Published in final edited form as:

J Diabetes Complications. 2015 ; 29(7): 918–922. doi:10.1016/j.jdiacomp.2015.04.013.

Factors associated with early relapse to insulin dependence in unprovoked A- β + Ketosis-Prone Diabetes

Ruchi Gaba^{1,2}, Dhiraj Gambhire³, Natalie Uy¹, Erica V. Gonzalez^{1,2}, Dinakar Iyer¹,
Christiane S. Hampe⁴, Nalini Ram^{1,2}, and Ashok Balasubramanyam^{1,2}

¹Translational Metabolism Unit, Diabetes Research Center, Division of Diabetes, Endocrinology and Metabolism, Baylor College of Medicine, Houston, TX

²Endocrine Service, Ben Taub General Hospital, Houston, TX

³University of Texas School of Public Health, Houston, TX

⁴Department of Medicine, University of Washington, Seattle, WA

Abstract

Objective—Unprovoked “A- β +” Ketosis-Prone Diabetes (KPD), a unique diabetic syndrome of adult-onset, obesity and proneness to ketoacidosis, is associated with rapid recovery of β cell function and insulin-independence. Whereas most patients experience prolonged remission, a subset relapses early to insulin dependence. We sought to define factors associated with early relapse.

Methods—We utilized a prospective, longitudinal database to analyze 50 unprovoked A- β + KPD patients with 2 measurements of β cell function and glycemia following baseline assessment.

Results—19 patients (38%) relapsed to insulin dependence <1y after the index DKA episode, while 31 (62%) remained insulin-independent for >1y (median 4.2y). Younger age at baseline (OR=0.947, P=0.033), and lower HOMA2- β (OR=0.982, P=0.001), lower HOMA2-IR (OR=0.582, P=0.046) and higher HbA1c at 1y (OR=1.71, P=0.002) were associated with early relapse. A multivariate model with these variables and the interaction of HOMA2- β and HbA1c at 1y provided a good fit (P<0.05).

Conclusions—Relapse to insulin dependence in unprovoked A- β + KPD patients is associated with younger age and, after 1y, lack of robust increase in β cell functional reserve, and suboptimal glycemic control. Measurements of these parameters 1y after the index DKA episode can be used to assess the need for insulin therapy.

Correspondence: Ashok Balasubramanyam, MD, Diabetes Research Center, ABBR 607, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, Ph: 713-798-8654, Fax: 713-798-4585, ashokb@bcm.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

None of the authors of this paper has a conflict of interest.

Keywords

ketoacidosis; beta-cell; HLA; multivariate; insulin-dependence

1. Introduction

Ketosis-Prone Diabetes (KPD), a widespread, emerging, heterogeneous syndrome characterized by patients who present with diabetic ketoacidosis [1], comprises four clinically and etiologically distinct subgroups classified by presence or absence of islet cell autoantibodies (“A+” or “A-”) and quantitative differences in β cell functional reserve (“ β +” or “ β -”) [2, 7]. Of the four subgroups, A- β + KPD is the most frequent and the most clinically unique. Patients belonging to this subgroup resemble type 2 diabetes patients in that they have adult-onset diabetes, are overweight or obese, lack islet autoantibodies and have substantial β cell functional reserve measured shortly after the index episode of DKA. A- β + KPD itself comprises two distinct phenotypes [5]. Approximately 50% of these patients (“unprovoked” A- β + KPD) present with DKA without a clinically evident precipitating factor at first diagnosis of diabetes, display a striking male predominance, have a low frequency of HLA Class II susceptibility alleles for type 1 diabetes (T1D), lack T cell reactivity to islet autoantigens [6], and demonstrate sustained preservation of β cell function following recovery from the index DKA with ability to discontinue insulin treatment while maintaining excellent glycemic control [3]. In contrast, the other 50%, with “provoked” A- β + KPD, develop DKA in association with a clinically evident precipitating factor such as acute illness, have long-standing diabetes with high frequencies of HLA class II T1D susceptibility alleles and T cell reactivity to islet autoantigens, and demonstrate progressive loss of β cell function and inability to achieve glycemic control without insulin treatment following recovery from the index DKA [5, 6].

Clinically, the most striking characteristic of unprovoked A- β + KPD patients is their ability to discontinue insulin therapy shortly after resolution of the index episode of DKA. We have shown, in prospective, longitudinal analyses, that the majority of this subgroup can discontinue insulin within 8–24 weeks after the index DKA episode, and maintain both excellent glycemic control and preserved β cell functional reserve during follow-up [2]. Other investigators (describing the same syndrome, denoted by different terms such as “ketosis-prone type 2 diabetes”) have reported the capacity of these patients to maintain “near-normoglycemic remission” from insulin therapy [2, 8, 9, 10, 11, 12, 13]. However, these studies have followed the patients for relative short periods of time (ranging from 6 to 12 months) following the index DKA episode, and the long-term natural history of this unique syndrome with respect to β cell function and insulin dependence remains unclear.

In our decade-long follow-up of KPD patients in a dedicated research clinic, we have observed that whereas the majority of unprovoked A- β + KPD remain in insulin-independent, near-normoglycemic remission for many years after recovery from the index DKA episode, approximately one-third relapse to ketosis, hyperglycemia and insulin dependence less than a year later. In the present study, we sought to characterize comprehensively the clinical and biochemical features associated with early compared to late relapse to insulin dependence

among unprovoked A- β + KPD patients, and to define the factors associated with early relapse to insulin dependence. To do so, we followed prospectively a large, longitudinally characterized cohort of patients with this subgroup of KPD, and analyzed the demographic, biochemical, immunogenetic and clinical features, as well as rates of change in β cell functional reserve, related to early relapse to insulin therapy.

2. Methods

2.1 Patients

The study was approved by the Institutional Review Boards for Human Studies of Baylor College of Medicine and the Harris Health System, Houston, Texas. Consecutive patients admitted with diabetic ketoacidosis to Ben Taub General Hospital from January, 1999 to December, 2012 were enrolled. The subjects provided informed consent to be followed prospectively in the KPD research clinic with a standard outpatient management and database protocol.

All patients were classified according to the A β classification scheme for KPD 3–4 weeks after the index DKA episode, based on fasting and stimulated C-peptide levels and circulating islet cell autoantibody levels, as previously described [1, 2]. A- β + KPD was defined by absence of all autoantibodies (i.e., antibodies directed against the 65 kDa glutamic acid decarboxylase (GAD65Ab), islet antigen-2 (IA2Ab) and zinc transporter T8 (ZnT8Ab)), and presence of β cell functional reserve (determined by fasting C-peptide (FCP) or area under the curve (AUC) for C-peptide during a glucagon stimulation test (GST) with validated cutoffs [1, 2]). A- β + KPD patients were further sub classified, on the basis of phenotypic distinctions and criteria previously defined [5] into two groups: “provoked” if they had a clinically evident precipitating event for the index episode of DKA, or “unprovoked” if they lacked such an event and if diabetes was first diagnosed at the time of the index DKA episode.

The index episode of DKA was treated in the hospital according to standard, well-established protocols [1]. Following complete resolution of DKA, a standard outpatient diabetes management protocol was followed, with a gradual, controlled attempt to reduce and eventually discontinue insulin therapy [1, 2]. If insulin was successfully discontinued, the patient was transitioned to therapy with metformin, with close monitoring for development of hyperglycemia and ketonuria. If glycemic control was inadequate with the maximum dose of metformin, sulfonylureas, sitagliptin, thiazolidinediones, acarbose or meglitinides were added to the regimen. If hyperglycemia persisted despite these attempts, or if ketonuria developed, insulin was reinstated.

Unprovoked A- β + KPD patients (n=121) were followed prospectively for 1–10 years with repeated clinical and biochemical measurements. β cell functional reserve was assessed every 6–12 months as described above, and HbA1c was measured by high performance liquid chromatography. We analyzed the data from 50 unprovoked A- β + KPD patients who had >2 annual measurements of both β cell function and glycemic control following baseline assessment after the index DKA episode. This subset of the target population was chosen to avoid any confounding effects of missing data. The proportions of these 50 patients with

early or late relapse to insulin therapy were representative of the complete cohort of 121 patients.

2.2 Statistical Analysis

Patient characteristics at baseline and after 1 year of follow-up (age, sex, race, family history of diabetes, body mass index (BMI), homeostasis model assessment (HOMA)2-% β , HOMA2-IR, HbA1c, fasting C-peptide, and HLA Class II T1D susceptibility (DRB1*07 DRB1*04) and protective (DRB1*15) alleles) were summarized using descriptive statistics. Patient characteristics were compared between two groups – those with relapse to insulin <1 year after the index DKA, and those who did not relapse to insulin 1 year after the index DKA), using the t-test (for normally distributed variables) and the Wilcoxon rank sum test for continuous variables. Fisher exact test was used to compare categorical variables. Univariate and multivariate logistic regression analyses were performed to identify baseline and 1-year characteristics associated with insulin dependence within 1 year of the index DKA event. Logistic regression was used to determine the most important factors associated with insulin dependence. The independent variables were selected based on significance in univariate settings and biological plausibility. Patient characteristics with overall model significance (type I error = 0.05) were then included in the multivariate model. In the multivariate analysis, the significance of the model was assessed using a likelihood ratio test with type I error level = 0.05. The fit of the model was assessed using a likelihood ratio test, Akaike information criterion (AIC), and Bayesian information criterion (BIC). The significance of individual variables was assessed using the Wald test with type I error = 0.05. Linearity of continuous variables was assessed using a locally weighted scatterplot. For non-linear variables, various transformations were explored to determine the best fit. Influential observations affecting the overall fit of the model were tested using Pearson residuals, deviance residuals, Pregibon leverage, difference of chi-squares and difference of deviances.

3. Results

Table 1 shows demographic and biochemical characteristics of the study cohort of 50 unprovoked A- β + KPD patients with 2 annual measurements of β cell function and glycemic control. All 50 patients were successfully withdrawn from insulin therapy (with excellent glycemic control, HbA1c <7% and absence of ketosis) 2–6 months after the index DKA. 38% relapsed to insulin requirement due to a significant rise in fasting glucose levels (persistently >250 mg/dL while on metformin with or without other oral antidiabetic drugs) within 1 year after the index DKA episode (early relapse), while 62% remained insulin independent for >1 year (late relapse or sustained insulin independence) after the index DKA episode (median 4.2 years).

Mean duration of diabetes was 0 years in both early and late relapse patients with unprovoked A- β + KPD, i.e., all patients presented with unprovoked DKA at initial diagnosis of diabetes. Ethnic distribution in the early relapse group was 15.8% Caucasian, 36.9% African American and 47.3% Hispanic, compared to 6.4%, 48.3% and 45% respectively in the late relapse group. Patients in both groups were similar in age, BMI, family history of

diabetes, baseline HbA1c, HOMA2-%B, HOMA2-IR, and fasting C-peptide levels. Similar proportions of both groups were treated with insulin sensitizers and insulin secretagogues ($p=0.20$). We also compared the baseline characteristics of the two groups of unprovoked A- β + KPD patients with those of provoked A- β + KPD patients (Table 2). The main demographic difference was that provoked A- β + KPD patients did not show the male predominance of unprovoked A- β + patients, consistent with our previous report [5]. The improvements in insulin secretory capacity and glycemic control ($p=0.001$) after one year were significantly greater for the unprovoked A- β + KPD patients who remained insulin-independent after 1 year, compared to both provoked A- β + KPD patients and early relapsing unprovoked A- β + KPD patients.

In univariate logistic regression, the following patient characteristics were significantly associated with relapse to insulin dependence <1 year after the index DKA episode: younger age at presentation with DKA (OR=0.947, $p=0.033$), lower HOMA2-%B at 12 months (OR=0.982, $p=0.001$), lower HOMA2-IR at 12 months (OR=0.582, $p=0.046$), higher HbA1c at 12 months (OR=1.71, $p=0.002$), smaller percent increase in HOMA2 %B at 12 months (OR=0.97, $p=0.03$) and smaller percent decrease in HbA1c at 12 months (OR=1.95, $p=0.01$) (Table 2).

A multivariate logistic regression model with these variables provided a good fit ($P<0.05$). The model correctly classified 84% of unprovoked A- β + KPD patients who experienced early relapse to insulin dependence.

4. Discussion

Patients with the phenotype of unprovoked A- β + KPD (denoted as “ketosis prone type 2 diabetes” [4, 11] or “KPD-NID” [10]) have been described by several investigators as having the striking characteristic of prolonged near-normoglycemic, insulinin-dependent “remission” beginning shortly after recovery from the index episode of DKA. However, no previous study has followed a large cohort of accurately classified patients for a sufficiently long period, with repeated objective measurements, to determine the natural history of this unique diabetic syndrome. One retrospective analysis suggested that up to 40% of these patients might relapse to unprovoked hyperglycemia and ketosis over 10 years [10]. Our prospective, longitudinal study, utilizing repeated objective measurements of β cell functional reserve and glycemia, demonstrates that although all unprovoked A- β + KPD patients demonstrate excellent β cell functional reserve and become insulin independent within 6 months after the index DKA episode, some relapse early (within one year) to insulin dependence. Amongst an array of relevant clinical, immunologic and biochemical parameters measured at baseline and 1 year after the index DKA episode, younger age at presentation with DKA, lower HOMA2-%B at 12 months, lower HOMA2-IR at 12 months and higher HbA1c at 12 months (with mean HbA1c value for the group >7%) are most strongly correlated with early relapse to insulin dependence. A multivariate logistic regression analysis incorporating these parameters yielded a model that correctly identified 84% of the unprovoked A- β + KPD patients who experienced early relapse.

Among the baseline measures, only younger age at the time of the index DKA was associated with early relapse. In previous studies, we reported that the fasting C-peptide level obtained within 4–8 weeks after the index DKA is a good predictor of long term β cell function and remission from insulin therapy [1, 2]; however, the follow up period in these reports did not exceed six months. Data from the much longer follow-up period in the current study indicate that baseline measures of β cell functional reserve do not reliably predict remission from insulin treatment beyond the first six months after the index DKA. Rather, they suggest that the lack of a marked increase in β cell function during the first 12 months is associated with relapse to insulin dependence within 1 year, underscoring the importance of repeated measurements of C-peptide levels during this period in all patients with unprovoked A- β + KPD. HOMA2-%B was similar among early and late relapsers at baseline – it also increased over time in both groups concomitantly with the ability to discontinue insulin therapy. However, at 12 months, HOMA2-%B had increased only ~50% over baseline among the early relapsing group, whereas it had increased ~7-fold among those with prolonged insulin independence. These results suggest that a several-fold increase in β cell functional reserve during the first 12 months may be required to permit sustained insulin-independent remission with excellent glycemic control among unprovoked A- β + KPD patients. Patients with less than a doubling of β cell functional reserve over 12 months from the index DKA experience only short-term remission.

These differences in the trajectory and extent of β cell functional recovery following the episode of DKA indicate that even in this well-circumscribed and relatively homogenous syndrome of diabetes, there are different underlying pathophysiologic mechanisms of β cell dysfunction. To a great extent, the clinical definition of unprovoked A- β + KPD rests on negative criteria – absence of islet autoantibodies, low frequency of HLA class II risk alleles, and lack of T cell reactivity to islet autoantigens [5, 6]. However, we have shown that the syndrome is also characterized by certain positively identifiable features, such as male predominance [5] and novel defects in the handling of the ketogenic amino acid leucine together with abnormalities in fat and ketone oxidation [14]. The present analysis indicates that these or additional factors affect either the kinetics of β cell recovery from the index episode of DKA, or the maximal degree of that recovery, which in turn translate to early loss of glycemic control with requirement for exogenous insulin therapy, or prolonged near-normoglycemic remission.

Treatment factors, management differences and compliance with therapy could certainly affect differences in glycemic control and the rate of relapse to insulin during the first 12 months after presentation. As described in “Methods”, all patients were treated and followed in the same dedicated research clinic, following a prescribed protocol for initial insulin management immediately following the episode of DKA, insulin withdrawal, transition to metformin therapy, and possible substitution or addition of another oral agent [1, 2]. We did not systematically assess medication compliance, but there were no differences between early relapsers and those with prolonged insulin independence in regard to clinic visits or frequency of contact with clinic staff.

These data have important clinical implications for the prognosis and follow-up of patients with unprovoked A- β + KPD. It is the experience of virtually all investigators of this

syndrome that the patients can be withdrawn from insulin therapy within 2–6 months after recovery from the DKA episode, and this decision is made on the basis of β cell functional reserve, sustained glycemic control and absence of ketosis within 4–8 weeks after recovery from the index DKA episode [1, 2, 4, 8–12]. The present data indicate that objective findings after 12 months of follow-up can be used reliably to justify this clinical decision and provide reassurance, if β cell function has improved several-fold over baseline, for continued insulin independence.

Acknowledgements

The authors thank Mary Lou Arvizu, RN, for excellent care of the patients in the KPD clinic at Ben Taub General Hospital.

This work was supported by RO1 DK1041411 (to A.B.)

References

1. Balasubramanyam A, Nalini R, Hampe CS, Maldonado M. Syndromes of ketosis-prone diabetes mellitus. *Endocr Rev.* 2008; 29:292–302. [PubMed: 18292467]
2. Maldonado M, Hampe CS, Gaur LK, D'Amico S, Iyer D, Hammerle LP, Bolgiano D, Rodriguez L, Rajan A, Lernmark A, Balasubramanyam A. Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and beta cell functional classification, prospective analysis, and clinical outcomes. *J Clin Endocrinol Metab.* 2003; 88(11):5090–5098. [PubMed: 14602731]. [PubMed: 14602731]
3. Nalini R, Gaur LK, Maldonado M, Hampe CS, Rodriguez L, Garza G, Lernmark A, Balasubramanyam A. HLA class II alleles specify phenotypes of ketosis-prone diabetes. *Diabetes Care.* 2008; 31:1195–1200. [PubMed: 18316396]. [PubMed: 18316396]
4. Umpierrez GE, Smiley D, Kitabchi AE. Narrative review: ketosis-prone type 2 diabetes mellitus. *Ann Intern Med.* 2006; 144(5):350–357. [PubMed: 16520476]. [PubMed: 16520476]
5. Nalini R, Ozer K, Maldonado M, Patel S, Hampe CS, Guthikonda A, Villanueva J, Smith E, Gaur L, Balasubramanyam A. Presence or absence of a known DKA precipitant defines distinct syndromes of A- β + KPD based on long term beta cell function, HLA class II alleles, and gender predilection. *Metabolism.* 2010; 59(10):1448–1455. [PubMed: 20170930]
6. Brooks-Worrell BM, Iyer D, Coraza I, Hampe CS, Nalini R, Ozer K, Narla R, Palmer JP, Balasubramanyam A. Islet-specific T-cell responses and proinflammatory monocytes define subtypes of autoantibody-negative ketosis-prone diabetes. *Diabetes Care.* 2013 Dec; 36(12):4098–4103. Doi: 10.2337/dc12-2328-Epub 2013 Oct. [PubMed: 24130366]
7. Balasubramanyam A, Garza G, Rodriguez L, Hampe CS, Gaur L, Lernmark A, Maldonado M. Accuracy and predictive value of classification schemes for ketosis-prone diabetes. *Diabetes Care.* 2006; 29(12):2575–2579. [PubMed: 17130187]. [PubMed: 17130187]
8. Umpierrez GE, Woo W, Hagopian WA, Isaacs SD, Palmer JP, Gaur LK, et al. Immunogenetic analysis suggests different pathogenesis for obese and lean African-Americans with diabetic ketoacidosis. *Diabetes Care.* 1999; 22:1517–1523. [PMID: 10480519]. [PubMed: 10480519]
9. Banerji MA, Chaiken RL, Huey H, Tuomi T, Norm AJ, Mackay IR, et al. GAD antibody negative NIDDM in adult black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4. *Flatbush diabetes.* *Diabetes.* 1994; 43:741–745. [PMID: 8194658]. [PubMed: 8194658]
10. Mauvais-Jarvis F, Sobngwi E, Porcher R, Riveline JP, Kevorkian JP, Vaisse C, et al. Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of beta-cell dysfunction and insulin resistance. *Diabetes.* 2004; 53:645–653. [PMID: 14988248]. [PubMed: 14988248]
11. Sobngwi E, Gautier JF. Adult-onset idiopathic Type I or ketosis-prone Type II diabetes: evidence to revisit diabetes classification. *Diabetologia.* 2002; 45(2):283–285. [PubMed: 11935161]

12. Sobngwi E, Mauvais-Jarvis F, Vexiau P, Mbanya JC, Gautier JF. Diabetes in Africans. Part 2: Ketosis-prone atypical diabetes mellitus. *Diabetes Metab.* 2002; 28:5–12. [PMID: 11938022]. [PubMed: 11938022]
13. Pinero-Pilona A, Raskin P. Idiopathic Type 1 diabetes. *J Diabetes Complications.* 2001; 15:328–335. [PMID: 11711327]. [PubMed: 11711327]
14. Patel SG 1, Hsu JW, Jahoor F, Coraza I, Bain JR, Stevens RD, Iyer D, Nalini R, Ozer K, Hampe CS, Newgard CB, Balasubramanyam A. Pathogenesis of ketosis-prone diabetes. *Diabetes.* 2013 Mar; 62(3):912–922. Epub 2012 Nov 16. [PubMed: 23160531]

Highlights

- Some patients with Unprovoked A- β + KPD suffer early relapse to insulin requirement.
- Understanding factors associated with early relapse would improve management.
- The factors are younger age, and lower beta cell function and higher HbA1c at 1 year.
- It is important to monitor fasting C-peptide and HbA1c repeatedly in these patients.

Table 1

Clinical, demographic and biochemical characteristics of the two groups of unprovoked A- β + KPD patients.

	Unprovoked A- β + KPD		P
	Required insulin within 1 y (N=19)	Remained insulin-independent >1 y (N=31)	
Race – Caucasian African-American Hispanic Asian	3 (16%) 7 (37%) 9 (47%)	2 (6%) 15 (48%) 14 (45%)	0.49
Family history of diabetes	14 (74%)	23 (74%)	1
Male sex	13 (68%)	21 (68%)	1
Age at baseline (y)	37.39 $\pm$ 10.13	44.71 $\pm$ 12.58	0.04
BMI (kg/m²)	34.57 $\pm$ 8.94	32.61 $\pm$ 8.63	0.42
HOMA2-%B at baseline	38.33 $\pm$ 31.69	34.55 $\pm$ 42.05	0.52
HOMA2-%B at one year	75.42 $\pm$ 58.15	152.01 $\pm$ 72.25	<0.01
HOMA2-IR at baseline	1.64 $\pm$ 1.06	2.18 $\pm$ 1.85	0.16
HOMA2-IR at one year	1.95 $\pm$ 1.34	2.83 $\pm$ 1.36	0.03
HbA1c at baseline (%)	13.24 $\pm$ 2.52	14.31 $\pm$ 2.67	0.17
HbA1c at one year (%)	8.62 $\pm$ 3.39	6.45 $\pm$ 1.02	<0.01
Fasting C-peptide at baseline (ng/ml)	1.81 $\pm$ 1.03	2.02 $\pm$ 1.85	0.66
Fasting C-peptide at one year (ng/ml)	2.68 $\pm$ 1.55	2.72 $\pm$ 1.63	0.89
Fasting plasma glucose at baseline (mg/dl)	201.74 $\pm$ 85.82	207.84 $\pm$ 70.01	0.63
Fasting plasma glucose at one year (mg/dl)	142.56 $\pm$ 51.20	128.68 $\pm$ 67.80	0.05
Oral Medications – Insulin Sensitizers Insulin Secretagogues Both None	14 (74%) 1 (5%) 1 (5%) 3 (16%)	21 (68%) 1 (3%) 9 (29%) 0 (0%)	0.2

Table 2

Clinical, demographic and biochemical characteristics of the two groups of unprovoked A- β + KPD compared to provoked A- β + KPD patients

	Unprovoked A- β + KPD		Provoked A- β + KPD	P
	Required insulin within 1 y (N=19)	Remained insulin-independent >1 y (N=31)	Provoked (N=29)	
Race – Caucasian African-American Hispanic Asian	3 (16%) 7 (37%) 9 (47%) 0 (0%)	2 (6%) 15 (48%) 14 (45%) 0 (0%)	3 (10%) 7 (24%) 18 (62%) 1 (3%)	0.35
Family history of diabetes	14 (74%)	23 (74%)	23 (80%)	1
Male sex	13(68%)	21 (68%)	9 (31%)	0.007
Age at baseline (y)	37.39 $\pm$ 10.13	44.71 $\pm$ 12.58	42.49 $\pm$ 13.84	0.14
BMI (kg/m²)	34.57 $\pm$ 8.94	32.61 $\pm$ 8.63	28.84 $\pm$ 9.25	0.08
HOMA2-%B at baseline	38.33 $\pm$ 31.69	34.55 $\pm$ 42.05	38.09 $\pm$ 47.83	0.84
HOMA2-%B at one year	75.42 $\pm$ 58.15	152.01 $\pm$ 72.25	65.20 $\pm$ 47.94	0.001
HOMA2-IR at baseline	1.64 $\pm$ 1.06	2.18 $\pm$ 1.85	1.85 $\pm$ 0.80	0.61
HOMA2-IR at one year	1.95 $\pm$ 1.34	2.83 $\pm$ 1.36	2.45 $\pm$ 1.62	0.58
HbA1c at baseline (%)	13.24 $\pm$ 2.52	14.31 $\pm$ 2.67	13.53 $\pm$ 2.36	0.31
HbA1c at one year (%)	8.62 $\pm$ 3.39	6.45 $\pm$ 1.02	7.82 $\pm$ 1.98	0.001
Fasting C-peptide at baseline (ng/ml)	1.81 $\pm$ 1.03	2.02 $\pm$ 1.85	1.68 $\pm$ 1.24	0.67
Fasting C-peptide at one year (ng/ml)	2.68 $\pm$ 1.55	2.72 $\pm$ 1.63	2.30 $\pm$ 1.60	0.6
Fasting Plasma Glucose at baseline (mg/dl)	201.74 $\pm$ 85.82	207.84 $\pm$ 70.01	259.77 $\pm$ 66.34	0.07
Fasting Plasma Glucose at one year (mg/dl)	142.56 $\pm$ 51.20	128.68 $\pm$ 67.80	113 $\pm$ 45.72	0.52
Oral Medications – Insulin Sensitizers Insulin Secretagogues Both None	14 (74%) 1 (5%) 1 (5%) 3 (16%)	21 (68%) 1 (3%) 9 (29%) 0 (0%)	12 (41%) 6 (21%) 0 (0%) 11 (38%)	0.47

Factors associated with relapse to insulin requirement among unprovoked A- β + KPD patients within one year of the index DKA episode - univariate analysis.

Table 3

	N	Odds Ratio	Standard Error	95% CI	P
Age	50	0.95	0.03	0.898–0.999	0.03
Sex	50	0.97	0.61	0.284–3.302	0.96
Race – African-American	50	0.31	0.32	0.042–2.302	0.51
Race-Hispanic		0.43	0.43	0.059–3.090	
Family history of diabetes	50	0.97	0.65	0.265–3.573	0.97
BMI	50	1.03	0.04	0.961–1.097	0.44
HOMA2-%B at baseline	40	1.00	0.01	0.986–1.020	0.76
HOMA2-%B at 1 year	37	0.98	0.01	0.969–0.995	0.00
HOMA2-IR at baseline	40	0.75	0.21	0.434–1.306	0.25
HOMA2-IR at 1 year	37	0.58	0.17	0.324–1.047	0.05
HbA1c at baseline	46	0.87	0.11	0.685–1.099	0.23
HbA1c at 1 year	46	1.71	0.42	1.052–2.778	0.00
Fasting C-peptide at baseline	50	0.91	0.20	0.595–1.383	0.63
Fasting C-peptide at 1 year	37	0.99	0.22	0.639–1.526	0.95
DRB1*04	35	1.16	0.99	0.216–6.207	0.86
DRB1*07	35	0.71	0.67	0.111–4.511	0.71
DRB1*15	35	0.42	0.38	0.071–2.449	0.31
% change in HOMA2-%B (odds ratio for every 10% change)	42	0.97	0.01	0.94–1.00	0.03
% change in HOMA-IR (odds ratio for every 10% change)	42	0.98	0.02	0.94–1.03	0.41
% change in HbA1c (odds ratio for every 10% change)	44	1.95	0.51	1.16–3.27	0.01
% change in fasting C-peptide (odds ratio for every 10% change)	37	0.94	0.05	0.85–1.04	0.21