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Ketoacidosis at the diagnosis of type 1 (insulin dependent) diabetes mellitus is related to poor residual β cell function

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Abstract

The determinants of the degree of metabolic decompensation at the diagnosis of type 1 (insulin dependent) diabetes mellitus (IDDM) and the possible role of diabetic ketoacidosis in the preservation and recovery of residual β cell function were examined in 745 Finnish children and adolescents. Children younger than 2 years or older than 10 years of age were found to be more susceptible to diabetic ketoacidosis than children between 2 and 10 years of age (<2 years: 53.3%; 2-10 years: 16.9%; >10 years: 33.3%). Children from families with poor parental educational level had ketoacidosis more often than those from families with high parental educational level (24.4% *v* 16.9%). A serum C peptide concentration of 0.10 nmol/l or more was associated with a favourable metabolic situation. Low serum C peptide concentrations, high requirement of exogenous insulin, low prevalence of remission, and high glycated haemoglobin concentrations were observed during the follow up in the group of probands having diabetic ketoacidosis at the diagnosis of IDDM. Thus diabetic ketoacidosis at diagnosis is related to a decreased capacity for β cell recovery after the clinical manifestation of IDDM in children.

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A chronic autoimmune destruction of the pancreatic β cells results in decreasing endogenous insulin secretion and the clinical manifestation of type 1 (insulin dependent) diabetes (IDDM). The clinical onset of the disease is often acute in children and adolescents, and diabetic ketoacidosis is present in 20-74% of the patients.[1-7] Young age and female sex have been associated with an increased frequency of diabetic ketoacidosis.[3] However, there are only limited data concerning the determinants of the degree of metabolic decompensation at the diagnosis of childhood IDDM.

It is well known that the capacity of residual β cells to secrete insulin is decreased at the time of diagnosis of IDDM, often improving in a few weeks after the initiation of exogenous insulin treatment.[8-11] The extent of improvement in insulin secretory capacity has been observed to be associated with age at diagnosis,[3] degree of metabolic decompensation,[9] mild clinical symptoms at diagnosis,[2 9 10] and strict initial blood glucose control.[12 13] Diabetic ketoacidosis is a serious consequence of insufficient insulin secretion.[14] In addition to possible acute complications, it may also influence the later outcome of diabetes.

To study the effect of age, sex, and socioeconomic factors on the clinical condition of the patient at the diagnosis of IDDM, and to find out whether metabolic decompensation at diagnosis is related to subsequent endogenous insulin secretion and impaired metabolic control, 745 Finnish children and adolescents, aged 0.8-14.9 years, were evaluated at the time of diagnosis of IDDM and then observed for two years.

Methods

PATIENTS

As a part of the Finnish nationwide 'Childhood diabetes in Finland' study,[15] 801 probands younger than 15 years, diagnosed as having IDDM during the recruitment period from 1 September 1986 to 30 April 1989, were offered the possibility of participating in the study. Of these 745 had analyses of blood pH, serum C peptide concentrations, and blood glycated haemoglobin levels at the time of hospital admission. At the time of admission, a clinical examination including assessment of consciousness and dehydration was performed, and the parents were asked to fill out a questionnaire concerning the socioeconomic status of the family. The subjects were then followed up in their own outpatient clinics (n = 31) for two years. At six month intervals, the recommended amount of insulin was recorded, blood specimens were taken for glycated haemoglobin and serum C peptide concentrations, and a clinical examination including height and weight recording was performed.

The mean age of the probands was 8.4 years (range 0.8 to 14.9 years). The majority of them were males (n = 412; 55.3%). The subjects were divided into two groups: those with and without diabetic ketoacidosis at diagnosis. In the longitudinal study the groups were compared at the time of diagnosis and at six, 12, 18, and 24 months after diagnosis.

LABORATORY MEASUREMENTS

Capillary or venous blood pH was measured at the time of hospital admission. Diabetic

ketoacidosis was defined as a blood pH of less than 7.30.

Serum C peptide concentrations were analysed in one central laboratory with a radioimmunoassay, as described earlier,[16] by using antiserum K6 (Novo Research Institute, Bagsvaerd, Denmark). The detection limit of the assay was 0.03 nmol/l.

Standard methods for blood glycated haemoglobin (HbA_1) and HbA_{1c} analysis were used in the various hospitals (n = 31) participating in the study. To make the results comparable, they were expressed as a SD score above the mean for non-diabetic subjects.

ASSESSMENT OF CONSCIOUSNESS AND DEHYDRATION

Degree of consciousness and dehydration was assessed by the clinician examining the patient at the time of hospital admission. Consciousness was estimated to be either normal or impaired. Dehydration was rated to be absent, mild (<8% in children younger than 12 years of age, <7% in older children), or severe (8% or more, 7% or more, respectively).

DAILY INSULIN DOSE AND REMISSION

The recommended amount of insulin and the weight of the proband were recorded at each six monthly visit, and the daily insulin dose (IU/kg/day) was calculated. Partial remission was defined as an insulin dose less than 0.5 IU/kg/day in combination with a glycated haemoglobin (HbA_1 or HbA_{1c}) not exceeding the mean laboratory specific reference level by 4 SD score or more.

SOCIOECONOMIC FACTORS

Families were divided into groups according to parental education, taxable income, and place of residence. Families in which at least one of the parents had an academic degree were classified as ones with high parental education, whereas other families were classified as ones with low parental education. Low income was considered as a reported annual income of less than FIM 90 000 ($US 18 000), medium income that of FIM 90-150 000 ($US 18-30 000), and high income that of more than FIM 150 000 ($US 30 000). Urban families had their homes in a city, town or suburb, while rural families lived in a village or outside a population centre.

STATISTICAL ANALYSIS

Statistical analyses were performed by using contingency table analysis with χ^2 statistics, the unpaired *t* test, Mann-Whitney U test, multiple linear regression analysis, correlation analysis, and one way analysis of variances (ANOVA) with covariance analysis or loglinear analysis.

Results

The clinical data of the study population at hospital admission are summarised in table 1, and the laboratory data in table 2. Sixty nine (42.9%) of the 161 subjects with a blood pH value of less than 7.30 were estimated to have impaired consciousness, while 21 (23.3%) of the probands with impaired consciousness had a blood pH value of 7.30 or more. Twenty one (21.4%) of the children who were rated to be severely dehydrated had a blood pH value of 7.30 or more. Sixteen (2.1%) children had a blood pH value of less than 7.00. One of them (6.2%) was considered to have normal consciousness, and four (25.0%) were considered to be only mildly dehydrated.

Table 1 Data on ketoacidosis, degree of consciousness, and dehydration in study population at the diagnosis of IDDM

		No (%)
pH	7.30 or more	584 (78.4)
	7.20-7.29	87 (11.7)
	7.10-7.19	40 (5.4)
	7.00-7.09	18 (2.4)
	< 7.00	16 (2.1)
Consciousness	Normal	655 (87.9)
	Impaired	90 (12.1)
Dehydration	No	274 (36.8)
	Mild	354 (47.5)
	Severe	98 (13.1)
	Unknown	19 (2.6)

Serum C peptide concentrations were analysed in 697 probands (93.6%). Fourteen of them (2.0%) had an undetectable serum C peptide concentration at diagnosis, and 141 (20.2%) had a concentration of less than 0.10 nmol/l. They were considered 'low' secretors. The clinical and laboratory data of 'low' and 'high' secretors are presented in table 3.

The mean age of the study population was 8.4 years (range 0.8 to 14.9 years). Thirty of the subjects (4.0%) were younger than 2.0 years of age (group A), 432 of them (58.0%) were 2.0-10.0 years old (group B), and 283 (38.0%) were older than 10.0 years (group C). More than half (58.4%) of the subjects in the oldest age group were pubertal at the diagnosis of IDDM. Ketoacidosis was more common in age group A (n = 16; 53.3%, p<0.001) and in age group C (n = 72; 25.4%, p<0.01) than in age group B (n = 73; 16.9%). Impaired consciousness was found more often in age group A (n = 10; 33.3%) than in age group B

Table 2 Laboratory data of study population at time of hospital admission

	No	*Mean*	*Median*	*SD*	*Range*
pH	745	7.34	7.37	0.11	6.83-7.58
B glucose (mmol/l)	739	21.6	20.2	9.6	3.2-107.0
C peptide (nmol/l)	697	0.19	0.15	0.14	0-1.29
GHb (SD score)	565	12.9	12.2	6.0	0.2-38.8

GHb = glycated haemoglobin.

Table 3 Clinical and laboratory data in diabetic children with serum C peptide concentrations < 0.10 nmol/l ('low' secretors) and in those with ≥ 0.10 nmol/l ('high' secretors). SD values are given in parentheses

	'Low' secretors (n=141)	*'High' secretors (n=556)*	*p*
Age (years)	6.7 (3.8)	8.9 (3.6)	< 0.001
B pH	7.29 (0.13)	7.36 (0.10)	< 0.001
B glucose (mmol/l)	26.5 (11.1)	20.4 (8.6)	< 0.001
GHb (SD score)	13.6 (5.1)	12.8 (6.1)	NS
Impaired consciousness	23.4%	9.2%	< 0.001
Dehydration	79.4%	59.5%	< 0.001

GHb = glycated haemoglobin.

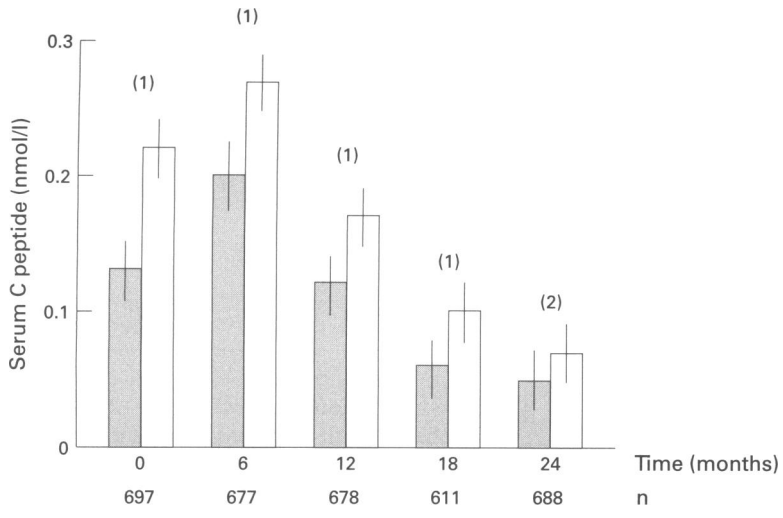

Figure 1 Mean (SEM) serum C peptide concentrations in the diabetic ketoacidosis group (shadowed columns) and non-diabetic ketoacidosis group (empty columns) at diagnosis and during the follow up period. (1) p<0.0001 (2) p = 0.004 (multiple linear regression analysis).

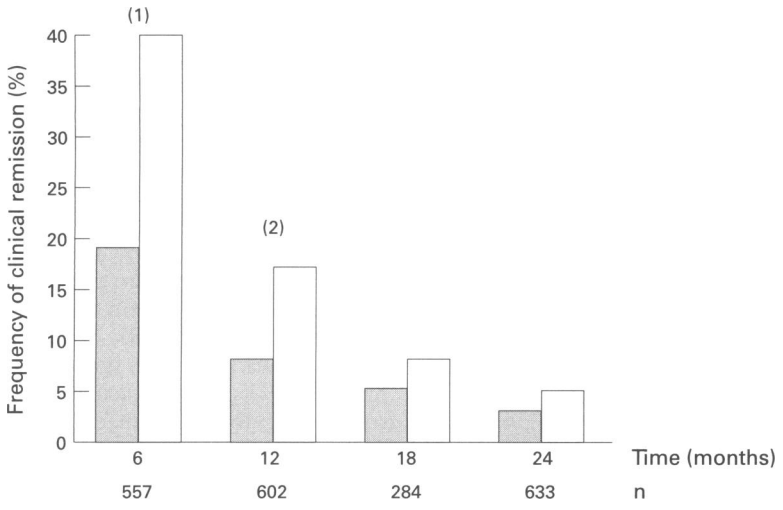

Figure 2 Frequency of clinical remission in the diabetic ketoacidosis group (shadowed columns) and non-diabetic ketoacidosis group (empty columns) during the follow up period. (1) p<0.0001, (2) p = 0.009, χ^2 test.

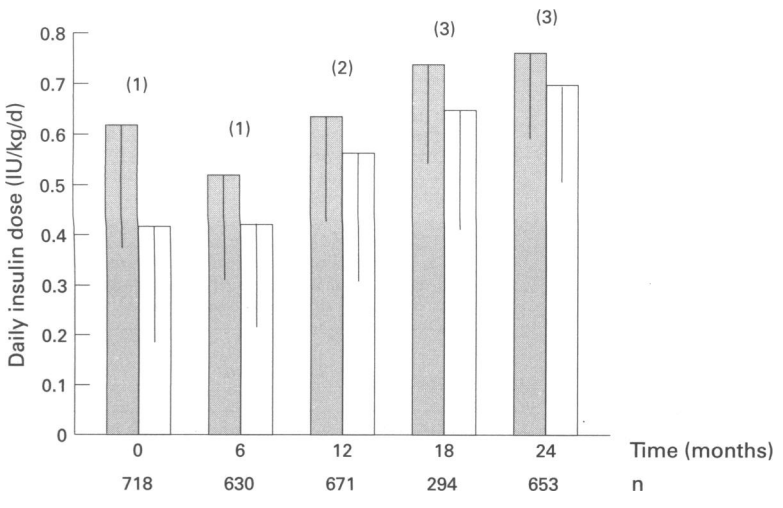

Figure 3 Mean (SD) daily insulin dose (IU/kg/day) in the diabetic ketoacidosis group (shadowed columns) and non-diabetic ketoacidosis group (empty columns) three weeks after diagnosis (time point 0) and during the follow up period. (1) p<0.0001, (2) p = 0.001, (3) p = 0.002 (multiple linear regression analysis).

(n = 48; 11.1%, p<0.001) or in age group C (n = 32: 11.3%, p<0.001).

Younger children had lower serum C peptide concentrations than older children. The mean (SD) serum C peptide concentration in age group A was 0.11 (0.10) nmol/l, in age group B 0.18 (0.13) nmol/l, and in age group C 0.22 (0.15) nmol/l (A *v* B: p<0.01; A *v* C and B *v* C: p<0.001).

Younger children had lower initial glycated haemoglobin values than older children. The mean (SD) glycated haemoglobin value in age group A was 10.1 (4.5) SD score, in age group B, 12.4 (5.1) SD score, and in age group C, 15.3 (6.7) SD score (p<0.001 between all groups).

The majority of the subjects were males (n = 412; 55.3%). Equal frequencies of diabetic ketoacidosis, impaired consciousness, and dehydration were observed in both sexes in each age group. There were no differences in blood pH between girls and boys. The mean (SD) serum C peptide concentration was 0.21 (0.16) nmol/l in females and 0.18 (0.12) nmol/l in males (p<0.01). Mean (SD) glycated haemoglobin value was 13.4 (5.8) SD score in females and 12.5 (6.1) SD score in males (p = 0.08).

Parental education was recorded in 685 subjects (91.9%), place of residence in 728 subjects (97.7%), and family income in 661 subjects (88.7%). The effects of the parental educational level are summarised in table 4. The income of the family had no influence on the variables, neither were there any differences between urban and rural families.

The mean serum C peptide concentration in the non-ketoacidosis group was significantly higher at the time of diagnosis and during the whole follow up period (fig 1) than in the ketoacidosis group. This held true even after adjustment for age and sex. Partial remission was less common in the ketoacidosis than in the non-ketoacidosis group (fig 2). The recommended amount of insulin was higher in the ketoacidosis than in the non-ketoacidosis group after adjustment for age (fig 3). Multiple insulin injection regimens were used more often in the ketoacidosis than in the non-ketoacidosis group (six months: 28% *v* 12%; 12 months: 38% *v* 24%; 18 months: 47% *v* 33%; 24 months: 56% *v* 49%). The ketoacidosis group had worse glucose control when assessed by glycated haemoglobin concentrations (table 5).

Table 4 Clinical condition at diagnosis of IDDM in the children from families with high or low parental education, mean (SD)

	High parental education (n=254)	*Low parental education (n=431)*	*p*
Age (years)	8.4 (3.8)	8.5 (3.8)	NS
pH	7.36 (0.10)	7.33 (0.12)	< 0.01
DKA	16.9%	24.4%	< 0.05
Dehydration	63.3%	63.3%	NS
Impaired consciousness	8.7%	14.4%	< 0.05
C peptide (nmol/l)	0.20 (0.15)	0.18 (0.13)	0.06
B glucose (mmol/l)	21.1 (9.0)	21.7 (9.0)	NS
GHb (SD score)	12.7 (6.1)	13.1 (6.0)	NS

GHb = glycated haemoglobin; DKA = diabetic ketoacidosis.

Table 5 Mean glycated haemoglobin values expressed as SD score above the mean level for non-diabetic subjects in diabetic ketoacidosis (DKA) and non-DKA groups (t test)

	DKA	No	Mean (SD)	p
At diagnosis	−	442	12.2 (5.9)	< 0.001
	+	123	15.5 (5.7)	
6 months	−	401	3.9 (3.4)	< 0.001
	+	118	4.9 (4.3)	
12 months	−	392	5.3 (3.7)	= 0.001
	+	111	6.7 (4.2)	
18 months	−	167	5.4 (3.7)	< 0.01
	+	49	7.1 (3.8)	
24 months	−	369	6.4 (4.0)	< 0.01
	+	107	7.7 (4.7)	

Serum C peptide concentrations at the time of diagnosis correlated strongly with later serum C peptide levels (six months: $r = 0.40$, $p<0.001$; 12 months: $r = 0.42$, $p<0.001$; 18 months: $r = 0.33$, $p<0.001$; 24 months: $r = 0.33$, $p<0.001$). There was also a significant correlation between initial glycated haemoglobin and subsequent glycated haemoglobin values (six months: $r = 0.20$, $p<0.001$; 12 months: $r = 0.26$, $p<0.001$; 18 months: $r = 0.12$, NS; 24 months: $r = 0.23$, $p<0.001$).

Discussion

At diagnosis, over one fifth (21.6%) of our diabetic children and adolescents had diabetic ketoacidosis, defined as a blood pH value of less than 7.30. This is quite a low proportion, since in a previous survey[2] more than one third (35.3%) of Finnish children and adolescents had diabetic ketoacidosis at the diagnosis of IDDM. The definition of diabetic ketoacidosis was the same as that in our study. Our observations indicate that the prevalence of diabetic ketoacidosis at the diagnosis of childhood IDDM has decreased over the last decade in our country.

Among other populations, a higher prevalence of diabetic ketoacidosis has been reported in children and adolescents at the presentation of IDDM. In the study of Elamin *et al* ketoacidosis was present at diagnosis in 73.9% of Sudanese children.[6] Drash reported at diagnosis a blood pH of 7.2 or less in 20%, and a bicarbonate concentration of 15 mmol/l or less in 42% of diabetic children and adolescents in Pittsburgh, USA,[3] and Couper *et al* observed a plasma pH of less than 7.30 in six of 25 Australian children (24%) with newly diagnosed IDDM.[5] In a recent study from southern England,[7] a blood pH value of less than 7.35 or a bicarbonate value of less than 21.0 mmol/l was observed in 29.7% of children younger than 15 years of age at the diagnosis of IDDM.

The low proportion of children presented with ketoacidosis at the diagnosis of IDDM is remarkable. Because of the high incidence of IDDM in Finland, its symptoms and signs are fairly well known, and the diagnosis is most often made before ketoacidosis occurs. Socioeconomic factors had only a minor effect on the clinical condition of the diabetic children at the diagnosis of the disease. However, children from families with high parental education were less prone to ketoacidosis, reflecting earlier suspicion and diagnosis of IDDM. These findings support the idea that, by effective diabetes education among the general population, it may be possible to further decrease the proportion of those with ketoacidosis at diagnosis.

Children under 2 years of age were more prone to diabetic ketoacidosis. This is probably because of the rapid progression of their disease, in combination with difficulties in recognising diabetic symptoms in this age group. The majority (62.5%) of patients with diabetic ketoacidosis were, however, older than 10 years. This disposition to diabetic ketoacidosis among subjects in the oldest age group is somewhat more surprising. It may be that they pay less attention to their symptoms, and are admitted to the hospital at a later stage. This is supported by the finding of a higher glycated haemoglobin in that age group, indicating a longer period of glucose intolerance before the diagnosis of their disease.

There were no differences in blood pH and frequency of diabetic ketoacidosis or impaired consciousness between sexes. However, females had significantly higher serum C peptide concentrations but they also tended to have higher glycated haemoglobin levels than males. These findings, which are in accordance with the observations of Drash,[3] are somewhat puzzling since in general there is an inverse correlation between serum C peptide and glycated haemoglobin levels during a follow up of diabetic patients. They may be explained by possible differences in insulin sensitivity between sexes, since an increased insulin requirement in adolescent females with IDDM, as well as an impaired insulin sensitivity in healthy adolescent girls, has been reported.[3 17-19] Our observation of higher endogenous insulin secretion probably reflects earlier clinical manifestation of IDDM in females than in males.

The discrepancy between the clinical and laboratory findings of the patients at the diagnosis of IDDM was remarkable. Nearly one fourth of the probands who were diagnosed as having impaired consciousness still had a blood pH value of 7.30 or more. The same was found in more than one fifth of the severely dehydrated patients. On the other hand, one of the 16 patients with a blood pH value of less than 7.00 was considered to have normal consciousness, and four of them were considered to be only mildly dehydrated. These observations are probably at least partly due to interobserver variation in the definition of consciousness and dehydration. They also clearly show the value of blood pH analysis in the evaluation of the child at the diagnosis of IDDM. Comparisons of the frequency of diabetic ketoacidosis between different populations should be based on blood pH measurements.

Reports on the residual β cell function at diagnosis of IDDM in children have been somewhat conflicting. Ludvigsson and Heding found detectable serum C peptide concentrations in all 12 newly diagnosed diabetic children,[9] while Sochett *et al* reported a median serum C peptide concentration of 0.03 nmol/l

before insulin treatment, undetectable low levels (less than 0.025 nmol/l) in 29% of their subjects, and concentrations below 0.10 nmol/l in 85% of the children.[20] In the present study, 98% of the subjects had measurable endogenous insulin secretion at diagnosis, identified by serum C peptide concentrations of 0.03 nmol/l or more. The median serum C peptide concentration was 0.15 nmol/l, which is in good accordance with an earlier report from Finland.[21] Four fifths (79.8%) of the children in the present study had serum C peptide concentrations of 0.10 nmol/l or more. These differences between different populations seem to be real, since Daneman *et al* reported the mean (SD) serum C peptide levels to be 0.15 (0.12) nmol/l in northern Finland,[4] and 0.05 (0.07) nmol/l in southern Ontario at clinical presentation. They may be explained by possible differences in the speed of β cell destruction, reflecting variations in the aetiology of IDDM. The other possible explanation would be different timing in diagnosis. This is, however, unlikely to be the only explanation, since we observed a mean (SD) serum C peptide of 0.12 (0.12) nmol/l even in the probands with diabetic ketoacidosis.

Young age was associated with lower serum C peptide concentrations. In particular, children younger than 2.0 years of age were low insulin secretors. This is in good agreement with earlier observations,[11 20] and reflects a smaller absolute β cell mass and a more aggressive β cell destruction in infants and young children.

Earlier data on the possible relationship between endogenous insulin secretion and metabolic decompensation at diagnosis are partly controversial. Käär[2] and Couper *et al* [5] reported an inverse relation between HbA_{1c} at diagnosis and both contemporaneous serum C peptide levels and those observed 7-14 days later. On the other hand, Sochett *et al* found no difference in mean C peptide concentration between children with diabetic ketoacidosis and those with normal acid-base status (pH ≥ 7.35).[20] In the present study, we observed a milder metabolic deterioration in children who had a serum C peptide concentration of 0.10 nmol/l or more than in children with a lower serum C peptide concentration. Our data indicate that even a relatively small amount of endogenous insulin secretory capacity prevents the child from serious metabolic decompensation at the diagnosis of IDDM.

Our data clearly show worse residual β cell function in children with diabetic ketoacidosis at the diagnosis of the disease. The serum C peptide concentrations were lower and insulin doses higher in the ketoacidosis group. Interestingly, most of the observed differences between the ketoacidosis and the non-ketoacidosis groups were preserved for the whole two year observation period. This is in contrast with the findings of Sochett *et al*,[20] who reported no relation between initial pH and basal or stimulated serum C peptide concentrations at diagnosis or during the first year of clinical disease. However, the number of probands in the Sochett's study (33 for follow up) may have been too small to discern a possible correlation between initial pH and C peptide concentrations during the follow up.

Partial remission was less common in the ketoacidosis group than in the non-ketoacidosis group. The remission is considered to be a result of the functional recovery of existing β cells and increasing peripheral insulin sensitivity after the initiation of insulin treatment. Accordingly, clinical remission reflects a better preserved β cell mass, which protects the child from developing diabetic ketoacidosis at diagnosis.

In spite of a larger dose of exogenous insulin, the ketoacidosis group had poorer metabolic control in the present study. This may be of importance, since poor metabolic control is related to higher risk of future diabetic retinopathy and nephropathy, at least in adult patients,[22] and possibly in paediatric patients as well.[23 24]

In conclusion, ketoacidosis at the diagnosis of IDDM is related to poorer subsequent β cell function and impaired metabolic control during at least the first two years of clinical disease. Both the metabolic decompensation assessed by the blood pH value at diagnosis and the initial serum C peptide concentrations predict the later β cell recovery. Together these observations indicate that diabetic ketoacidosis at diagnosis reflects a more advanced β cell destruction leading to reduced β cell recovery and poorer metabolic control after the institution of exogenous insulin treatment. Accordingly, avoidance of initial diabetic ketoacidosis may facilitate good metabolic control over the first years of manifest IDDM.

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