Heterogeneity of diabetes mellitus in the Hong Kong Chinese population. The Chinese University of Hong Kong–Prince of Wales Hospital Diabetes Research and Care Group

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Diabetes mellitus is a massive public health problem that has major socio-economic implications. There are now local and international data that confirm the high prevalence of diabetes in Chinese populations living in affluent societies such as Hong Kong. The heterogeneity of diabetes mellitus, especially among patients with a young onset of the disease, is being increasingly recognised. Genetic factors appear to be a particularly important factor in these young diabetic patients, who face a long duration of disease. Understanding the pathogenesis and genetic basis of diabetes mellitus and its complications are of fundamental importance to improving the diagnosis and treatment of this heterogeneous disease. Despite its potential complications, diabetes mellitus is a very treatable and preventable disease. The challenge lies in the effective delivery of quality and affordable care to high-risk individuals. To this end, these concerted efforts among academics, clinicians, scientists, health care professionals, administrators, and policy makers are required to defuse this health care time bomb.

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Prevalence of diabetes mellitus and the metabolic syndrome

Two large-scale population-based epidemiological studies that used the 1985 World Health Organization (WHO) diagnostic criteria for diabetes mellitus were performed in Hong Kong in 1990[1] and 1995.[2] The earlier study involved 1513 subjects who were recruited from two workforces aged between 28 and 65 years. The age-adjusted prevalence of diabetes mellitus was found to be 7.7%, whereas the crude prevalence ranged from less than 1% in subjects younger than 30 years to more than 20% in the middle-aged group.[1] The 1995 population-based survey involved 2900 subjects who were aged between 25 and 74 years, and showed an age-adjusted prevalence of 8.5%. The crude prevalence ranged from 1.7% in the 25-to-34-year age-group to more than 25% in those older than 65 years.[2] Due to different sampling methods, these figures are not directly comparable; nevertheless, they support an overall rising trend in the age-adjusted prevalence of diabetes mellitus. In both studies, only 30% of diabetic subjects had been previously diagnosed. The body mass index (BMI), waist to hip ratio, a family history of diabetes, and an older age were independent predictors of diabetes mellitus.[1,2] There were also close associations between glucose intolerance, dyslipidaemia (high levels of triglyceride and low levels of high-density lipoprotein [HDL]–cholesterol), obesity, hyperinsulinaemia, albuminuria, and high blood pressure in these subjects.[3] These findings suggest that diabetes mellitus in the Hong Kong Chinese population is often part of a multifaceted syndrome, commonly known as the 'metabolic syndrome'.[4] Using statistical modelling, most of the components of the syndrome can be explained by obesity, family history, and increased age.[4]

Prevalence of impaired glucose tolerance

Individuals have impaired glucose tolerance (IGT) if they fail to maintain a normal plasma glucose (PG) concentration 2 hours after a glucose load, but their PG levels do not reach values in the diabetic range (ie fasting PG, <7 mmol/L and 2-hour PG, 7.8-11.1 mmol/L). Similar to the local trend in the prevalence of diabetes

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mellitus, the prevalence of impaired glucose tolerance (IGT) has increased markedly, from 7% in both men and women in 1990[5] to 14% in men and 17% in women in 1995.[2] As with Caucasians,[6,7] Hong Kong Chinese people with IGT have an increased number of cardiovascular risk factors.[8,9] For example, the prevalence of hypertension in 1990 was 7.5%, 23.9%, and 15% in Hong Kong Chinese men with normal glucose tolerance, IGT, and diabetes, respectively; in women, the corresponding figures were 3.4%, 8.7%, and 14%.[3] Retinopathy[10] and albuminuria[3] have also been observed in Chinese subjects with IGT. Three large-scale population-based studies of Caucasians have found clear relationships between the fasting PG level and mortality, even in non-diabetic people.[11]

In a typical cohort of subjects with risk factors for diabetes mellitus (usually a positive family history or a history of gestational diabetes mellitus), 50% of those with IGT progressed to develop diabetes mellitus in 4.34 years, giving a crude annual conversion rate of 11.6%.[12] The 2-hour post–glucose loading PG level was the major predictor of the progression of glucose intolerance. For those with a 2-hour PG level of ≥10.1 mmol/L, the progression from IGT to diabetes mellitus was three times faster than for those with a 2-hour PG level of <10.1 mmol/L.[12]

Prevalence of obesity and its relationships with cardiovascular risk factors

The WHO defines overweight as a BMI between 25 and 29.9 kg/m^2, and obesity as a BMI of ≥30 kg/m^2 in Caucasians.[13] The National Diabetes Data Group, however, defines obesity as a BMI of ≥25 kg/m^2 in Caucasian women and ≥27 kg/m^2 in men.[14] Based on the WHO criteria, the prevalence of overweight in the Hong Kong Chinese population increased from 28% (in 1990) to 36% (in 1995) and that of obesity from 3% to 6%.[1,2] In the 1990 survey, however, the mean BMI of Hong Kong men and women of working age was 23 kg/m^2, whereas the mean BMI of diabetic individuals was 24 kg/m^2.[1] Hence, when the WHO definitions are applied to Asian populations, whose body frames are generally smaller than those of Caucasians, they are often erroneously considered to be non-obese.[15] The International Obesity Task Force recently recommended the following weight for Asians according to BMI value: overweight, ≥23 kg/m^2; at-risk, 23 to 24.9 kg/m^2; obese I, 25 to 29.9 kg/m^2; and obese II, >30 kg/m^2.

Despite the differences in adiposity indices between Chinese and Caucasian populations, there are continuous relationships between anthropometric measurements—in particular, waist circumference—and cardiovascular risk factors in the Hong Kong Chinese population. The threshold BMI value taken to indicate cardiovascular risk factors such as diabetes, hypertension, or dyslipidaemia has been shown to be approximately 24 kg/m^2 in both Hong Kong men and women.[16] Taken together, the cardiovascular risks associated with blood pressure, and blood lipid and blood glucose levels,[17] and obesity represent a continuum, and their interactions are more important than absolute values.[15,17-19]

Mortality and morbidity of type 2 diabetes

In 1989, we examined the clinical characteristics of 493 consecutive Hong Kong Chinese patients attending a hospital diabetes clinic.[20] Less than 3% of the patients had classical type 1 diabetes mellitus, defined as acute presentation with either diabetic ketoacidosis or heavy ketonuria (>3+) or continuous requirement of insulin within 1 year of diagnosis. However, 25% of the patients with type 2 diabetes mellitus received insulin treatment. Among the study population, 50% had hypertension, 50% had increased albuminuria, and 50% had dyslipidaemia. In type 1 diabetes there are close relationships between hypertension, proteinuria, and retinopathy. However, these relationships are usually less consistent in the type 2 disease. For example, in Chinese patients with type 2 diabetes mellitus, 60% to 80% of patients with microalbuminuria or macroalbuminuria had hypertension. However, 40% of the normoalbuminuric patients also had hypertension thus suggesting that essential hypertension often coexists with type 2 diabetes.[20] These findings emphasise the heterogeneous nature in the clustering of these risk factors in Chinese patients.

Approximately 30% of patients admitted to Hong Kong public hospitals with stroke,[21,22] acute myocardial infarction,[23] and heart failure[24] in the early 1990s were found to also have diabetes mellitus. Many cases of diabetes were diagnosed only as the result of these diabetic complications. Until recently, 30% of diabetic patients showed clinical evidence of retinopathy when they were first referred to hospital. The recent reduction of this figure to less than 10% in the past 2 to 3 years has been attributed to an increased awareness and earlier referral of patients to hospital clinics.[25,26] Between 30% and 40% of Hong Kong Chinese patients receiving dialysis had diabetes during 1995 to 1999,[27] and many were not enrolled into the renal replacement programme because of concurrent medical problems such as visual loss or stroke. Despite receiving dialysis, these patients often have a reduced survival rate and poor quality of life. In a 1990 survey,

drug-induced hypoglycaemia, mainly due to oral drugs, was the main cause of hospital admissions to treat adverse drug events. Impaired renal function and old age were the major predisposing factors.[28]

In a local prospective study involving 400 type 2 diabetic patients followed up for a mean period of 26 months, the annual mortality rate was found to be 3.5%. The majority of deaths were due to cardiovascular diseases (mainly stroke) and renal failure.[29] The independent predictors of death were the fasting PG level and albuminuria. In this study, a spot urine albumin to creatinine ratio (ACR) of 5.6 to 38.0 mg/mmol corresponded to a 24-hour urinary albumin excretion of 30 to 300 mg/d. These higher cut-off values might have been because of the lower body mass of the Hong Kong Chinese population. The relative risk of death was 3.7 in patients with microalbuminuria and 11 in those with macroalbuminuria (ACR ≥38 mg/mmol) when compared with the normoalbuminuric patients.[29] In another cohort of 102 hypertensive patients with type 2 diabetes mellitus who were followed up for a mean period of 5.5 years, 50% of patients with macroalbuminuria (24-hour urinary albumin excretion, ≥300 mg/d on at least two occasions) had at least one clinical end-point, which was defined either as death, significant cardiovascular disease, or renal failure.[30]

There were also close relationships between albuminuria and the rate of deterioration of renal function. By using multivariate analysis, the fasting PG level, the glycated haemoglobin HbA_{1c} level, albuminuria, a high total cholesterol and low-density lipoprotein–cholesterol were found to be independent predictors of clinical events.[30] Apart from the duration of disease, and metabolic and blood pressure control, genetic factors have also been implicated in the development of diabetic complications.[31] In the Hong Kong Chinese population, the *Z-2* allele—an $(AC)_n$ dinucleotide repeat upstream to the aldose reductase gene—has been shown to be associated with severe retinopathy in young patients with type 2 diabetes mellitus.[32] The angiotensinogen M235T (*TT*) genotype and its possible interaction with the angiotensin converting enzyme deletion/insertion polymorphisms (*DI/DD*) have also been reported in Chinese diabetic patients who have increased albuminuria.[33] However, these findings need to be reproducted in other patient populations and their clinical significance requires prospective evaluation.

Childhood diabetes

In Caucasians, autoimmune type 1 diabetes mellitus is the main form of diabetes in young patients and the diagnosis is unlikely to be missed. In contrast, the type 1 disease remains uncommon in most non-Caucasian populations,[34] even among Chinese children or patients with a young onset of the disease (younger than 35 years).[20] Epidemiological studies performed in Hong Kong and mainland China have revealed that there is a wide variation of incidence rates of type 1 diabetes within the Chinese population; the highest rate was found in Hong Kong (overall annual incidence, 2 per 100 000).[35,36]

The incidence rates of both type 1 and type 2 diabetes mellitus in Chinese children are increasing. Currently, 10% to 15% of cases of childhood diabetes in Hong Kong are type 2 diabetes mellitus. Most of the young patients are adolescents with a strong family history of the disease (G Wong, written communication, 2000). The high prevalence of childhood obesity (>120% of the reference mean of body weight for a certain height) is 10% to 14% in Hong Kong children,[37,38] and the incidence of type 2 diabetes mellitus in adolescents and young adults is expected to increase further.

Autoimmune status in patients with young- or acute-onset diabetes

In 1990, 28% of adults who attended the Prince of Wales Hospital Diabetes Clinic were shown to have diabetes before the age of 35 years. Among these patients, only 10% had classical type 1 diabetes mellitus, of which 50% received insulin treatment.[20] In two separate cohorts of patients with either acute-[39] or early-onset diabetes,[40] antibodies to glutamic acid decarboxylase (GAD), a marker for autoimmunity, were found in only 10% to 30% of patients, depending on the acuteness of their modes of presentation and insulin secretory status. Patients with an earlier onset of disease also tended to have a higher detection rate of anti-GAD antibodies. These findings suggest that although autoimmune destruction of β cells remains a rare event in the local population, it may adopt a more important role in patients with early-onset disease. A similar form of slow-onset autoimmune diabetes has also been reported in Caucasians.[41]

In patients with type 1 presentation, there was also heterogeneity of pancreatic β-cell function; only 75% of patients were classified as being truly insulin deficient,[39] as determined by either basal (<0.2 nmol/L)[42] or post–glucagon-stimulated plasma C-peptide levels (<0.6 nmol/L).[43] Despite presenting with diabetic ketoacidosis, some patients no longer required insulin at a later stage. Although these patients did not have

antibodies against GAD, they had severe to moderate insulin deficiency, based on C-peptide level, which suggests that they may eventually require insulin treatment.[44,45] A similar form of diabetes, sometimes known as 'type $1^1/_2$' or 'flatbush diabetes' has also been described in African Americans.[46] The acute presentation in these patients might be related to the effects of severe hyperglycaemia on insulin resistance and pancreatic β-cell function. Our findings suggest that, as with childhood type 1 diabetes mellitus, both acute- and young-onset diabetes in the Hong Kong Chinese population are heterogeneous conditions in which autoimmunity remains an uncommon cause.

In our 1990 survey, we reported that younger patients had a higher prevalence of a family history of type 2 diabetes mellitus and obesity than patients whose disease started later in life.[20] Since 1995, all patients attending the Prince of Wales Hospital Diabetes Clinic undergo comprehensive assessment modified from the Europe DiabCare protocol.[47] In 1997, the database consisted of more than 3000 patients, 28% of whom were diagnosed before the age of 35 years and 16% of whom were younger than 35 years at the time of assessment. Among these young patients, 56% had a family history of diabetes, compared with 45% in the older-onset group.[48] In addition, 1% of these index patients had members of three successive generations affected by diabetes. In agreement with reports in other populations, patients who had a positive family history of diabetes were more likely to have a maternal history of the disease.[49,50] These findings emphasise the importance of genetic factors, especially in patients with a young onset of disease.

Genetic heterogeneity of patients with maturity-onset diabetes of youth

Our findings suggest that some young patients in Hong Kong might have maturity-onset diabetes of youth (MODY),[51] which is a monogenic form of diabetes that is characterised by autosomal dominant inheritance, early onset (usually before 25 years of age), and a primary defect in pancreatic β-cell function. This form of diabetes can result from mutations in at least five different genes—namely, those encoding glucokinase; the hepatocyte nuclear factors, HNF-1α, HNF-1β, and HNF-4α; and insulin promoter factor 1 (IPF-1).[52-56]

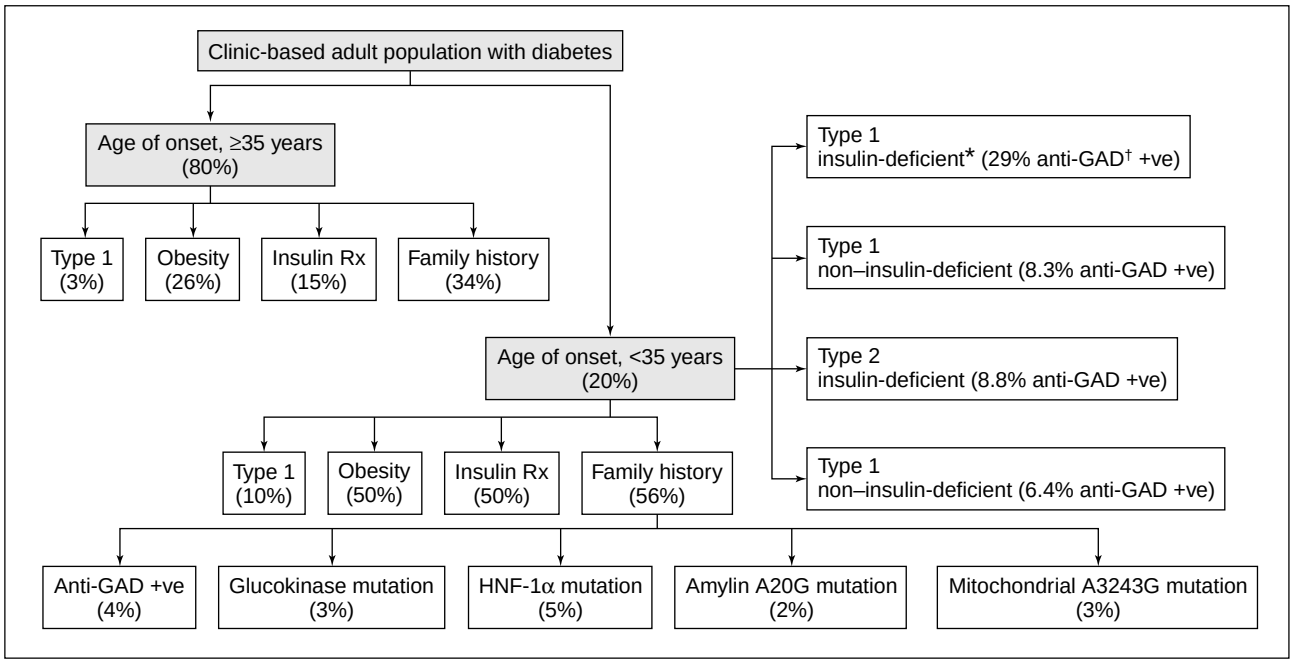
In a cohort of 92 unrelated Chinese patients with the familial form of early-onset type 2 diabetes, direct sequencing revealed mutations in the genes encoding glucokinase and the transcription factor HNF-1α genes in three (3%) and five (5%) patients, respectively. No mutations were found in the coding region of the HNF-4α gene. The three mutations found in the glucokinase gene were novel missense mutations that corresponded to amino acid changes I110T, A119D, and G385V. The mutations found in the HNF-1α gene also represented new mutations and included four missense mutations (G20R, R203H, S432C, and I618M) and one splice acceptor site mutation (IVS2nt-1G→A). Despite the cosegregation of mutations with diabetes in one of these families, two siblings presented with severe complications due to delayed diagnosis while the other two siblings (who had been diagnosed by screening) remained free of complications after 10 years of disease.[57-59]

Among a cohort of 150 young patients with a family history of diabetes, 3% had an A→G mutation in the mitochondrial DNA encoding $tRNA^{Leu(UUR)}$ at position 3243 and 2% had an A→G mutation in the amylin gene. In addition, antibodies to GAD were present in 4% of the young patients.[60] The presence of these gene mutations and autoimmune markers is associated with a reduced insulin secretion and is likely to have contributed to MODY either directly or indirectly by gene-gene or gene-environmental interactions (Fig 1).

The role of genetic factors in causing diabetes in young patients is further highlighted by the increased heritability of diabetes mellitus among their family members. All but two of the 55 families screened so far had at least one other affected family member. Among the 200 family members of patients with young onset of disease, approximately 40% had PG either in the diabetic or IGT range during a 75-g oral glucose tolerance test. The majority of cases, however, had not been diagnosed previously. This figure compares with a 1% to 2% prevalence of diabetes in a random population of similar age.[2] Furthermore, 90% of the parents of the index patients who underwent formal oral glucose tolerance testing were found to have diabetes mellitus. This figure compares with a prevalence of 20% to 25% in a random population aged 60 years or older.[61]

Obesity in young-onset diabetic patients

Obesity affects 50% of young diabetic patients in Hong Kong.[20] Compared with patients who had antibodies to GAD, those who did not were more obese, had a higher blood pressure, higher triglyceride levels, lower HDL-cholesterol levels, and increased albuminuria. These findings suggest that the metabolic syndrome



* Post–glucose-stimulated plasma C-peptide level of < 0.6 nmol/L
† GAD glutamic acid decarboxylase

Fig. 1 Heterogeneity of diabetes in the Hong Kong Chinese population

may have an earlier presentation in young patients in Hong Kong[40] and corroborate the rising prevalence of childhood obesity in the local population.[37,38]

Obesity is a multifactorial disease that involves genetic, environmental, hormonal, and cultural factors. There are complex hormonal interactions in the regulation of food intake, energy expenditure, and fat deposition.[15] In this respect, it has been hypothesised that a reduced level of growth hormone (partly due to physical inactivity), changes in sex hormones, and stress-related hypercortisolaemia may enhance the deposition of visceral adipocytes. The latter have increased lipolytic activities in response to catecholamines. Increased production of free fatty acids can in turn lead to insulin resistance and reduced glucose-stimulated insulin secretion (Fig 2).[4,62] Against this background, 51% of the variance in waist circumference in young Hong Kong Chinese patients can be explained by a reduced secretion of growth hormone and increased cortisol, and insulin levels.[63] We are currently exploring the interactions between these hormonal factors and other candidate genes for obesity in these young patients.

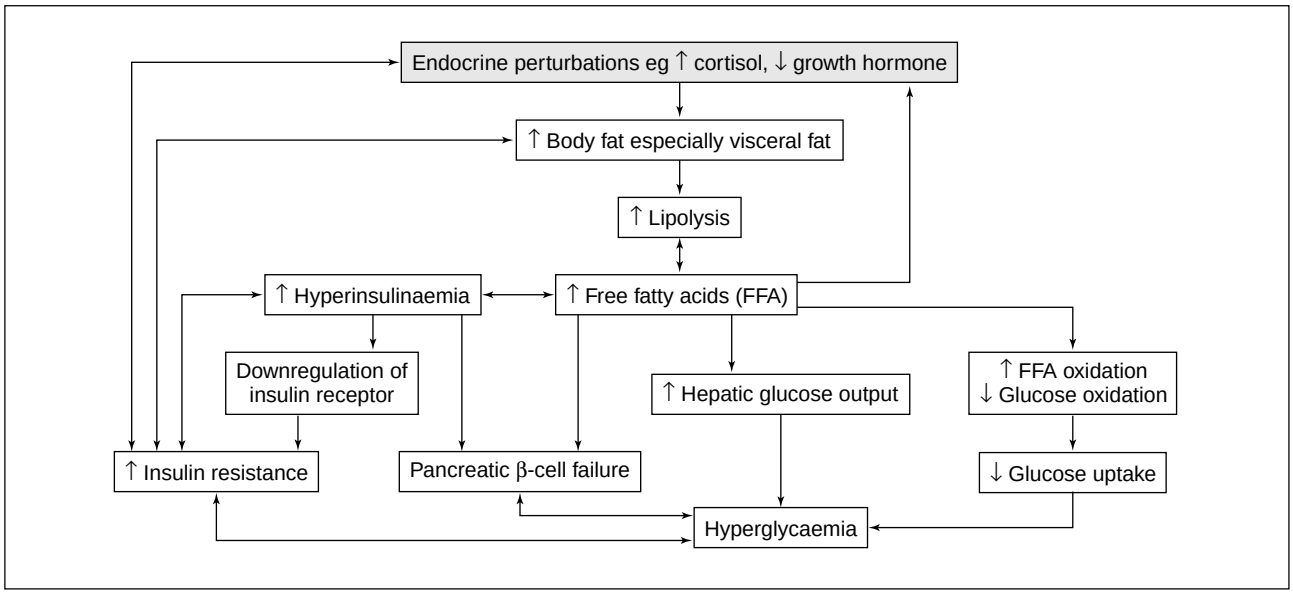


Fig. 2 Relationship between obesity and young-onset diabetes

The importance of quality care of diabetic patients

Diabetes mellitus—particularly type 2 diabetes mellitus, which accounts for 97% of all cases of diabetes—is a massive public health problem that has major socio-economic implications.[64] According to the WHO, rapid changes in lifestyles and socio-economic developments in Asia will cause major increases in the prevalence of diabetes in mainland China and India.[65] It is estimated that 18 million people in China have diabetes mellitus and that 50% of cases will remain undiagnosed. The figure is expected to increase to 34 million in 2025 and will occur mainly in the 40- to 50-year age-group.[65]

The effective management of diabetes depends on a holistic and multidisciplinary approach that emphasises prevention and patient education. Owing to the complexity and chronicity of diabetes, a structured disease management programme that uses periodic assessments, evidence-based medicine to achieve treatment targets, and patient empowerment is necessary to ensure the quality of diabetes care. To maximise the efficient use of finite health care resources, there is an increasing trend for patients with chronic diseases such as diabetes to be discharged to the community using a 'shared care' model.[66] Under this scheme, carefully selected patients who are discharged to community clinics are followed up according to a protocol designed by both specialists and community doctors. Since the implementation of the shared care model in the Prince of Wales Hospital in 1995, more than 1000 patients have returned to the community. The majority of patients who have returned for reassessment had stable metabolic and blood pressure control. More than 80% of these patients were satisfied with this mode of care and showed good knowledge about the disease and its management.[67]

Because only a small proportion of diabetic patients in Hong Kong has access to shared care, many cases of diabetes will remain undiagnosed, untreated, or suboptimally treated. There is a need for structural changes within the health care system and increased awareness of diabetes among both the general public and health care professionals. Increased training opportunities for dedicated health care providers in diabetes education and management are also urgently needed if quality and affordable diabetes care is to become easily and widely available.

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