1 Sick-Day Management in type 1 Diabetes

2 Detection of Ketonemia and its Relationship with Hyperglycemia in type 1 Diabetic Patients

3 When Should Determination of Ketonemia be Recommended?
Risk of metabolic decompensation and Diabetic Ketoacidosis (DKA)

- Any intercurrent illness [even relatively mild] can disrupt metabolic balance in patients with type 1 diabetes
- In these patients such illnesses can cause increased secretion of counterregulatory hormones which increase hepatic glucose production, induce state of insulin resistance with decreased peripheral glucose use, and stimulate ketogenesis
- If associated metabolic disturbances of hyperglycemia and ketosis are not adequately monitored and treated relatively mild illness can progress to life-threatening consequences in a person with type 1 diabetes

Demographics of DKA

- DKA is one of the acute, life threatening complications of diabetes, mainly occurring in patients with type 1 insulin-dependent diabetes mellitus
- The overwhelming majority of patients of all ages who require treatment for DKA have previously diagnosed diabetes; only 10% of patients with DKA have previously undiagnosed diabetes
- DKA is the presenting complaint in 20% to 30% of patients with type 1 diabetes and in as many as 40% of patients with Type 1 diabetes undiagnosed at less than 4 years of age
- In the US, mortality from DKA is fairly stable but remains significant

Causes of hyperglycemia, ketosis and DKA

In patients with type 1 diabetes, insulin needs increase associated with infection, injury, surgery, inadequate insulin replacement secondary to poor compliance or accidental or intentional errors in medication or other stressful stimulican trigger a DKA episode

- New-onset diabetes
- Infection
- Trauma
- Surgery
- Emotional stress
- Errors in insulin administration
- Pump failure
- Intentional manipulation of insulin dosing
- Myocardial infarction
- Medications
- Substance abuse
- Eating disorders
- Comorbidities
Ketone bodies: physiology, significance and measurement

- Ketone bodies, a by-product of fat metabolism, are produced in the liver as an alternative energy source when insufficient insulin is available to use glucose effectively.
- The two main ketone bodies are acetoacetate (AcAc) and β-hydroxybutyrate (β-OHB); acetone is the third and least important ketone body.
- Ketogenesis is the process by which fatty acids released from the adipocytes are converted into AcAc and β-OHB in the mitochondria of hepatocytes.
- Ketosis is the term that refers to the excessive presence of ketones in the blood; ketonuria refers to the presence of ketones in the urine.
- Marked concentrations in circulating levels of ketone bodies are present in DKA.

Most investigators agree on the threshold for pathological values of ketonemia:

<table>
<thead>
<tr>
<th>Serum levels of ketone bodies</th>
<th>Clinical interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.5 mmol/L</td>
<td>Normal</td>
</tr>
<tr>
<td>&gt; 1 mmol/L</td>
<td>Hyperketonemia</td>
</tr>
<tr>
<td>&gt; 3 mmol/L</td>
<td>Ketoacidosis</td>
</tr>
</tbody>
</table>

- Hyperketonemia and ketoacidosis are considered to be forms of ketosis.
- Physiologic ketosis occurs when mildly to moderately elevated levels of circulating ketone bodies are present in response to fasting (especially during infancy or pregnancy), prolonged exercise, or a ketogenic (high fat) diet; understanding the physiologic states associated with mild ketosis can help determine the significance of elevated ketone levels in persons with diabetes.
- DKA is the most common pathologic cause of ketosis. The ketone body ratio, defined as the ratio of circulating β-OHB to AcAc, is approximately equal to 1 following a meal, whereas it rises to values of 10 or more during DKA.
- In patients with Type 1 diabetes, ketosis occurring in association with hyperglycemia confirms the presence of insulin deficiency and the need for supplemental insulin to avoid further deterioration and the development of DKA.
- There are potential advantages to measuring blood β-OHB over traditional urine ketone determination.

Some studies have shown that β-OHB levels determination can be very useful in some clinical situations:

**Usefulness of 3HB determination**

- Useful in the detection of underinsulinization and avoidance of DKA.
- Useful as a sensitive metabolic marker of the adequacy of insulin therapy (especially levels determined before breakfast).
- Useful in patients with poorly controlled diabetes (elevations in blood levels are extremely common in these patients); ketonemia can be underestimated in the presence of ketonuria.
Conventional ketone testing with nitroprusside test has been associated with several problems:

### Problems associated with conventional ketone testing

- Patients negative perception (unpleasant and time consuming experience)
- Expiration of strips or incorrect home storage
- Significant rate of false-positive and false-negative results
- Test based on nitroprusside reagent which only detects AcAc and not β-OHB
- There may be dissociation between urine ketone levels and serum β-OHB levels

### Prevention

- **Approximatively 50% of admissions to the hospital for DKA may be preventable** with improved outpatient treatment programs and better adherence to self-care. With frequent monitoring of metabolic parameters, including glycemia and ketosis, timely interventions with supplemental insulin and enteral fluids **can avert the need for emergency room management or hospitalization**
- Prevention is the most important opportunity for improved outcomes of DKA in patients with known diabetes. **Steps should include increased awareness of sick-day management and improved patient (and family) education regarding diabetes management (monitoring blood glucose and identifying the presence of ketone bodies)**
Cornerstones of sick-day management

1 Never omit insulin
   - Insulin must always be administered during illness, even at times when eating is markedly diminished
   - Infection induces insulin resistance, often necessitating increased or supplemental doses of insulin
   - The patient should always receive the usually prescribed insulin dose supplemented by fast- or rapid-acting insulin in the form of regular or lispro
   - The additional or supplemental dose is needed to manage the hyperglycemia and ketosis
   - The blood sugar level and the presence of ketones help to determine the optimal supplemental insulin dosage

2 Prevent dehydration and hypoglycemia
   - Fluid intake must be encouraged to prevent dehydration
   - Oral hydration is preferred but may be impossible at times of nausea and vomiting- if recurrent vomiting exists, the health care team should be called immediately
   - Attempts at oral hydration with frequent small quantities of clear fluids are recommended
   - A reassessment of hydration status is important to avoid decompensation. Evidence of dehydration, such as weight loss, sunken eyes or dry tongue, indicates a need for prompt medical assessment

3 Monitor blood sugar frequently
   - Self monitoring or family monitoring of blood sugar should be performed at least every 2 to 4 hours. More frequent monitoring is recommended if the blood glucose is low

4 Monitor for ketosis
   - Blood measurement of b-OHB can be a good guide to insulin therapy in home management of ketosis
   - During any intercurrent illness, blood sugars and ketone levels should be monitored every 2 to 4 hours. When the glucose exceeds 300 mg/dL on two or more occasions, patients and their families should monitor for the presence of ketones

5 Provide supplemental fast-acting or rapid-acting insulin
   - Supplemental doses of fast-acting (regular) or rapidly acting (lispro) insulin should be administered in addition to usual insulin dosages whenever hyperglycemia and ketosis are present
   - The degree of hyperglycemia and the presence or absence of ketones determine the amount of supplemental insulin

6 Treat underlying triggers
   - Any acute infectious process should be evaluated and treated accordingly
   - Patients with a history of recurrent DKA, patients with known eating disorders or psychosocial problems, and patients with poor glycemic control are at risk for decompensation and should be advised to call their health care team at the onset of symptoms and signs of illness or decompensation

7 Maintain frequent contact with the medical team
   - Patients and their family should be advised to look for signs that medical attention is needed: vomiting more than 2 to 4 hours duration, blood glucose that exceeds 300 mg/dL or persistent ketones for more than 12 hours, signs of dehydration, symptoms suggesting DKA (nausea, abdominal or chest pain, vomiting, ketotic breath, hyperventilation or altered consciousness)
Conclusions

- Illness and stress are common occurrences; for the person with Type 1 diabetes, these events can be triggers for counterregulation and subsequent metabolic deterioration if there is no attention to diabetes management tasks
- Sick-day management requires increased monitoring of blood glucose and assessment for ketosis
- Although urine testing for ketones has been the standard approach to sick-day management, new technology for self-monitoring of blood β-OHB levels is now available
Background

Although it is advisable to measure blood ketones when glycemia exceeds 250–300 mg/dL, the relationship between blood ketones and glycemia levels is still not fully understood.

Aims

- To assess the prevalence of ketosis in Type 1 diabetic patients with casual hyperglycemia (> 250 mg/dL)
- To establish the relationship between glycemia and ketonemia during daily life (to find a cutoff point at which blood ketone testing is advisable)
- To determine the potential practical advantage of measuring capillary blood ketones over urine ketones during daily life

Patients and methods

- 562 patients who had Type 1 diabetes for more than 3 months, aged 20–75 years, admitted to diabetes clinic in any of the seven Spanish Endocrinology units were included in the study
- Baseline HbA1c was 7–11% in all patients at the time of screening; all of them were in daily insulin injections and their weight had been stable for two months prior the study
- The majority of blood glucose monitoring was carried out during the postprandial state; patients who had glycemia values > 250 mg/dL were measured for ketones, both in the urine and capillary blood
- Positive ketosis was defined as values of β-hydroxybutyrate (β-OHB) ≥ 0.5 mmol/L for capillary blood and ketone bodies ≥ 4 mmol/L for ketonuria

Results

- Of 562 screened patients, 155 (81 men and 74 women) had glycemic values > 250 mg/dL (27.58%); in this hyperglycemic population, the prevalence of asymptomatic ketonemia was 8.39%
- 110 out of 155 patients (70.96%) had blood ketone levels between 0 and 0.1 mmol/L and 32 out of 155 patients (20.63%) had blood ketone levels between 0.2 and 0.4 mmol/L; surprisingly the mean glycemia levels were consistently high (around 300 mg/dL) in these two subgroups

![Blood ketone levels in hyperglycemic patients* (n=155)](image)

*mean glycemia levels in these subgroups was consistently around 300 mg/dL
As a result of the statistical approach made in this study, the glucose cutoff point from which ketonemia measurement is advisable was around 270 mg/dL.

Some discrepancies between determination of ketonuria and ketonemia were observed: in 20 patients with positive ketonuria, ketonemia was not detected, probably because ketosis was already resolved. Besides, urine ketone testing was not possible in some patients due to difficulties in obtaining a urine sample.

Conclusions

- Asymptomatic ketosis can occur in hyperglycemic Type 1 diabetic population with a significant prevalence
- Relationship between glycemia and ketonemia is not always constant: in this study a variety of glycemia/ketonemia pairs were observed; therefore glycemia is not the only parameter which has to be taken into account for metabolic control
- Blood ketone testing is simpler and more user-friendly than urine ketone testing

Remarks

This study supports the opinion that the presence of ketosis, detected by β-OHB levels, even below levels considered as pathologic, together with hyperglycemia, must be taken into account for proper monitoring and therapeutic control of diabetic patients.
Background

Hyperketonemia is frequently encountered in Type 1 diabetic patients. Whether hyperketonemia can contribute to the increase in lipid peroxidation levels in diabetes is not known.

Aim

To analyse the effect of ketosis on plasma peroxidation levels in diabetic patients.

Patients and Methods

- Plasma levels of lipid peroxidation products (malondialdehyde, MDA) and ketone bodies (acetoacetate and β-hydroxybutyrate) were determined in 70 diabetic patients and age-matched with 25 normal volunteers.
- Total ketone body levels >1.0 mmol/L were considered as hyperketonemia; levels ≤1.0 mmol/L as normoketonemia.

Results

- After normalization versus total lipids, levels of lipid peroxidation were significantly higher in the plasma of hyperketonemic diabetic patients (p < 0.05), but not in normoketonemic diabetic patients, compared with age-matched volunteers.
- In addition, low ketonemia was associated with lower lipid peroxidation levels in the same patient (n=7) at two different clinic visits.

Conclusions

- This study suggests that hyperketonemia can increase blood lipid peroxidation levels in diabetes and may provide a biochemical explanation for the increased risk of vascular disease in diabetic patients with frequent episodes of ketosis.