

Severe Diabetes in Remission: A Singapore's Perspective

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Abstract

Introduction: Diabetic ketoacidosis is generally thought to be the classical presentation of individuals with Type 1 diabetes. Clinicians are beginning to see individuals with atypical diabetes presenting with severe hyperglycaemia associated with or without ketosis and after the initial period of intensive insulin therapy, becoming non-insulin dependent and remaining in remission for years. So far, these patients have only been identified amongst African Americans and have only recently been reported amongst the Japanese and the Chinese in Hong Kong. We therefore set out to identify the existence of such patients in our population. **Materials and Methods:** We have a database of patients admitted for diabetic ketoacidosis. From this, we recruited patients who fulfilled the criteria for atypical diabetes and proceeded to perform a retrospective analysis together with a prospective analysis of their outcome. **Results:** We identified 10 individuals with atypical diabetes with characteristics similar to those previously described. Our data showed that these patients differed from classical individuals with Type 1 diabetes in the following ways—older age of onset, relatively higher BMI, marked elevation in HBA1c suggesting a significant period and degree of hyperglycaemia and prolonged remission after reversal of hyperglycaemia. **Conclusions:** Atypical Type 2 diabetes exists in our population. Clinicians looking after individuals with diabetes should be made aware of this as there are important implications in the subsequent management of such patients.

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Introduction

Diabetic ketoacidosis is generally believed to be the result of an acute and severe degree of insulin insufficiency, classically occurring at the presentation of a newly diagnosed individual with Type 1 diabetes. Patients who recover from this acute condition almost invariably need insulin injections for the rest of their lives. It is also known that 15% to 20% of individuals with new onset Type 1 diabetes treated with intensive insulin therapy at the start of presentation will go into a complete or partial remission of hyperglycaemia that lasts for several months.¹ This so-called “honeymoon” period has, however, been known to be transient, reflecting the progressive autoimmune destruction of pancreatic β -cells in these individuals with Type 1 diabetes.

There is, however, a group of individuals with Type 2 diabetes that have aroused much attention recently. These are mostly individuals with adult-onset diabetes presenting with severe hyperglycaemia associated with or without ketosis and after the initial period of intensive insulin

therapy, become non-insulin dependent and remain in remission for years. This group of individuals with atypical diabetes was first described in African Americans.²⁻⁶ Recently, it was also reported among the Japanese⁷⁻⁹ and the Chinese in Hong Kong.¹⁰ We have identified such patients in our clinics and done a retrospective analysis, together with a prospective follow-up on their outcome. We now present our data with a review of current literature on severe diabetes in remission.

Materials and Methods

The Singapore General Hospital is a tertiary hospital with a 1,600-bedded capacity. We have a database of patients admitted for diabetic ketoacidosis from 1990 to 1999. From this, the records of 200 patients were reviewed and patients were recruited into the study if they fulfilled the following criteria:

1. Diabetes developed acutely as diabetic ketoacidosis (DKA) or ketosis without precipitating events;
2. Negativity in anti-GAD (glutamic acid decarboxylase)

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antibodies;

3. Establishment of non-insulin dependency: a period of at least 1 week off insulin without the development of ketonuria or severe symptoms of hyperglycaemia.

The above criteria were used as they summarised the salient features of atypical diabetes described in current literature. There is yet a standard definition used for this form of diabetes.

We identified 10 patients that fulfilled the above and proceeded to perform a retrospective analysis together with prospective follow-up of their outcome. The data were analysed for ethnic distribution, characteristics of clinical presentation, biochemical indices, age, sex, age of onset of diabetes, body mass index (BMI), family history of diabetes, C-peptide levels and overall diabetes management.

Results

The clinical characteristics of the 10 patients at their first presentation of diabetes are shown in the Table I.

Eighty per cent (8) of the patients were Chinese; the other 2 were a Malay and an Indian. They were all male patients. A family history of diabetes mellitus was elicited in 4 patients (40%). All except 1 had been tested for anti-GAD antibodies, and all those tested were negative for the antibodies. All the patients had presented with severe symptoms of diabetes mellitus and had required hospitalisation for intravenous rehydration and insulin therapy. Symptoms of polydipsia, polyuria and weight loss were relatively uniform complaints. All of the patients presented with severe hyperglycaemia with 3 of the patients in ketoacidosis while the rest with 2 to 4+ presence of urine ketones. There was no identifiable precipitating cause of sepsis in any of the cases, although 2 of the patients were noted to have mild balanitis and another was recovering

from an upper respiratory tract infection (URTI). Only 3 patients gave a history of a change in a diet that consisted mainly of an increase in beverages with high sugar-content prior to presentation.

Table II gives pertinent information relative to the development and duration of the normoglycaemia remission in the 10 patients.

Upon their subsequent reviews, all had consistently maintained excellent control of their diabetes. Most of the patients had their insulin requirements gradually decreased as they were experiencing and had documented hypoglycaemic episodes on self home glucose monitoring. In fact, 3 of the patients took themselves off their insulin even before seeing their doctors because of repeated hypoglycaemia. Most of the patients were placed on dietary control alone upon withdrawal of insulin therapy. Patient 4 was the only one showing signs of relapse of hyperglycaemia after a recent bout of URTI symptoms and was placed on metformin.

Discussion

The main finding of our paper is that there are individuals with atypical Type 2 diabetes amongst our diabetic population. Our data showed that these patients deferred from classical individuals with Type 1 diabetes in the following ways—older age of onset, relatively higher BMI, marked elevation in HBA1c suggesting a significant period and degree of hyperglycaemia and prolonged remission after reversal of hyperglycaemia. Since the 1940s, there have been sporadic case reports on patients with amelioration of severe diabetes to the extent of complete omission of insulin for months or years.¹¹⁻¹³ In 1957, Harwood¹³ described one such case in a 24-year-old youth and in this review suggested that “restoration of function of the islands of Langerhans in early diabetes is always a

TABLE I: CLINICAL CHARACTERISTICS OF THE 10 PATIENTS STUDIED

Patient	FH	Ethnic group	At presentation					
			Age (y)	BMI (kg/m ²)	Duration of symptoms (days)	pH	HBA1c (%)	Plasma glucose (mmol/L)
1	+	C	40	28.7	7	7.36	12.6	52.8
2	-	M	39	27.7	14	7.12	13.4	28.1
3	-	C	38	23.8	8	—	14.5	17.7
4	-	C	34	24.6	14	—	15.0	42.2
5	-	C	48	23.5	10	7.41	17.0	35.9
6	+	C	38	24.4	7	7.19	13.4	30.6
7	+	C	44	22.8	3	7.15	14.3	27.7
8	-	C	43	28.7	28	7.34	—	31.2
9	+	I	47	18.5	30	7.41	13.2	27.4
10	-	C	27	20.2	14	7.41	16.6	20.8
Mean ± standard deviation (SD)			40 ± 6	24.3 ± 3.4	12.9 ± 8.7	7.30 ± 0.1	14.4 ± 1.5	31.4 ± 10.2

FH: family history; C: Chinese; I: Indian; M: Malay

possibility, and that attempts to achieve this by the strictest control with diet and insulin should make such remissions a more common occurrence”.

Since then, investigators have gone on to review and study series of patients with such description of diabetes in detail, characterising them in terms of metabolic, genetic and immunological investigations.³⁻¹⁰ We searched the literature and found 6 series on such patients. Table III summarises some of the features of these studies. Winter et al⁴ coined the term “atypical diabetes” to describe this group of patients, similarly used by the authors from Hong Kong; while Banerji et al⁵ used “flatbush diabetes” in one of her many articles on such patients, the Japanese chose to call theirs “ketosis-onset” Type 2 diabetes.⁷⁻⁹ The above showed the bias in current literature of this form of diabetes towards a predominant occurrence amongst blacks. It was not until the past couple of years that such patients were being described in the Japanese and the Chinese in Hong Kong. Our series further illustrated the presence of this form of diabetes amongst other ethnic groups such as the Malays and Indians.

One of the reasons why this form of diabetes has aroused much attention is that their initial presentation of severe hyperglycaemia and ketosis closely mimicked that of individuals with Type 1 diabetes. These patients usually

had no identifiable precipitating cause for the acute deterioration except for an obvious state of insulin insufficiency.

Hence, investigators had attempted to differentiate these patients by characterising them in terms of their immunological status such as the presence of anti-GAD antibodies, islet-cell antibodies and thyroid microsomal antibodies, fasting and stimulated C-peptide assays and HLA typing. The consensus drawn so far was that these individuals with atypical diabetes generally lacked typical markers for Type 1 diabetes and possessed phenotypic features of individuals with Type 2 diabetes.

This holds true in our cohort as all tested were negative for anti-GAD antibodies. Unfortunately, since our study was done on a retrospective analysis, the information on C-peptide status of these patients being retrieved was from whatever records were available at the time of study. We realise the limitations of such information but with the preliminary results of a mean fasting C-peptide level and stimulated levels way above those expected of Type 1 diabetes,^{14,15} there was definite evidence to suggest the presence of relatively adequate pancreatic β -cell reserves.

Utilising BMI as a measure of obesity with the mean $\pm$ SD of BMI of an average Chinese male estimated to be $22.3 \pm 3.8 \text{ kg/m}^2$,¹⁶ majority of our patients were above the

TABLE II: CHARACTERISTICS OF THE 10 PATIENTS DURING NORMOGLYCAEMIC REMISSION

Patient	Period on insulin (mo)	Period off insulin (y)	C-peptide (ug/L)	BMI (kg/m ²)	Current HBA1c (%)	Current therapy
1	16	1.0	6.2 (s)	28.1	5.3	Diet
2	12	0.6	21.5 (s)	29.1	6.5	Diet
3	1	8.8	1.8 (f)	21.1	6.6	Diet
4	11	6.3	4.4 (f)	25.8	7.8	Metformin
5	1	1.3	1.8 (s)	25.5	5.6	Diet
6	12	1.4	4.4 (s)	26.3	7.1	Repaglinide
7	18	0.4	4.3 (s)	23.0	5.4	Diet
8	16	8.1	3.1 (f)	28.7	5.2	Diet
9	1	0.7	2.7 (s)	21.1	6.2	Diet
10	4	8.6	1.6 (f)	20.3	7.4	Diet
Mean $\pm$ SD	9.6 ± 6	3.7 ± 3.7 (median: 1.4)	2.7 ± 1.3 (f) 6.8 ± 7.4 (s)	24.9 ± 3.3	6.3 ± 0.9	

s: stimulation with IV glucagon; f: fasting

TABLE III: CHARACTERISTICS OF PATIENTS STUDIED IN THE 6 STUDIES

Authors	Year published	No. of atypical patients in study cohort	Mean age of atypical patients (y)	Race of atypical patients	No. of atypical patients with family history
Winter et al ⁴	1987	12/129	13 ± 4	African American	12/12
Banerji et al ³	1994	7/21	45 ± 9	African American	14/21
Umpierrez et al ⁶	1995	35/67	40 ± 2	African American	29/35
Tanaka et al ⁷	1999	24/146	44 ± 2	Japanese	12/24
Katakura et al ⁸	1999	9/9	26 ± 7	Japanese	5/9
Tan et al ¹⁰	2000	11/11	28 ± 3	Chinese	5/11

average BMI. Most of the patients described in previous studies were also normal to mildly overweight. Interestingly, obesity did not feature markedly amongst all of the studies and most authors felt that the impairment of insulin at presentation, rather than insulin resistance contributed more significantly to the pathogenesis of this form of diabetes.^{6,17} Studies done earlier had also supported these findings, with less sophisticated investigation tools.^{18,19} The group from Hong Kong also felt that the difference in insulin sensitivity did not matter much in their patients. We were, however, unable to substantiate our deductions in this retrospective evaluation.

Our cohort was male predominant with a positive family history of diabetes mellitus in less than half of them. They were middle-aged, mostly presenting during the fourth to fifth decades of their lives. This is in concordance with the findings of most of the earlier studies, although some of the studies did stress upon the importance of a positive family history in their studies.

Most of our patients were symptomatic for almost 2 weeks prior to their presentation. Somewhat surprising was the severity of the hyperglycaemia with which the majority of these patients presented. As can be seen in Table I, 8 of 10 patients presented with plasma glucose above 27 mmol/L. Their average HBA1c at presentation was more than 14%, suggesting a significant long period of exposure to high levels of glucose prior to their presentation.

The Japanese group had implied in their studies that the excessive intake of soda drinks might have precipitated the acute presentation.⁸ Three of our patients had also given the history of recent excessive consumption of sweetened beverages prior to their admission. No such history was obtained from the Chinese in Hong Kong. This observation is, however, provocative as most of these patients had no other identifiable precipitating cause leading to the episode of severe hyperglycaemia.

We found that the management strategy common to the successful remission of these individuals with atypical Type 2 diabetes was the intensive management they had received at their initial presentation. These patients were by default being treated as Type 1 in view of their acute presentation. Many previous studies have shown that initial intensive management of diabetes to normoglycaemia with diet, oral hypoglycaemic agents or insulin has led to many individuals with diabetes going into remission.²⁰⁻²³ Most, however, eventually relapsed due to inability to maintain dietary restrictions, muscular activity or ideal body weight or having concurrent infections. Several therapeutic strategies have been proposed to maintain diabetes in remission. Both Umpierrez et al²¹ and Banerji et al^{22,23} have in separate studies shown a significant difference in the number of relapses if these patients were

placed on low dosages of sulphonylurea during their remission. All these measures play their role in preserving pancreatic β -cell reserves by preventing hyperglycaemia from recurring.²⁴⁻²⁸

Similarly, we propose that one of the reasons why diabetes remit and remain in remission in these patients might be related to their vigilance with the monitoring of blood glucose at home, preventing the onset of even mild hyperglycaemia. Home monitoring of blood glucose has not yet been advocated for the management of Type 2 diabetes. Chronic hyperglycaemia, even at mildly elevated levels, has been shown to desensitise the pancreas through uncertain mechanisms.²⁴⁻²⁹ This effect maybe reversible in the short run. With toxic levels over longer periods of exposure, however, irreparable damage would inevitably arise.^{27,28}

Conclusions

In conclusion, atypical Type 2 diabetes exist in our population. These are patients who first present with severe diabetes associated with ketosis and eventually go into remission if initially treated intensively and attained normoglycaemia.

Clinicians treating individuals with diabetes should therefore consider intensive treatment for newly diagnosed young to middle-aged patients to achieve normoglycaemia soon after diagnosis. Clinicians should also be aware that diabetic ketoacidosis is not unique to Type 1 patients. Patients therefore should not be wrongly classified and continued on insulin especially if they were experiencing frequent hypoglycaemic episodes. The value of C-peptide level measurements in the classification and further management of newly diagnosed patients is clearly highlighted by the presentation of such atypical Type 2 diabetes.

REFERENCES

1. Agner T, Damm P, Binder C. Remission in IDDM: Prospective study of basal c-peptide and insulin dose in 268 consecutive patients. *Diabetes Care* 1987; 10:164-9.
2. Pinhas-Hamiel O, Dolan L M, Zeitler P S. Diabetic ketoacidosis among obese African-American adolescents with NIDDM. *Diabetes Care* 1997; 20:484-6.
3. Banerji M A, Lebovitz H E. Remission in non-insulin dependent diabetes mellitus: Clinical characteristics of remission and relapse in black patients. *Medicine* 1990; 69:176-85.
4. Winter W, Maclaren N K, Riley W J M, Clarke D W, Kappy M S, Spillar R. Maturity onset diabetes of youth in black Americans. *N Engl J Med* 1987; 316:285-91.
5. Banerji M A, Chaiken R L, Huey H, Tuomi T, Norin A J, Mackay I R, et al. GAD antibody negative NIDDM in adults black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4: Flatbush Diabetes. *Diabetes* 1994; 43:741-5.
6. Umpierrez G E, Casals M M C, Gebhart S S P, Mixon P S, Clark W S,

- Phillips L S. Diabetic ketoacidosis in obese African-Americans. *Diabetes* 1995; 44:790-5.
7. Tanaka K, Moriya T, Kanamori A, Yajima Y. Analysis and long term follow up of ketosis-onset Japanese NIDDM patients. *Diabetes Res Clin Pract* 1999; 44:137-46.
 8. Katakura M, Aizawa T, Naka M, Funase Y, Komatsu M, Yamauchi K, et al. Long-term prognosis of islet cell antibody-negative ketosis-onset diabetes with subsequent non-insulin dependency [letter]. *Diabetes Care* 1999; 22:1584-6.
 9. Aizawa T, Funase Y, Katakura M, Asanuma N, Yamauchi K, Yoshizawa K, et al. Ketosis-onset diabetes in young adults with subsequent non-insulin-dependency, a link between IDDM and NIDDM [letter]? *Diabet Med* 1997; 14:989-94.
 10. Tan K C B, Mackay I R, Hawkins B R, Lam K S L, Zimmet P Z. Metabolic and immunologic features of Chinese patients with atypical diabetes mellitus. *Diabetes Care* 2000; 23:335-8.
 11. Carlstrom S, Ingemansson C A. Juvenile diabetes with long-standing remission. *Diabetologia* 1967; 3:465-7.
 12. Peck F B, Kirtley W R. Complete remission of severe diabetes. *Diabetes* 1958; 7:93-7.
 13. Harwood R. Severe diabetes with remission. *N Engl J Med* 1995; 257:257-61.
 14. The Diabetes Control and Complications Trial (DCCT). Design and methodological considerations for the feasibility phase. The DCCT Research Group. *Diabetes* 1986; 35:530-45.
 15. The Diabetes Control and Complications Trial (DCCT). Effects of age, duration and treatment of insulin-dependent diabetes mellitus on residual beta-cell function: observation during eligibility testing for DCCT. *J Clin Endocrinol Metab* 1987; 65:30-6.
 16. Tan C E, Tan B Y, Emmanuel S C, Jacod E. Prevalence of diabetes and ethnic differences in cardiovascular risk factors. *Diabetes Care* 1999; 22:241-7.
 17. Banerji M A, Lebovitz H E. Insulin-sensitive and insulin-resistance variants in NIDDM. *Diabetes* 1989; 38:784-92.
 18. Park B N, Soelder J S, Gleason R E. Diabetes in remission: Insulin secretory dynamics. *Diabetes* 1974; 23:616-23.
 19. Genuth S M. Clinical remission in diabetes mellitus: studies of insulin secretion. *Diabetes* 1970; 19:116-21.
 20. Leahy J L. Natural history of β -cell dysfunction in NIDDM. *Diabetes Care* 1990; 13:992-1010.
 21. Umpierrez G, Clark W S, Steen M T. Sulfonylurea treatment prevents recurrence of hyperglycemia in obese African-American patients with a history of hyperglycemic crisis. *Diabetes Care* 1997; 20:479-83.
 22. Banerji M A, Chaiken R L, Lebovitz H E. Prolongation of near-normoglycemia remission in black NIDDM subjects with chronic low-dose sulfonylurea treatment. *Diabetes* 1995; 44:466-70.
 23. Banerji M A, Chaiken R L, Lebovitz H E. Long term normoglycemic remission in blacks newly diagnosed NIDDM subjects. *Diabetes* 1996; 45:337-41.
 24. Gjessing H J, Reinhold B, Pedersen O. The effect of chronic hyperglycemia on the islet β -cell responsiveness in newly diagnosed Type 2 diabetes. *Diabet Med* 1992; 9:601-4.
 25. Unger R H, Grundy S. Hyperglycemia as an inducer as well as a consequence of impaired islet cell function and insulin resistance: implications for the management of diabetes. *Diabetologia* 1985; 28:119-21.
 26. Leahy J L, Cooper H E, Deal D A, Weir G C. Chronic hyperglycemia is associated with impaired glucose influence on insulin secretion. *J Clin Invest* 1986; 77:908-15.
 27. Jarvinen Y. Glucose toxicity. *Endocr Rev* 1992; 13:415-31.
 28. Robertson R P, Olson L K, Zhang H J. Differentiating glucose toxicity from glucose desensitization: a new message from the insulin gene. *Diabetes* 1994; 43:1085-9.
 29. Shah S C, Malone J I, Simpson N E. A randomised trial of intensive therapy in newly diagnosed insulin-dependent diabetes mellitus. *N Engl J Med* 1989; 320:550-4.