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Clinical characteristics, beta-cell dysfunction and treatment outcomes in patients with A−β+ Ketosis-Prone Diabetes (KPD): The first identified cohort amongst Asian Indians

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ABSTRACT

Objective: Ketosis-prone diabetes (KPD), an atypical form of diabetes, has emerged as a heterogeneous syndrome in multiple ethnic groups. The objectives of this study were to look into the clinical characteristics of adult Asian Indian patients with recently diagnosed, antibody negative diabetes presenting with unprovoked ketoacidosis (A−β+ KPD) and to determine the natural course of recovery of beta-cell functions on serial follow-up over one year.
Research design and methods: Newly diagnosed adult diabetes patients (n = 11) with suspected KPD (A−β+) were prospectively studied over a period of 1-year with serial evaluations of clinical, biochemical and beta-cell secretion characteristics. These were compared with a control group (n = 23) of KPD (A+β−) (classical Type 1A diabetes) with similar presentation. Beta-cell secretion was assessed by fasting and stimulated C-peptide values after a standard mixed meal challenge. Glycaemic control and treatment outcomes were also documented.
Results: In comparison to the A+β− KPD controls, the A−β+ KPD patients had a significantly older age, higher BMI, stronger family history of type 2 diabetes, more severe ketoacidosis and higher fasting and stimulated C-peptide level at presentation. On serial follow-up, the patients with KPD achieved complete recovery of their beta-cell function with remission from insulin-dependence within 3–4 months without further recurrences of DKA.
Conclusions: This is the first reported series of A−β+ KPD from India. The phenotype of Indian A−β+ KPD patients differs from their Western counterparts in that they are relatively younger and leaner, though the male preponderance and natural history of recovery of beta-cell dysfunction bears similarity.

1. Introduction

Diabetic ketoacidosis (DKA) is a complex metabolic state characterized by hyperglycaemia, ketoacidosis and ketonuria. Though traditionally associated with type1 diabetes, an increasing prevalence of DKA is being reported in type 2 diabetes as well. The prevalence rate of DKA between 2008 and 2010 was reported as 31.1% and 5.7% for type 1 and type 2 diabetes respectively.[1] Type 2 diabetes patients with DKA are older, have higher levels of C-peptide, a similar degree of hyperglycaemia but less severe acidosis than type 1 diabetic patients.[1]

Banerji et al.[2] had initially described the entity of new onset diabetes with absent autoimmune markers and acute transient insulin deficiency presenting as ketosis or ketoacidosis, with remission in the beta-cell secretory dysfunction over a period of time. Several reports have been published since then from African, Japanese, Hispanic, Chinese and Pakistani cohorts suggestive of a worldwide prevalence of this Ketosis prone diabetes (KPD).[3–7] One case report has also been published from India.[8] Different names have been attributed to this heterogeneous syndrome such as Flatbush diabetes,[2] Idiopathic type 1 diabetes,[9] Atypical diabetes,[10] Phasic insulin-dependent diabetes and Ketosis-Prone diabetes (KPD).[11] Balasubramanyam et al. compared the several classification schemes been used in these newly diagnosed KPD patients with varying accuracy, like the ADA scheme (sensitivity 89.7%, specificity 22.7%), the modified ADA classification (sensitivity 34.5%, specificity 100%), BMI based classification (sensitivity 72.2%, specificity 76.2%) and the Aβ classification (sensitivity 99.1%, specificity 95.5%).[9,11–14] They concluded that the Aβ classification most accurately classifies patients with KPD and strongly predicts their long-term clinical and biochemical behaviour.[14] This Aβ classification system is based on the presence or absence of autoantibodies (A+, A−) and presence or absence of beta-cell secretory function (β+, β) consists of four categories: A+β− type 1 diabetes with positive autoantibodies and absent beta-cell function; A+β+ Latent autoimmune diabetes of adults

Abbreviations: A−, Autoantibodies absent; A+, Autoantibodies present; β−, absent beta-cell secretory function; β+, present beta-cell secretory function; BMI, Body mass index; DKA, Diabetic Ketoacidosis; GAD65, Glutamic acid decarboxylase; IA2, Islet antigen; KPD, Ketosis Prone Diabetes; MMCT, Mixed meal challenge test.

Conflict of interest: The authors have no conflicts of interest.

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(LADA) with positive autoantibodies but preserved beta-cell function; A−β− type 1 diabetes without autoantibody and absent beta-cell function and A−β+ Ketosis prone diabetes without autoimmunity but preserved beta-cell function and propensity for unprovoked ketosis/ketoacidosis.[11] Unprovoked A−β+ KPD are thus a distinct syndrome of reversible beta-cell dysfunction lacking evidence of humoral or cellular islet autoimmunity.[15] The objective of this study was to ascertain the presence of unprovoked A−β+ KPD in India and to study their characteristics in this ethnic group.

2. Research designs and methods

2.1. Study design

A prospective study of 81 consecutive cases of DKA admitted in the Christian Medical College (CMC), Vellore, India, over a period of one year (January 2014 to December 2014) was done. Only adult patients (>16 years age) with a definite diagnosis of DKA defined as a blood glucose level > 250 mg/dl, positive urine ketones (Keto-Diastix; Bayer), arterial blood gas analysis with a pH < 7.30, serum bicarbonate < 18 mmol/l and a positive anion gap (>15 mmol/l) were recruited.[16] Patients with concomitant conditions that might result in anion gap acidosis or ketosis such as pregnancy, kidney injury, lactic acidosis, acute alcohol intoxication or poisoning were excluded. Informed consent was obtained from the patients who were willing to participate in the study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (and revised in 2013) and was approved by the Institutional Review Board of Christian Medical College & Hospital, Vellore, India (IRB Min. No. 9547). A total of 51 DKA patients with new onset diabetes were subsequently included in the study as outlined (Fig. 1).

2.2. Study population

In this study, A−β+ KPD, was defined by the Aβ classification scheme as those patients with new-onset diabetes, presenting with unprovoked ketoacidosis in the absence of GAD65 and IA2 autoantibodies (A−) with subsequent complete recovery of beta cell functions (β+).[3,14] According to the same classification, A+β− KPD, included in the study was defined as those patients with new-onset diabetes, presenting with ketoacidosis in the presence of GAD65 and IA2 autoantibodies (A+) with subsequent failure of recovery of beta cell functions (β−). This A+β− group thus represented the classical antibody positive Type 1 Diabetes group. Initially, thirteen such probable A−β+ KPD patients were identified and planned for longitudinal follow up for 1 year. However two patients were lost to follow up after the initial admission with DKA and hence were excluded from the study. Thus the total number of A−β+ KPD patients in the study was eleven (cases). Twenty-three patients with newly detected A+β− KPD admitted with DKA were included as the control group. Serial C-peptide levels and insulin requirements over the one year follow-up period were monitored for the eleven cases and twenty-three controls. Recovery of beta-cell dysfunction and remission from insulin-dependence on follow up was the defining feature in all KPD patients. Remission from insulin dependence was defined as having an HbA1c ≤ 6.3% (45 mmol/mol) and a fasting plasma glucose <124 mg/dl

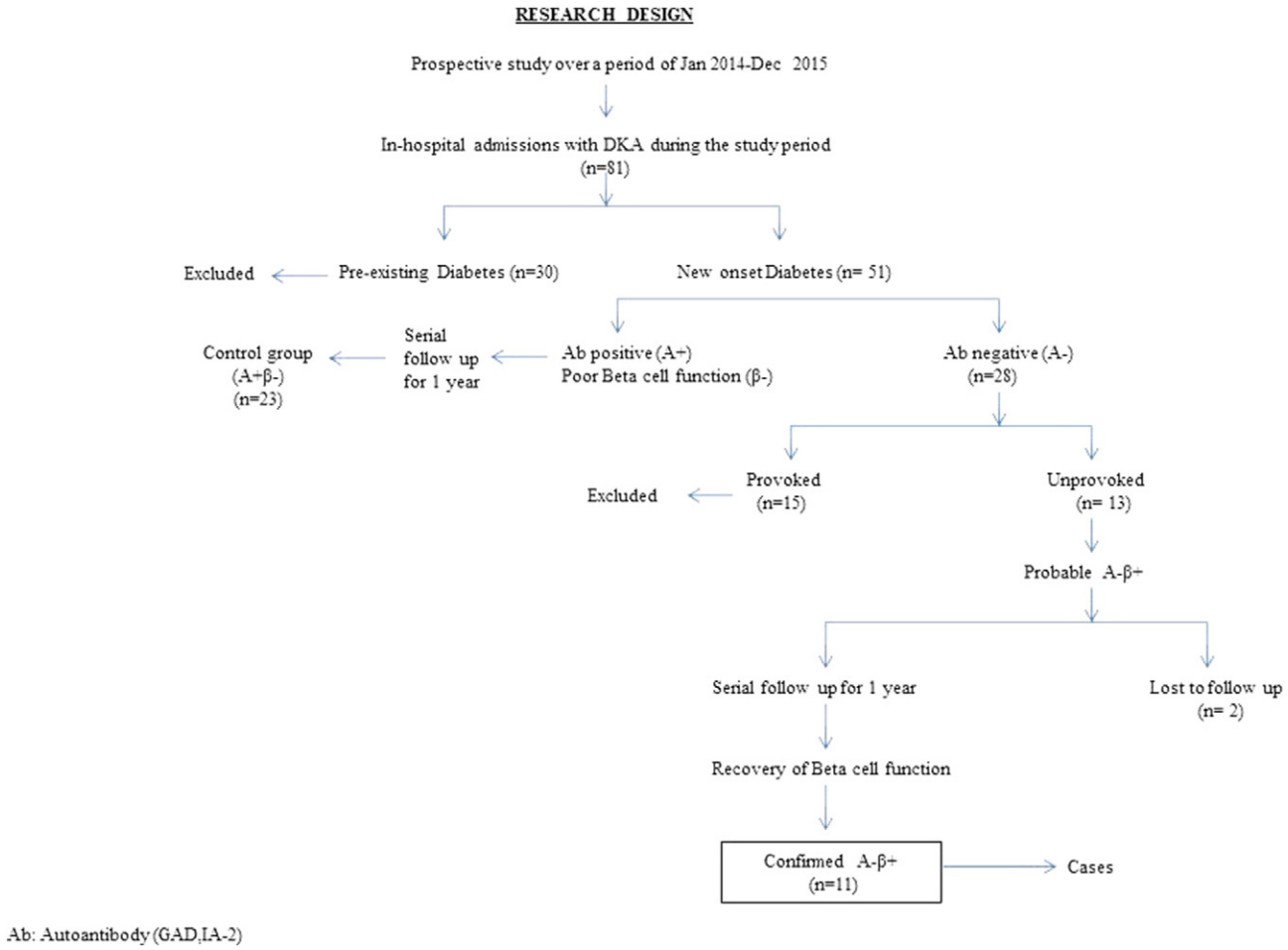

Fig. 1. Research design.

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three months after discontinuing all pharmacological agents.[17] Autoantibody negative diabetes patients admitted with provoked ketoacidosis (n = 15) were excluded from the study (Fig. 1).

2.3. Clinical characteristics

Eligible patients were interviewed within 48 h of admission. Initial assessment included obtaining the detailed medical history including their duration of symptoms, co-morbidities, family history of diabetes, treatment history, history of any exogenous drug intake and likely precipitating factors of DKA (infections, stress, drugs, etc). A detailed pedigree chart with a three generation family history of diabetes was obtained for all subjects. Thorough physical examination including BMI (Body mass index) and markers of insulin resistance were documented. Haematological (complete blood count and blood picture), biochemical (HbA1c, lipid profile, liver function, renal function, electrolytes), radiological (Chest X-ray, Ultrasound abdomen), microbiological (urine and blood cultures) investigations were done as per the clinical requirement.

2.4. Clinical course

All patients were managed as per the standard protocol for DKA management.[16] They were discharged on a basal-bolus insulin regimen with advice to self-monitor blood glucose (SMBG) at home. The cases and controls were longitudinally followed up for 1 year after the index episode of DKA. HbA1c (High performance liquid chromatography method) was monitored every 3 months. The dose of insulin was titrated as per SMBG and discontinued and switched to oral antidiabetic agents or lifestyle measures, once the fasting and post prandial blood glucose and HbA1c values were within the ADA targets at two consecutive clinic visits made 2–4 weeks apart.[12] None of the patients developed ketosis, ketoacidosis or hyperglycaemias on down titration of insulin.

2.5. Autoantibody analysis

Autoantibodies to GAD65 and IA2 were analyzed by Quantitative Sandwich Immunoassay method (RSR Limited, Cardiff, UK) with assay range of upto5 to 2000 U/ml for GAD65 and upto 7.5 to 4000 U/ml for IA2.Standards were calibrated against the WHO reference NIBSC (97/550).[18] The cut-off level was set to 5 WHO Units/ml for GAD65 and 7.5 WHO Units/ml for IA2, which are the lowest standard concentration and also the recommended cut-off by the manufacturer for serum samples. Patients were classified as antibody positive (A+) if the value for at least one of the measured serum antibodies was positive or antibody negative (A−) if the value for both antibodies were negative.

2.6. Measurement of beta-cell secretory reserve

The pancreatic beta-cell secretory functions during the initial admission were assessed in the fasting state and with a mixed meal challenge test (MMCT) after control of DKA. At the time of the MMCT, the patients were off intravenous insulin, subcutaneous long-acting or intermediate-acting insulin for at least 24 h and off subcutaneous short or rapid acting insulin for at least 6 h prior to the test. In addition, it was ensured that the patients had completely recovered from the DKA and were taking normal oral feeds for at least 48 h prior to the test. The patients were usually subjected to the test after a week of the initial presentation with DKA. During follow-up, patients were off sulfonylureas for at least 36 h prior to the MMCT. Further, the subjects underwent an overnight fast for at least 8 h prior to the test with limitations placed on strenuous exercise, alcohol, caffeine and tobacco use on the day prior to the MMCT. The simultaneous blood glucose levels at the start of the MMCT were maintained below 150 mg/dl. A standard MMCT, rather than an OGTT (Oral Glucose Tolerance Test), represents a more physiologically relevant stimulus as it more closely mimics the metabolic changes experienced by individuals in daily life and is better tolerated. Following an overnight fast, subjects were administered a mixed meal of Ensure nutritional powder (carbohydrate 54%, fat 32% and protein 14%, Abbott Healthcare Ltd., USA) in a dose of 6 ml/kg (maximum of 360 ml) to be consumed over 5–10 min. The Ensure nutritional powder provides a standardized, well-tolerated liquid mixed meal challenge and has been widely used in research studies.[19] Fasting and stimulated C-peptide levels (90 min after the mixed meal challenge) were measured by use of a chemiluminescent immunometric assay (Siemens Medical Solutions Diagnostics, USA) with assay range of 0.1–20.0 ng/ml. A longitudinal evaluation of beta-cell secretory function was similarly done at 3, 6 and 12 months of follow up in the study group and at 0 and 12 months in the A+β− group. Preserved beta-cell function (β+) after the index DKA was defined as fasting serum C-peptide level > 1 ng/ml or the maximum stimulated serum C-peptide level > 1.5 ng/ml.[20]

2.7. Statistical analysis

Data was checked for normality and analyzed using SPSS (Version 11). Independent samples "*t*" test was applied to check for significance in differences in Mean & SD. The p value < 0.05 was considered statistically significant.

3. Results

3.1. Case group (A−β+ KPD)

The cases consisted of 11 patients who fulfilled the criteria of unprovoked DKA with newly diagnosed antibody negative diabetes. The mean age of the study patients was 39.8 ± 6.5 years with a predominant male distribution, 8/11 (72%). The mean duration of osmotic symptoms were 16 ± 7 days preceding the index DKA episode along with a history of weight loss of about 1.4 ± 1.2 kg per week. A positive family history of type 2 diabetes was elicited in 7 (64%) patients. The mean BMI was 25.3 ± 1.6 kg/m^2, with a waist hip ratio of 1.0 ± 0.16. Physical signs of insulin resistance were documented in 4 out of 11 patients (36%). Biochemical parameters were suggestive of uncontrolled hyperglycaemia with mean admission glucose values of 586 ± 138 mg/dl, an HbA1c of 11.3 ± 1.8% (100 ± 19.7 mmol/mol) and severe ketoacidosis with mean arterial pH of 7.14 ± 0.08 and bicarbonate level of 15.4 ± 6.1 mmol/l. The beta-cell functional capacity assessed after a week of the initial presentation with DKA showed a fasting C-peptide value of 0.46 ± 0.08 ng/ml and the stimulated C-peptide of 1.02 ± 0.10 ng/ml. All of them were intensively managed with a stable insulin infusion protocol for DKA and were discharged after a week on a basal bolus regimen of insulin. The average insulin dose needed at discharge was 0.8 ± 0.2 U/kg.

3.2. Control group (A+β−)

The control group of A+β− diabetes (n = 23) had a mean age of 26.9 ± 8.3 years at the time of DKA, with age-wise distribution showing 3 patients aged between 16 and 20 years, 9 patients aged between 21 and 25 years, 8 patients aged between 26 and 30 years and 2 patients aged above 30 years. The control group had a male predominance of 17/23 (74%) with the mean duration of osmotic symptoms for 14 ± 6 days and a weight loss of 1.6 ± 0.8 kg per week preceding the index DKA episode. Only 5/23 (22%) patients in this group had a positive family history of type 2 diabetes. Their mean BMI was 19.8 ± 2.5 kg/m^2, with a waist hip ratio of 0.9 ± 0.14. At admission, the mean glucose value was 412 ± 132 mg/dl with mean HbA1c of 10.8 ± 2.6% (95 ± 28.4 mmol/mol), arterial pH of 7.26 ± 0.11 and bicarbonate of 17.8 ± 5.5 mmol/l. The baseline fasting C-peptide was 0.10 ± 0.04 ng/ml and the stimulated C-peptide was 0.48 ± 0.12 ng/ml. They were discharged on basal bolus regimen of

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insulin with the average insulin dose of 0.6 ± 0.15 U/kg after successful management of DKA as per the standard protocol.

3.3. A−β+ KPD (cases) vs. A+β− (controls)

On comparison with the A+β− control group (Table 1), it was found that the A−β+ KPD patients presented with DKA at an older age (p = 0.01) with a higher BMI (p = 0.01) but with similar sex distribution (p = 0.12). The A−β+ group was associated with a significant positive family history of type 2 diabetes as compared to A+β− group (p = 0.03). There was no significant difference in the preceding history of weight loss (p = 0.45), duration of osmotic symptoms (p = 0.56), HbA1c on admission (p = 0.95), plasma triglycerides (p = 0.65) or low density lipoproteins (p = 0.45) amongst the groups.

The A−β+ KPD group had significantly higher glucose values on admission (p = 0.02) with more severe ketoacidosis (pH-p = 0.02, bicarbonate-p = 0.03).Both the groups responded well to the initial DKA management without any mortality and were discharged within a week. The A−β+ KPD patients at discharge required a higher dose of insulin (0.8 ± 0.2 U/kg) than the A+β− diabetes patients (0.6 ± 0.15 U/kg). The analysis of beta-cell secretory function at baseline, done using the fasting (p = 0.01) and stimulated C-peptide values (p = 0.01) were suggestive of relatively better beta-cell function in the A−β+ KPD group.

3.4. Natural course of A−β+ KPD

Serial monitoring of the fasting and stimulated C-peptide values in the A−β+ KPD group done at 0, 3, 6 and 12 months of follow up showed statistically significant progressive improvement of beta-cell secretory function (Table 2). The average duration to remission was 93 ± 4.5 days. Glycemic control was sustained without insulin for rest of the follow up period. 27% (n = 3) A−β+ KPD patients were on sulfonylurea alone, 18% (n = 2) were on metformin alone and 45% (n = 5) were on combination of sulphonylureas plus metformin (Fig. 2). One patient could maintain his glycaemic targets on diet and lifestyle modification alone.

Table 2
C-peptide values on follow up A−β+ group.

A−β+ group	0 month	3 month	6 month	12 month
Basal C-peptide (ng/ml)	0.46 ± 0.08	0.89 ± 0.04	1.1 ± 0.03	1.36 ± 0.09
Stimulated C-peptide (ng/ml)	1.02 ± 0.10	1.67 ± 0.08	2.65 ± 0.07	3.42 ± 0. 47

3.5. Comparative characteristics at 1 year follow up

At the end of one year follow up, all 11 patients in the A−β+ KPD group were off insulin. Though the HbA1c at the time of the index DKA was similar in the two groups, at 12 months of follow up it had significantly improved in the A−β+ KPD group compared with the A+β− group (p = 0.02). The C-peptide values showed remarkable improvement in the A−β+ KPD group in contrast to the A+β− group (p < 0.01). None of the 11 A−β+ patients had recurrence of ketosis or ketoacidosis till end of 1 year follow-up. All the A+β− group patients were continued on a basal bolus insulin regimen (Table 3).

4. Discussion

This study, conducted at a tertiary care centre in India, is the first reported series of adult patients demonstrating A−β+ pattern of KPD with prospective delineation of the natural course of recovery of beta-cell function over a one year period.

4.1. Ethnicity

KPD has been predominantly reported amongst people of African and Caribbean ethnicity.[3,10,21] Maldonado et al. reported significant differences in the characteristics of indigent, KPD patients based on their ethnicity like the Hispanic had greater beta-cell functional reserve and less dependence on chronic insulin therapy.[22] Though independent case reports have been published from South Asia,[8,23] there are no reports of A−β+ cohorts of KPD described from this ethnic group.

Table 1
Baseline Characteristics of A−β+ and A+β− groups.

Characteristics	A−β+ (n = 11)	A+β− (n = 23)	p-Value
	Mean ± SD	Mean ± SD	
Clinical characteristics			
Age (years)	39.8 ± 6.5	26.9 ± 8.3	0.001
Male gender (%)	8 (72%)	17(74%)	0.12
Duration of symptoms (days)	16 ± 7	14 ± 6	0.56
Weight loss at presentation (kg/week)	1.4 ± 1.2	1.6 ± 0.8	0.45
Family history of type 2 diabetes (%)	7 (64%)	5 (22%)	0.01
BMI (kg/m^2) at presentation	25.3 ± 1.6	19.8 ± 2.5	0.01
Waist hip ratio	1.0 ± 0.16	0.9 ± 0.14	0.22
Biochemical characteristics - baseline			
HbA1c (%) (mmol/mol)	11.3 ± 1.8 (100 ± 19.7)	10.8 ± 2.6 (95 ± 28.4)	0.95
Triglyceride (mg/dl)	160 ± 26	149 ± 32	0.65
LDL-c (mg/dl)	98 ± 12	101 ± 19	0.45
GAD/IA2 antibodies positive (U/ml)	0	23	NS
Biochemical characteristics - during DKA			
Admission glucose (mg/dl)	586 ± 138	412 ± 132	0.02
pH (arterial)	7.14 ± 0.08	7.26 ± 0.11	0.01
Bicarbonate (mmol/l)	15.4 ± 6.1	17.8 ± 5.5	0.01
Beta-cell secretory function - baseline			
Fasting C-peptide (ng/ml)	0.46 ± 0.08	0.10 ± 0.04	0.01
Stimulated C-peptide (ng/ml)	1.02 ± 0.10	0.48 ± 0.12	0.01
Treatment prescribed - at discharge			
Insulin	11/11 (100%)	23/23 (100%)	NS
Oral antidiabetic drugs	0/11	0/23	NS
Insulin dose at discharge (U/kg)	0.8 ± 0.2	0.6 ± 0.15	NS

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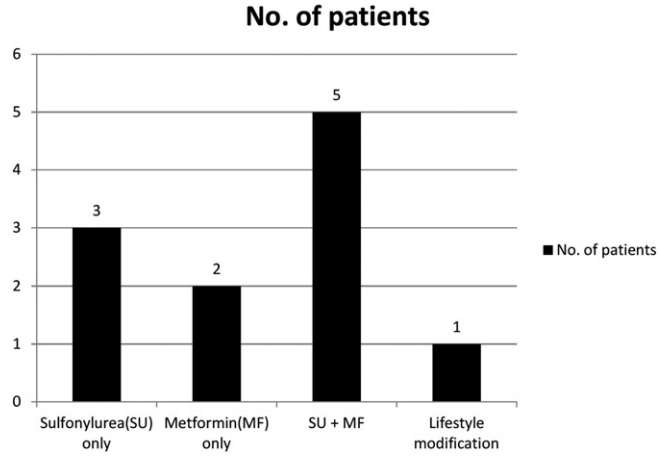

Fig. 2. Therapeutic management at end of 1 year follow-up in A−β+ KPD group.

Hence, our study, that aimed to look at the clinic-biochemical, immunological and therapeutic characteristics of A−β+ KPD patients of Indian origin, assumes significance.

4.2. Age

In comparison to A+β− group which usually manifests at an earlier age, A−β+ patients present with DKA in the 4th or 5th decade, with the mean age varying from 33 to 53 years.[13] The mean age at presentation in our group was 39.8 ± 6.5 years. Though this is lower than that reported in some of the western cohorts,[24,25] the finding is consistent with the mean age reported in the Houston cohort[11] and other East Asian cohorts. The isolated case report from India was of a patient aged 39 years.[8] However, reports of A−β+ KPD in the paediatric population have been described including one case report from Pakistan.[23] Therefore, this warrants further larger studies including the paediatric population.

4.3. Gender

All available literature has reported male predominance in A−β+ KPD.[3,9] Our cohort has also shown a striking male predominance with a gender ratio of 8:3, which is comparable to that reported by Sobngwi[10] and Maldonado in the Houston cohort.[11] The percentage of females in our study group was around 30% which is relatively more when compared to the western reports of 25%[3,9] but similar to studies from Asia.[4,6] Thus, though the male preponderance in A−β+ KPD is maintained in our cohort, gender specific mechanisms of etio-pathogenesis and occurrence in females needs to be further studied in this population.

Table 3
Characteristics at 1-year follow up in A−β+ and A+β− groups.

Characteristics at 1 year follow up	A−β+ (n = 11)	A+β− (n = 23)	p-Value
	Mean ± SD	Mean ± SD	
BMI (kg/m^2)	26.2 ± 2.7	20.1 ± 3.2	0.01
Insulin dose (U/kg)	Nil	0.7 ± 0.2	–
HbA1c (%) (mmol/mol)	6.1 ± 0.3 (43 ± 3.3)	8.2 ± 1.5 (66 ± 16.4)	0.01
Fasting C-peptide (ng/ml)	1.36 ± 0.09	0.09 ± 0.03	<0.01
Stimulated C-peptide (ng/ml)	3.42 ± 0.47	0.41 ± 0.18	<0.01
Treatment with insulin	0/11 (0%)	23/23 (100%)	–
Treatment with			
Oral anti-diabetic drugs	10/11 (91%)	0/23 (0%)	–
Lifestyle modification alone	1/11 (9%)	0/23 (0%)	

4.4. Body mass index

The mean BMI in our cohort was 25.3 ± 1.6 kg/m^2. Reported literature suggests that A−β+ KPD is predominant in the obese.[17] However compared to all western literature reviewed (e.g. 28.9 kg/m^2 reported by Banerji, 37 kg/m^2 by Umpierrez, 30.3 kg/m^2 by Maldonado) the mean BMI in our cohort was significantly lower. It is known that Asians in general are less overweight than their Western counterparts, though they have similar or even higher prevalence of diabetes and the BMI based cut-offs for obesity for Asian Indians are much lower than the West.[24,25] This is further supported by the similarity of our findings to the mean BMI reported in other East Asian cohorts.[4,6] According to the BMI based classification proposed by investigators at Emory University, Atlanta, Georgia, which differentiated A−β+ KPD patients into "lean" (BMI < 28 kg/m^2) and "obese" (BMI > 28 kg/m^2) subtypes, our cohort fits into the former. It would be worthwhile to investigate the different immunogenic mechanisms suggested by Umpierrez et al. for the pathogenesis of DKA in lean and obese patients in our cohort as well.[26]

4.5. Family history of diabetes

Positive family history of type 2 diabetes was noted in 64% (7/11) of our A−β+ KPD patients which is almost similar to that reported by Chihaoui (56%), Banerji (67%) and Mauvais Jarvis (67.6%). None of our patients had young onset diabetes (<30 years) in their three generations as analyzed by the detailed pedigree chart, thereby making the possibility of MODY rather unlikely.[27] The high prevalence of familial aggregation of type 2 diabetes in general in the Indian subcontinent reflects both inherited genetic susceptibility and shared environments like cultural factors and diet amongst others.[28]

4.6. Symptoms

In general, A−β+ KPD patients have been reported to have a short symptomatic period preceding DKA. Our study group was symptomatic for a mean duration of 3 ± 1.2 weeks similar to that reported as <4 weeks by Mauvais Jarvis et al.[3] A−β+ patients had a similar presentation when compared to A+β− patients featuring most common symptoms such as fatigue, osmotic symptoms, pain abdomen and nausea. Previous studies have reported weight loss ranging between 4 and 12 kg prior to admission with DKA.[3,9,13,17] A mean weight loss of 4.2 kg was reported in our study group which was consistent with the available reports. None of our A−β+ patients had any precipitating cause for metabolic decompensation that could have attributed to DKA at presentation.

4.7. DKA at onset

More than 75% of A−β+ KPD patients present with ketoacidosis at the time of diagnosis of diabetes.[3,22] Most studies have included patients with both ketosis and ketoacidosis. All 11 patients (100%) included in our study had presented with definite ketoacidosis at the point of time of first diagnosis of diabetes, similar to that reported by Mauvais Jarvis in the sub-Saharan population[3] and Banerji et al. in their original cohort of Flatbush diabetes.[2] Inclusion of patients with ketosis can be a confounding factor, since several causes may be contributing (e.g. dehydration, alcohol, poisoning etc). Beiyan et al. had proposed an alternative classification for KPD stating that 'Ketosis Prone Diabetes' and 'Ketosis Onset Diabetes' are two separate entities.[6] Our study suggests that the Indian phenotype is probably more similar to the Ketosis-Onset type.

4.8. Biochemical profile

The baseline biochemical profile of the A−β+ KPD group, including the renal functions, liver functions and lipid profile were

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comparable to that of the control group and were within the normal range. At admission with DKA, our cohort of A−β+ patients had higher mean blood glucose levels, with more severe acidemia and required a higher dose of insulin at the time of discharge from hospital and during the initial follow up period, when compared to A+β− patients. The mean HbA1c at presentation in the KPD group was 11.3 ± 1.8% (100 ± 19.7 mmol/mol) which was comparable to that reported by Beiyan Liu et al. but much higher when compared to 9.5% (80 mmol/mol) reported by Pinero-Pilona, 6.7% (50 mmol/mol) by Umpierrez or 7.5% (58 mmol/mol) by Maldonado et al. The high HbA1c reflects prolonged undiagnosed hyperglycaemia with either low grade symptoms in the initial period or a delay in seeking medical attention due to socioeconomic constraints.

4.9. Clinical course: natural history of pancreatic beta-cell function

This study shows that both the A−β+ and A+β− patients do not differ significantly in their initial presentation. The natural history of A−β+ KPD has been best elicited in large cohorts with longer longitudinal follow-up.[3] Umpierrez et al. had suggested that the initial aggressive management with insulin might contribute to improvements in beta-cell function and that approximately 50% of adults with KPD will be able to discontinue insulin treatment in the due course.[29] The remission rate (HBA1c <6.3% (45 mmol/mol) and fasting blood glucose <124 mg/dl) is reported to be around 43% to 62%.[3,17,22] All of our patients (100%) could successfully be weaned off insulin therapy with a mean remission time of 93 ± 4.5 days. McFarlane[30] has reported that 42% of patients achieved remission after a mean duration of 83 days while Banerji et al.[31] had reported near-normoglycaemic remission in 70% of patients after 9 weeks (63 days). Mauvais-Jarvis et al., found that only 23% patients in their cohort remained insulin dependent after follow up for 10 years. None of our A−β+ KPD patients had recurrence of DKA till the end of 1 year of follow up.

Progressive improvement in C-peptide response to MMCT confirmed the recovery of pancreatic beta-cell dysfunction. The 90-minute stimulated C–peptide value in our A−β+ KPD group, at 1 year of follow up, was 3.42 ng/ml which is comparable to that reported by Sobngwi (3.7 ng/ml).[10] The preserved beta-cell functional reserve at the end of 1 year follow up, along with the glycaemic improvement ruled out the probability of a diagnosis of A+β− diabetes in the poorly defined honeymoon period.[9] The HbA1c, at the end of one year of follow up, was 6.1 ± 0.3% (43 ± 3.3 mmol/mol) in our cohort which was significantly better compared to that reported by Sobngwi as 8.8% (73 mmol/mol), Maldanodo as 7.5% (58 mmol/mol) or Umpierrez as 6.8% (51 mmol/mol). It thus suggests beta-cell propensity to glucose toxicity and possible recovery of the beta-cell dysfunction after adequate control of hyperglycaemia.[32]

Our study group did not have any recurrence of DKA or hyperglycaemia over the1 year follow up period. Reports have suggested that most A−β+ KPD patients relapse within 2 years of their initial presentation, especially if not treated with some sort of antidiabetic regimen.[3,31] In the study with longest follow up (10 years), Mauvais-Jarvis had quoted that the probability for relapse was 90% within 10 years.[3] Since our data was based on only one year follow up, further monitoring of this cohort may reveal a subset of KPD patients who may have recurrence of hyperglycaemia or ketosis requiring insulin in future. Our study did not measure ZnT8 (Zinc Transporter 8) antibody in the A−β+ KPD group, and as evidenced by the Houston cohort,[11] the possibility of some of the cases in the study group being antibody positive for ZnT8 (A^+) cannot be excluded. Thus future studies in the Indian KPD cohort should take into account measuring ZnT8 antibodies as well. While our study was focussed specifically on the A−β+ subtype of KPD in Indian subjects, larger prospective studies aimed at estimating the prevalence and comparative clinical characteristics of all four subtypes of KPD in India would be extremely useful in understanding the pathogenesis of reversible and irreversible beta-cell dysfunction.

Our series of A−β+ KPD patients had a distinct clinical, biochemical and beta-cell specific characteristics that differentiated it from new onset A+β− group of patients presenting with DKA. Hence the differential diagnosis of A−β+ KPD must be considered in all adult Asian Indians presenting with DKA at diagnosis of diabetes, especially if the antibody status is negative.

5. Conclusions

This is the first prospective study to report the existence of a cohort of A−B+ variety of KPD in India with prospective evaluation of the natural course of their diabetes. Our data showed that 11 out of the 51 adult patients who were admitted with DKA at diagnosis of diabetes had characteristics of A−β+ KPD which suggested a prevalence rate of 21.6%. Even though this is a study from a single tertiary care centre and not representative of the general population, we have definite evidence of A−β+ KPD being present in the Indian population. In agreement with the available literature, our patient group is characterized by middle age, male preponderance and severe DKA at onset. Moreover, in agreement with literature from other East Asian cohorts, a lower BMI at presentation probably characterize the Indian cohort.

The significant glycaemic improvement, on follow up, in a group of DKA patients who can be classified as A−β+ KPD, must alert the physicians to continue serial monitoring of the beta-cell secretory function and enable treatment with oral antidiabetic agents and/or diet and exercise alone ensuring compliance, reducing hypoglycaemias and diabetes related complications in future. Given the heterogeneous nature of this disease, larger studies are warranted to delineate the clinical and immunological characteristics and therapeutic outcomes of indigent, ketosis-prone diabetes patients in the Indian population. Our study, which provides the first evidence of the presence and natural course of A−β+ KPD amongst newly diagnosed adult diabetes patients in the Indian population, can provide a platform for future etiopathogenetic research.

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Authors' contributions

Dr. Riddhi Das Gupta designed the study, recruited the volunteers, and undertook the metabolic assessment, contributed to the interpretation of the data and write up of the manuscript. Dr. Roshna contributed in the data analysis, manuscript writing and editing and review of literature, Drs Praveen and Shajith contributed in the research data, analysis and write-up of the manuscript. Drs Surjit, Anil and Samantha assisted in the clinical workup and follow up of these patients. Drs Nihal Thomas and Asha helped in reviewing and editing the manuscript. Dr. Nihal Thomas is the guarantor of this work and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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