and fetal complications were to be expected. Black et al. [20] demonstrated that clinical outcomes of pregnancies complicated by GDM based on IADPSG criteria differ according to combinations of abnormal OGTT values. In the present study, LGA and shoulder dystocia appeared to be more strongly associated with categories of GDM based on abnormal fasting glucose values (IFG isolated or combined with IGT) whereas, in contrast, preterm delivery, gestational hypertension and hyperbilirubinemia appeared to be more closely related to elevated post-load glucose [20]. The absence of differences in maternal outcomes between our study groups should be treated with caution given the small size of our population and the subsequent insufficient power to detect statistically significant differences for most of the outcomes. However, a higher rate of LGA neonates was seen in the IFG group in comparison to the two other groups, whereas 2-h OGTT glucose levels were not associated with LGA occurrence on logistic regression analysis of the whole population.

It has previously been reported that LGA is the most common complication of GDM and is linearly related to maternal plasma glucose levels [6]. Given the characteristics of the women of our IFG group, it could be proposed that the increased LGA occurrence in this group was related to their excess body weight and fat. Indeed, it was recently reported that antepartum overweight and obesity account for a high proportion of LGA even in the absence of GDM [17]. Interestingly, our study has demonstrated that LGA babies were still associated with FPG after adjusting for BMI on multivariate logistic regression. Ben-Haroush et al. [21] previously demonstrated that only maternal weight at the time of delivery and fasting glucose levels were independently and significantly associated with LGA neonates. Moreover, recent data suggest that FPG > 89 mg/dL or BMI > 33.5 kg/m² at 28–32 weeks of gestation can detect rates of adverse outcomes similar to IADPSG criteria [22]. Using ROC analysis of our whole study population, the fasting glucose value was the only parameter of glucose homeostasis significantly predictive of LGA neonates, while the cut-off value of > 5.1 mmol/L was highly predictive of such an outcome. Thus, if the importance of FPG in LGA neonate occurrence is confirmed in larger cohorts, this could simplify both the diagnosis and monitoring of pregnant women at high risk, as has already been proposed in less economically developed countries [23].

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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