

## TREATMENT OF DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS

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### ABSTRACT

The incidence of Type 1 Diabetes continues to increase around the world. Advances in technology of insulin delivery systems including closed loop and continuous glucose monitoring are improving the possibilities of maintaining desirable glucose control. Type 2 Diabetes is increasing in the adolescent age groups across the world, in certain populations especially including Native Americans, Pacific Islanders, Hispanics, African Americans, and South East Asians. For Type 2 Diabetes, the pharmacological armamentarium has markedly increased by the addition of GLP-1 agonists, DPP4 antagonists, and SGLT2 inhibitors, each of which has improved metabolic control and cardiovascular outcomes. To date, these newer modalities are being tested in adolescents with T2DM but several are not yet officially approved for this age group. Diabetic Ketoacidosis (DKA) remains the initial presentation of some 30%-40% of pediatric patients, and DKA remains the leading cause of death, sometimes associated with Cerebral Edema; complications are also very high in children/adolescents presenting with Hyperglycemia/Hyperosmolar syndrome in the context of a T2DM clinical picture. Appropriate treatment in medical centers with trained personnel and modern laboratory facilities has markedly reduced the mortality and morbidity associated with DKA and Hyperglycemic-Hyperosmolar Syndrome.

### DIABETIC KETOACIDOSIS

#### Pathophysiology

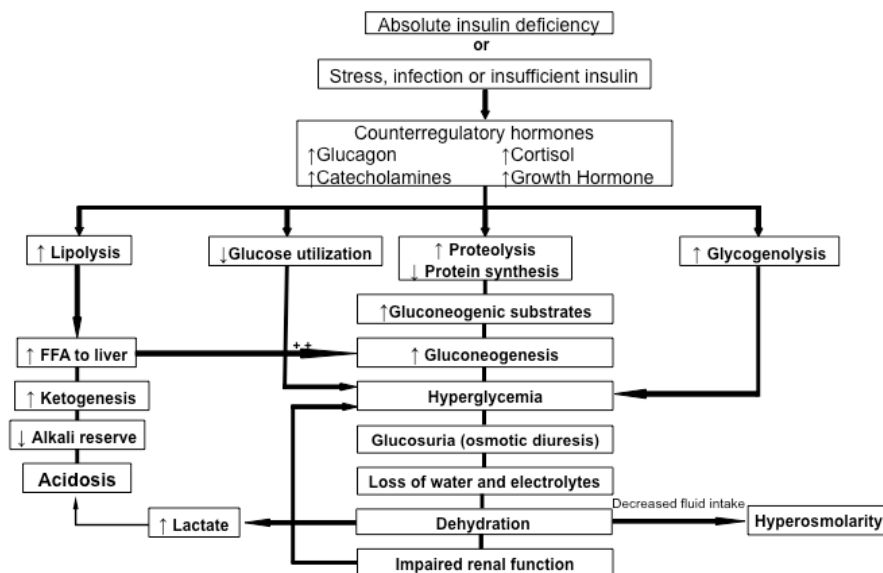
Diabetic ketoacidosis (DKA) is a life-threatening metabolic decompensation considered to be a medical emergency and caused by a combination of insulin deficiency and the action of counter-regulatory hormones(1). The biochemical, metabolic and acid-base abnormalities that occur have been extensively documented at a physiologic level and to some extent at a molecular level (2-4). Briefly, deficiency of insulin prevents the entry of glucose into insulin-sensitive cells in tissues such as liver, muscle, and fat and its appropriate metabolism. Sensing intra-cellular glucopenia, the organism responds by increased secretion of the 4 counter-regulatory hormones, glucagon, cortisol, growth hormone, and catecholamines. Acting synergistically, these hormones increase glucose production via glycogen breakdown and gluconeogenesis, induce lipolysis and ketogenesis and result in hyperglycemia, osmotic polyuria, dehydration, increased thirst, and acidosis from the accumulation of ketoacids, principally  $\beta$ -hydroxybutyrate, (B-OHB) which exceed buffering capacity, as well as lactic acidosis from the ensuing dehydration and limited tissue perfusion. Hence, the symptoms and signs are polyuria, polydipsia, dehydration, tachycardia, deep sighing respiration (Kussmaul breathing), and the smell of acetone on the breath, and abdominal pain and nausea imitating an acute abdominal condition; paradoxically, despite

dehydration, blood pressure may be normal or elevated reflecting the effects of catecholamines (Table 1). These manifestations develop over hours or days, in contrast to hypoglycemia which can occur suddenly. In cases of new diabetes, weight loss, increased appetite, and nocturia, or enuresis in previously toilet-trained child, are almost universally present if a careful history is elicited. Left untreated, clouding of consciousness due decreased cerebral oxygen perfusion, acidosis, and neural biochemical changes lead to coma and eventually death. Absolute insulin deficiency occurs most often at onset of

evolving T1DM, but it may also occur after deliberate or inadvertent omission of insulin in a child or adolescent responsible for their own care, or with kinking or obstruction of tubing in insulin pumps. Relative insulin deficiency occurs with major physiological stressors such as sepsis, infection, or severe trauma that result in profound increased secretion of the counter-regulatory hormones which overwhelm the actions of insulin. Recurrent episodes of DKA are almost the result of psycho-social mal-adjustment. These concepts are summarized in figure 1.

<b>TABLE 1. Clinical and Biochemical Manifestations of Diabetic Ketoacidosis</b>	
<b>Clinical</b>	<b>Biochemical</b>
Dehydration	Hyperglycemia (11-50mmol/l)
Rapid, deep, sighing (Kussmaul respiration)	Variable degrees of acidosis (PH<7.3; HCO <sub>3</sub> <15meq/l)
Nausea, vomiting, and abdominal pain mimicking an acute abdomen	Ketosis-serum BOHB (>3mmol/l)
Progressive obtundation and loss of consciousness	Elevation of BUN and Creatinine Increased leukocyte count with left shift
Fever only when infection is present	Non-specific elevation of serum amylase

## Pathophysiology of Diabetic Ketoacidosis



**Figure 1. Pathophysiology of diabetic ketoacidosis(7).** Copyright © 2006 American Diabetes Association. From *Diabetes Care*, Vol. 29, 2006:1150-1159. Reprinted with permission of *The American Diabetes Association*

### Criteria for Defining DKA

The criteria for a diagnosis of DKA are hyperglycemia with glucose  $\geq 200\text{mg/dl}$  ( $\geq 11\text{mmol/l}$ ), pH  $\leq 7.30$  or bicarbonate ( $\text{HCO}_3$ )  $\leq 15\text{mmol/l}$ , and ketonuria or B-OHB  $\geq 2.0\text{mmol/l}$ . Severity of DKA is defined by the degree of acidosis; mild=pH 7.20-7.30,  $\text{HCO}_3$  10-15mmol/l; moderate=pH 7.1-7.2,  $\text{HCO}_3$  5-10mmol/l; severe =pH $<7.1$ ,  $\text{HCO}_3<5$  mmol/l. Hyperglycemia usually ranges between 200-1000mg/dl (16.6-50.5mmol/l); values  $>1000\text{mg/dl}$  should raise the possibility of hyperosmolar hyperglycemia, separately discussed below. The reported frequency of DKA varies from about 13% to 80% in various countries and

is generally higher in less developed countries; it is inversely related to socio-economic development, level of education of the family, and to the incidence of diabetes mellitus in the location. In the United States, about 30-40% of newly diagnosed patients with DM present in DKA, reflecting delay in establishing the diagnosis of diabetes in a child, particularly in children  $<5$  years of age (8-11).

Table 2 illustrates the average losses of fluids and electrolytes in diabetic ketoacidosis and maintenance requirements in normal children adapted from references (4, 7, 9).

TABLE 2. Fluid and Electrolyte Losses and Maintenance Requirements in DKA		
	Average (range) losses	24-hour maintenance requirements
Water	70 mL/kg (30-100)	≤10 kg: 100 mL/kg/24hrs 11-20 kg: 1000 mL+ 50 mL/kg/24 hr for each kg from 11-20 >20 kg: 1500 mL+ 20 mL/kg/24 hr for each kg >20
Sodium	6 mmol/kg (5-13)	2-4 mmol/kg
Potassium	5 mmol/kg (3-6)	2-3 mmol/kg
Chloride	4 mmol/kg (3-9)	2-3 mmol/kg
Phosphate	1 mmol/kg (0.5-2.5)	1-2 mmol/kg

## Principles of Treatment

The principles of treatment enunciated here are based on those of the International Society for Pediatric and Adolescent Diabetes, the American Diabetes Association, and the Pediatric Endocrine Societies of Europe and the USA (4, 7, 11).

Mild cases of DKA such as might occur in a patient using an insulin pump in which the tubing has become obstructed, or mild upper respiratory or mild abdominal infection without significant vomiting or diarrhea in an educated patient and strong family support might be managed via telephone instructions. When fluids are tolerated, 3-4 ounces of clear fluids (approximately 100ml) can be offered hourly. In addition, rapid acting insulin 0.1-0.2U/kg is given every 2-4 hours, glucose levels are checked via home meters and urinary ketones are checked via strips. Resolution of hyperglycemia and ketonuria, and tolerance to oral fluid intake indicates successful management and return to customary regimens including pump settings and/or subcutaneous basal-bolus insulin regimens.

For new onset patients, those that cannot tolerate oral fluid intake, and those with moderate to severe DKA, we recommend admission to a unit with capabilities similar to those of an ICU, possessing written guidelines on management, physicians and nursing staff trained in the management of DKA, bedside

glucose and blood gas monitoring, vital sign monitoring (pulse, blood pressure, respiration), and laboratory back-up of acid-base and electrolyte status. A thorough physical examination including level of consciousness should determine the overall clinical status, degree of dehydration, and consider the need to evaluate for infection. Supplemental oxygen may be provided via mask or nasal cannula, and a gastric tube passed if the patient is vomiting. Urine output should be measured via bag collection and catheterization avoided if possible. A blood sample should be obtained for measurement of glucose, electrolytes,  $\beta$ -OHB, acid-base status, hematocrit, and complete blood count; blood cultures and imaging studies should be considered in cases of suspected sepsis as the precipitating cause and appropriate antibiotics given. A modest increase in WBC with neutrophil predominance may reflect an acute phase response rather than sepsis; even if an acute abdominal condition is suspected, surgery should be deferred until several hours of resuscitation with fluids and electrolytes has occurred. Access for IV infusion should be established; this or preferably a separate IV site can serve as source of blood sampling.

The initial resuscitation consists of intravenous saline bolus infusion at 10-20 ml/kg over 1-2 hours depending on the degree of dehydration. Clinical assessment of dehydration is based on physical findings such as heart rate, blood pressure, speed of capillary refill, tissue turgor, and dry coated tongue

and is generally rated as 5% (mild), 10% (moderate) or greater than 10% (severe). Urine output is not a reliable sign as it usually continues due to the osmotic diuresis of hyperglycemia; diminished urine output may reflect evolving renal failure. Clinical judgment of degree of dehydration is notoriously inaccurate and can result in over or under estimation; hematocrit or a very recent weight may aid in assessment of the degree of dehydration so as to more accurately guide the amount and composition of fluids to be infused and in turn reduce the risk of the occurrence of cerebral edema (12, 13). Hence initial estimates of dehydration and osmolality of plasma based on glucose and electrolyte status, as well as acid base resolution, require re-assessment as treatment progresses. The initial resuscitation period with normal (0.9%) sodium chloride solution provides an opportunity to elicit a careful history and formulate the plan of management focused on provision of fluid, electrolytes, insulin, and monitoring to anticipate and correct complications.

## FLUID

The amount of fluid to be administered is based on the estimated degree of dehydration, e.g., 5% of body weight in Kg, plus daily maintenance (see table 2) evenly infused over 24-36 hours, subtracting the fluid administered as resuscitation. For example, a 30kg child with estimated dehydration of 5% would require 1500 ml for deficit plus 1700 ml for daily maintenance, yields a total of 3200 ml (table2); subtracting the 20ml/kg bolus of normal 0.9% saline from this total (600ml), leaves 2600 ml, or approximately 100 ml/hour over the initial 24 hours with adjustments made according to response. The total daily fluid infused should rarely exceed 1.5-2.0 times daily maintenance.

## COMPOSITION OF FLUID

### *Sodium Chloride*

Normal isotonic saline is the initial crystalloid of choice to be given over the initial 4-6 hours. This fluid is hypotonic relative to the osmolality of the patient's

plasma which can be calculated as  $2(\text{Na meq/dl} + \text{K meq/dl})$  plus glucose in mmol, or mg/dl divided by 18. Assuming a Na of 140meq, K 4.0meq and glucose of 450 mg/dl, the osmolality is  $284+25 = 309$  mosm. Normal (0.9%) saline has an osmolality of 286meq/l; the difference between the osmolality of the infused saline and patient's plasma becomes greater as the glucose concentration in plasma rises. But it is important to note that the infusate remains hypotonic relative to plasma as long as the hyperglycemia persists; decline in plasma osmolality must be carefully monitored to avoid rapid osmotic shifts that facilitate entry of water to the intracellular /intracerebral compartment. After the first 4-6 hours, 0.5-0.75 N saline plus added potassium(K) as the phosphate, acetate or chloride maintains an osmolality of the infusate close to that of the patient's plasma. Because of the concerns regarding use of chloride in worsening acidosis, some have recommended the use of lactated Ringers solution or sodium acetate in lieu of normal saline (7).

### *Potassium*

During acidosis K moves from the intra cellular to the extracellular compartment and considerable K is then lost in urine. As a result, total body K stores are almost always depleted and with correction of acidosis, K returns to the intracellular compartment resulting in hypokalemia, which may precipitate cardiac arrhythmia. Hyperkalemia is less common and may reflect impaired renal function. **Hence, after initial resuscitation, as soon as urine output is documented, K should be added to the infusate at a concentration of 20-40 meq/l.** The potassium may be in the form of potassium chloride, but this adds to the hyperchloremia which may result in persistent hyperchloremic acidosis. Hence, some recommend that the K may be administered, at least in part, as the acetate or phosphate, which may have additional benefit as described below. Total amounts of potassium replacement should not exceed 0.5mm/kg/hour. Potassium replacement should continue throughout the period of IV therapy to assist

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in the repletion of potassium stores. This may not be fully accomplished during IV therapy and continues when oral intake is resumed. The measurement of K concentration is an essential component of biochemical monitoring as described below; additional rapid monitoring of K concentration in plasma is in the evaluation of the EKG which may show high peaked T waves with hyperkalemia and low amplitude of T waves, T wave inversion, prolonged PR interval and prominent U waves with hypokalemia.

### *Phosphate*

As with potassium, phosphate stores are depleted in ketoacidosis and further losses occur with ongoing diuresis during treatment and the effects of insulin in promoting intracellular entry. Severe hypophosphatemia (<1mg/dl) may be associated with depletion of ATP and the resultant deleterious effects on any energy requiring processes, including muscle function, CNS disturbances, hemolysis, and rhabdomyolysis. In addition, phosphate participates in the regulation of the oxygen dissociation curve, so depletion impairs oxygen release to tissues and further exacerbates acidosis by promoting lactate accumulation. On the other hand, infusing phosphate is associated with hypocalcemia and limited trials have not shown consistent beneficial effects in the treatment of DKA. An advantage however, is its cautious use in limiting hyperchloremia and hence acidosis by providing some of the potassium requirement as phosphate rather than chloride, alternating KCl with KPO<sub>4</sub> and monitoring calcium concentration to avoid or treat hypocalcemia. We use this approach in our practice recommendations.

### INSULIN THERAPY

Fluid therapy alone incompletely corrects many of the biochemical features of DKA, but full resolution of DKA requires insulin to switch off ketogenesis, restore acid-base balance, and resume anabolic processes. For moderate to severe acidosis, we recommend a starting dose of insulin(regular) at 0.1 U/Kg/hour,

infused intravenously until acidosis is curtailed; insulin should be continued even if the blood glucose concentration has declined to ~300mg/dl or less and additional glucose provided as 5%-10% solution to maintain glucose at ~300mg/dl. Temporarily switching off the insulin infusion may result in rebound or persistence of acidosis, as insulin is essential to curtail keto-acid production and enable metabolism of keto-acids to bicarbonate. It is permissible to reduce the insulin dose to 0.05U/Kg/hr if there is difficulty in maintaining glucose at ~300mg/dl, even with additional glucose infusion, **but insulin infusion should not stop until acidosis is resolved and pH is 7.3 or higher.** In those admitted with mild acidosis, or those who administered basal insulin prior to admission, the starting dose of insulin should be 0.05U/Kg/hr, in order to avoid too rapid decline in the glucose concentration. Monitoring of blood glucose decline may require upward adjustment of the insulin dose if glucose is not declining at least 50 mg/dl/hour. An intravenous insulin bolus of insulin is not recommended to be given at the start of therapy and may not be effective as acidosis promotes dissociation of hormone binding to its cognate receptor. Where venous access is not possible, IM or SQ fast acting insulin (aspart or lispro) may be given at a starting dose of 0.2-0.3U/Kg and doses of 0.1-0.2 U/kg repeated 1-2 hours apart depending on response in terms of decline in glucose and correction of acidosis.

### BICARBONATE THERAPY

In controlled trials in adults, bicarbonate therapy has not been effective in shortening the time of acidosis; bicarbonate actually may cause harm. Harm may occur because HCO<sub>3</sub><sup>-</sup> combines with the H<sup>+</sup> to form H<sub>2</sub>CO<sub>3</sub> which dissociates to H<sub>2</sub>O and CO<sub>2</sub>. Whereas HCO<sub>3</sub><sup>-</sup> does not cross the blood-brain barrier, CO<sub>2</sub> diffuses readily across the blood-brain barrier and may exacerbate acidosis. In addition, large doses of bicarbonate may induce alkalosis and promote hypokalemia. Although controlled trials have not been performed in children, observational outcomes in pediatric studies show resolution of acidosis with



provision of fluids and insulin; bicarbonate therapy is not recommended in published guideline (4, 7, 12). In severe acidosis, with pH <7.0, myocardial contractility may be impaired and here bicarbonate may be helpful. In these circumstances, bicarbonate may be infused at 1-2mmol/Kg over 60 minutes and acid -base status reassessed thereafter. Bicarbonate therapy may be

useful in treatment of severe hyperkalemia. Bicarbonate must not be given as a bolus in treating DKA.

An example of the losses and management of DKA in a child with weight 30kg (Surface area 1M<sup>2</sup>) are shown in Tables 3 and 4.

**TABLE 3. Fluid and Electrolyte losses Based on Assumed 7% Dehydration in a Child with Diabetic Ketoacidosis\***

Fluid and electrolyte	Approximate accumulated losses with 7% dehydration	Approximate requirements for maintenance (36hrs)	Approximate working total
Water (mL)	2100	2550	4650
Sodium (mEq)	180	180	360
Potassium (mEq)	120	90	210
Chloride (mEq)	120	90	210
Phosphate (mEq)	30	45	75

\*Weight 30 kg; surface area 1 M<sup>2</sup>; See tables 2 and 3, references (4, 7, 12) and text for source of losses of water and electrolytes

**TABLE 4. Replacement Therapy for a Child with Assumed 7% Dehydration and DKA**

Duration	Fluid composition/amount	Sodium (mEq)	Chloride (mEq)	Potassium (mEq)	Phosphate (mEq)
Hour 0-2:	500 mL N. SALINE (0.9%NaCl)	75	75	0	0
Hour 2-6: 150mL/hr INSULIN 0.1 U/kg/hr	600mL N. SALINE + 40mEq KCl/L	90	115	25	0
Hour 6-12: 150mL/hr INSULIN 0.1 U/kg/hr	900ML 0.5N. SALINE +40mEq KCl/L	~70	105	35	0
Subtotal: initial 12 hr	2000ML	235	295	60	0
Next 24 hr: 100mL/hr INSULIN 0.1 U/kg/hr	2400 mL 0.5N SALINE 1 <sup>ST</sup> LITER ADD KPO4 40mEq	75 75	75 95	40 20	40 0

	2 <sup>nd</sup> LITER ADD KCl 20 mEq 3 <sup>rd</sup> LITER ADD KPO4 20 mEq	30	30	8	8
Total 36 hr:	4400 ml	415	495	128	48

\*Weight 30 kg; surface area 1 M<sup>2</sup>; In this formulation, calculated fluid deficit has been corrected by about 12 hours and basal requirement over the ensuing 24 hours; total fluid over the 36 hours has not exceeded 2 times daily maintenance. Total sodium infused only modestly exceeds the calculated deficit, but total chloride excess is considerable and may be associated with persistent (hyperchloremic) acidosis. Potassium and phosphate repletion is incomplete and continues after transition to oral intake of nutrition and subcutaneous insulin therapy. This example is for illustrative purposes only; the actual amount and composition of infused fluids is dictated by the biochemical responses monitored and recorded during therapy. Detailed discussion of electrolyte replacement can be found in references (12) and (13).

## MONITORING

A flow sheet to record clinical and biochemical progress is an essential component of therapy. Actual real-time monitoring of vital signs should be complemented by hourly recordings. Initial chemical laboratory tests must include blood glucose, serum electrolytes with emphasis on sodium, chloride, and potassium, as well as phosphate, calcium, pH, pCO<sub>2</sub>, HCO<sub>3</sub>, base excess, BUN and creatinine as indices of renal function and  $\beta$ -hydroxybutyrate(B-OHB) as a measure of ketosis. Measurement of urine output, urine glucose and ketones also must be recorded. The urine ketone measurement uses the sodium nitroprusside reaction which measures aceto-acetic acid and weakly acetone, but not B-OHB, the predominant ketone in blood. Hence, the major contributor to ketoacidosis is not reflected in the urinary ketone measurement. Bedside blood glucose, electrolyte, and acid base, and ketone meters are very useful but must be verified by periodic formal laboratory measurements. Initially, hourly measurement of glucose, electrolytes, and acid base status are recommended for the first 4 hours and 2-4 hourly thereafter depending on indices of improvement and resolution of acidosis, defined as pH $\geq$ 7.3 or bicarbonate  $\geq$ 15 mm/l. At this time transition to oral intake and discontinuation of IV therapy can be undertaken; absence of ketonuria should not be a criterion as this may continue for some time due to

conversion of B-OHB to aceto-acetate as ketosis resolves. After the first day, once daily measurement of electrolytes, acid base and renal function should be performed until restoration of normal function is confirmed.

## TRANSITION TO ORAL INTAKE

Oral intake may be begun when clinical recovery has occurred even if the acid base status and ketonuria have not completely resolved. Oral sips of clear liquids precede the introduction of oral fluids to gradually supplant the IV provision and total daily fluid restricted to no more than 1.5 times calculated daily maintenance. The first dose of regular or fast acting insulin is given subcutaneously approximately 1-2 hours before discontinuing the IV insulin to allow for absorption. For patients on a basal-bolus insulin regimen, the first dose of basal insulin may be administered in the evening while the IV insulin is maintained till the morning and then discontinued.

## Mortality and Morbidity of DKA

Mortality of DKA has declined markedly in the past 2 decades largely due to greater referral of patients to specialized centers (5, 6, 14). Cerebral edema (CE) is responsible for the majority of deaths and survivors of CE may have severe or mild residual impairment of CNS function including memory impairment (15-17).



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Several other causes of mortality and morbidity occur, but each is individually rare and include venous and arterial CNS thromboses, pulmonary embolus, rhabdomyolysis, pancreatitis, ARDS, and infections such as rhino-cerebral mucormycosis and other rare entities. These rarer complications are more fully described in prior reviews (4, 7, 16).

## CEREBRAL EDEMA

Cerebral edema is the most feared complication of DKA occurring either early (cerebral ischemia/reperfusion injury) or later during the course of therapy; mechanisms have not been clearly defined and whether the composition of IV fluids and their rate of administration contribute to or may prevent this complication is hotly debated (12-19). New onset, younger age and indices of severity have been associated with greater risk of this complication (20). Symptoms and signs include severe headache and development of bradycardia and hypertension as evidence of raised intracranial pressure, restlessness and irritability, localizing neurological features such as nystagmus and incontinence or polyuria without glucosuria as indicators of evolving diabetes insipidus, as well as evidence of papilledema. Clinical diagnosis based on bedside evaluation of neurological state as shown below has been proposed (16). In this formulation, one diagnostic criterion, two major criteria, or one major and two minor criteria have a sensitivity of 92% and a false positive rate of only 4% (16). Signs that occur before treatment should not be included in the diagnosis of cerebral edema. *Diagnostic criteria include* abnormal motor or verbal response to pain; decorticate or decerebrate posture; cranial nerve palsy (especially III, IV, and VI), and abnormal neurogenic respiratory pattern such as grunting, or Cheyne-Stokes respiration. *Major criteria include* altered mentation/fluctuating level of consciousness; sustained heart rate deceleration (decrease more than 20 beats per minute) not attributable to improved intravascular volume or sleep state; and age-inappropriate incontinence with a rise in serum sodium indicative of loss of free

water(diabetes insipidus). *Minor criteria include* vomiting, headache; lethargy or not easily arousable; diastolic BP >90 mm Hg; *young age* (<5 years) (16). The mechanisms responsible for the development of cerebral edema in DKA appear to be both osmotic (12-14, 18, 20) and vasogenic (21, 22), and the timing of appearance as early or late in the course of treatment may depend in part on the major contribution of the mechanism involved. Treatment should begin with reduction in the rate of fluid administration, elevating the head of the bed, administration of mannitol, 0.5-1 g/kg IV over 10-15 minutes, and repeating the dose of mannitol if there is no initial response in 30 minutes to 2 hours. Hypertonic saline (3%), at a dose 2.5-5 mL/kg over 10-15 minutes, may be used as an alternative to mannitol, especially if there is no initial response to mannitol. After these measures have begun, imaging of the CNS should be arranged to identify intracranial pathology such as thrombosis and treat as appropriate.

## Caveats

- A. Ketone bodies measured in urine grossly underestimate the degree of ketosis, because the common method uses sodium nitroprusside which reacts strongly with aceto-acetate, weakly with acetone, *and not at all with  $\beta$ OHB*. Yet the actual amount of  $\beta$ OHB may be 5 times or more than aceto-acetate, especially in the presence of acidosis. As acidosis is corrected and more of the  $\beta$ OHB is converted to aceto-acetate, it *appears* as if the ketosis is getting worse, when in fact acidosis and clinical parameters are improving. Measurements of  $\beta$ OHB via bedside meters or formal laboratory methods are better means to monitor “ketone” status.
- B. After commencing treatment, acidosis may appear to worsen initially for 3 reasons (4). First, dilution of the total bicarbonate in the expanding fluid volume lowers the apparent bicarbonate concentration because the  $\text{HCO}_3^-$  is expressed as mmol/L, and while the total mmols may not have changed, they are distributed in a greater volume.

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Second, with initially rapid rehydration, accumulated lactic acid enters into the circulation. Third, the  $\beta$ OHB acid is excreted in urine after it is converted to Na Butyrate; the Na derives from  $\text{NaHCO}_3$ , leaving bicarbonate which combines with  $\text{H}^+$  to yield  $\text{CO}_2$  and  $\text{H}_2\text{O}$  and permits loss of the  $\text{CO}_2$  in respiration. In these processes, bicarbonate ( $\text{HCO}_3$ ) and Na are lost, further depleting the bicarbonate content of plasma. With rehydration and insulin, which together curtail ketogenesis, acid base balance gradually returns to normal (4).

- C. The use of phosphate as potassium phosphate or acetate rather than KCl, may reduce the large amount of chloride used and hence reduce hyperchloremic acidosis, as well as improving oxygen dissociation to enable lactate to be converted to pyruvate. However, this is not accepted by all authorities and some claim no additional benefit from using phosphate. In addition, the use of phosphate may result in hypocalcemia. However, with severe phosphate depletion, the use of phosphate is indicated and likely to be beneficial.

### **Recurring Episodes of DKA**

A small subset of patients experience repeat episodes of DKA, and with each episode the prognosis for short-term and long-term outcome worsens. Recent data confirm that the majority of such recurrences reflect psycho-social maladjustments that require careful attention via medical and social support to avoid disastrous consequences (5, 6).

### **HYPERGLYCEMIA HYPEROSMOLAR SYNDROME (HHS)**

The hyperglycemia-hyperosmolar syndrome (HHS) is characterized by blood glucose concentrations  $>600\text{mg/dl}$  ( $>33.3\text{ mmol/l}$ ), serum hyper-osmolality  $\geq 330\text{mmol/l}$ , and minor acidosis and ketosis; serum bicarbonate remains  $>15\text{meq/l}$  and urinary “ketones” (aceto-acetate) are usually negative or only trace

positive on testing urine via dipstick (7, 21, 22). Hospital admissions for HHS are increasing in incidence, have high morbidity, and though classically considered to occur in obese patients with T2DM it may occur in T1DM as frequently as in T2DM (23). Although there are similarities to diabetic keto-acidosis, the fundamental difference is a greater degree of dehydration and less acidosis, so that treatment should focus on fluid and electrolyte replacement, and less on provision of insulin; indeed, insulin should be withheld initially to prevent a too rapid fall in serum glucose and lowering of serum osmolality which might result in fluid shifts into the cerebral compartment and cerebral edema (CE). However, CE is rarer in HHS than in DKA. The degree of insulin deficiency and the magnitude of counter-regulatory response appear to be less severe, so that the symptoms and signs of DKA are absent or less pronounced; abdominal pain and Kussmaul respiration are absent, and vomiting is less severe. These milder features also lead to greater time in evolution, greater degrees of dehydration and electrolyte losses resulting from the polyuria, and are often compounded by intake of highly glucose-enriched carbonated soft drinks consumed due to thirst. Glucose concentrations commonly exceed  $1000\text{mg/dl}$ , dehydration may be as much as twice that occurring in DKA and may be difficult to estimate due to co-existing obesity and hypertonicity which retains fluid in the intra-vascular compartment. Persistence of the polyuria due to the persistence of glucose concentrations exceeding renal threshold of  $\sim 200\text{mg/dl}$  during treatment, requires careful monitoring of clinical status and fluid replacement to avoid dehydration and vascular collapse. The risk of thrombosis is greater in HHS than in DKA, possibly as a result of osmotic disruption of endothelial cells, with release of thromboplastins facilitating coagulation.

Treatment should assume dehydration of 10%-15% and initially isotonic (normal) saline should be provided at  $20\text{ml/kg}$  bolus infusions to restore fluid deficits and maintain vascular volume with assessment of serum chemistries every 1-2 hours;

subsequently, 0.5-0.75 N saline, with added potassium and phosphate should be infused to replace calculated losses over 24-48 hours, guided by laboratory chemistry every 2-4 hours and ongoing clinical monitoring performed in an ICU or equivalent setting. The aim should be to control the decline in blood glucose to 100 mg/dl per hour; if glucose is not declining at a rate of at least 50 mg/dl, or ketosis is more than mild, insulin at a rate of only 0.025-0.05U/kg/hour may be used with caution and careful clinical and laboratory monitoring. Potassium, phosphate and magnesium losses may be considerable; potassium should be infused at 40meq/l added to each liter of saline, with balanced mixtures of potassium chloride and potassium phosphate, the latter to replete phosphate depletion which may predispose to rhabdomyolysis and hemolytic anemia. As in DKA, use of bicarbonate is not recommended. Magnesium also may be severely depleted in HHS and predispose to hypocalcemia; the recommended doses of magnesium replacement are 25-50mg/kg/dose given every 4-6 hours at a maximum infusion rate of 150mg/min(2gm/hr.) for 3-4 doses. In

addition to cerebral edema, thrombosis, and rhabdomyolysis, malignant hyperthermia is reported as a complication. Monitoring for these complications is based in part on clinical anticipation e.g., hyperthermia, and supplemented by appropriate biochemical testing e.g., serum creatinine kinase for rhabdomyolysis. Some patients have features that combine DKA and HHS that reflect the degree of insulin deficiency; clinical acumen, earlier use of insulin, and careful monitoring of the patient's vital signs and chemistries guide treatment, especially the earlier use of insulin in appropriate doses. This syndrome of HHS in adolescents and young adults was classically considered a feature of T2DM (24), an entity that is increasing at an annual rate of 4.8% in the obese population of the USA (25). Hence, the frequency of HHS as a presenting feature is also likely to increase, so that physicians caring for these patients in an ICU or equivalent setting must be alert to the differences in management with the greater focus on fluid and electrolyte replacement in HHS rather than the use of insulin as in DKA.

**Table 5. Monitoring of Patients with HHS in the ICU (1)**

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| <ul style="list-style-type: none"> <li>A. Continuous cardiac, respiratory and blood pressure monitoring</li> <li>B. Hourly glucose and clinical assessment</li> <li>C. 2-4hourly assessment of fluid balance(input/output); serum electrolytes, BUN, creatinine, CPK (creatine-phospho-kinase)</li> <li>D. 4-6 hourly Calcium, phosphate, magnesium</li> <li>E. Be alert to complications-thrombosis, rhabdomyolysis, hyperpyrexia, cerebral edema.</li> </ul> |
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## ROUTINE MANAGEMENT OF DIABETES

The goals of treating diabetes mellitus in children are to maintain metabolism as near to normal by the appropriate provision of insulin, maintaining nutrition by meeting caloric requirements and balanced composition of food choices within the cultural preferences of the family, and to balance both insulin and nutrition with recommended exercise and activity

to allow normal growth and development. In order to prevent diabetes related complications, especially long-term microvascular disease, glycemic control is crucial. This optimal diabetes regimen requires intensive management by patients and their families along with a multidisciplinary approach with psychosocial support. Glycemic control is assessed by periodic measurement of hemoglobin A1C levels.

**Table 6. The American Diabetes Association Guidelines for the Target Glucose and HbA1C Levels (26)**

A1C	<7%
Pre-prandial plasma glucose	90-130 mg/dl
Overnight plasma glucose	70-180 mg/dl

## TYPE 1 DIABETES

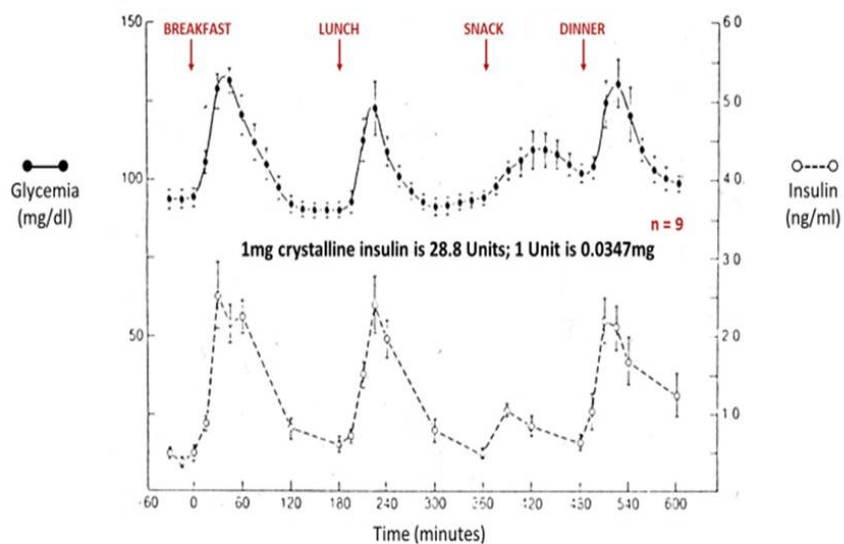
### Insulin Therapy

The management of diabetes can be cumbersome. In caring for children and adolescents with Type 1 diabetes, providers must take into account unique factors such as a child's pubertal stage and growth, ability to provide self-care, supervision of care, school environment, and neurological vulnerability of hypoglycemia in young children.

However, it is crucial to normalize glucose levels in order to prevent long-term consequences of diabetes especially from microvasculopathies, leading to neuropathy, renal failure, and blindness. In 1993, The Diabetes Control and Complications Trial (DCCT)

reported results demonstrating that the intensive therapy of T1DM reduces the risk of development and progression of microvascular complications. Furthermore, these benefits outweighed the increased risk of hypoglycemia that accompanied intensive diabetes therapy (27). Thereafter, The Epidemiology of Diabetes Interventions and Complications (EDIC) study assessed whether these benefits persisted after the end of DCCT. The findings of this study provide further support for the DCCT recommendation that most adolescents with T1D receive intensive therapy aimed at achieving glycemic control as close to normal as possible to reduce the risk of microvascular complications (28). This goal is not easily achieved even with a multi-dose insulin regimen of basal and short acting insulin that attempt to mimic normal patterns (Figure 2).

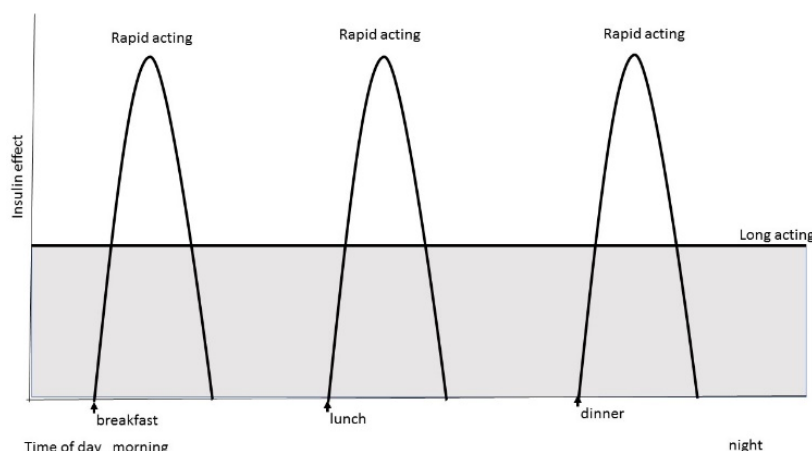
### Normal glucose / insulin profiles



## Figure 2. Normal Glucose and Insulin Profiles

This pattern is difficult to achieve because the perfect alignment of glucose and insulin in the normal person depends on a complex interaction of neural, hormonal, and nutritional signals that are absent in type 1 DM. Moreover, the “first pass” of endogenous insulin is via the portal vein to the liver, whereas SQ insulin injections first reach the liver via the systemic

circulation. Hence the common problem of postprandial hyperglycemia due to delay in the action of insulin during and immediately after a meal, and rebound hypoglycemia sometime after the meal. The following describes the insulin regimens recommended as standard of care attempting to reproduce the normal situation.



**Figure 3. Time Course of Rapid and Long-Acting Insulin**

Insulin Glargine and Detemir provide day-long basal insulin without significant peaks of action. In some children, however, Glargine may not be fully effective for a whole 24 hours and for this reason is usually given at night. This synthetic insulin cannot be safely mixed with other insulins in the same syringe due to pH incompatibilities. Throughout the day, short acting insulin preparations such as Insulin Aspart, Lispro, and Glulisine are given to normalize blood glucose levels and cover calories consumed during meals and as possible snacks. As 3 meals are eaten by most on a daily basis, short acting insulins should be given at least 3 times daily to prevent excessive hyperglycemic excursions.

Prepubertal children typically require a total daily insulin dose of  $\sim 0.7 - 1$  U/kg/day whereas pubertal children may require total daily insulin doses up to 1.2-1.5 U/kg/day; greater than 2.0 U/kg/day suggest

extreme insulin resistance or non-compliance (29). Of the total daily insulin dose, 40-60% should be given as basal insulin. The actual dose depends upon the level of glycemia and the quantity of calories and carbohydrates consumed. A fast-acting insulin bolus is given to cover meals, calculated from an estimation of the carbohydrate content in grams and an individual factor (insulin to carbohydrate ratio) relating insulin dosage to the amount of carbohydrate to be consumed. When using carbohydrate counting, the ‘500-rule’ can be used to obtain an initial carbohydrate ratio by dividing 500 by the total daily insulin dose.(29) The range is from 1 unit per 10-50 grams. In addition to the meal bolus, the difference between the blood glucose recorded immediately before the meal and the target glucose concentration (120 mg/dl for older children; 150 mg/dl for younger children) is used to calculate a correction bolus, based on a theoretical Insulin Sensitivity Factor or ISF. This may range from

1 unit for 10- 200 mg/dl blood glucose depending upon age and body size. The '1800-rule' can be used to

obtain an initial ISF by dividing 1800 by the total daily insulin dose.

<b>Table 7. Types of Insulin Preparations and Action Profiles (30)</b>			
<b>Insulin</b>	<b>Onset</b>	<b>Peak</b>	<b>Duration</b>
Insulin lispro (rapid acting)	15-30 mins	0.5-2 hrs	2-5 hrs
Insulin aspart (rapid acting)	15 mins	1-3 hrs	3-5 hrs
Insulin glulisine (rapid acting)	12-30 mins	1.5 hrs	5-6 hrs
Fiasp (ultra-rapid acting)	5 mins	0.5 hrs	3-5 hrs
Regular (short acting)	0.5-1 hrs	2-4 hrs	5-8 hrs
NPH (medium acting)	2-4 hrs	4-10 hrs	8-16 hrs
Insulin glargine (long acting)	2-4 hrs	None	24 hrs
Insulin detemir (long acting)	1-2 hrs	6-12 hrs	20-24 hrs
Insulin degludec (ultra-long acting)	0.5-1.5 hrs	none	42 hrs
Insulin glargine U300 (ultra-long acting)	6 hrs	none	24-36 hrs

The intermittent, short acting insulin given as a bolus should be injected 15 minutes before the meal in order to have its full effect when glucose rises during and after the meal. For infants and toddlers, these short acting insulin doses may be given after the meal if food consumption has been found to be unpredictable. In addition to the 3 meals, additional amounts of short acting insulin may be taken to cover snacks, and to reduce blood glucose concentration as appropriate at bedtime. An insulin "pen" is a convenient way of carrying multiple doses in a single dispenser but this pen device does not reduce the burden of multiple insulin injections. Super long-acting insulin preparations e.g. Degludec or super-fast acting insulin e.g. Fiasp(Ultra-Fast acting insulin Aspart) are available and may have advantages in specific situations. In particular, a super-fast acting insulin

would allow more rapid equilibration between the systemic and portal circulations, so offering advantages to prevent excessive rise in glucose after a meal and avoiding later development of post-prandial hypoglycemia (31, 32). The half-life of insulin degludec exceeds the dosing interval resulting in a very low peak:trough ratio at steady state.

An alternative and better method of insulin delivery is the use of continuous subcutaneous insulin infusion (CSII) through use of an insulin pump. In this case, only short acting insulin e.g., lispro, glulisine), aspart, or Fiasp is taken as a continuous basal infusion and multiple boluses of insulin are given as above. The newer generation of CSII pumps automatically calculate meal and/or correction boluses based on input insulin-to carbohydrate ratios and insulin



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sensitivity factors plus estimates of the amount of carbohydrate consumed. The infusion site is best changed every 2 days to avoid skin infections. The advantages of CSII when used correctly are that insulin is delivered only as needed, and not in an anticipatory fashion as with long-acting insulin. Insulin boluses are also delivered only as needed, nutritional intake may be more liberal, glycemic excursions both as hyperglycemic and hypoglycemic episodes can be reduced, and the system is convenient and portable. Patients receiving insulin via CSII and their parents have generally reported improved treatment satisfaction. The one disadvantage of CSII is that since only short acting insulin is used (effects of rapid acting insulins are dissipated within 3 hours), any blockage in the tubing or pump failure can lead to rapid onset of hyperglycemia, accumulation of serum ketones, and an uncontrolled diabetic state. Thus, patients and their care-givers must be educated on treatment of hyperglycemia with an insulin pen or syringe in case of suspected pump malfunction which can be a common cause of DKA.

With advanced technology, insulin therapy is becoming more physiologic. Continuous subcutaneous insulin infusion (CSII) therapy is transforming care of T1DM while continuous glucose monitoring (CGM) of interstitial fluid has become widely available and increasingly used in the US. Without continuous glucose monitoring, manual adjustment of insulin doses in response to changes in blood glucose are based only upon intermittent blood glucose testing and corrections. Moreover, as previously mentioned, insulin injections or infusions are given subcutaneously and initially enter the systemic circulation, whereas endogenous insulin is secreted into the portal vein and act directly and immediately on the liver.

Currently, we are entering a new era of diabetes care for children, with the adoption of closed loop systems (33). All systems in development rely on glucose measurements via CGM transmitted to an insulin delivery system (pump) which uses a computerized

algorithm to adjust insulin infusion based on upper and lower limits and the rate of change in increase or decrease of glucose values (34-36). Modified versions of the closed-loop system that are semi-automated are FDA approved for use in children. Semi-automated closed-loop systems, also known as hybrid closed loop systems, are characterized by the combination of automated insulin delivery via an algorithm for basal requirement and user-initiated insulin delivery for meals. A setting to suspend insulin delivery when glucose is low or rapidly downward trending can be utilized to avoid hypoglycemia. To improve ease of mobility, a tubeless insulin pump that can be operated by a third party through a wireless receiver is available and useful for very young children with control exercised by a parent.

Bi-hormonal systems (insulin and glucagon) can rapidly alter high or low glucose values and be used with safety during normal activity and exercise (37, 38). This system has not yet been approved for commercial use. However, the next decade should see application of these tools to an increasing number of patients with T1DM.

The clinical management for patients with T1DM is based on adequate insulin replacement matched to food intake and modified by exercise. Insulin is required throughout the whole day to prevent development of a starvation state and ketosis i.e., the basal insulin requirement.

Recurrent hypoglycemia represents a mismatch between insulin provided and caloric expenditure, which occurs as a result of not covering the basal amount or a bolus with appropriate food intake, malabsorption of food e.g., celiac disease, or exercise without adjustment in the insulin dose or omission of additional calories before or after the exercise. unexplained episodes of hypoglycemia require re-evaluation of the insulin regimen, exclusion of concurrent conditions such as acute illness with diminished food intake, and testing for celiac disease, hypothyroidism, and Addison's disease.

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In special circumstances where adherence to recommended regimens is not being followed due to various psycho-social limitations, a twice daily regimen of pre-mixed insulin (NPH/Reg70/30) may be prescribed, though it is known not to be ideal. In developing countries with limited resources to treat diabetes, this twice daily dosing regimen of NPH and regular continues to be vital to avoid DKA but is associated with less optimal glycemic control.

### **Glucose Monitoring**

Patients on insulin regimens are encouraged to check glucose levels prior to meals and snacks, at bedtime, prior to exercise, and when they suspect low blood glucose. This typically amounts to 4-6 glucose levels per day. Blood glucose monitoring allows patients and families to evaluate their individual response to therapy, assess whether achieving glycemic targets, and help guide treatment decisions.

Continuous glucose monitors and intermittently scanned monitors measures interstitial glucose which correlates well with plasma glucose. Time in range is defined as percentage of the day with blood glucose levels between 70 and 180 mg/dL. A time in range target of more than 70% is recommended (39). Time in range is becoming a key glycemic metric, in addition to glycosylated hemoglobin (HbA1c) (39). A correlation between improved HbA1c levels and fewer diabetes complications has been demonstrated (40). Percent time in range provides real-time insights into glycemic variability and frequency of hypoglycemia and hyperglycemia. Time in range also correlates with complications of diabetes and HbA1c values and is being used to compare diabetes technology (40).

### **Nutrition**

The goal of nutrition is to support normal growth and development, improve diabetes outcomes, and reduce cardiovascular risk factors. Dietary recommendations should be based on healthy eating principles

appropriate for all children and their families. Typically, distribution of energy sources recommended is 50-55% carbohydrates, <35% fat, and 15-20% protein (41). Regular meals are recommended. A commonly prescribed meal plan consists of 20% of calories at breakfast, 30% at lunch and 30% at dinner with 2 snacks of 10% each one of which is at bedtime to avoid nocturnal hypoglycemia. In the basal-bolus insulin regimen, insulin doses are matched to the amount of carbohydrates consumed during each meal.

Protein and fat are not typically accounted for in the meal time insulin dose calculation though this issue is controversial and some authorities recommend that these protein-fat derived calories must be included. The predominant effect of dietary fats and protein is late postprandial hyperglycemia. Bolus corrections for insulin pump use when eating fatty meals have been devised and recommended (42-44). Studies have found that lower glycemic index diets improved glycemic control compared to traditional higher glycemic index diets (45, 46). Low glycemic index foods include whole-grain breads, pasta, temperate fruits, and dairy products

Dietary advice should be given in the context of cultural, ethnic and family traditions to be successful. Continuous nutritional education regarding a healthy diet and carbohydrate counting is recommended. Food labeling requirements have simplified the process, as many foods are clearly labeled with the amount of carbohydrate grams per serving. Additionally, apps, such as Calorie King, provide information on carbohydrate content of foods provided by many large restaurants.

### **Exercise**

Establishing and maintaining an active lifestyle should be the goal for all children. Increased physical activity is associated with better glucose utilization and increased insulin sensitivity leading to lower insulin requirements. However, blood glucose levels can be

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difficult to regulate during these intervals of exercise. Hypoglycemia is common during exercise and can possibly last up to 24 hours afterwards, due to increased insulin sensitivity (47). This increases the risk of nocturnal hypoglycemia. Factors during exercise frequently associated with hypoglycemia are excessive insulin dosing prior to exercise, prolonged duration, and higher intensity aerobic exercise (47).

To reduce the risk of hypoglycemia during prolonged exercise, reductions in bolus and basal insulin are typically needed. In children using CSII pumps, simply suspending or reducing the basal infusion rate can markedly reduce the risk of hypoglycemia during exercise. If insulin doses prior to exercise are not reduced, a snack of 1-1.5 grams of carbohydrates per kilogram is recommended (47). Meals with high carbohydrate content should be consumed shortly after exercise. As the effects of exercise can be prolonged, blood glucose should be measured before bed and a decrease in basal insulin (either long acting or overnight basal) should be considered after exercise later in the day.

Any exercise should be avoided if blood glucose prior to exercise are high (>250 mg/dl) and associated with ketonuria. Exercise during such insulinopenic states is dangerous owing to the effects of uninhibited counterregulatory hormones and may precipitate diabetic ketoacidosis.

### **Sick Day Management**

Children with intercurrent illnesses such as fever or vomiting, should be closely monitored for the development of hyperglycemia and ketonuria. On sick days, blood glucose levels should be checked every 2-3 hours when not tolerating food and urine should be checked for the presence of ketones with every void. Correction doses with rapid-acting insulin should be given approximately every 3 hours. Persistent vomiting and/or ketonuria are signs of diabetic ketoacidosis; patients with such signs and symptoms

should be evaluated in an emergency department immediately.

Adequate fluid intake is crucial to preventing dehydration and accumulation of ketones. For blood glucose >200 mg/dl, rehydration with sugar free fluids is recommended. Sugar containing fluids such as flat soda or diluted juice may be necessary to maintain normoglycemia if blood glucose is <140 mg/dl.

### **Management of Co-Morbid Conditions**

Besides insulin replacement therapy for T1DM, co-existing hypertension and dyslipidemia should be aggressively treated; it is important to use age-appropriate references for determining the presence of hypertension and upper levels of acceptable lipid values of LDL and triglycerides.

Increased urinary protein excretion is the earliest clinical finding of diabetic nephropathy. Measurement of the urine albumin-to-creatinine ratio in an untimed urinary sample is the preferred screening strategy for moderately increased albuminuria in all patients with diabetes and should be repeated yearly. Screening for increased urinary albumin excretion can be deferred for five years after the onset of disease in patients with type 1 diabetes because increased albumin excretion is uncommon before this time; screening should begin at diagnosis in patients with type 2 diabetes because many have had diabetes for several years before diagnosis. Abnormal results should be confirmed by repeat testing before establishing a diagnosis because of the large number of false positives that can occur. The normal ratio of microalbumin to creatinine is less than 30 mg/g. Thus, a persistently elevated ratio of 30-300 mg/g signifies microalbuminuria. Microalbuminuria and/or hypertension should be a call for use of angiotensin converting enzyme (ACE) inhibitors to minimize progression to chronic glomerulosclerotic damage. ACE inhibitors may induce angio-edema and can produce a troublesome dry cough.

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Poorly controlled diabetes induces an increase in VLDL and triglyceride levels, when acute or chronic, pancreatitis may be induced. Diet reduced in animal fat and administration of fibrates (e.g., gemfibrozil or fenofibrate) may be used to combat hypertriglyceridemia. Co-existing Hashimoto's thyroiditis should be periodically sought through thyroid autoantibody analyses, and hypothyroidism when identified by elevated TSH levels, treated by thyroid hormone replacement. Celiac disease also should be regularly checked via titers of tissue transglutaminase antibody titers, and treated via gluten exclusion when diagnosis is confirmed by endoscopically obtained biopsy specimens. Addison's disease and atrophic gastritis/pernicious anemia should always be considered in patients with T1DM, especially with unexplained frequent episode of hypoglycemia, and if found, treated accordingly.

## **TYPE 2 DIABETES**

The increased incidence of T2DM is attributed to the increase in obesity worldwide. Approximately 3700 youths are diagnosed with T2DM every year in the US (25) and it is estimated that the number of youths with T2DM will almost quadruple from 22,820 in 2010 to be approximately 85,000 adolescents with T2DM by 2050 (48). Similar rates of increases in youths with T2DM are reported from the UK, India, China and Japan (48). The child with T2DM as part of the insulin resistance syndrome (IRS) should be aggressively treated to prevent the burgeoning complications of the condition. The development of complications associated with T2DM is accelerated in youth, with reported rates of 6% with renal failure within 5 years of diagnosis, and 2.3% end stage renal disease by 10 years.

Initial education for T2DM should focus on dietary and lifestyle modifications and this education should continue to be reinforced with the goal being to decrease insulin resistance. The approaches should include an exercise program such as walking or swimming for 30-40 minutes most days of the week, since at the level of the muscle, exercise provokes

glucose entry into muscle without the involvement of insulin. Sedentary time including homework, computer and phone related activities, and video games should be assessed and established for appropriateness in each family setting. Caloric restriction, particularly of carbohydrates, is the key to reducing weight, a task that has proven resistant to success in many instances. Elimination of sugar containing sodas and juices has been shown to result in significant weight loss (49). Barriers include older age at diagnosis, difference in socioeconomic status, and poor diet within the household (50). Also, clinicians should understand the health beliefs and behaviors of the family and community and take into account cultural food preferences and the use of food during celebrations and cultural festivals in order to collaborate with the family on diabetes management.

The use of metformin as first-line therapy is based on its glucose-lowering efficacy, safety profile, weight neutrality, and reasonable cost. In most countries, metformin is currently approved for use in children. Metformin is approved for the treatment of T2DM in children, but is also the drug of choice for insulin resistance syndrome, also known as metabolic syndrome (IRS) and impaired glucose tolerance because of its property in improving insulin sensitivity. Monotherapy with metformin was associated with durable glycemic control in approximately half of children and adolescents with T2DM (51). Some suggest that it is the gastro-intestinal side effects of the drug that accounts for much of its beneficial effects. However, the drug is effective in T2DM even without weight loss, an action attributed to reduced hepatic glucose output.

The guidelines from the ADA and EASD indicate that any FDA-approved second agent can be used in combination with metformin to improve glycemic control, whereas the American Association of Clinical Endocrinologists recommends either incretin-based therapy or sodium glucose transporter 2 (SGLT2) inhibition agents (52). Sulfonylureas are approved for use in adolescents in some countries; these agents


bind to receptors on the K<sup>+</sup>/ATP channel complex resulting in insulin secretion. The PPAR- $\gamma$  agonists are effective at insulin sensitization but are less useful in supporting weight loss. Further, they promote salt retention and a tendency for edema. A new class of drugs which inhibit the sodium co-transporter 2 (SGLT2) resulting in glycosuria at a lower blood glucose threshold than normal have become available, though not currently approved for use in children (canagliflozin, dapagliflozin, empagliflozin). Use of SGLT2 inhibitors has been associated with an increase in fungal infections of the genital areas and missed symptoms of evolving keto-acidosis.

Two drug classes were developed that target the incretin system and increase endogenous insulin secretion: glucagon-like peptide (GLP)-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. GLP-1 receptor agonists (e.g., liraglutide and exenatide) resist degradation by DPP-4 resulting in increased circulating levels of the administered drug (53). DPP-4 inhibitors (e.g., sitagliptin, vildagliptin and saxagliptin) reduce endogenous GLP-1 degradation, thereby maintaining circulating levels of GLP-1 with biological effect. Both these classes of drugs improve glycemic control with a low incidence of hypoglycemia

because of their glucose-dependent mechanism of action. In addition to their effects on improving insulin secretion, these drugs lower glucagon and delay gastric emptying, and potentiate weight loss, in part through decreased appetite.

Whereas the glucagon like peptide one (GLP-1) analogue exenatide given by subcutaneous injection will lower blood glucose levels and complement metformin in provoking weight loss, it should be reserved for more severely diabetic adults and teenagers who have become unresponsive to diet and exercise programs. Some formulations of GLP-1 analogues can be given once weekly. In 2019, liraglutide was approved for adjunct use to improve glycemic control in pediatric patients 10 years and older with T2DM. (54, 55) Sitagliptin blocks the dipeptidyl peptidase-4 (DPP-4) enzyme preventing it from inactivating GLP-1, thus prolonging the action of GLP-1 once induced by a meal. Whereas the latter agent is in general weight neutral, it can be of adjunctive help in lowering hyperglycemic excursions. When these additional agents also fail to maintain near normoglycemia, then insulin should be given instead of the secretagogues.

**Table 8. Glucose Management for Adult Patients with Type 2 Diabetes (52)**

IRS/IGT  Diabetes Mild  	Step 1: Dietary and lifestyle education- 3-5% weight loss; 150 min/week exercise					
	Step 2: Addition of metformin- Maximum daily dose of 2000 mg					
	Step 3: Addition of second antihyperglycemic drug					
		Pioglitazone	DPP4 inhibitor	GLP-1 agonist	SGLT2 inhibitor	Sulfonylurea
	HbA1C	↓	↓	↓	↓	↓
	Weight	↑	--	↓	↓	↑
	Hypoglycemia	--	--	--	--	↑
	Major CV events	--	--	↓	↓	-
	Heart failure	↑	↑*	--	↓	-
	Step 4: Addition of insulin Basal insulin with or without prandial insulin					



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Severe	
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\*Saxagliptin is a DPP4 inhibitor associated with heart failure. Other DPP4 inhibitors have not been shown to cause heart failure. Whereas studies of these agents are under investigation, only a GLP-1 agonist is currently approved by the FDA for use in children and adolescents

One of the main goals of therapy in IRS/T2DM should be to achieve an ideal body mass index (kg/m<sup>2</sup>) for age and gender. This is not readily achievable with lifestyle modification and medical therapy in many subjects; bariatric surgery is emerging as a successful and durable treatment in adults and adolescents with IRS, obesity, and their associated complications (56-58). In adults the ADA recommends bariatric surgery in those with BMI of 30 kg/m<sup>2</sup> or greater and poorly controlled DM (59). Bariatric surgery is an effective treatment for severe obesity that results in the improvement or remission of many obesity-related comorbid conditions, as well as sustained weight loss and improvement in quality of life. Mortality owing to cardiovascular diseases, diabetes, and respiratory conditions is reduced after bariatric surgery (60). A prospective follow up studies of bariatric surgery in adolescents with severe obesity showed a substantial and durable weight reduction and cardio-metabolic benefits (57, 58). Changes in glucoregulatory hormones produced by the gastrointestinal tract, bile acid metabolism, and GI tract nutrient sensing and glucose utilization are proposed mechanism for improvement in glycemic control after bariatric surgery (61). Currently, bariatric surgery is considered only in children with BMI  $\geq 40$  kg/m<sup>2</sup> with comorbidities or BMI  $\geq 50$  kg/m<sup>2</sup> regardless of comorbidities (62, 63). Indications in adults are much less stringent; adults with BMI  $\geq 35$  kg/m<sup>2</sup> with comorbidities are candidates for these procedures. Updated recommendations for adolescents provide more aggressive recommendations similar to those for adults (64). Bariatric surgery is now safe, with mortality comparable to common elective general surgical operations. Level 1 evidence show that bariatric surgery provides superior short-term and long-term

weight loss and improvement of T2DM compared with conventional medical therapy. However, patients require life-long follow up and monitoring for nutritional deficiencies and abdominal issues, and to date, results in adolescents are relatively short term. Pediatric patients who are being considered for bariatric surgery should be evaluated by a multidisciplinary team dedicated to providing long-term follow-up care postoperatively. In addition, selection criteria often exclude the population most in need of this proven procedure.

### **Treatment of Associated Comorbidities**

The typical dyslipidemia associated with IRS and T2DM should be treated by reduced intake of animal fat and a fibrate such as gemfibrozil or fenofibrate. Where there is an increased level of triglycerides, restriction of animal fats and simple sugars should be recommended. However, those patients who have prominent elevations in LDL-cholesterol should be treated with a statin. The mixed use of a statin and a fibrate should be undertaken cautiously since the risks of muscle necrosis (rhabdomyolysis) with renal failure has been. In patients taking a statin gemfibrozil should not be used and fenofibrate is the fibrate of choice as the risk of myositis is less. Hypertension and microalbuminuria, when present, should be aggressively treated, preferably with angiotensin converting enzyme inhibitors (ACE) and angiotensin receptor blockers (ARBs), at least initially.

Oral contraceptive agents are often prescribed in IRS when there is evidence of hyper-androgenization, where they may counteract the effects of androgens. However, oral contraceptives also increase the level



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of hormonal binding globulins, including sex hormone binding globulin that binds testosterone, thereby lowering the level of free and bio-available testosterone. Estrogen containing therapies in a prepubertal patient increases the risk of premature closure of the epiphyses and hence risks loss of adult height; they also promote thrombosis and mitigate against weight loss.

## **TREATMENT OF MONOGENIC FORMS OF DIABETES**

Monogenic forms of diabetes constitute a heterogeneous group of disorders classified according to clinical features that suggest possible type 1 diabetes, type 2 diabetes, and neonatal diabetes, all in the absence of markers of autoimmunity such as circulating antibodies to various islet antigens. The genes responsible for these forms share a role in the formation or function of the pancreatic  $\beta$ -cell, limiting normal insulin secretion that depending on severity, and under certain conditions, results in clinical diabetes. Increasingly, it is being recognized that there is a continuum in the spectrum of these disorders such that the severity of the genetic defect responsible for insulin secretion or action determines the clinical pattern (65-68). This is perhaps best exemplified in the genetic defects of the ATP-regulated potassium channel (KATP) involving the *ABCC8* gene coding for the sulfonylurea receptor SUR1, and *KCNJ11* coding for the subunits of Kir, the inward rectifying potassium channel itself. Severe activating mutations in these genes maintain the KATP in an open state and result in permanent neonatal diabetes, sometimes associated with developmental delay and epilepsy (DEND). Progressively less severe functional mutations may result in transient neonatal diabetes, or in a form of maturity onset diabetes of youth (MODY), or in T2DM. These activating mutations typically respond to sulfonylurea therapy, high dose for the severe mutations and lower doses for the less severe mutations, inducing endogenous insulin secretion mediated in part by GLP-1, and improved metabolic control superior to that obtained by exogenous insulin

injection. Similar considerations apply to transcription factors such as hepatocyte nuclear factor1 $\alpha$  (HNF1A) and hepatocyte nuclear factor 4 $\alpha$  (HNF4A), respectively responsible for MODY3 and MODY1, which may respond to oral sulfonylurea drugs, avoiding the need for injected insulin, at least initially. Heterozygous inactivating mutations in the glucokinase gene responsible for MODY2 delay insulin secretion and result in a mild diabetes that is not associated with an increased risk of macrovascular or microvascular complications, so that treatment with exogenous insulin or other drug therapies is not indicated (69). Hence, knowledge of the genetic mutation drives therapy, permits more precise genetic counselling, and may indicate prognosis. In an era of precision medicine and progressive decline in the cost of sequencing, genetic testing should be considered in those with a strong family history of diabetes, early onset diabetes, and in children or adolescents who present with features suggestive of T1DM, are negative for islet auto-antibodies, and have residual c-peptide secretion as determined by measurement or reflected in persistently low insulin requirements extending beyond 1 year after diagnosis. These concepts are discussed in greater detail in several recent publications (65-69).

### **Maturity Onset Diabetes of Youth (MODY)**

The term MODY refers to Maturity Onset Diabetes of Youth, a term coined by Fajans and Tattersall for a mild type of diabetes with autosomal dominant inheritance and varying degrees of impaired insulin secretion (70). The molecular basis for these entities was discovered initially to be due to transcription factors or the enzyme glucokinase responsible for phosphorylating glucose to enable its metabolism to yield ATP; numbering followed the timing of discovery of the genetic-molecular basis (70). There are now 14 entities considered to be MODY as listed in the table in our chapter on the “Etiology and Pathogenesis of Diabetes Mellitus in Children and Adolescents” in Endotext. Of the original 6 “classical” MODY entities,

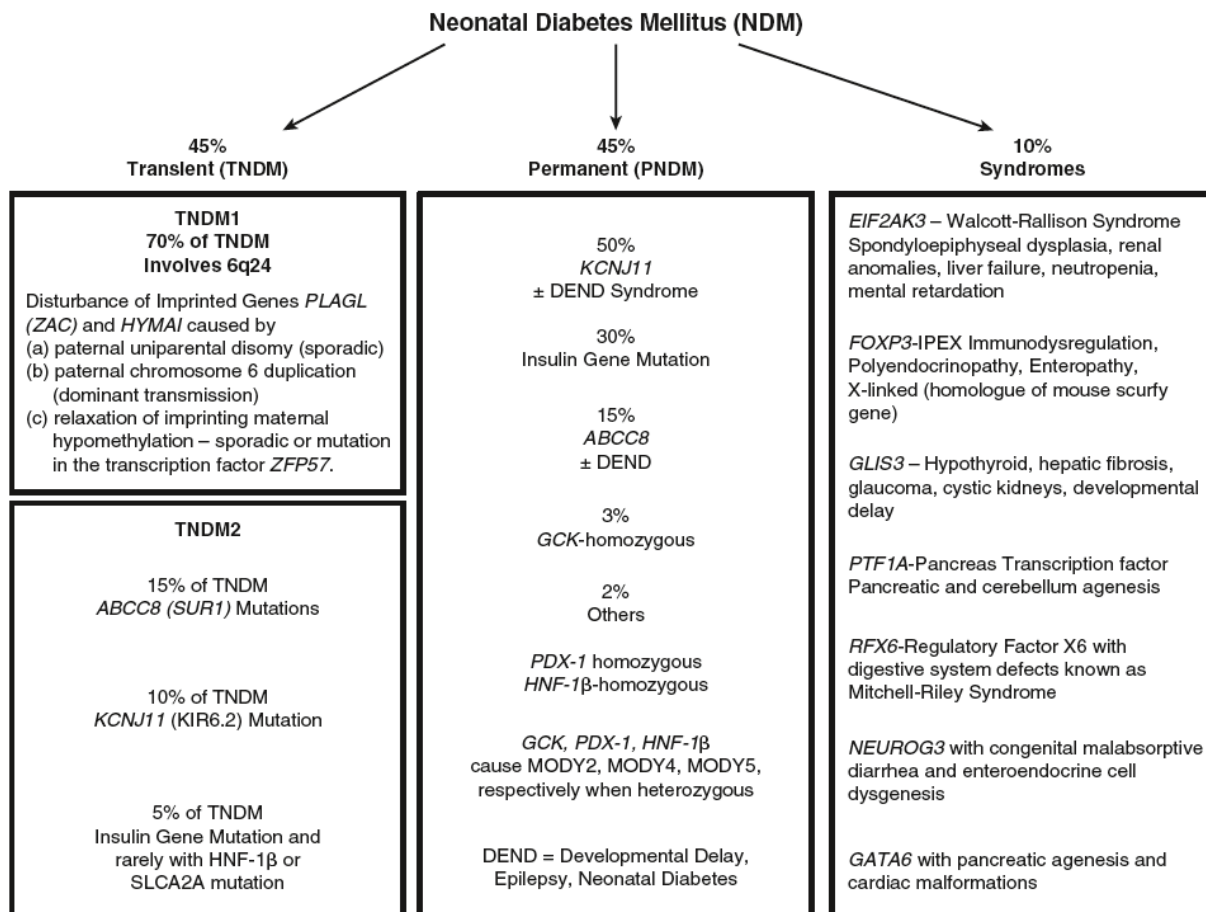
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MODY3 (*HNF1A* mutation), MOY2 (*GCK* (glucokinase) mutation) and MODY1 (*HNF4A* mutation) constitute about 85% of all MODY cases (65-68). With rare exceptions, these patients present as milder types of diabetes before age 30-35 years, with a positive family history involving at least 2-3 generations, and negative for islet cell antibodies; a daily dose of insulin less than 0.5U/Kg /day after 1 year of diagnosis should raise suspicion for MODY. MODY affects both sexes and is found in all races, with a prevalence of ~2%-4% of patients diagnosed with diabetes  $\leq$  30 years (71, 72). The majority are misdiagnosed as type1 or type 2 diabetes and incorrectly and unnecessarily treated with insulin or ineffective drugs such as metformin. MODY 2 affects about 1:1000 people and in females may be noted for the first time during oral glucose tolerance testing in pregnancy, again resulting in inappropriate classification and treatment (73). Biomarkers such as the urinary C-peptide to creatinine ratio ( $\geq 0.2$ nmol/mmol), and negative islet cell antibodies (GAD and IA2) should lead to molecular genetic testing (72). Using this approach, the minimum prevalence of monogenic diabetes was found to be 3.6% of patients diagnosed  $\leq 30$  years of age with diabetes (72). In a study screening for MODY in all antibody negative children with diabetes in a national population-based registry in Norway, the prevalence of MODY was found to be 6.5%, and in a study from Japan, 11/89 children with insulin requiring diabetes but negative for islet cell antibodies were found to have monogenic forms of diabetes involving mutations in *INS*, the insulin gene, and in *HNF1A* or *HNF4A* (74, 75). Mutations in *HNF4A* may be associated with large size at birth and neonatal hypoglycemia with hyperinsulinemia that resolves spontaneously, only later becoming manifest as diabetes. Family history is helpful but not essential; de novo mutations occur.

In summary, there should be a high index of suspicion for MODY in milder forms of diabetes and in those children who are islet cell negative; using biomarkers

followed by molecular diagnostics, the yield becomes quite high for discovering a form of MODY. As the cost of molecular diagnostics declines, and newer algorithms to apply these tools to differentiate apparent type1 from monogenic forms of diabetes are being developed (76, 77), it is becoming apparent that some of these mutations also contribute to the genetics of apparent type 2 diabetes (78, 79). For MODY3 and MODY1, oral sulfonylurea medication (Glipizide) is likely to be effective inducing endogenous insulin secretion; MODY2 does not require treatment. Genetic counselling should inform patients of the 50% likelihood of each of their offspring having MODY, so that inappropriate diagnosis and treatment is avoided. In addition, the prognosis for vascular complications is improved especially in MODY2, though not absolute in MODY3. MODY12 (*ABCC8*) and MODY13 (*KCNJ11*) are also responsive to oral sulfonylurea medication, but may require careful upward titration. For the remaining forms of MODY, insulin is likely to be necessary to control diabetes. In particular, these less frequent forms of MODY may have involvement of other organ systems, e.g., kidney cysts and dysfunction in MODY5(*HNF1B*), gastrointestinal involvement in MODY8 (*CEL*), exocrine pancreatic disturbances in MODY4 (*PDX-1*), blood abnormalities in MODY11(*BLK*), as well as other abnormalities (see references (65-68) for details). Thus, establishing a diagnosis for a form of MODY has several important consequences. First, it guides treatment, obviating the need for insulin with its costs and discomforts in several forms of MODY, as well as anticipation for possible associated abnormalities. Second, it permits a more accurate prediction of the course and prognosis for complications, e.g., MODY2, which in turn has ramifications on the cost and ability to obtain life insurance policy, or the choice of occupations which may be restricted to a person with T1DM. Third, it permits precise genetic counselling for risk of occurrence in offspring, and targeted molecular screening for the existence of the mutation in suspected family members.

## NEONATAL DIABETES MELLITUS



**Figure 4. Causes of Neonatal Diabetes**

Neonatal diabetes mellitus (NDM) is defined as diabetes occurring in the first 6 months of life; for some authorities, the window extends to 9 months of age, but several of the mutations may manifest only later (65, 80, 81). For convenience, NDM is classified into 3 categories; transient NDM which constitutes about 45%, permanent NDM also constituting about 45%, and NDM associated with various other syndromic features, about 10% (Figure 4).

### Transient Neonatal Diabetes

The transient forms are characterized by a period of remission during which glucose tolerance is normal, but diabetes usually recurs later in life. Of these transient forms, about 2/3<sup>rd</sup> involve methylation

abnormalities in chromosome 6q24 which lead to malfunction of imprinted genes *PLAGL*, also known as *ZAC*, and *HYMAI* that arise by the mechanisms listed in the Figure. These infants display small size at birth due to inadequate in utero secretion of insulin, a major regulator of anabolic growth; there is rapid catch-up growth when insulin is provided by sub-cutaneous injection or via pump therapy with insulin diluted 1:10 so that 1 ml contains 10 U rather than the standard 100U/ml. Hyperglycemia and glucosuria are present but may be missed if not sought. Rare variants of these methylation defects may have initial hypoglycemia and devolve into hyperglycemia. Most are sporadic, but duplication of paternal chromosome 6 leads to dominant transmission (see figure). Of the remaining 1/3<sup>rd</sup> of TNDM, the majority harbor

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mutations in the KATP genes *ABCC8* and *KCNJ11* which respond to therapy via oral hypoglycemic agents such as glipizide; dosage requires titration to individual responsiveness. Approximately 5% of transient cases involve mutation in the insulin gene *INS*, the  $\beta$ -cell glucose transporter *SLCA2A*, or other genes as listed in Figure 4.

### Permanent Neonatal Diabetes

Permanent NDM primarily involves 3 genes; severe mutations in *KCNJ11* or *ABCC8*, and the insulin gene *INS*. Because the KATP channel and its' genes are also expressed in the CNS, severe mutations also may affect neural function and development. **Developmental delay, Epilepsy, and Neonatal Diabetes** constitute the DEND syndrome, with associated physical and neuropsychological features; early treatment with oral sulfonylurea medication benefits neuropsychological function and timing of treatment influences outcome, i.e., the earlier the better (82-84). There is debate whether treatment with oral sulfonylurea should be started before confirmation of the genetic defect, but we recommend that it not be started, as the transition to oral agents with concomitant reduction in the injected insulin dose, essential to control the severe hyperglycemia and sometimes associated with DKA, is potentially dangerous and the dose of sulfonylurea needed is much higher than that used in adults with T2DM. If successful, transition to oral therapy is associated with remarkable improvement of metabolic control due to stimulation of endogenous insulin secretion and neuropsychological improvement; it is also easier and less traumatic to the patient than insulin injection (80). We therefore recommend that such transitions be performed in a hospital setting according to a

published protocol (85). When insulin therapy is used, either in mutations of the KATP channel or where it must be in mutations of *INS* which do not respond to sulfonylurea, using continuous subcutaneous infusion via a pump and diluted insulin, appears to be the best option (86).

### Neonatal Diabetes and Associated Syndromes

About 10% of cases of NDM are associated with a spectrum of syndromic disorders; the more common ones are listed in the figure 4 and greater details can be found in the references (65-68, 77, 80, 81). In all forms of neonatal diabetes, children are born small for gestational age; the smaller the child, the more severe the defect in insulin synthesis, secretion or action is likely to be. The associated abnormalities provide clinical clues, and it was the clinical associations that often defined the syndrome, before the genetic mutation was known. Next generation sequencing with a panel specifically designed for NDM can provide a rapid diagnosis and guide therapy, predict associated abnormalities, and infer possible interventions before some of the classical features have evolved (77, 81). Indeed, this is the approach now recommended, i.e., non-selective genetic testing in any case of neonatal diabetes. In addition, exome sequencing of unusual cases not covered by the panel may uncover new entities, as recently described for a form of autoimmunity associated with NDM that is responsive to a CTL4 mimetic (87). For most of the syndromic forms, insulin is the required therapy to control diabetes; an exception may be thiamine responsive megaloblastic anemia and diabetes which is due to mutation in the thiamine transporter *SLCA29* and initially responsive to thiamine replacement (77, 80).

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