Review Article

DIABETIC KETOACIDOSIS: A COMMON DEBUT OF DIABETES AMONG AFRICAN AMERICANS WITH TYPE 2 DIABETES

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Running Title: DKA in AA with T2D

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Abstract

Objective: More than half of African Americans (AA) with a new diagnosis of diabetic ketoacidosis have clinical and metabolic features of type 2 diabetes during follow-up. This particular presentation of diabetes has been termed as ketosis-prone type 2 diabetes (KPDM) or atypical diabetes.

Methods: We review the epidemiology, diagnosis, pathophysiology and acute and long-term management of AA with KPDM and compare these similarities to patients with type 2 diabetes.

Results: In contrast to the long-term insulin requirement of autoimmune type 1 diabetes, patients with KPDM are able to discontinue insulin after a few months of therapy and maintain acceptable glycemic control for many years on either diet or oral agents. Patients with KPDM have significant impairment of both insulin secretion and insulin action at presentation; however, at the time of near-normoglycemia remission, insulin secretion and action improve to levels similar to hyperglycemic patients with ketosis-resistant type 2 diabetes. At long-term; however, patients with KPDM have a decline in beta-cell function similar to patients with type 2 diabetes. Recent studies indicate that treatment with metformin and DPP4-inhibitors can prolong the period of near-normoglycemia remission for several years compared to placebo therapy.

Conclusion: KPDM is a unique but common presentation of newly diagnosed African Americans with type 2 diabetes.
According to the Centers for Disease Control, the incidence of diabetic ketoacidosis (DKA) is increasing in the United States. Since 1980, the number of hospital discharges for DKA increased from 80,000 in 1988 to ~140,000 in 2009 (1). The majority (66%) of primary DKA episodes occur in patients diagnosed with type 1 diabetes. The rest (34%) of primary DKA episodes occur in patients with type 2 diabetes. DKA, which was previously thought of as a key clinical feature of type 1 diabetes, has been shown to occur in children and adult patients with newly diagnosed type 2 diabetes (2-4). Patients with type 2 diabetes and poor metabolic control can also develop DKA under stressful conditions such as trauma, surgery or infections (2, 4). In addition, DKA can be the clinical presentation of many newly diagnosed children, adolescents and adult patients with type 2 diabetes without a precipitating cause (5-10). Their clinical presentation is acute with severe hyperglycemia and ketosis similar to classic type 1 diabetes, but after a few months of insulin therapy, patients are able to stop insulin therapy and remain in near-normoglycemia remission with diet and/or oral antidiabetic agents (8-12).

During the past two decades, many investigators considered such patients as having a unique subtype of diabetes referred to in the literature as idiopathic type 1 diabetes, atypical diabetes, Flatbush diabetes, diabetes type 1 ½ (somewhere between type 1 and type 2 diabetes), and more recently as ketosis-prone type 2 diabetes mellitus (KPDM). Despite their acute presentation, several cross-sectional and longitudinal studies by our group and others have indicated that DKA...
is a unique common clinical presentation in newly diagnosed patients with type 2 diabetes rather than a unique subtype of “atypical” diabetes.

While there is considerable heterogeneity in patients who present with DKA, in this review, we will discuss the clinical, immunogenic and metabolic features, and management of patients with newly diagnosed diabetes presenting with KPDM and highlight similarities to patients with ketosis-resistant type 2 diabetes.

**Historic background of Ketosis-Prone Diabetes**

Since the 1960’s, several reports from Africa of “temporary diabetes” (13, 14) described patients presenting with DKA, but did not follow typical course of patients with type 1 diabetes. Rather, these patients were able to discontinue insulin after a short course of insulin therapy and be controlled with oral antidiabetic agents. Subsequently, Winter et al. (6) published a report on 12 obese African Americans youth who presented with DKA, but followed an atypical course similar to patients with non-insulin dependent diabetes. These patients despite presenting with DKA, had low prevalence of islet-cell autoantibodies. After initial treatment with insulin, they were able to discontinue and stay off insulin without recurrence of DKA. After discontinuation of insulin, these patients had C-peptide response to a mixed-meal that was similar to patients without diabetes (6). In the 1990’s, studies by our group and by Banerji et al. further characterized Black patients of Caribbean and African origin who presented with DKA and low pancreatic autoantibodies; a majority of whom were able to discontinue insulin after intensive insulin therapy (12, 15, 16). Our group and others showed that obese African American patients, unlike patients with type 1 diabetes, were able to achieve and maintain adequate glycemic control without insulin therapy (near-normoglycemia remission) due to recovery of pancreatic beta (β)-cell function and improvement in insulin sensitivity (11, 12). This presentation and
clinical course of diabetes has been called diabetes type 1b, atypical diabetes or type 1.5 diabetes, or ketosis-prone diabetes (KPDM) to distinguish it from the typical presentation of type 2 diabetes and from the insulin dependent form of diabetes or type 1 diabetes (17, 18) (Table 1).

Clinical Presentation

DKA can present in both patients with newly diagnosed diabetes as well as patients with preexisting diabetes. Most patients with KPDM are overweight or obese with newly diagnosed diabetes and usually present with an acute and short history of hyperglycemic symptoms (12). Even though there are no studies that show the duration and severity of the period of antecedent hyperglycemia prior to DKA, most patients report a short duration (< 4 weeks) of polyuria, polydipsia and weight loss. Patients usually present with markedly elevated glucose of >500 mg/dL, a mean hemoglobin A1c >10% and a pH < 7.30 accompanied by ketoacidosis, such as that seen with presentation of DKA in type 1 diabetes (10, 12, 19, 20). Unlike patients with type 1 diabetes, most patients with KPDM have physical signs consistent with type 2 diabetes such as acanthosis nigricans, obesity, and abdominal adiposity (12). Further, almost 80% of patients with KPDM have a strong family history of type 2 and there is a higher prevalence in men compared to women (17, 21). KPDM has been well described in blacks, (11, 12, 15, 22) but has also been shown to affect other populations at high risk for type 2 diabetes such as the Chinese, Japanese, Hispanic (7, 22, 23) and South Asian populations (24).

Clinical Course

The time to resolution of DKA and response to insulin infusion is similar to that reported in patients with type 1 diabetes. After the acute treatment, patients with KPDM are insulin resistant frequently requiring an initial subcutaneous starting insulin dose of 0.8-1.2 units/kg/day (12). Unlike the insulin dependence seen in type 1 diabetes, after a few weeks, which is quite variable
ranging from 2 to 12 weeks, insulin requirements decrease and approximately 70% of patients who present with obese DKA achieve near-normoglycemia remission (21) and are able to remain off insulin therapy (Table 2). The definition of near-normoglycemia remission varies but near-normoglycemia remission is defined by our group as HbA1c < 7% and the ability to maintain fasting blood glucose < 130 mg/dL off subcutaneous insulin therapy for at least one week (12). McFarlane et al. (11) defined near-normoglycemia remission as being off all anti-hyperglycemic therapy for at least 3 months with an HbA1c < 6.3% and fasting plasma glucose < 124 mg/dL. After presentation of KPDM, with their definition of remission, 42% of patients were able to achieve near-normoglycemia remission and were able to sustain near-normoglycemia remission for at least 20 months. Similar to the results by our group, Mauvais-Jarvis et al. (8) described a cohort of 111 obese African patients of Sub-Saharan origin who presented with DKA; of them, >70% of patients were able to achieve near-normoglycemia remission from insulin lasting for several years.

Several factors affect the long-term clinical course of patients who present with KPDM such as the presence of autoimmune and HLA antibodies and lack/presence of a precipitating cause of DKA. Balasubramanyam et al. (25) and Maldonado et al. (7) proposed a classification system for patients who present with new-onset DKA based on presence of pancreatic autoantibodies (A+/−) and β-cell reserve (β +/-). β-cell reserve was defined as fasting C-peptide >1 ng/ml or stimulated C-peptide level ≥ 1.5 ng/ml one year after the initial DKA episode. This classification system showed that patients who presented with DKA with A-β+ status follow a clinical course to that of patients described by our group (12, 26) and Banerji et al (27, 28). Unlike the patients with A+ β- who were patients with type 1 diabetes, patients who are A-β+ show β-cell recovery with intensive insulin treatment and are able to maintain near-normoglycemia remission from insulin.
for many years. Further studies by the group also examined the role of masked or overt antibodies to the DPD epitope of the 65-kDa glutamate decarboxylase (GAD-65). In patients who presented with masked autoantibodies to DPD epitope of GAD-65, there was increased β-cell reserve even in the presence of pancreatic autoantibodies and lack of these masked antibodies to the DPD epitope were associated with type 1 diabetes susceptibility HLA alleles (29).

The clinical course also differs for patients with a lack/presence of a precipitating cause for the DKA. Nalini et al. (30) characterized the differences in long-term outcomes in a subset of patients who are A-/β+ and presenting with new-onset provoked compared to unprovoked DKA. The patients with precipitating cause for the DKA were mostly Hispanic, presented with a lower glucose and HBA1c level at presentation along with lower measures of pancreatic β-cell function over the long-term compared to patients with unprovoked new-onset diabetes. Patients who did not have a precipitating cause of DKA were mostly African American, males and had higher HbA1c at presentation. However, over the long-term, patients with unprovoked DKA had higher beta-cell function and were characterized by recovery of insulin secretion after a few weeks of insulin treatment (30). Further studies by the group showed that in patients who present with unprovoked DKA and are A-β+, there is an increased frequency of the protective HLA class II DQB1*0602 allele (30) and a lack of islet-specific T-cell response (31).

The long-term clinical course of patients who present with new-onset unprovoked DKA with negative pancreatic autoantibodies is similar to that of patients with type 2 diabetes. Despite the ability to achieve remission from insulin and antidiabetic agents, many patients with KPDM exhibit insulin resistance of muscle, adipose tissue and liver, similar to patients with type 2 diabetes (32). Mauvais-Jarvis et al. (8) followed a cohort of 111 obese African patients of Sub-
Saharan origin who presented with unprovoked DKA for 10 years; of them, >70% of patients were able to achieve near-normoglycemia remission from insulin lasting for several years. In a subset of these patients, they also measured longitudinal measures of β-cell function using glucagon stimulated C-peptide levels and compared them to patients with type 2 diabetes that presented without DKA and patients with type 1 diabetes. In the patients who attained β-cell recovery, long-term decline in β-cell function was similar to patients with type 2 diabetes. Even though, 40% of patients remained in remission for up to 10 years, most patients needed oral antidiabetic agents and almost 50% needed to be on insulin due to declining endogenous insulin secretion. Despite a few patients having ketotic relapses, the clinical course seen in patients who achieve remission is similar to that seen in patients with a more typical presentation of type 2 diabetes, where declining β-cell function frequently necessitated escalation of therapy (33). Our group and others have also studied obese African American patients who presented with hyperglycemia without ketosis with similar glucose levels as obese patients who present with DKA. These patients who are ketosis-resistant have a similar clinical course as patients who present with DKA. At presentation, these patients who present with severe hyperglycemia also require similar amounts of insulin as patients who present with DKA (21). With intensive insulin treatment, these ketosis-resistant patients also achieve near-normoglycemia remission from insulin (11, 12, 27). Our group along with McFarlane et al. showed that similar remission from insulin occurs in obese African American patients who present with severe hyperglycemia (glucose levels > 400 mg/dl) without the presence of ketoacidosis (11, 12, 21, 26).

Pathophysiology of KPDM

Pancreatic beta-cell function in KPDM
The unique aspect of KPDM is the initial episode of ketoacidosis despite the physical features of type 2 diabetes. While several studies show the initial decompensation of β-cell function and subsequent recovery, the etiology for why patients have initial β-cell decompensation and recovery is not known and the reason for propensity for ketosis is poorly understood. The study by Patel et al. (30) used the novel approach of dynamic testing with tracers and metabolomics to show that patients with KPDM have reduced β-hydroxybutyrate oxidation along with increased branched chain amino acid catabolism leading toward ketogenesis. While the development of DKA is unique, the long-term β-cell decline seen in ketosis-prone diabetes is similar to patients with ketosis-resistant type 2 diabetes.

Since ketotic relapses are preceded by a period of hyperglycemia (8), our group determined if exposure to sustained elevated glucose and free fatty acid (FFA) levels induce β-cell decompensation by causing gluco- and lipo-toxicity (31). Obese patients who presented with DKA and severe hyperglycemia received 10% dextrose infusion at 200 mg/m2/min for 20-hours during near-normoglycemia remission. β-cell function was assessed by arginine stimulation before and after glucose load. We reported a remarkable improvement in β-cell function, with comparable response to sequential arginine stimulation comparable to the response observed in obese patients with history of type 2 diabetes and obese non-diabetic controls (31). We also investigated if patients with KPDM were susceptible to experience acute lipotoxicity by infusing high levels of free fatty acids (FFAs) (32) in patients who already achieved near-normoglycemia remission. Despite increasing FFAs levels four-fold from baseline during intralipid infusion for 48 hours, we found that increased FFAs were not associated with impaired insulin secretion or β-cell lipotoxicity. The results of these studies found that at near-normoglycemia remission, even
with exposure to large amounts of glucose and free fatty acids, the β-cells responded appropriately to arginine stimulation as ketosis-resistant patients with type 2 diabetes.

Autoimmune etiology

Given the presentation of DKA, several studies have examined the role of HLA subtypes in KPDM. An extensive discussion on the role of HLA markers and pancreatic autoantibodies in the clinical course of KPDM was discussed previously. Not all but some studies showed that patients with KPDM lack the autoimmune antibodies such as GAD-65 antibodies, islet cell antibodies and insulin autoantibodies (6, 15). However, in the study by Banerji et al. there was an increased prevalence of HLADR3 and DR4 alleles in the black patients who presented with DKA, which are known to confer risk of type 1 diabetes (15). Our study in patients presenting with KPDM and with severe hyperglycemia showed that patients with KPDM have similar pancreatic autoantibody and HLA type 1 risk allele prevalence to patients who presented with type 2 diabetes and hyperglycemia (16).

Viral Etiology

Due to the association between type 1 diabetes and DKA and studies with viral infections causing acute insulin resistance (33-36), a reversible viral etiology by the herpes virus was investigated as the etiology of KPDM. A cross-sectional study found increased prevalence of antibodies to HHV8 in KPDM compared to type 2 diabetes that did not present with diabetes (37). However, a follow-up study showed that HHV8 status does not correlate with insulin sensitivity, non-esterified fatty acid release or endogenous glucose production during a euglycemic-hyperinsulinemic clamp study (38).

Genetic Etiology
A study of Maldonado et al. proposed that DKA patients with A-/β+ included a heterogeneous type of diabetes with glucose toxicity playing a role in β-cell dysfunction (7). Further, they also showed that KPDM is not a monogenic form of diabetes (44) and genetic studies showed that KPDM does not have a unique genetic etiology. While there were no specific genetic mutations found, several studies investigated the role of candidate genes in KPDM. A missense mutation Gly574Ser in the MODY candidate gene HNF-1α, was found to be significantly associated with KPDM in children (45). However, the same mutation occurred in similar frequency in adult patients with KPDM, type 1 diabetes and with type 2 diabetes (46). The same group showed that patients with KPDM have an increased prevalence of a mutation in PAX-4 (47) and NGN3 (48), both genes involved in β-cell development. Given the high prevalence of KPDM in males, they also examined the role of an X-linked disorder in glucose-6-phosphate dehydrogenase (G6PD) deficiency in the pathogenesis of KPDM. Even though, they found an increased G6PD deficiency in patients who presented with KPDM, they did not find an increased prevalence of gene mutations (49) and were not able to find any association between hyperglycemia and G6PD activity (50).

**Maintaining Near-Normoglycemia Remission**

In KPDM, after initial treatment, the period of near-normoglycemia remission is variable. The period of near-normoglycemia has varied from 6 months to 120 months (8). Despite the initial remission from insulin, many patients continue to have insulin resistance and develop hyperglycemia. Similar to patients with type 2 diabetes, glycemic control can be maintained with oral agents. We and others have shown that treatment with sulfonylureas can prolong the period of near-normoglycemia remission (25, 41). More recently, we also showed that treatment of metformin or sitagliptin is equally efficacious in prolongation of near-normoglycemia remission.
We studied 48 African American patients who presented with severe hyperglycemia and DKA. We randomized the patients who achieved remission from insulin to metformin, sitagliptin or placebo. Serial oral glucose tolerance tests were performed to assess measures of insulin sensitivity and beta-cell function. We found that patients who received metformin or sitagliptin sustained near-normoglycemia remission significantly longer than patients randomized to placebo (Figure 1) (21). The prolongation of near-normoglycemia remission was due to higher $\beta$-cell function in the patients who sustained near-normoglycemia remission compared to those that had hyperglycemic relapse.

This type of remission in KPDM is similar to that reported in patients with type 2 diabetes where early intensive insulin therapy shows improvement in $\beta$-cell function (27). In a study of 382 patients in China, short-term treatment with insulin in patients with type 2 diabetes restored $\beta$-cell function when compared to oral hypoglycemia agents with patients achieving remission from treatment in approximately 5-6 days (26). After one year of follow-up, the patients that continued to remain in remission had higher insulin secretion compared to patients who did not achieve or maintain remission. A pilot study looked at the effect of sitagliptin in prolonging remission off anti-diabetic therapy after short-term intensive insulin therapy in patients with early type 2 diabetes (51). This study showed that $\beta$-cell function declined similarly in patients with randomized to placebo or sitagliptin. A possible reason for the lack of difference between the groups could be that both groups received metformin in addition to the study drug. Similar to our trial, it is possible that metformin was enough to sustain near-normoglycemia remission. However, the same group conducted a subsequent study showing that remission can be prolonged by treatment with a GLP-1 receptor agonist due to increased beta-cell function (27).
KPDM has been described as a unique subtype of diabetes or atypical diabetes. However, the current data shows that the clinical course, prevalence of autoimmune markers, and improvement of insulin secretion and insulin action of KPDM patients is similar to patients with type 2 diabetes over the long-term. Their initial presentation is characterized by significant impairment in β-cell function and insulin resistance, which can improve with intensive short-term insulin therapy in obese patients to levels similar to patients with ketosis-resistant type 2 diabetes. These data suggest that KPDM is not a unique subtype of diabetes, but rather that it is a common presentation in newly diagnosed obese African Americans with ketoacidosis. Even though most of the studies were performed in African Americans, KPDM also presents in other minority populations. Future studies are needed to characterize the underlying mechanisms of ketoacidosis and outline differences in clinical course in different minority populations.

Funding and Duality of Interest.

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**Table 1**: Differences and Similarities between Type 1, Type 2 and Ketosis-Prone Diabetes Mellitus

<table>
<thead>
<tr>
<th></th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
<th>KPDM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of presentation</strong></td>
<td>Childhood, adolescence</td>
<td>Adolescence, adulthood</td>
<td>Adolescence, adulthood</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>Lean</td>
<td>Overweight-Obese</td>
<td>Overweight-Obese</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td>Predominantly Caucasian</td>
<td>Multi-ethnic</td>
<td>Predominantly Blacks and other minorities</td>
</tr>
<tr>
<td><strong>Family history of type 2 diabetes</strong></td>
<td>No</td>
<td>Frequent</td>
<td>Frequent</td>
</tr>
<tr>
<td><strong>Male:Female ratio</strong></td>
<td>1:1</td>
<td>1:1</td>
<td>3:1</td>
</tr>
<tr>
<td><strong>Acanthosis</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Presentation**

<table>
<thead>
<tr>
<th></th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
<th>KPDM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ketosis</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Insulin secretion</strong></td>
<td>None</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td><strong>Insulin sensitivity</strong></td>
<td>Higher than non-diabetics</td>
<td>Similar to obese non diabetics</td>
<td>Lower than obese non diabetics</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Insulin</td>
<td>Oral hypoglycemic agents/Insulin</td>
<td>Insulin</td>
</tr>
</tbody>
</table>

**Remission from insulin**

<table>
<thead>
<tr>
<th></th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
<th>KPDM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ketosis</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Insulin secretion</strong></td>
<td>Absent</td>
<td>Present but decreases over time</td>
<td>Markedly reduced at presentation. β-cell recovery with intensive therapy. Decreases over time</td>
</tr>
<tr>
<td><strong>Insulin sensitivity</strong></td>
<td>Higher than non-diabetics</td>
<td>Reduced. Similar to obese non diabetics</td>
<td>Reduced. Similar to obese non diabetics</td>
</tr>
<tr>
<td><strong>Long-term treatment</strong></td>
<td>Insulin</td>
<td>Treat with oral agents, may progress to insulin</td>
<td>Transient insulin requirement at presentation. Oral agents may prolong insulin remission phase</td>
</tr>
</tbody>
</table>
Table 2: Clinical Course of Patients Presenting with Ketosis-Prone Diabetes Mellitus

<table>
<thead>
<tr>
<th></th>
<th>At Presentation</th>
<th>Near-Normoglycemia Remission</th>
<th>Long-Term Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Polyuria, polydipsia, weight loss</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Plasma glucose, mg/dl</td>
<td>&gt; 400</td>
<td>&lt; 126</td>
<td>Variable, risk of recurrence</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>&gt; 10</td>
<td>&lt; 7%</td>
<td>Variable</td>
</tr>
<tr>
<td>pH</td>
<td>&lt; 7.30</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Bicarbonate, mmol</td>
<td>&lt; 18</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>β-hydroxybutyrate, mmol/l</td>
<td>Positive, &gt; 3</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>B-cell autoantibodies</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Fasting and stimulated insulin secretion</td>
<td>Markedly reduced</td>
<td>Improved, similar to patients with T2D</td>
<td>Variable, progressive decline as in T2D</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Markedly reduced</td>
<td>Improved, similar to patients with T2D</td>
<td>Variable, progressive decline as in T2D</td>
</tr>
<tr>
<td>Need for insulin treatment</td>
<td>Yes</td>
<td>None</td>
<td>May be needed with long-term follow-up</td>
</tr>
<tr>
<td>Response to oral antidiabetic agents</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Figure 1**: Cox Proportional Hazards of Failure Free Survival Between Metformin, Sitagliptin, and Placebo in Obese African American Patients Presenting with DKA and Severe Hyperglycemia.

Figure Legend: There was a significant difference was found between the placebo, metformin and sitagliptin groups (p=0.015). There was no significant difference between the sitagliptin and metformin groups (p=0.75)

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The graph shows the comparison of hyperglycemia relapse-free survival among three groups: Metformin, Sitagliptin, and Placebo. The log-rank test revealed a significant difference with p = 0.015.

- **Number at Risk**:
  - Metformin, n = 17, 15, 11
  - Sitagliptin, n = 16, 8, 7
  - Placebo, n = 15, 8, 7

- **Days**:
  - 6
  - 4
  - 2
  - 1

The survival rates are noted as follows:
- **Metformin**
- **Sitagliptin**
- **Placebo**