

Metabolic and Immunologic Features of Chinese Patients With Atypical Diabetes Mellitus

KATHRYN C.B. TAN, MD
IAN R. MACKAY, MD
PAUL Z. ZIMMET, MD, PHD

BRIAN R. HAWKINS, PHD
KAREN S.L. LAM, MD

OBJECTIVE — To determine whether atypical diabetes mellitus (ADM) is present in the Chinese population in Hong Kong.

RESEARCH DESIGN AND METHODS — The records of Chinese patients who attended the Diabetes Clinic at Queen Mary Hospital were reviewed. We identified 11 patients who initially presented with acute diabetic ketoacidosis but subsequently displayed clinical features more typical of type 2 diabetes. Metabolic studies and HLA typing were performed to characterize this group of Chinese patients with ADM.

RESULTS — C-peptide response of the patients with ADM 1 h after a standard meal was intermediate between that of type 1 diabetic patients (matched for age and duration of diabetes) and that of nondiabetic control subjects (matched for age and BMI) (analysis of variance, $P = 0.02$). Insulin sensitivity measured by a short insulin tolerance test was not significantly different between patients with ADM and their matched nondiabetic control subjects. HLA typing showed that none of the patients with ADM had the DR3 allele and that the frequency of DR9 was not increased. Only one patient had significantly increased levels of antibodies to GAD and islet cell antigen 512.

CONCLUSIONS — ADM, which was first described in African-Americans, is seen also in Chinese subjects. These patients have significant residual C-peptide secretory capacity and should not be misdiagnosed and treated as patients with type 1 diabetes with life-long insulin therapy.

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Several studies in recent years have reported that, in a subset of African-American patients with diabetes, the clinical course of diabetes is rather atypical and that these patients cannot be classified as having either type 1 or type 2 diabetes. Winter et al. (1) first described atypical diabetes in African-American youths who presented with acute symptoms of insulin deficiency with or without diabetic ketoacidosis (DKA) and who subsequently dis-

played clinical and metabolic features more typical of type 2 diabetes. They used the phrase atypical diabetes mellitus (ADM) of youth to describe these patients. Rosenbloom et al. (2,3) suggested that ADM can be differentiated from type 2 diabetes by its consistent genetic pattern (autosomal dominant), its type of onset, its consistency and severity of insulinopenia, and its normal insulin sensitivity. Banerji et al. (4) also reported on 21 adult African-American

patients with DKA who had similar clinical features, except for older age at onset.

The exact etiology of ADM is not known. The absence of either HLA association or autoantibodies makes β -cell autoimmunity unlikely (4–6). House et al. (7) demonstrated that the first-phase insulin response was lost in ADM and that there was marked suppression of fasting C-peptide-to-glucose ratios at a level intermediate between type 1 and type 2 diabetes. The group of adult patients in the study by Banerji et al. (4) was found to be insulin resistant and had lower insulin secretion than nondiabetic control subjects. The strong family history in patients with ADM suggests that a genetic component may be present in this form of diabetes. Nakamura et al. (8,9) have identified a mutation in the glucokinase gene in a patient with ADM and a mitochondrial mutation in another family. A missense mutation in the hepatocyte nuclear factor-1 α gene, Gly 574 to Ser, has recently been shown to be a marker of ADM in African-American children (10).

Yamada and Nonaka (11) recently reported on four cases of young obese Japanese men with ADM. To our knowledge, ADM has not been described in Chinese subjects. The incidence of diabetes is rising in Asia, and the majority of Chinese diabetic patients have type 2 diabetes. The incidence of type 1 diabetes is much lower than that in Caucasian populations (12). We have identified 11 Chinese patients who have clinical profiles similar to those described by Winter et al. (1). Metabolic studies and HLA typing were performed to characterize this group of Chinese patients with ADM.

RESEARCH DESIGN AND METHODS

Subjects

The records of >3,000 Chinese patients who were followed up at the Diabetes Clinic at Queen Mary Hospital from 1994 to 1996 were reviewed. The majority of the patients who attend the clinic have type 2 diabetes, and ~5% of the patients have type 1 diabetes. The patients' ages ranged from ~15 to >80 years. All patients who were identified

From the Department of Medicine (K.C.B.T., K.S.L.L.), Queen Mary Hospital; the Department of Pathology (B.R.H.), University of Hong Kong, Hong Kong, China; the Department of Biochemistry and Molecular Biology (I.R.M.), Monash University, Clayton; and the International Diabetes Institute (P.Z.Z.), Melbourne, Victoria, Australia.

Address correspondence and reprint requests to Kathryn C.B. Tan, MD, Department of Medicine, Queen Mary Hospital, Pokfulam Rd., Hong Kong, China.

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Abbreviations: ADM, atypical diabetes mellitus; DKA, diabetic ketoacidosis; ICA512, islet cell antigen 512; K_{it} , glucose disappearance rate.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Clinical characteristics of Chinese patients with ADM

Patient no.	Sex	Family history of type 2 diabetes	Age at presentation (years)	BMI at presentation (kg/m ²)	Blood pH at presentation	Plasma glucose at presentation (mmol/l)	Duration of initial insulin treatment (months)	Duration of diabetes (years)	Current therapy	Duration during which insulin therapy was stopped
1	M	Yes	16	27.3	7.24	44.4	4	13	Insulin	8 years
2	M	No	30	28.3	7.04	36.7	70	13	Insulin	5 years
3	F	Yes	15	30.7	7.16	24.3	22	9	Diet	7 years
4	M	No	16	24.3	7.21	41.5	18	8	Insulin	2 years
5	M	No	28	28.1	7.10	31.2	5	6	Insulin	4 years
6	F	No	13	33.1	7.15	31.3	2	5	OHA	4 years
7	M	No	23	28.0	7.18	30.1	34	4	Diet	12 months
8	M	Yes	37	24.4	7.00	22.9	2	2	OHA	22 months
9	M	Yes	46	26.6	7.22	30.6	2	2	OHA	21 months
10	M	No	38	29.7	7.31	67.4	3	2	OHA	21 months
11	F	Yes	42	27.9	6.99	33.8	7	2	OHA	18 months

OHA, oral hypoglycemic agent.

with an atypical clinical course ($n = 11$) participated in the study. They all presented with acute DKA and were initially diagnosed with type 1 diabetes and were treated with insulin therapy. However, they were able to subsequently discontinue insulin completely for >1 year after diagnosis without the development of ketonuria or severe symptoms of hyperglycemia. The clinical characteristics of the patients are shown in Table 1. No identifiable precipitating factor for DKA could be found except in patient 1, who had sepsis. Each patient with ADM was compared with a type 1 diabetic patient matched for age, sex, and duration of diabetes (within 1 year) and with a nondiabetic control subject matched for age, sex, and BMI who was recruited from the hospital personnel (Table 2).

Metabolic studies and HLA typing

Insulin secretion was assessed in all three groups of subjects. C-peptide response after a standard test meal was measured, and levels of C-peptide were assayed by use of a radioimmunoassay (Incstar, Stillwater, MN). The test meal consisted of 50.7% carbohy-

drates, 35.8% fat, and 13.6% protein (13), and the coefficient of variation of the peak response after the standard meal was 16%. Insulin sensitivity was estimated by measuring the glucose disappearance rate (K_{it}) during a short insulin tolerance test (14) in patients with ADM and in the matched nondiabetic control subjects. Intravenous insulin was given at a dose of 0.1 U/kg. Measurement of glucose concentration was performed at $-5, 0, 1, 3, 5, 7, 9, 11, 13,$ and 15 min on arterialized venous samples obtained from an indwelling venous catheter, and the test was terminated by an injection of glucose to prevent hypoglycemia. K_{it} was calculated by linear regression to estimate the slope of decline in logarithmically transformed blood glucose concentration. The coefficient of variation of K_{it} was 9%. Long-acting insulin or oral hypoglycemic agents were withheld the evening before the tests. HLA typing was performed by either serological methods (15) or polymerase chain reaction amplification with sequence-specific primers (16). Screening for autoantibodies to GAD and

islet cell antigen 512 (ICA512) was performed with radioimmunoprecipitation assays using radiolabeled porcine brain GAD and ICA512 as antigens, respectively, as previously described (17).

RESULTS — The results of the C-peptide response to a standard meal are shown in Fig. 1. The peak C-peptide response of the patients with ADM was intermediate between that in patients with type 1 diabetes and that in nondiabetic control subjects. Insulin sensitivity was not significantly different between patients with ADM and their matched nondiabetic control subjects (3.0 ± 1.5 vs. $3.7 \pm 1.0\%$). There was no significant difference in the C-peptide response or in insulin sensitivity within the ADM group according to the duration of disease or type of treatment. Previous studies have shown that HLA alleles associated with type 1 diabetes are DR3 and DR9 in Chinese (15,16,18). None of the patients with ADM had the DR3 allele, whereas 4 of 11 type 1 diabetic patients had the DR3 allele. The DR9 allele was found in 3 of 11 patients with ADM vs. 5 of 11 patients with type 1 diabetes. No specific association between ADM and DR alleles could be identified. Only one patient with ADM (patient 11) and one patient with type 1 diabetes had elevated levels of GAD autoantibodies (75 and 61 reference units, respectively; cutoff <18 reference units). The results of autoantibodies to ICA512 showed similar results. Only patient 11 from the ADM group and the patient with type 1 diabetes who was GAD positive had elevated levels of autoantibodies to ICA512 (24 and 81 reference units, respec-

Table 2—Demographic data and glycemic control of patients with ADM, matched control subjects, and patients with type 1 diabetes

	ADM patients	Control subjects	Type 1 diabetic patients
Age (years)	34.8 \pm 10.6	34.3 \pm 8.3	32.5 \pm 8.9
BMI (kg/m ²)	28.6 \pm 2.3	29.3 \pm 2.0	22.6 \pm 2.3
Duration of diabetes (years)	4 (2–13)	—	4 (2–14)
HbA _{1c} (%)	7.1 \pm 2.3	5.8 \pm 0.5	8.9 \pm 2.2

Data are means \pm SD or medians (range).

tively; cutoff <12 reference units). At 2 years from diagnosis, the patient with ADM who was GAD and ICA512 positive has remained stable on only a small dose of sulfonylurea. She had the DR9 allele, and her C-peptide responses after a standard meal were 0.31 ng/ml at baseline, 0.87 ng/ml at 1 h, and 0.69 ng/ml at 2 h.

CONCLUSIONS — We have described a group of Chinese diabetic patients who initially presented with acute DKA but subsequently displayed clinical metabolic features more typical of type 2 diabetes. At presentation, all of the patients were either overweight or had BMI at the upper end of the normal range for our population; they certainly would not fit into the classification of patients with phasic type 1 diabetes, which is associated with malnutrition (19). In fact, their clinical profile was similar to that of African-Americans with ADM (1–4). ADM has also been described in Japanese individuals (11). Compared with the four reported cases of ADM in Japan, our Chinese patients with ADM had older age at onset and were less obese. A history of overconsumption of sugar-containing soft drinks was present in the four Japanese cases, which could be a contributory factor in the development of DKA at presentation. No similar history was obtained in any of our Chinese patients with ADM.

All our patients with ADM were initially treated with insulin therapy after presenting with DKA. However, unlike patients with type 1 diabetes, they were all able to discontinue insulin therapy for ≥ 1 year (Table 1). Of these patients, four subsequently resumed insulin therapy (after stopping insulin for a period ranging from 2 to 8 years) because of unsatisfactory glycemic control. Similarly, in the study by Banerji et al. (4) on adult African-Americans with ADM, 42% of their patients were on insulin therapy, 29% were administered oral hypoglycemic agents, and 29% were on dietary therapy. In a recent retrospective review that examined the occurrence of DKA in 226 adult patients, 27% of the patients had DKA as the initial manifestation of the disease, 47% of the patients admitted with DKA had type 1 diabetes, and 26% had type 2 diabetes (20). The study group comprised Caucasian, Hispanic, African-American, and Native American patients. It is interesting to note that in the group of newly diagnosed diabetic patients presenting with DKA, 9 of the 37 patients who had follow-up information

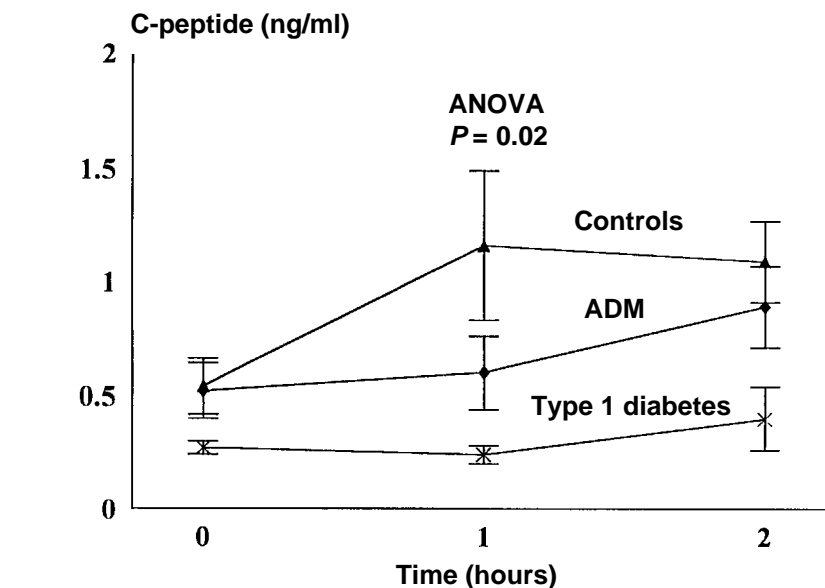


Figure 1—C-peptide response after a standard meal. Values are means \pm SD. ANOVA, analysis of variance.

available at least 12 months after the episode of DKA were able to discontinue insulin (4 were on sulfonylureas and 5 were on diet therapy). It is probable that some of these patients may have ADM.

It has been reported that in adult African-American patients with ADM, insulin secretion was impaired, and these patients were more insulin resistant compared with nondiabetic control subjects who were less overweight (4). Similar to the African-American patients with ADM, our patients exhibited a certain degree of insulin deficiency that was intermediate between that of type 1 diabetic patients and that of nondiabetic control subjects, which suggests that a defect in insulin secretion might play a significant role in the etiology of ADM. In contrast, we found that Chinese patients with ADM were not more insulin resistant when compared with equally overweight nondiabetic control subjects. Our findings differ from those of Banerji et al. (4), probably because we did not compare our ADM patients with normal-weight control subjects. The degree of insulin sensitivity, as reflected by the measurement K_{itt} , of our overweight nondiabetic control subjects is comparable to that reported in other studies: Bonora et al. (14) showed that obese nondiabetic subjects had a mean K_{itt} value of 4.1%, 2.7% in patients with type 2 diabetes and 5.7% in normal-weight nondiabetic subjects, which suggests that our patients with ADM would be more insulin resistant if

they were compared with normal-weight nondiabetic control subjects.

In African-American youths with ADM, no association between ADM and HLA type or autoantibodies has been found. However, Banerji et al. (4) found an increase in the frequency of HLA-DR3 and -DR4 in their group of adult African-American patients, but antibodies to GAD and islet cell cytoplasmic proteins were not detected. Previous studies in Chinese subjects have shown that the HLA specificities associated with type 1 diabetes are DR3 and DR9 (15,16,18). We did not find an association between DR3 and ADM in our patients, and the frequency of DR9 (27%) was not increased compared with that previously reported in control subjects in Hong Kong (29%) (16).

Autoantibodies to ICA512 and GAD are useful immune markers for type 1 diabetes in Caucasians (17,21). The presence of autoantibodies to GAD has also been shown to be useful in identifying patients with latent autoimmune diabetes (22). According to other studies, autoantibodies were not detected in African-American or Japanese patients with ADM (4–6,23). Autoantibody titers are generally less useful in classifying diabetic patients in Asian populations, because the prevalence of autoantibodies to islet cell antigens and GAD is much lower in Asian populations than in Caucasian populations (24–26). Of Caucasian patients with type 1 diabetes, >60% have at least one autoantibody (17,21). In

contrast, islet cell autoantibodies are present in only 20% of Chinese patients with type 1 diabetes in Singapore (24). The prevalence of autoantibodies to GAD is only 29% in patients with type 1 diabetes and 6% in those with type 2 diabetes in Hong Kong (26). In our study, we did not find any differences in the prevalence of autoantibodies between patients with type 1 diabetes and those with ADM. Measuring autoantibodies may not help distinguish the two because of the low prevalence of autoantibodies in Chinese patients with type 1 diabetes.

In conclusion, ADM, which was first described in African-Americans, is also seen in Chinese subjects. ADM appears to be a separate entity of type 1 diabetes. Although these patients present acutely with severe symptoms of insulin deficiency, such as DKA, and require insulin therapy initially, they have significant residual C-peptide secretory capacity, and insulin therapy can be subsequently withdrawn for long periods. Unlike patients with type 1 diabetes, these patients tend to be overweight or even obese at presentation. Physicians who care for Chinese patients should be aware of ADM so that these patients are not misdiagnosed and treated as patients with type 1 diabetes with life-long insulin therapy.

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