

Incidence of type 2 diabetes in southern Spain (Pizarra Study)

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ABSTRACT

Background Few European studies have used an oral glucose tolerance test (OGTT) to examine the incidence of type 2 diabetes. We determined the incidence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and type 2 diabetes in a population from southern Spain.

Material and methods A population-based cohort study was undertaken in Pizarra, Spain. Baseline data were recorded on age, sex, weight, height, waist and hip circumferences, and diabetes status for 1051 persons, of whom 910 were free of type 2 diabetes (at-risk sample). Of these, 714 completed the 6-year follow-up study. Body mass index, waist-to-hip ratio and weight increase since baseline were calculated. The homeostasis model assessment equations were used to estimate the indices of insulin resistance and β -cell function. Each person received an OGTT at baseline and after 6 years.

Results Type 2 diabetes developed in 81 people for a total of 4253 person-years, representing an incidence of 19.1 cases per 1000 person-years (95% confidence interval, 15.3–23.6). Age and the presence of obesity, central obesity and carbohydrate metabolism disorders [IFG (cut off = 100 mg dL⁻¹, capillary blood glucose level), IGT or both] at baseline were significant markers for the onset of type 2 diabetes during follow-up. After adjusting for these variables, multivariate analysis showed weight increase, waist-to-hip ratio and the indices of insulin resistance and β -cell function were significantly associated with the risk for type 2 diabetes.

Conclusions The incidence of type 2 diabetes in a population from southern Spain is high. It is probably associated with the high prevalence of obesity and weight increase in this population.

Keywords Cohort population-based study, impaired fasting glucose, impaired glucose tolerance, incidence rate, relative risk, type 2 diabetes.

Eur J Clin Invest 2008; 38 (2): 126–133

Introduction

The prevalence of type 2 diabetes mellitus varies widely in different parts of the world [1]. The World Health Organization (WHO) has predicted that the prevalence of type 2 diabetes mellitus in people 20 years of age or over will increase five fold by 2025 [2]. The prevalence of type 2 diabetes mellitus in Europe is moderate or low compared with other parts of the world [3]. In Spain, numerous studies have evaluated the prevalence of type 2 diabetes mellitus [4–10], which ranges from 5.6% [5] to 15.9% [10], though it appears to be increasing over the years [4].

Type 2 diabetes mellitus is a potentially preventable disease [11], and studies of the incidence of the disease have led to examination of those variables associated with a greater risk for developing type 2 diabetes. Various prospective studies have been carried out

in populations with a high prevalence of diabetes or in subgroups with a greater risk, such as people with impaired glucose tolerance (IGT) [12,13]. Variables associated with the risk for type 2 diabetes include fasting blood glucose levels and post oral glucose tolerance test (OGTT) glucose level [12,13], obesity [14], the pattern of insulin sensitivity [15] or variables associated with lifestyle and physical exercise [16]. However, population-based studies of the incidence of type 2 diabetes, and the conversion to type 2 diabetes of people with a normal OGTT, or with impaired fasting glucose (IFG) or IGT, are less frequent. Two prospective, population-based studies have been undertaken, both in northern Spain [17,18]; the incidence of type 2 diabetes was 8 and 10.8 cases/1000 person-years, respectively.

The aim of this study was to determine the incidence of IFG, IGT and type 2 diabetes in southern Spain in a population with a known prevalence for type 2 diabetes [19].

Materials and methods

Baseline study

In 1997–98 a study was undertaken in Pizarra, a town in the province of Malaga (Andalusia, southern Spain). The characteristics of the study have been reported previously [19]. The sample size was calculated assuming a population prevalence of type 2 diabetes of 7%, hypertension of 25% and obesity of 15%, using reference data from previously published prevalence studies in Spain [4]. A total of 1051 people completed the baseline study, giving a participation index of 70.3%. People were selected randomly from the municipal census. The inclusion age was 18–65 years, and people were excluded from the study if they were institutionalized for any reason, were pregnant or had a severe clinical or psychological disorder.

The subjects were requested by mail to attend their local health centre for a medical examination. Those who failed to attend their first appointment were sent a second letter giving them another appointment, and all those still not attending were visited at home in order to ascertain the reason. The final sample distribution by age and sex was not significantly different from the population distribution. All the participants were informed about the nature of the study and gave their written consent. The study was approved by the Ethics and Clinical Research Committee of Carlos Haya Hospital.

Follow-up

The cohort was re-evaluated in 2003–04. All those who had completed the baseline study ($n = 1051$) were invited by letter or by phone to attend for another clinical and anthropometric examination and another OGTT. In total, 824 people completed the follow-up study (78.4%). Of the 227 who did not complete the study, 19 had died, 90 could not be traced and 118 no longer wished to collaborate in the study.

The 141 people who had type 2 diabetes at baseline were excluded from all the calculations of the incidence. Thus, the at-risk sample included 910 people, of whom 714 completed the follow-up (78.5%).

Procedures

The same methodology was used for both the prevalence and the incidence studies. All the participants were interviewed and given a standardized clinical examination [20]. Measurements were made of weight, height, body mass index (BMI) ($\text{weight}/\text{height}^2$), waist and hip circumferences and waist to hip ratio (WHR). The increase in the BMI was calculated as the difference between the BMI at follow-up and the baseline measurement, divided

by the BMI of the baseline study, expressed as a percentage. Questions relating to a family history of diabetes were only asked in the follow-up study.

Capillary blood glucose level was measured in both studies using the glucose oxidase method (Accu-Chek, Roche Diagnostics, Barcelona, Spain) at fasting and 120 min after an OGTT with 75 g of glucose. The fasting serum insulin level was measured by radioimmunoassay (Coat a Count RIA kit, DPC, Los Angeles, CA, USA).

Insulin-resistance and β -cell function indices were estimated with the homeostasis model assessment (HOMA) equations, as follows [21]:

$$\text{Insulin resistance index (IR}_{\text{HOMA}}) = (\text{fasting insulin } (\mu\text{U mL}^{-1}) \times \text{fasting glucose (mmol L}^{-1})/22.5$$

$$\beta\text{-cell function index } (\beta\text{CF}_{\text{HOMA}}) = ((20 \times \text{fasting insulin } (\mu\text{U mL}^{-1}))/\text{fasting glucose (mmol)}) - 3.5$$

Classification criteria

The WHO 1998 criteria were used to classify the people with diabetes, IGT and IFG [22]. People were considered to have known diabetes if they were already receiving treatment with oral anti-diabetics. Those people being treated with diet only received an OGTT to verify the diagnosis. No incident diabetes case required treatment with insulin. Subjects with a baseline capillary blood glucose level $< 100 \text{ mg dL}^{-1}$ and a post OGTT blood glucose level $< 140 \text{ mg dL}^{-1}$ were considered to have a normal OGTT. Subjects with a capillary blood glucose level between 100 and 110 mg dL^{-1} and a post OGTT blood glucose level $< 140 \text{ mg dL}^{-1}$ were considered to have IFG. Subjects with a capillary blood glucose level $< 100 \text{ mg dL}^{-1}$ and a post OGTT blood glucose level between 140 and 200 mg dL^{-1} were considered to have IGT. Finally, subjects with a capillary blood glucose level $> 110 \text{ mg dL}^{-1}$ or post OGTT blood glucose level $> 200 \text{ mg dL}^{-1}$ were diagnosed with type 2 diabetes.

People were considered to be obese if their BMI was $\geq 30 \text{ kg m}^{-2}$ [23]. Subjects were considered to have hypertension if their blood pressure was $> 130/85 \text{ mmHg}$ or they were receiving antihypertensive treatment [24]. Central obesity was defined by waist circumference ($\geq 94 \text{ cm}$ in men and $\geq 80 \text{ cm}$ in women) or by the waist-to-hip ratio (≥ 1.00 in men and ≥ 0.85 in women). They were considered to have dyslipidaemia if their triglycerides were $\geq 150 \text{ mg dL}^{-1}$ or HDL cholesterol $< 40 \text{ mg dL}^{-1}$ in men or $< 50 \text{ mg dL}^{-1}$ in women [24].

Statistical analysis

Data are presented as means \pm SD, medians and 25th and 75th percentiles (in case of non-normality) or proportions. Differences between the baseline study and follow-up were determined by the t -test for paired samples or the Wilcoxon test. The incidence rates (IRs) (number of events/person-time at risk) and

Table 1 Baseline and follow-up characteristics of the full and final study samples. Data are means \pm SD, median (25th–75th percentile) or proportions

	Baseline			Follow up
	Full sample N = 1051	At-risk sample* N = 910	Final sample† N = 714	Final sample N = 714
Age (years)	40.0 \pm 13.8	38.1 \pm 13.2	38.9 \pm 13.0	45.0 \pm 13.4
Sex (male/female)	396/655	329/581	252/462	252/462
Weight (kg)	71.7 \pm 13.9	70.6 \pm 13.7	70.4 \pm 13.0	73.3 \pm 14.0
Waist (cm)	91.9 \pm 13.7	90.2 \pm 13.2	90.3 \pm 12.9	98.1 \pm 13.0
Body mass index (kg m ⁻²)	27.5 \pm 5.2	27.1 \pm 5.1	27.1 \pm 4.9	28.3 \pm 5.2
Waist-to-hip ratio	0.91 \pm 0.09	0.90 \pm 0.09	0.90 \pm 0.09	0.95 \pm 0.09
IR _{HOMA}	2.2 (1.4–3.4)	2.1 (1.3–3.0)	2.0 (1.3–3.0)	2.1 (1.3–3.2)
β CF _{HOMA}	87.7 (53.1–126.5)	89.7 (56.1–129.2)	89.8 (56.6–126.4)	88.7 (54.6–123.3)
Obesity (%)	28.8	24.8	25.5	32.8
Family history of DM (%)	–	–	–	58.4
OGTT normal (%)	62.0	71.6	71.1	69.3
Impaired fasting glucose‡ (%)	12.3	14.2	13.9	7.8
Impaired glucose tolerance (%)	8.4	9.7	10.4	7.6
Impaired fasting glucose + impaired glucose tolerance (%)	3.9	4.5	4.6	3.9
DM unknown (%)	8.8	–	–	9.5
DM known (%)	4.6	–	–	1.8
Hypertension (%)	53.8	49.8	50.4	58.2
Dyslipidaemia (%)	43.7	41.4	41.9	–

*People in the at-risk sample were those without diabetes at baseline. †People in the final sample were those in the at-risk sample who could be classified according to their diabetes status during follow up. ‡Capillary blood glucose level > 100 mg dL⁻¹.

Abbreviations: IR_{HOMA}, insulin resistance index; β CF_{HOMA}, β Cell Function index; (both calculated by homeostatic model assessment equations); DM, diabetes mellitus; OGTT, oral glucose tolerance test.

relative risks (RRs) (IR exposed/IR non-exposed) for diabetes were calculated for each exposure variable. Comparisons between RRs were made by Z-test [25]. In all cases the level of rejection of a null hypothesis was $\alpha = 0.05$. Multivariate analysis was performed using stepwise logistical regression. For IRs and RRs, 95% confidence intervals were computed. Analyses were made using SPSS v10 (SPSS Inc., Chicago, IL, USA) and EpiBasic (URL: <http://www.folkgesundhed.au.dk/uddannelse/software>; accessed 20 December 2007).

Results

Table 1 shows the characteristics of the subjects who completed the baseline study ($n = 1051$), the at-risk sample (subjects without diabetes at baseline, $n = 910$), and the baseline and follow-up characteristics of the final sample (subjects from the at-risk group who completed the follow-up, $n = 714$; participation index, 78.5%). The mean

follow-up was six years. During this period significant increases were noted in weight ($P < 0.0001$), waist circumference ($P < 0.0001$), BMI ($P < 0.0001$) and WHR ($P < 0.0001$), but not in IR_{HOMA} or β CF_{HOMA}.

Of those people with a BMI ≥ 30 kg m⁻² at baseline, 10.8% reduced it below 30 kg m⁻², but 14.3% of the people who had a BMI < 30 kg m⁻² increased it above 30 kg m⁻², which represents a net increase in obesity in the population studied of 7.4%. Just over 58% of the subjects had a relative with type 2 diabetes and 82.8% of the subjects being treated for type 2 diabetes had a relative with the disease. The total prevalence of type 2 diabetes rose from 13.4% at baseline to 20.3% after six years, with over half the subjects unaware of their disease. Hypertension rose from 50.4% to 58.2% in the follow-up study. The presence of dyslipidaemia was found in 41.9% of the participants in the baseline study. No lipid data were available in the follow-up study.

Table 2 shows the incident cases and the incidence rates of diabetes for the whole sample and according to exposure variables.

Table 2 Incidence of diabetes (per 1000 person-years) in the cohort overall and by exposure variables

	Cases of incident diabetes	Person-years	Incidence rate per 1000 person-years	95% CI	RR	95% CI
Whole cohort	81	4253	19.1	(15.3–23.6)	–	–
Sex						
Men	35	1541	22.7	(16.3–31.6)	1	
Women	46	2712	17.0	(12.7–22.7)	0.75	(0.48–1.16)
Age group						
18–35 years	15	1754	8.6	(5.1–14.2)	1	–
36–45 years	21	1085	19.4	(12.6–29.7)	2.26	(1.17–4.39)
46–55 years	24	755	31.8	(21.3–47.4)	3.70	(1.95–7.09)
> 56 years	22	659	33.4	(21.9–50.7)	3.90	(2.00–7.51)
Obesity						
BMI < 30 kg m ⁻²	42	3075	13.7	(10.1–18.5)	1	
BMI ≥ 30 kg m ⁻²	39	1070	36.4	(26.6–49.9)	2.66	(1.73–4.13)
Central obesity (Waist ≥ 94 cm in men and ≥ 80 cm in women)						
No	11	1577	6.9	3.8–12.6	1	
Yes	68	2593	26.2	(20.7–33.3)	3.8	(2.0–7.1)
Central obesity (WHR ≥ 1.00 in men and ≥ 0.85 in women)						
No	33	2945	11.2	(7.97–15.76)	1	
Yes	48	1199	40.0	(30.17–53.12)	3.57	(2.29–5.57)
OGTT						
Baseline capillary blood glucose level ≤ 90 mg dL ⁻¹	13	1806	7.2	(4.2–12.4)	1	
Baseline capillary blood glucose level > 90 mg dL ⁻¹ and < 100 mg dL ⁻¹	17	1181	14.4	(8.9–23.2)	2.0	(0.9–4.1)
Baseline capillary blood glucose level ≥ 100 mg dL ⁻¹ and < 110 mg dL ⁻¹	23	604	38.1	(25.3–57.3)	5.3	(2.7–10.4)
Impaired glucose tolerance	14	450	31.1	(18.4–52.5)	4.3	(2.0–9.2)
Impaired fasting glucose* + impaired glucose tolerance	14	212	66.0	(39.1–111.5)	9.2	(4.3–19.5)
Family history of DM						
No	33	1861	17.7	(12.60–24.90)	1	
Yes	46	2457	18.7	(14.02–25.00)	1.06	(0.66–1.70)
Hypertension						
No	27	1992	13.5	(9.3–19.8)	1	
Yes	52	2183	23.8	(8.2–31.3)	1.76	(1.10–2.80)
Dyslipidaemia						
No	42	2415	17.3	(12.8–23.5)	1	
Yes	38	16.96	22.4	(16.3–30.7)	1.29	(0.83–2.00)

*Capillary blood glucose level > 100 mg dL⁻¹.

Table 3 Incident impaired fasting glucose, impaired glucose tolerance and diabetes multivariate analysis (data are relative risk (95% CI) calculated by stepwise logistical regression. Independent variables: age, sex, obesity, increase in BMI, IR_{HOMA}, β CF_{HOMA}, family history of diabetes, a large waist (≥ 94 cm in men and ≥ 80 cm in women), increase in waist circumference, a high waist-to-hip ratio, hypertension and dyslipidaemia

	Relative Risk (95% CI)	P
Impaired fasting glucose vs. normal OGTT		
IR _{HOMA}	1.54 (1.16–2.05)	0.003
Impaired glucose tolerance vs. normal OGTT		
Central obesity		
No	1	–
Yes (WHR > 1 in men, WHR > 0.85 in women)	2.95 (1.57–5.52)	0.001
Hypertension		
No	1	–
Yes	1.95 (1.53–5.95)	0.001
Diabetes vs. normal OGTT		
Obesity		
No	1	–
Yes	2.22 (1.18–4.15)	0.01
BMI increase*	1.25 (1.13–1.38)	0.0001
IR _{HOMA}	2.09 (1.50–2.90)	0.0001
β CF _{HOMA}	0.98 (0.97–0.99)	0.0001
Central obesity		
No	1	–
Yes (WHR > 1 in men, WHR > 0.85 in women)	4.80 (2.63–8.75)	0.0001

*BMI increase = (BMI baseline – BMI follow up)/BMI baseline. Abbreviations: OGTT, oral glucose tolerance test; IR_{HOMA}, insulin resistance index; β CF_{HOMA}, β Cell Function index; (both calculated by homeostatic model assessment equations); WHR, waist-to-hip ratio.

None of the incident cases required treatment with insulin. We cannot rule out the presence of people with latent autoimmune diabetes in adults (LADA). The risk for diabetes increased significantly with age (over 35 years), the presence of obesity or central obesity (WHR or waist circumference criteria). The risk of developing diabetes was greater in the subjects with IFG (capillary blood glucose level = 100 mg dL⁻¹) or IGT; subjects with a capillary blood glucose level between 90 and 100 mg dL⁻¹ showed no significantly higher risk of diabetes than those with a blood glucose level ≤ 90 mg dL⁻¹. However, this risk rose significantly ($P < 0.05$) in the subjects with IFG and IGT (RR = 9.2) versus the subjects with isolated IGT. Hypertension, but not dyslipidaemia, was associated with the development of diabetes.

The stepwise logistical regression analysis was made with the following independent variables: age, sex, obesity (BMI = 30 kg m⁻²), increase in BMI, IR_{HOMA}, β CF_{HOMA}, family history of diabetes, waist circumference, increase in waist circumference, and a high waist-to-hip ratio (WHR > 1 in men or > 0.85 in women). Dependent variables were the presence of a carbohydrate metabolism disorder versus normal OGTT (Table 3). Logistical regression models showed that only IR_{HOMA} in the baseline study significantly predicted the onset of IFG after six years. Central obesity and hypertension were significant predictors of the onset of IGT. Finally, obesity, central obesity (WHR > 1 in men or > 0.85 in women), and the increase in BMI, IR_{HOMA} and β CF_{HOMA} were all significantly associated with the risk of developing type 2 diabetes. Neither age, sex, waist circumference, increase in waist circumference, hypertension, dyslipidaemia nor a family history of diabetes contributed to the risk of developing carbohydrate metabolism disorders in the multivariate analyses.

Discussion

The prevalence of type 2 diabetes is increasing worldwide [1]. This increased prevalence is probably associated not only with longevity, but also with an increase in the side-effects of a modern, western lifestyle [12,14]. Indeed, mention has been made of the catastrophic status of public health due to the epidemic of obesity and diabetes mellitus [26].

Although numerous studies have examined the prevalence of type 2 diabetes, fewer studies have assessed its incidence and comparisons between them are not always easy. Type 2 diabetes is a disease which has a silent onset that may pass unnoticed, as shown by the fact that in all population studies an important number of cases are diagnosed during the field study itself [18]. This, too, was the case in our study, in which most of the subjects with diabetes were unaware of their status.

The results depend on the diagnostic criteria used or on the presence of numerous confounding variables associated with the risk of type 2 diabetes. Several studies have evaluated the impact of the change in the classification criteria for diabetes mellitus on the prevalence and incidence of type 2 diabetes [27,28].

The incidence found in our study is greater than that of other studies [17,18,28]. In Spain, the prevalence of type 2 diabetes has risen over recent years [29]. However, only two population-based studies have examined the incidence of type 2 diabetes in Spain, reporting annual incidence rates of 8 and 10.8 cases per 1000, respectively [17,18], both lower than that found in our study, despite the fact that the minimum ages in their studies were 30 and 35 years. Large differences in the incidence of type 2 diabetes over one decade were already noted in the San Antonio Heart Study, where it rose from 2.6% for the participants enrolled in 1980 to 9.4% for those enrolled in 1988 [30]. Age and obesity are two variables that are associated in all studies with the risk and

incidence of type 2 diabetes [3,12,14,17,30–32]. Age was strongly associated with all the exposure variables (data not shown), though its bivariate relation with alterations in blood glucose level disappeared in the stepwise multivariate analysis. Weight increase and central obesity have also been associated with the risk of type 2 diabetes mellitus, independently of the presence of obesity.

The role of obesity as a risk factor for type 2 diabetes is well known. The prevalence of obesity in the population studied here is 28.8% [33,34], greater than that of other studies in Spain [35,36]. Over the study period, the mean increase in weight was 3 kg, and the prevalence of obesity in the cohort without diabetes rose from 25.5% to 32.8%. Considering the very important role of obesity in the risk for type 2 diabetes it is highly likely that the high incidence of type 2 diabetes in our study was due to the high prevalence and incidence of obesity in the study population. Because of their high correlation BMI, WHR and waist circumference have similar associations with incident diabetes [37]. Although these three variables in our study were associated with the incidence of diabetes, BMI displaced WHR and waist circumference from the models in the multivariate analysis.

One limitation of our study is the use of capillary blood glucose levels for the diagnosis of blood glucose level disorders. Alberti and Zimmet (22) proposed capillary blood glucose levels of 100 and 110 mg dL⁻¹ for the diagnosis of IFG and diabetes, respectively, equivalent to 110 and 126 mg dL⁻¹ of plasma glucose. To our knowledge, no capillary value equivalent to 100 mg dL⁻¹ of plasma glucose has been proposed to define IFG. A low cut-off for blood glucose levels increases the diagnostic sensitivity, but at the cost of reduced specificity [38], and some authors have found no greater diagnostic efficacy after reducing the cut-off [39]. As our data indicate that a capillary blood glucose level between 90 and 100 mg dL⁻¹ is not predictive of type 2 diabetes, we have continued using the value of 100 mg dL⁻¹ for IFG and 110 mg dL⁻¹ for type 2 diabetes.

Type 2 diabetes is a disease with a polygenic hereditary component. Different studies have found that the incidence of type 2 diabetes is greater in those persons who have a family history of the disease [40,41]. Two family studies have estimated that the risk of being diagnosed with diabetes mellitus increases from 2- to 4-fold [42] and from 3.5- to 6-fold [43] depending on whether one or both parents are affected. In our study, 67.4% of the people who were diabetic had some Relative with diabetes, a higher proportion than for those who were not diabetic (57.5%). This greater proportion was mainly at the expense of the group of people with known diabetes, a group in which 82.8% had a family history of diabetes ($P < 0.001$), though after adjustment for other variables the association was not significant. The absence of significance in the hereditary component of type 2 diabetes suggests that, in our environment, the increases in incidence and prevalence are associated more with the presence of environmental factors rather than truly genetic factors.

Data from pathophysiological studies show that insulin resistance and β -cell dysfunction are precursors of type 2 diabetes [44]. However, the evidence for the role of the pattern of insulin resistance and insulin secretion in the risk for type 2 diabetes in low- or medium-risk populations is scarce. At the baseline study we evaluated the indices of insulin resistance and insulin secretion in the same population, according to carbohydrate metabolism [43]. Six years later we determined that the risk for type 2 diabetes in non-diabetic people was positively and significantly associated with the previous index of insulin resistance and negatively associated with the index of insulin secretion. Similar results were found in the Bruneck Study [31] and in the Botnia Study [44], as well as others [32]. A debate exists in the medical literature regarding the relevance of insulin resistance and insulin secretion in the progression to type 2 diabetes [5,31,33,43,44]. The results of the epidemiological studies mentioned, as well as those of our study, support the idea that both defects characterise the natural history of type 2 diabetes.

In conclusion, the results of our study provide information about the high incidence of type 2 diabetes in a population from southern Spain, probably associated with the high prevalence of obesity and the increase in weight. The study also confirms the importance of early β -cell malfunction as a risk factor for the onset of type 2 diabetes. The study suggests the need to set up prevention programmes to avoid obesity and the early intervention of carbohydrate metabolism disorders in order to reduce insulin resistance and avoid β -cell secretory dysfunction.

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Received 17 April 2007; accepted 30 November 2007

Acknowledgements

We are grateful to Ian Johnstone for his help with the English language version of the manuscript. This study was undertaken with finance from the Fondo de Investigación Sanitaria (PI041883, PI051307, C03/08), Junta de Andalucía (0124/2005) and the Asociación Maimónides.

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