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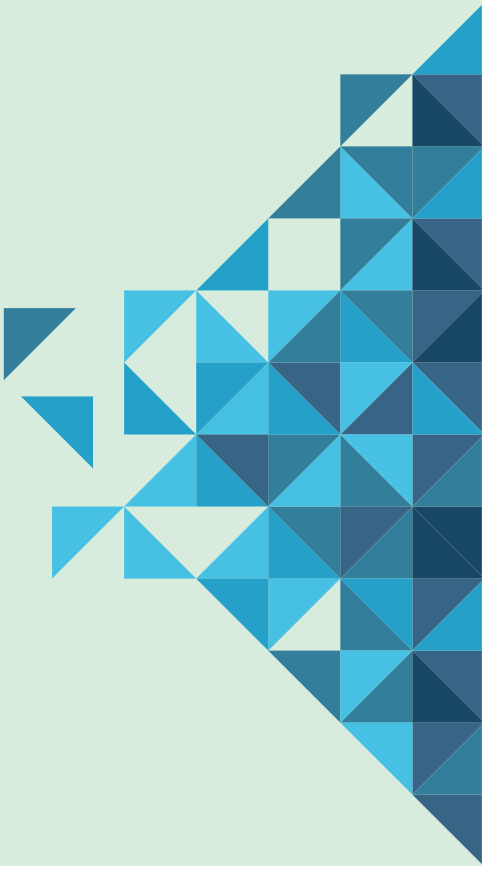

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# Luminary Learnings

## Diabetes

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# Contents

## Continuing Education



## Connect the Dots

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# Diabetes in Pregnancy

**Agustin Busta, Alberto Franco-Akel, Yuriy Gurevich, Adina Schneider, Elliot Rayfield**

## Abstract

Maternal diabetes is a significant cause of short-term and long-term morbidity for the infant and the mother. Infants born from mothers with gestational diabetes have a high prevalence of overweight, obesity, and risk to develop type 2 diabetes later in life. Gestational diabetes affects 18% of pregnancies. Its increasing incidence and prevalence worldwide are mostly attributed to the progressively increasing rates of obesity and a changing lifestyle in the general population. Gestational diabetes is an independent risk factor for the future development of overt postpartum diabetes.

Maternal and fetal complications are more frequent in patients with pre-existing diabetes than those with gestational diabetes. Nondiabetic women should receive universal screening for gestational diabetes, and women at risk for diabetes should be screened on the first prenatal visit. At present, there is general agreement on the strategy for diagnosis as well as the management of labor and delivery and postpartum follow-up in women with pre-existing diabetes and gestational diabetes.

The first-line treatment for gestational diabetes consists of dietary modification and increased physical activity. Subsequent pharmacologic therapy is warranted if this strategy fails. Early diagnosis of pre-existing diabetes, as well as proper diagnosis of gestational diabetes, warrants early

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treatment and a strict clinical follow-up since early intervention has been shown to improve fetal and maternal outcomes in randomized controlled trials.

**Keywords:** Gestational diabetes mellitus, Perinatal, Insulin resistance, Macrosomic, Large-for-gestational-age infants, Preeclampsia, Target glucose levels, Maternal ketonemia, Low-glycemic-index diet, Diabetic retinopathy, Teratogenic effects, Pre-existing diabetes, Pre-gestational

## Introduction

Gestational diabetes mellitus (GDM) is glucose intolerance that first occurs, or is first identified during pregnancy [1]. GDM affects up to 18% of pregnancies [2]. The prevalence of GDM in the USA has more than doubled from 1.5% in 1989–1990 to 4.2% in 2001–2004 [3]. Based on the 2013 birth data in the USA [4, 5], maternal diabetes affects more than 235,000 of the almost four million pregnancies that result in birth and is a significant cause of maternal and fetal morbidity [6]. The majority of these cases are attributed to GDM. Both pre-gestational T1DM and T2DM confer significantly greater risk for complications than GDM [7].

In North America, the prevalence of GDM is higher in Asians, African-Americans, Native-Americans from Canada, and Hispanics, than in non-Hispanic whites [8]. A subset of women with GDM have circulating islet cell antibodies. These patients might have a latent form of T1DM [9].

The majority of complications arise in patients with gestational and undiagnosed T2DM. Patients with GDM usually develop hyperglycemia during the second half of pregnancy. Hyperglycemia at this stage of gestation clearly causes fetal macrosomia and neonatal hypoglycemia. Patients with pre-gestational diabetes are at risk for hyperglycemia early in pregnancy; this hyperglycemia is associated with significantly increased rates of fetal loss and fetal malformations.

Based on information reported from a 12-year outcome database [10], women with T2DM have a less satisfactory pregnancy outcome compared to the general population, with infants having a twofold higher risk of stillbirth, a 2.5-fold higher risk of a perinatal mortality, a 3.5-fold higher risk of death within the first month, and a sixfold higher risk of death up to 1 year, along with an 11 times higher risk of a congenital malformation. Nevertheless, randomized controlled trials (RCT) have demonstrated the benefit of treating maternal hyperglycemia in GDM based on the fact that the achievement of euglycemia decreased the risk of adverse perinatal outcomes [11, 12].

The association between maternal diabetes and birth defects and perinatal mortality has been recognized since the late nineteenth century [13, 14]. About 6–10% of newborns from mothers with T1DM and T2DM have major congenital defects [15]. Developmental malformations in the infants of diabetic mothers exhibit great diversity of these malformations, ranging from congenital structural defects, functional defects, and low birth weight to macrosomia [16, 17]. In the pre-insulin era, maternal diabetes-associated perinatal mortality reached 70%, and maternal mortality was as high as 30–40% [18, 19]. After the introduction of insulin, maternal mortality decreased dramatically, while perinatal mortality was reduced down to the current rates of 4–13% [20, 21].

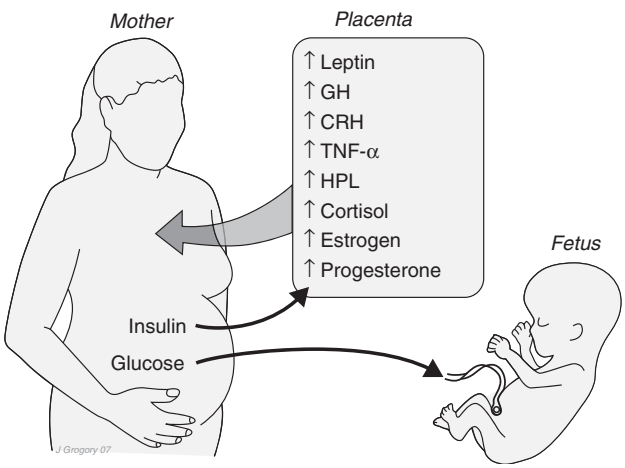


**Fig. 1.** Movement of hormones and glucose across the placental barrier.

## Pathophysiology of Glucose Intolerance in Pregnancy

Fasting glycemia is 10–20% lower in pregnant women as compared to nonpregnant women. This physiological adaptation process has been attributed to several mechanisms such as increased storage of glycogen in tissues, increased utilization of peripheral glucose, diminished hepatic glucose production, and fetal utilization of glucose, which occurs predominantly through a glucose transporter (GLUT)-1 isoform on the trophoblast [22].

Development of insulin resistance in late gestation is a process common to all human pregnancies. The underlying pathophysiology of GDM is a function of decreased maternal insulin sensitivity or increased insulin resistance, which is defined as the inability of a defined concentration of insulin to effect a predictable biological response of nutrient metabolism at the level of the target tissue [23] (see Fig. 1).

Maternal insulin resistance is a normal physiologic response that begins in the second trimester and peaks in the third trimester. This occurs as a result of increased placental secretion of diabetogenic hormones such as growth hormone (GH), corticotropin-releasing hormone (CRH), chorionic somatomammotropin (HCS), also called human placental lactogen (hPL), and progesterone. hPL plays a major role in maternal insulin resistance [24]. In addition, the placenta produces somatostatin, which has the ability to inhibit hPL. Thus, reduction in the secretion of somatostatin in the later part of pregnancy may contribute to insulin resistance [25].

Several other changes that occur in GDM might further impact insulin resistance. Elevated leptin concentrations have been observed in GDM [26]. It has been shown that levels of tumor necrosis factor-alpha (TNF-α) increase from early to late pregnancy [27]. Some investigators suggest that TNF-α is the most important contributor to insulin resistance in pregnancy [28]. In late gestation, hepatic glucose production was reported to increase in women with GDM in comparison with a control group [29].

Secretion of pituitary GH is diminished by 20 weeks and supplanted by placental GH. Human placental growth hormone has been shown to cause insulin resistance in transgenic animals [17].

ACTH levels increase during pregnancy, probably secondary to placental CRH, leading to an increase in plasma cortisol levels.

According to the data presented at the Fifth International Workshop-Conference on GDM, post-receptor mechanism of insulin resistance in GDM involves β-subunit of insulin receptor as well as IRS-1 in the skeletal muscle [30].

## Gestational Diabetes

Gestational diabetes mellitus is defined as carbohydrate intolerance resulting in hyperglycemia with onset or first recognition during pregnancy [1, 2]. The prevalence of GDM is increasing, which has health implications for the mother and the fetus, during pregnancy and later in life [31, 32].

Women with GDM are more likely to give birth to macrosomic or large-for-gestational-age infants. GDM may result in obstructed labor, the death of the mother and the baby, and birth injury for the infants. GDM also has long-term health impact, with more than 50% of women with GDM going on to develop T2DM within 5–10 years of delivery. Moreover, infants of women with GDM have a higher prevalence of overweight and obesity and higher risk of developing T2DM later in life [32].

### Screening and Diagnosis of Gestational Diabetes

For women at risk of pre-existing diabetes, early screening is warranted. They should be tested for undiagnosed diabetes at the first prenatal visit using the American Diabetes Association diagnostic criteria for nonpregnant adults [33, 34].

For women without pre-existing diabetes, a universal screening test is recommended at 24–28 weeks of pregnancy [35]. Universal screening is preferred rather than selective screening based on practicality, since only 10% of the general obstetric population in the USA has been found to meet all the low-risk criteria for developing GDM [36], whereas 90% of pregnant women have at least one risk factor for glucose impairment during pregnancy. Furthermore, it has been observed that 2.7–20% of women who are diagnosed with GDM had no risk factors [37, 38].

Diagnosis of GDM can be accomplished with either of two strategies in all pregnant women. The "one-step" approach with a 75-g OGTT or, the "Two-step" approach with a 50-g (non-fasting) screen followed by a 100-g OGTT for those who screen positive [39].

### One-Step Strategy

In 2011, the ADA recommended for the first time that all pregnant women not known to have prior diabetes undergo a 75-g OGTT at 24–28 weeks of gestation, based on a recommendation of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) [2]. In 2015, the AACE/ACE recommend screening for GDM in all pregnant women using the criteria described in this one-step strategy [40]. This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5–6% to ~15–20%), primarily because only one abnormal value, not two, became sufficient to make the diagnosis.

## Two-Step Strategy

In 2013, the National Institutes of Health (NIH) convened a consensus development conference on diagnosing GDM. The panel had representatives from obstetrics/gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other fields, to consider diagnostic criteria [41], and recommended the two-step approach of screening with a 1-h 50-g glucose load test (GLT) followed by a 3-h 100-g OGTT for those who screen positive. This is a strategy commonly used in the USA.

The lack of clinical trial interventions demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large new group of women with GDM (e.g., medicalization of pregnancy with increased interventions and costs) were important determinant factors in the NIH panel's decision-making process.

The American College of Obstetricians and Gynecologists (ACOG) updated its guidelines in 2013 and supported the two-step approach [42].

As the IADPSG criteria have been adopted internationally, further evidence has emerged to support improved pregnancy outcomes with cost savings [43]. In addition, pregnancies complicated by GDM per IADPSG criteria, but not recognized as such, have comparable outcomes to pregnancies diagnosed as GDM by the more stringent two-step criteria [44].

Nevertheless, screening with a 50-g GLT does not require fasting and is therefore easier to accomplish for many women. In addition, treatment of higher threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births, and shoulder dystocia, without increasing small-for-gestational-age births [45].

The conflicting recommendations from expert groups underscore the fact that there is data to support each strategy. The decision regarding which strategy to implement must therefore be made based on the relative values placed on factors that have yet to be measured (e.g., cost-benefit estimation, willingness to change practice based on correlation studies rather than clinical intervention trial results, relative role of cost considerations, and available infrastructure locally, nationally, and internationally).

There remains a strong consensus that establishing a uniform approach to diagnosing GDM will benefit patients, caregivers, and policy makers. Longer-term outcome studies are currently underway.

To deal with disparity in diagnostic testing used throughout the world and its impact on estimation of prevalence of GDM and pregnancy outcomes, a Hyperglycemia and Adverse Pregnancy Outcome (HAPO) prospective observational study was undertaken [46]. Investigators analyzed several pregnancy outcomes in over 23,000 women with impaired glycemic control as determined by 75-g oral glucose tolerance test (OGTT) at 24–32 weeks gestation. Average fasting and 1- and 2-h plasma glucose levels were 80.9 mg/dL, 134.1 mg/dL, and 111.0 mg/dL, respectively. The study demonstrated that primary outcomes (neonatal insulinemia, measured by means of umbilical cord-blood C-peptide level, birth weight, neonatal hypoglycemia, and rate of cesarean delivery) were directly related to the levels of fasting, plasma glucose, and 1- and 2-h post-challenge glucose.

Despite the aforementioned criteria for diagnosis of GDM, there is evidence to suggest that one abnormal glucose tolerance test value is associated with increased risk of macrosomia, preeclampsia, and eclampsia [47]. It has also been demonstrated that treatment of women with one abnormal OGTT value results in reduction of such complications [48].

## Morbidity, Long-Term Consequences, and Benefits of Treatment

Gestational diabetes mellitus is characterized by the increased risk for adverse perinatal outcomes. These risks have a greater prevalence among GDM women compared to those who are normoglycemic. GDM has been associated with maternal risks such as hypertension, cesarean delivery, and preterm birth [49].

Fetal and neonatal adverse outcomes result from excessive maternal glucose crossing the placenta, which can lead to fetal hyperinsulinemia and subsequently fetal overgrowth, fat deposition, and demand for oxygen [50].

Other clinically important adverse perinatal outcomes associated with GDM are hyperbilirubinemia, respiratory distress, and prematurity [49].

A multicenter-randomized trial aimed to determine whether pregnancy outcomes were modified by treatment in women with mild GDM. Results of this trial showed that the frequency of stillbirth, perinatal mortality, and complications from maternal hyperglycemia (e.g., hypoglycemia, hyperbilirubinemia, neonatal hyperinsulinemia, and birth trauma) were not significantly reduced. However, this study did show a lower risk of fetal overgrowth, shoulder dystocia, cesarean delivery, and preeclampsia if treatment was provided [51] (see Table 1).

The Australian Carbohydrate Intolerance Study (ACHOIS) in patients with GDM reported a significant lower rate of serious adverse perinatal outcomes, defined as infant death, shoulder dystocia, bone fracture, and/or nerve palsy, in women who received intervention (e.g., dietary advice, blood glucose monitoring, and insulin therapy) than those who received routine care [52]. GDM entails an increased risk for maternal diabetes after pregnancy [53]. A systematic review of the incidence and the factors associated with this conversion to overt diabetes showed a widely variable cumulative incidence of T2DM among studies. These differences could be explained by the length of follow-up, retention of cohort studies, and selection of initial population with GDM.

**Table 1. Morbidity of gestational diabetes.**

| Maternal | Fetal and newborn |
|---|---|
| Preeclampsia | Neonatal hypoglycemia |
| C-section | Macrosomia |
| Polyhydramnios | Shoulder dystocia |
| | Polycythemia |
| | Hypocalcemia |
| | Hyperbilirubinemia |
| | Future diabetes mellitus, obesity |

Women from mixed cohorts or non-white cohorts seemed to have a similar rate of progression to T2DM. The rate of progression to T2DM had a steep increase within the first 5 years upon delivery and showed a plateau afterward [54]. Moreover, women who had a diagnosis of GDM have a risk greater than 50% of developing subsequent GDM and later T2DM [55].

Emerging evidence suggests that in utero programming related to the degree of glycemic control in pregnancy may prompt an increased risk of metabolic syndrome, obesity, and diabetes among children of GDM mothers [56].

A systematic review and meta-analysis done in 2013, which included randomized controlled trials and cohort studies, revealed that treating GDM resulted in decreased rates of preeclampsia, shoulder dystocia, and macrosomia [57].

The children of women who have had GDM have an increased risk of developing obesity and abnormal glucose tolerance by the time of puberty. The health-care providers of these children should be aware of this risk so that they can encourage their patients to make appropriate lifestyle changes [58].

### Target Glucose Levels

The primary goal of treating GDM is to decrease the risk of adverse perinatal outcomes. The goals for glycemic control in GDM are derived from the Fifth International Workshop-Conference on Gestational Diabetes Mellitus [30]. Once the diagnosis of GDM is established, patients should start monitoring their blood glucose levels, ideally fasting levels and 1 or 2 h after meals. Fasting glucose target level should be ≤95 mg/dL, 1-h postprandial should be ≤140 mg/dL, and 2-h postprandial should be ≤120 mg/dL [30, 42]. If glucose targets are achieved by means of diet and exercise, less intensive glucose monitoring is acceptable [34, 42].

### Lifestyle Modification

The first-line treatment for GDM consists of diet and physical activity. GDM women should receive individualized nutrition counseling from a dietitian. It is generally recommended to limit carbohydrate intake to 33–40% of calories [30].

Aerobic exercise and resistance training have been shown to improve glycemic control in patients with diabetes; nevertheless, these effects have been inconsistent in clinical trials of women with GDM [59, 60].

Maternal obesity, excessive gestational weight gain, and GDM are well-established independent and additive risk factors for fetal macrosomia. Hence, it makes sense that all possible efforts are made to minimize maternal weight gain [61].

### Diet Therapy

A nutritionist or other professional should provide dietary advice to women with gestational diabetes. The Fifth International Workshop-Conference recommends 30 min of physical activity a day if possible, consisting of brisk walking or seated arm exercises for 10 min after each meal [30].

There are several strategies to nutritional therapy for patients with GDM. The American Diabetes Association recommends an average of 30 kcal/kg/day based on prepregnant body weight. The ACOG recommends a maximal caloric restriction of 33% and focuses on the avoidance of ketonemia, because of old data that suggests an inverse association between maternal ketonemia and intelligence quotient of the offspring [62]. A low-glycemic-index diet is considered essential in the nutritional management of patients with non-gestational diabetes, although its effectiveness has not been well explored in patients with GDM. Based on results of small pilot open-label studies, it has been suggested that a low-glycemic diet improved postprandial glucose compared with controls [63]. Although it is reasonable to assume that a low-glycemic diet should be established in the treatment of GDM, data supporting this strategy is not strong. We can conclude that a well-balanced diet that restricts concentrated sweets and simple carbohydrates is culturally sensitive and as much as possible is adapted to the patient's preferences should be implemented.

## Exercise

The benefit of physical exercise in the treatment of T2DM is well established. Aerobic exercise rapidly improves glycemia, whereas sustained exercise has been shown to improve insulin sensitivity. As insulin resistance is the basic underlying process in GDM, it is likely that exercise confers short- and long-term benefits. In addition, low-impact activity such as walking, swimming, and resistance training may have great potential benefits with very small risks.

A prospective randomized controlled study of obese pregnant women (BMI ≥ 30) in the first trimester, looked into the effects of lifestyle modification, including an exercise component, compared to a control group which received routine prenatal care. The intervention group subjects gained less weight in pregnancy and did not have any increased risk of preeclampsia, cesarean delivery, or low birthweight [64].

A randomized trial of 64 women with diet-controlled GDM looked into the impact of resistance band exercise versus routine management on insulin sensitivity. Results of this study showed that women in the exercise group compared to the control group had >50% reduction of required insulin (56.3% vs. 21.9%) and a higher percentage of time with glycemia in the target range, with no increased rates of hypoglycemia [65].

## Pharmacologic Therapy

Women with greater initial degrees of hyperglycemia may require early initiation of pharmacological therapy. Nevertheless, in cases of mild to moderate hyperglycemia, if a trial of lifestyle modification does not result in satisfactory glucose control, pharmacologic therapy can be initiated.

Insulin is the first-line agent recommended for treatment of GDM in the USA. Glyburide is a suitable alternative to insulin therapy, except for those women with diagnosis of GDM before 25 weeks gestation [66] and for those women with fasting plasma glucose levels above 110 mg/dL, [67] in which case insulin therapy is preferred. Nevertheless, recent meta-analyses and large observational studies examining maternal and fetal outcomes suggested that glyburide

may be inferior to insulin and metformin due to increased risk of neonatal hypoglycemia and macrosomia [53].

Metformin is a suitable alternative when patients are not good candidates for glyburide [68].

Neither glyburide nor metformin have been approved by the U.S. FDA for the treatment of GDM. Both of these medications cross the placenta but have not been associated with birth defects or short-term adverse neonatal outcomes [42, 69]. Clinicians may consider counseling patients on the lack of long-term safety data for these medications.

### Insulin

Historically, insulin has been the recommended treatment for GDM in the USA. Insulin is required in women who have uncontrolled blood glucose levels despite lifestyle modification, especially if oral medications have failed to achieve target pre- and postprandial plasma glucose values.

Insulin does not cross the placenta, and most insulin types are considered safe for use in pregnancy [70, 71]. Women who require basal insulin should be started on the insulin analog detemir (pregnancy category B). Neutral Protamine Hagedorn (NPH) insulin is also an option, although it has been associated with problematic hypoglycemia, even if given at appropriate doses [72]. Insulin detemir may also be continued in those women with pre-gestational diabetes who have already successfully taken it before pregnancy.

Whereas insulin detemir is approved by the FDA for use during pregnancy, insulin glargine does not have such approval. It has been suggested that insulin glargine could be continued during pregnancy in women who were already on it and had satisfactory glucose control before getting pregnant [68]. Women treated with insulin glargine during the first trimester have a similar rate of congenital malformations as those treated with NPH insulin [73, 74].

Rapid-acting insulin analogues lispro and aspart are preferred over regular soluble insulin and pregnant women with diabetes. These two analogues allow greater lifestyle flexibility, greater patient satisfaction, and improved quality of life [75]. These also provide better postprandial glucose control [76] and hemoglobin $A_{1c}$ reduction [77]. Insulin glulisine (pregnancy category C) does not have FDA approval for use in pregnancy.

Women who were on subcutaneous insulin infusion before pregnancy should continue it once they get pregnant [68].

Insulin therapy can be started by calculating a total daily dosage of 0.7–1.0 units/Kg. Half of this total daily requirements is to be given as long-acting insulin, and the other half is administered as rapid-acting insulin in three divided doses before meals. The dose should be individualized and tailored as needed [78].

### Oral Hypoglycemic Medications

When lifestyle modification does not result in satisfactory glucose control, generally after a trial of one week, pharmacologic therapy is indicated. Randomized controlled trials support the efficacy and short-term safety of glyburide (pregnancy category B) [79].

Metformin therapy can also be used for glucose control in women with GDM who do not have satisfactory glycemic control despite medical nutrition therapy and who are not good candidates, or cannot use insulin or glyburide [68].

There is no consensus on the threshold values for which these two oral medications should be initiated. Different approaches have been used. One approach is to start therapy if more than two values on the same meal during a 2-week period are above target by more than 10 mg/dL [80]. Another approach would be to start medications if 50% of the values in a given week are above target levels [51]. Between 15% and 40% of women who are prescribed oral medications for GDM will ultimately require insulin [42]. Glyburide may be associated with lower failure rates than metformin [80]. Nearly half of the women with GDM treated with metformin monotherapy have glycemic control failure rates requiring conversion to insulin therapy [81]. Other than that, glycemic control, maternal and neonatal outcomes, and adverse effects are similar among patients treated with oral agents versus insulin [82, 83].

### Labor and Delivery

As the placenta is delivered, there is a considerable reduction in pregnancy-related insulin resistance. Most women with GDM will not require insulin once active labor begins and rarely require insulin after delivery. Blood glucose needs to be obtained on the day after delivery to make sure hyperglycemia is resolved.

There is no data to support delivery of women with GDM before 38 weeks gestation if evidence of maternal or fetal compromise is absent. There is a lack of information on the risk of perinatal morbidity and mortality in the infants of women with well-controlled GDM if pregnancy proceeds beyond 40 weeks of gestation. However, it is prudent to intensify fetal surveillance when pregnancy continues beyond this point [30].

### Postpartum Management

According to the Fifth International Workshop, there is evidence that suggest that breastfeeding might have a beneficial effect on the development of postpartum diabetes in women with GDM. Therefore, breastfeeding is encouraged [30].

Since insulin is degraded in the digestive tract of the infant, women who are breastfeeding can safely use any type of insulin. Glyburide and glipizide may also be utilized [82].

There is some data to suggest that metformin is excreted into breast milk in small amounts. However, this seems not to have any deleterious effects on the infant [84]. At present, larger studies are needed to determine safety of metformin in breastfeeding mothers (see Fig. 2).

### Fetal Surveillance

The intensity of fetal monitoring is determined by the severity of GDM. At a minimum, patients treated with diet alone should be taught to measure fetal movements during the last 8–10 weeks

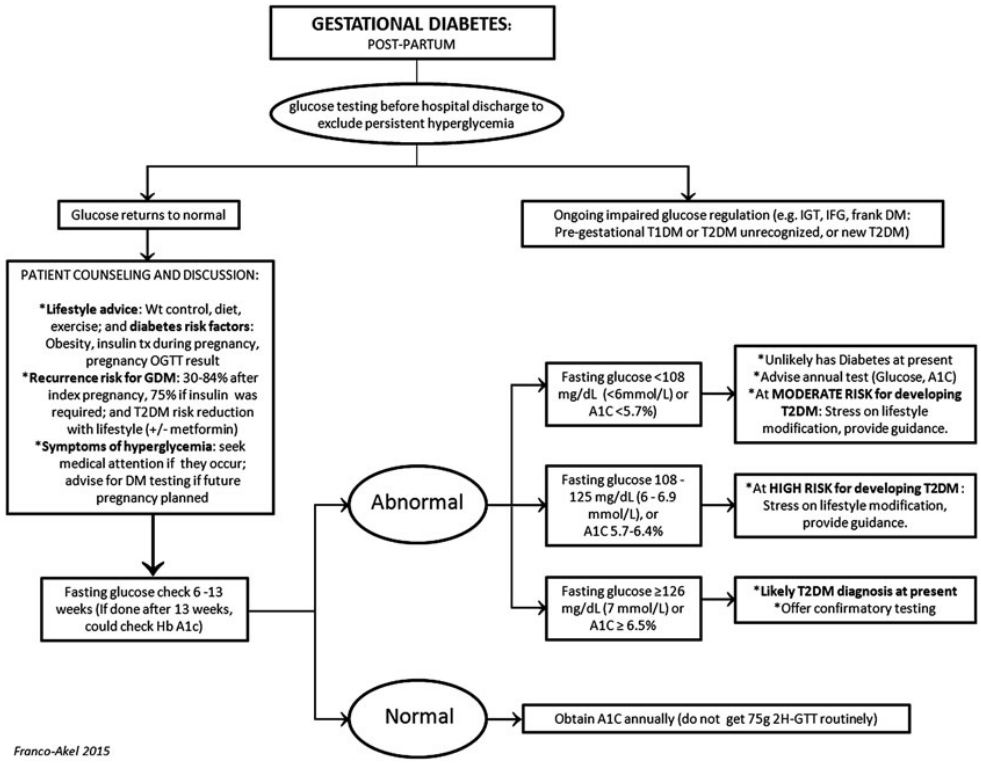


**Fig. 2.** Postpartum follow-up in gestational diabetes women.

of pregnancy. Patients who are being treated with insulin should undergo nonstress testing beginning at 32 weeks of gestation. Fetal ultrasound may be used to assess fetal size at 29–33 weeks and should be used for detection of fetal anomalies in patients who had GDM diagnosed during the first trimester or who have fasting plasma glucose of >120 mg/dL [58]. Recent evidence suggests the use of fetal ultrasound rather than strict glycemic parameters as a guide for initiation of insulin therapy. This approach would minimize glucose testing and insulin utilization in low-risk pregnancies [85].

## Pre-Gestational Diabetes

Both pre-existing T1DM and T2DM significantly represent a greater maternal and fetal risk than GDM. Among them, spontaneous abortion, fetal anomalies, preeclampsia, intrauterine fetal demise, macrosomia, neonatal hypoglycemia, and neonatal hyperbilirubinemia are the most clinically important. In addition, diabetes in pregnancy may increase the risk of obesity and T2DM in the offspring later in life [86, 87]. Therefore, it is imperative that all efforts are directed toward the achievement of glucose control before conception.

## Congenital Malformations

Before the introduction of insulin, diabetic women were rarely able to produce viable offspring. The level of glycemic control early in organogenesis has been shown to impact rates of malformations. Miller et al. showed that a hemoglobin $A_{1c}$ in the first trimester of >8.5% was associated with a malformation rate of 22.4%, a hemoglobin $A_{1c}$ 7–8.4% was associated with a rate of 5%, while a hemoglobin $A_{1c}$ <6.9% was associated with no excessive malformations [88]. The duration of diabetes and the presence of vasculopathy have also been shown to be associated with an increased risk of anomalies [89].

## Pre-Conception Care

Pregnancy must be a planned event for women with T1DM and T2DM. It has been pointed out that women with T2DM are less likely to receive pre-conception care because the disease has often gone undiagnosed [90]. In addition, T2DM is also more prevalent in minority groups who may have limited access to care.

Family planning should be discussed, and an effective plan for contraception should be prescribed and used until a woman is ready to become pregnant [53]. Pre-conception counseling should be provided, addressing the importance of glycemic control as close to normal, and as safely possible, ideally with a hemoglobin $A_{1c}$ <6.5% (48 mmol/mol) to reduce the risk of congenital anomalies [53].

Women with pre-existing diabetes who desire pregnancy or who have become pregnant should receive extensive counseling on the risk of development and/or progression of diabetic retinopathy [53]. If no such counseling takes place and a woman with pre-existing diabetes presents to the office at the beginning of her pregnancy, it is imperative to establish glycemic control as soon as possible, only after an ophthalmologic evaluation by a specialist is performed, since the rapid normalization of glycemia is known to play a role in the progression of diabetic retinopathy [6] (see section "Diabetic Retinopathy").

Evaluation of renal function and thyroid function is essential component of the initial visit. Hypertensive women should be treated with agents which have been shown to be safe in pregnancy. ACE inhibitors, diuretics, and beta blockers should be avoided because of the associated risk of congenital malformations [91]. Also, statin drugs need to be discontinued in anticipation of conception due to potential teratogenic effects [92] (see Table 2).

## Diabetic Retinopathy

The association of pregnancy with rapidly progressing diabetic retinopathy has been well established [93, 94]. This progression can lead to sight-threatening damage, which can occur during pregnancy and up to 1 year after delivery [95–97]. The absence of diabetic retinopathy before conception confers a very small risk to develop severe retinal disease during pregnancy; although, even if not identified before conception, important retinopathy can develop during pregnancy

**Table 2. Pre-conception care – initial visit.**

| |
|---|
| Hemoglobin $A_{1c}$ |
| Blood glucose record |
| 24-h urine microalbumin/creatinine |
| TSH |
| Blood pressure/medication reconciliation |
| Retinal exam |
| Cardiovascular evaluation/medication reconciliation |
| Neurological exam |
| Nutritional evaluation |
| Counseling on risks of pregnancy |

[96]. Therefore, it is reasonable that women with diabetes not known to have retinopathy get an eye evaluation soon after pregnancy is achieved [68].

There is a direct relationship between the severity of pre-conception retinopathy and the risk for progression of retinopathy during gestation [96]. For this reason, women with a diagnosis of pre-gestational T1DM or T2DM and who plan to become pregnant, or are already pregnant, should receive counseling on this risk [68, 98]. These women should have a detailed ocular evaluation by a qualified ophthalmologist [68].

Risk factors associated with progression of retinopathy in pregnant women are pre-conception hypertension [99], uncontrolled hypertension during pregnancy [100], preeclampsia [101], and poorly controlled glycemia at the beginning or during pregnancy [97]. Paradoxically, rapid establishment of tight glycemic control in women with diabetic retinopathy has been associated with worsening of retinal disease [95].

The main goal of screening for diabetic retinopathy is preventing and/or reversing vision loss by means of treatment of retinopathy [98]. If retinopathy has been identified and it is severe enough to warrant therapy, it is strongly recommended to defer conception until retinopathy is treated appropriately and stabilized [98]. In addition, once women with established background retinopathy get pregnant, they should be followed by their ophthalmologist every trimester, then within 3 months of giving birth, and then as needed [68].

Women with GDM do not need retinal examination during pregnancy, as they appear to lack an increased risk for retinopathy during pregnancy, in contrast to those with pre-existing diabetes [102].

## Diabetic Kidney Disease

Women with diabetes who plan pregnancies should receive pre-conception kidney function evaluation, by means of creatinine and urinary albumin-to a -creatinine ratio testing [53], as well as estimated glomerular filtration rate (eGFR) [68].

Mild degree of diabetic kidney disease may worsen during pregnancy. Mild renal dysfunction is usually both modest and reversible once pregnancy is completed [103]. Mild renal dysfunction, however, can result in more significant degrees of proteinuria and renal impairment when blood pressure and blood glucose are not well controlled during pregnancy [104]. Therefore, all women with diabetes and any degree of pre-conceptional renal dysfunction should be monitored regularly during pregnancy [68].

In women with more severe pre-conceptional renal dysfunction (e.g., reduced GFR and elevated serum creatinine), renal function can further deteriorate during pregnancy and may be irreversible [105, 106]. These women should be assessed by a nephrologist before pregnancy [68].

Angiotensin-converting enzyme inhibitors (ACEI) are the first-line medical therapy for diabetic kidney disease, although these are contraindicated during pregnancy. Alpha methyldopa is considered safe during early pregnancy. Diltiazem, which is a more effective agent in preventing progression of nephropathy, can be used at the end of the first trimester [107]. Preeclampsia is the most common complication in patients with overt nephropathy; other maternal complications include anemia and nephrotic syndrome. Fetal complications include fetal distress, intrauterine growth retardation, preterm delivery, and stillbirth. Diabetic kidney disease, in the absence of hypertension, impacts fetal outcome when renal function is impaired by at least 50% [90]. With improved control of pre-conception and perinatal glycemia, and blood pressure, perinatal mortality has decreased to 5% [90].

### Treatment: Pharmacologic Therapy and Monitoring

Close follow-up by a diabetes team is required throughout gestation to assure maintenance of strict glycemic control. Office visits every 2–3 weeks are usually necessary with more frequent telephone contact as needed (see Table 3).

Multiple blood glucose measurements and insulin injections are often required to achieve tight glycemic control. As noted previously, postprandial monitoring seems to result in improved fetal outcome. Indeed, postprandial blood glucose levels are the most important predictor of fetal macrosomia [108]. Hemoglobin $A_{1c}$ should be monitored to confirm the level of control. The usual insulin requirements in women with pre-existing T1DM are similar to those in women with GDM who required insulin, as outlined above. Insulin pump therapy can achieve glucose control and perinatal outcomes equal to multiple injection regimens [109]. As discussed for women with GDM, women with T2DM must be treated with insulin during pregnancy. Again, insulin requirements in these patients are often high due to obesity and insulin resistance.

### Diet and Exercise

As discussed for women with GDM, the patients with pre-gestational diabetes should receive appropriate dietary counseling by a nutritionist or other professional and followed closely. Exercise may be beneficial for pregnant patients with T2DM. Exercise in pregnant women with T1DM may lead to increased hypoglycemic episodes and is only permitted in women who participated in an exercise program prior to becoming pregnant [90].

**Table 3. Plan of care in diabetic pregnancy.**

| |
|---|
| Five to nine blood glucose measurements/day |
| Hemoglobin $A_{1c}$ every 4–6 weeks |
| Office visits every 2–3 weeks |
| Telephone contact (as needed) |
| Fetal surveillance |

## Hypoglycemia

Hypoglycemia is an important complication of tight glucose control during pregnancy. Early pregnancy is associated with decreased fasting glucose levels due to increased glucose uptake by the placental fetal unit and decreased hepatic glucose production. The majority of hypoglycemic episodes occur during the first trimester. Recurrent episodes of hypoglycemia may be associated with small-for-gestational-age infants [58], and severe prolonged episodes of hypoglycemia can result in intrauterine fetal demise [110].

## Diabetic Ketoacidosis

Although the frequency of diabetic ketoacidosis (DKA) has decreased markedly, it remains a serious emergency in a pregnant woman with T1DM, and it is associated with increased fetal morbidity and mortality. Ketogenesis appears to be accelerated during the third trimester. The mechanism by which DKA results in poor fetal outcome is not clear but is hypothesized to involve fetal hypoxia. Another possibility is that the fetus develops acidosis and hypokalemia with subsequent cardiac arrest [111]. The fetal heart rate should be continuously monitored while the mother is undergoing intensive treatment for DKA. It is also prudent to alert a neonatologist. In a retrospective, matched control study of 90 patients, there was an increased risk of maternal DKA when subcutaneous insulin infusion was used versus multiple insulin injections during pregnancy in women with overt diabetes [112].

## Labor and Delivery

Women with diabetes, regardless of type (e.g., T1DM, T2DM, and GDM), experience rapid changes in serum levels of placental hormones in the postpartum period; thus, maternal hypoglycemia is a concern. It has been described that elevated glucose levels in the maternal serum in the peripartum period increase the risk for neonatal hypoglycemia and fetal academia [113, 114], birth asphyxia, and abnormal fetal heart rate [115], potentially causing fetal distress. Although these associations have been demonstrated mostly in observational studies of women with T1DM, it is reasonable to consider that avoidance of maternal hyperglycemia is a crucial aspect in the management in this period [113].

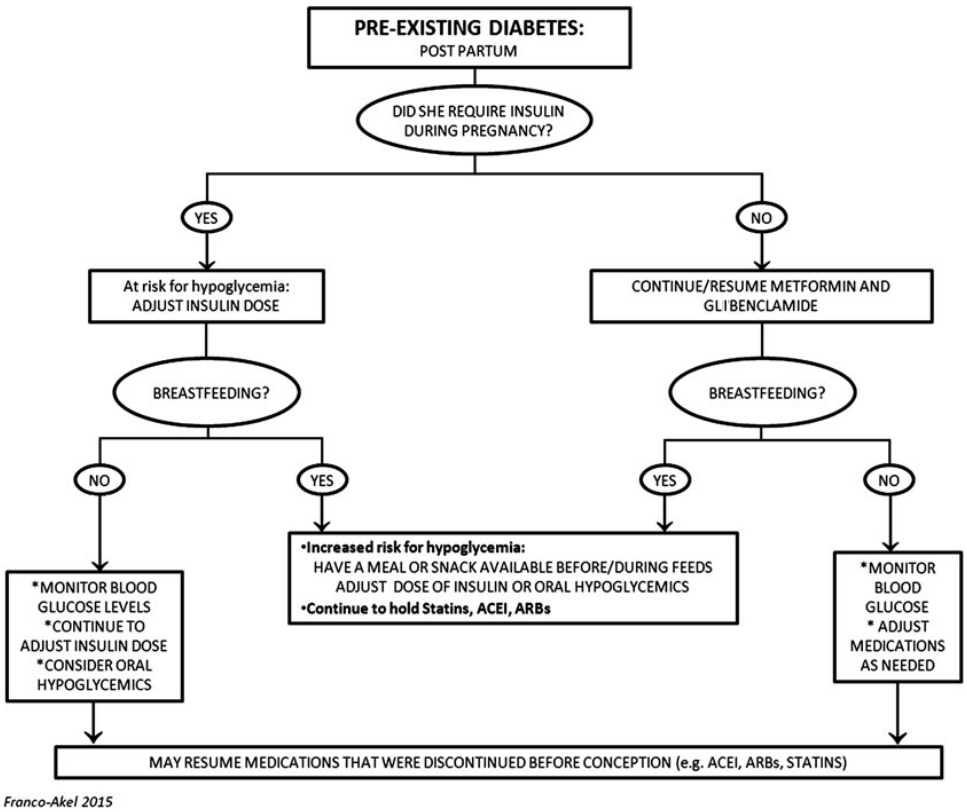


**Fig. 3.** Postpartum follow-up in women with pre-existing diabetes.

Women with GDM receiving insulin therapy, commonly will not require it once labor begins. Blood glucose levels should be monitored closely during labor to determine the patient's insulin requirements [116].

Several factors are implicated in determining insulin requirement in the intrapartum period. The most important of those is the type of maternal diabetes (e.g., T1DM, T2DM, or GDM). In addition, insulin requirements are influenced by the specific phase of labor. Usually these remain stable during the latent phase of labor and decrease significantly in the active phase. In addition, it has been observed that the degree of glucose control during gestation may impact the requirements of insulin during the peripartum period [116, 117].

Women with poorly controlled glucose levels throughout pregnancy may require higher doses of insulin in the peripartum period. Also, infants born from mothers with uncontrolled diabetes are at risk for severe neonatal hypoglycemia due to hyperinsulinemia from secondary hyperplasia of the pancreas. This becomes a challenging situation, since even with tight glycemic control in the peripartum period, neonatal hypoglycemia becomes difficult to prevent [118]. An ideal strategy to maintaining target glycemia in these phases has not been determined. The

management strategy should be implemented by the individual provider in order to achieve safe glucose levels. A target glycemia of 72–126 mg/dL (4.0–7.0 mmol/L) during labor and delivery in women with overt or GDM has been recommended [68] (see Fig. 3).

### Fetal Surveillance

Fetal surveillance may be deferred until the 35th week in patients with pre-gestational diabetes who have been under strict metabolic control. Those patients with poor control, nephropathy, hypertension, or vascular disease should begin surveillance at week 26. The best method of surveillance is via fetal ultrasound, which can estimate gestational age, screen for anomalies, determine amniotic fluid volume, and assess fetus status through Doppler and biophysical profiles [90].

## Summary

The presence of diabetes in a pregnant woman can result in serious maternal and neonatal morbidity and mortality if not treated appropriately. Screening pregnant women for gestational diabetes and attainment of euglycemia, either by diet or insulin therapy, clearly prevents potentially catastrophic maternal and fetal events. Pregnancies that suffer from hyperglycemia early in gestation are at high risk for fetal loss and malformations. Thus, pre-conception care is essential for all women with diabetes type 1 and type 2. Diabetic women of reproductive age must be continuously reminded of the need to plan their pregnancies. Maintenance of strict glycemic control requires tremendous effort on the part of the patient and the health-care team. This should be considered an achievable goal in all pregnant women with diabetes.

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# 2

# Diabetes in the Elderly

**Vincent Yen**

## Abstract

Diabetic phenotypes in the elderly are extremely diverse. The many different manifestations of hyperglycemia in this population in part result from a dichotomy of patients. Some patients present at an earlier age and progress through their life with diabetes. This group exhibits higher burden of complications which contribute to geriatric syndromes, thus demonstrating how the complications of diabetes promote accelerated aging. Other patients develop diabetes at a later age and can thus be viewed as examples of aging itself being a risk factor for loss of glycemic control. The management of diabetes in the elderly, as with younger patients, involves lifestyle changes, education, and monitoring, as well as multiple classes of medications. The goals of therapy in the elderly need to be individualized based on many factors. The prime directive of "do no harm" in the elderly is vital, particularly in regard to avoidance of hypoglycemia.

**Keywords:** Diabetes and geriatric syndromes, Diabetic syndromes as accelerated aging, Individualization of goals, Hypoglycemia, Aging as risk factor for diabetes, Diabetes and geriatric syndromes, Individualization of treatment goal, Hypoglycemia

## Introduction

Two representative cases will serve as a starting point for discussion:

1. Mr. JB is an 82-year-old male with a 30-year history of type 2 diabetes, stroke with residual right hemiparesis, dementia, chronic kidney disease stage II, coronary artery disease, and congestive heart failure, with coronary bypass surgery 20 years ago. He has been on metformin, glipizide, and sitagliptin for his diabetes. He is additionally on lisinopril, atorvastatin,

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amlodipine, and carvedilol twice daily, furosemide daily, vitamin D once daily, oxycodone twice daily as needed, gabapentin at bedtime, Colace three times daily, omeprazole daily, and Risperdal at bedtime. He is seen today after a 5-day admission to the hospital because of a fall, in a febrile state and with evidence of delirium. He had been on basal insulin as well as liraglutide as recently as 2 years ago, but these were discontinued after the death of his wife, who was his main caregiver, administering his medication and performing his fingersticks. Notably, his blood glucose and his overall functionality have deteriorated since then. His last Hgb $A_{1c}$ was 10.2%. Since his doctor was concerned about this level adversely reflecting on his institution's performance measures, the addition of canagliflozin is considered. The patient's daughter who lives in a neighboring state has not wanted to place him in a nursing home.

2. Mr. PC is a 72-year-old male with a history of hypertension, on atenolol daily and rosuvastatin daily. He is still working as a lawyer and has been physically active until recently, when his level of activity was reduced because of low back pain. He has been mildly overweight with a BMI of 28 kg/m$^2$. He sees his urologist for an increase in urination at night; a random glucose of 190 mg/dL is found. His $HbA_{1c}$ is 7.3%.

## Key Principles

These cases reflect some key principles regarding different aspects of diabetes care in the geriatric population:

1. **The epidemiology**: Elderly patients with diabetes can be divided into those who developed diabetes in earlier or middle age and have since progressed to geriatric status and those who have developed diabetes later in life. These different patients, who will often have a different burden of conditions, provide some reflection on how aging itself is a risk factor for the development of diabetes.
2. **Geriatric syndromes** can be both cause and effect of diabetes. These include cognitive impairment, falls and fractures, frailty and functional disability, incontinence, depression, pain, and polypharmacy, in addition to the characteristic micro- and macrovascular complications; these syndromes lend support to the role of glycemia in the aging process.
3. **Individualization** of treatment goals is based on overall status, functionality, level of support, expected lifespan, current level of complications, and the risks of overtreatment as well as undertreatment.

## Epidemiology

Among adults over 65 years old, about 15% to nearly 30%, have diabetes [1]. This is about twice the prevalence in middle age. About one third of these individuals are elderly-onset diabetic patients [2]. Elderly diabetic patients have highest rates of amputation, visual impairment, end-stage renal disease, and cardiovascular disease, as well as doubled rates of mortality after cardiovascular events and after procedures [3]. The incidence of diabetes in a nursing home in one study

was 26.4%, with the majority of these patients having cardiovascular morbidity, as well as depression, and total or extensive dependence; one half had pain; one third had cognitive impairment [4]. One cross-sectional analysis of nursing home residents found an incidence of cardiovascular disease of nearly 80% in diabetic patients [5] (Tables 1 and 2).

## Pathophysiology of Diabetes in the Elderly

Glucose intolerance is associated with aging (although it is not an inevitable consequence) and is due to a combination of age-related increases in insulin resistance, as well as age-related decreases in insulin secretion dynamics. During oral glucose tolerance testing, there is a loss of the first-phase insulin response, a finding that is similar to that seen in younger type 2 diabetes patients. There is also a decreased overall insulin response. The incretin response seems to be maintained as reflected by gastric inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP-1) [6]. Possible predisposing factors in the elderly for these findings include:

1. Increased abdominal adiposity
2. Decreased physical activity
3. Sarcopenia, with decreased muscle uptake of glucose

**Table 1. Geriatric syndromes affected by diabetes.**

| |
|---|
| Dementia |
| Frailty/sarcopenia/falls |
| Depression |
| Incontinence |
| Chronic pain |
| Polypharmacy |
| Osteoporosis |

**Table 2. Aging as a risk factor for diabetes.**

| |
|---|
| 1. Adiposity |
| 2. Decreased physical activity |
| 3. Sarcopenia |
| 4. Mitochondrial dysfunction |
| 5. Oxidative stress |
| 6. Hormonal changes |
| 7. Beta cell dysfunction |
| 8. Comorbidities |

4. Mitochondrial dysfunction [7] – decreased mitochondrial oxidative phosphorylation in lean healthy elderly compared to matched younger subjects
5. Increased burden of oxidative stress and inflammatory cytokines (numbers 1–5 relate to an age-related increase in insulin resistance)
6. Hormonal changes (decreased IGF-1, sex hormones)
7. Beta-cell dysfunction: with age-related decline in insulin secretion
8. Burden of drugs (including statins, psychiatric and other centrally acting drugs) and of coexisting illness

**Geriatric syndromes and diabetes:** Overall, geriatric syndromes and diabetes involve the issue of bidirectional cause and effect. Unanswered questions remain as to whether earlier treatment aimed at Hgb $A_{1c}$ lowering will prevent or ameliorate the course of these syndromes (in a manner similar to prevention of microvascular disease).

1. **Frailty**: Muscle function as measured by knee extensor strength seems to have an inverse relationship to Hgb $A_{1c}$ [8]. There are changes in protein synthesis related to insulin resistance, with a resulting vicious cycle because of the need for muscle as a site of glucose uptake. There is likely some association of frailty with neuropathy as well as with inflammatory markers.
2. **Depression**: There is a higher incidence of depression in diabetes (up to a 50% increase) [9]. Since age and cognitive dysfunctions are additional risks for depression, the burden can be considerable. Importantly, weight gain and hyperglycemia can be related to the use of some psychiatric medications, such as atypical antipsychotics olanzapine and clozaril [10].
3. **Cognitive dysfunction**: This is a significant factor in diabetes management as it affects a patient's ability to self-manage and self-medicate, to monitor, to obtain nutrition, and to recognize comorbidity including hypoglycemia [11]. A prospective cohort of 13,000 patients with median age of 57 years (13% with DM) was followed for 19 years. The average decline on cognitive function scores was 19% greater among diabetic than in nondiabetic individuals [11]. This decline increased with higher baseline Hgb $A_{1c}$ and with longer duration of diabetes. One study in Japan [12] and a meta-analysis [13] found Alzheimer's disease and multi-infarct dementia to occur about twice as often in diabetic patients as in those without diabetes. The Health, Aging, and Body Composition Study group [14] followed 2,895 functional adults (ages 70–79) for 3.5 years; 24% had diabetes at the start. Patients with diabetes and a high inflammatory burden (measured by C-reactive protein and IL-6 levels) had the highest risk for functional decline. Even in the setting of higher glucose levels without overt diabetes, there is a higher incidence of dementia [15]. In one study, 2,067 participants with mean age of 76 years (the majority without diabetes) were followed for median 6.8 years. Five hundred twenty-four developed dementia; among patients without diabetes, a glucose of 115 mg/dL compared to 100 mg/dL showed a hazard ratio of developing diabetes of 1.18 (1.04–1.33). In the patients with diabetes, a glucose of 190 versus 160 mg/dL showed a hazard ratio of 1.40 (1.12–1.76). There was some suggestion that diabetes and glucose were independent risk factors [16]. One study showed an inverse relation between $HbA_{1c}$ and mini-mental status exam scores and clock drawing performance in 60 patients, mean age 79 years [16]. Of

note, in the ACCORD trial, about 20% of the older patients had cognitive dysfunction which did not improve with tighter blood pressure or glucose control [17].

4. **Chronic pain**: In diabetic individuals, chronic pain can be due to the contribution of neuropathy as well as of vascular disease. Age itself was found to be a risk factor for pain in diabetic patient [18].
5. **Falls**: Falls are a significant cause of morbidity and mortality in the elderly. The falls can be related to frailty and can be multifactorial, with contributions of neuropathy, sensory loss, sarcopenia with gait and balance disturbance, postural hypotension, and medications. One review [9] noted an increased risk of any fall of 1.39 (1.04–1.81), of recurrent falls of 1.69 (1.18–2.43), and especially of significant falls of 2.76 (1.52–5.01) in the insulin-treated patients with diabetes.
6. **Urinary incontinence**: It is increased in elderly in general and worsened by the presence of diabetes. One meta-analysis estimated a doubled risk of urinary incontinence in the setting of diabetes [9]. Contributing factors to incontinence include prostate disease; bladder dysfunction, including that from diabetic autonomic neuropathy; and the use of diuretics. Urinary incontinence is often cited by patients as a primary quality-of-life offender.
7. **Polypharmacy**: As noted, diabetes can contribute significantly to the medication list (see below).
8. **Osteoporosis**: Some data suggest that DM is a risk factor for osteoporosis. Diabetic women have about double fracture risk after controlling for age, body mass index, and bone mineral density. There is consideration that perhaps this is related to the presence of advanced glycosylated end products. Additionally, thiazolidinedione medications are known to be related to bone loss as well.
9. **Erectile dysfunction**: Another syndrome that is more prevalent in both diabetic men and the elderly.
10. **Visual and hearing decline** (visual loss is seen in >20% of the elderly with DM): note also that hearing loss is more prevalent in elderly diabetic patients.
11. **Need for caregivers**: Greater than 60% of elderly diabetic individuals use spouse as the main caregiver. Elderly diabetic patients require more home care hours/week (10 h for diabetic patients, 14 if using insulin, vs. 6 h per week for individuals without diabetes).

All of the above issues are vital when assessing the elderly diabetic patient, as well as for deciding on the type of therapy.

## Treatment

Because of the high prevalence of cardiovascular disease in the diabetic elderly (44% coronary artery disease, 28% cerebrovascular disease seen in the study of 467 diabetic patients, mean age 80 years) [19], the ongoing issue is whether intensive glycemic control can reduce cardiovascular morbidity in type 2 diabetes. This debate can be broken down into macrovascular vs. microvascular implications and elderly vs. younger (note that the elderly are often excluded from trials, such as in the UKPDS) and by duration of diabetes. A recent systematic review [20] analyzed 20

randomized controlled trials for a total of nearly 30,000 patients (mean age 62 years, duration of diabetes up to 12.5 years) and found no significant difference in cardiovascular mortality but did find a reduced risk of amputation (RR 0.64; 0.43–0.95), retinopathy (RR 0.79; 0.68–0.92), and nephropathy (RR 0.78; 0.61–0.99 with intense control); intensive control produced a 30% increase in hypoglycemia.

A sensible rule for treating diabetic patients who are elderly is to individualize glycemic goals based on their current complications and comorbidities and their quality of life. If the patient is robust and doing well, then it is reasonable to aim for tighter control. Otherwise, less stringent targets are acceptable and warranted.

**Treatment**: The rationales and goals for treatment of diabetes in the elderly would include the following:

1. Prevention of acute syndromes leading to hospitalization: hyperosmolar states/dehydration.
2. Prevention of **symptoms** as they relate to quality-of-life issues such as urinary incontinence, fatigue, and increased infections. There are questions regarding diabetic control and mental status, depression, pain, falls, and loss of function; it is not clear whether tighter control reduces rates of admission to nursing homes.
3. Prevention of the development or worsening of **microvascular complications**. Here, the distinction between prevalent and recent-onset diabetes becomes significant. It is also with this issue that life expectancy and the time course to show benefit from treatment become important.
4. Prevention of **macrovascular complications** (this is debatable regarding the contribution of glucose control compared to blood pressure and lipid management).

**Risks of Overtreatment**

1. **Hypoglycemia**: Virtually all intensive therapy studies show increased rates of hypoglycemia. In the ACCORD study, the older patients had 50% more hypoglycemia in both groups [21]. The issue of hypoglycemia will be discussed later in this article.
2. **Polypharmacy** in the elderly: The use of greater than six medications increases fall risk, as well as the risk of drug interactions. Diabetes often requires the use of multiple agents, including injectables [22]. In a retrospective analysis of over 20,000 patients over 20 years on oral monotherapy intensified to combination oral therapy vs. oral medications changed to insulin with initial $A_{1c}$ 9–10%, there was a u-shaped curve regarding all-cause mortality. The lowest mortality occurred at $HbA_{1c}$ of 7.5% overall. Both groups had the highest mortality at highest $A_{1c}$ (>10%) and lowest $A_{1c}$ (6.4%) [22].

As mentioned above, the **individualization** of goals of therapy is an important concept in the care of diabetes in the elderly. There is unlikely to be a benefit from tighter control if life expectancy is less than 5–10 years [23]. In the California Health Care Foundation's guidelines for improving the healthcare of the older person, a window of 8 years of tighter control shows a microvascular complication benefit. Therefore, the outcomes describe the concept of goals based on status: for instance, if healthy, then a goal of less than 7.5% is suitable; if complex, then a goal of less than 8.0% is convenient; if very complex or in poor health, then a goal of less than 8.5% is

appropriate. Others have promoted frailty scales [24] that can be used to help with these designations and with "expected lifespan" (for frailty, the life expectancy is 28 months; for mild frailty, the patient needs help with some instrumental activities of daily living (IADLs), e.g., stairs and driving; for severe frailty, the patient is completely dependent for ADLs with progression up to terminal disease). Note that American Diabetes Association data regarding patients in their 80s with diabetes show dramatic decreases in cardiovascular disease incidence of up to 70% within 3 years with blood pressure control. An LDL decrease to less than 70 ng/% can decrease cardiovascular endpoints by up to 20% in the same period. Therefore, in the treatment of blood pressure and lipids, one can consider a shorter time frame regarding obtaining a benefit – as low as a 2–3-year time frame (with differences in secondary vs. primary prevention). In all types of patients, there should be enough treatment to avoid acute hyperosmolar states or dehydration [25].

## Treatment Options

1. **Lifestyle changes** involving exercise and diet should generally be used. In the Diabetes Prevention Program where 20% of the patients are greater than 65 years of age (although none >70 or with cognitive impairment), a greater effect in the elderly was observed with lifestyle change, compared with metformin [26]. Self-reported sedentary lifestyle in older women had HR for death 2.08 (1.79–2.41) [27]. Restricting diets in the elderly can be counterproductive: there is a risk of provoking malnutrition, worsening sarcopenia, and bone density with weight loss, especially in the long-term healthcare setting. Depending on functionality, there can be issues of anorexia, impaired taste and smell, dental loss, dysphagia, and aspiration. Functionality figures heavily into food preparation. Body mass index (BMI) thresholds for obesity in the elderly may be different [24]. Using a 2010 Australian cohort of 9,000 patients aged 70–75 years, at 10 years the overweight cohort (BMI 25–29.9) had decreased hazard ratio for death at 0.87 kg/mL (0.78–0.94) [27]; in another study of 2,400 patients, aged 70–85 years, in Israel, followed up to 18 years, women with BMI > 25 kg/mL had lower mortality compared to those with BMI < 25 kg/mL [28].

**Medications**: Once the decision to use medications is made, issues to take into account include:

1. Changes in renal and hepatic function (and risk of hypoglycemia)
2. Duration of diabetes and presumed beta cell function as those contribute to predicting efficacy of oral agents versus insulin
3. Age-related changes in pharmacokinetics and dynamics
4. Consideration of other caretakers needed
5. Cost
6. Polypharmacy

1. **Sulfonylureas**: The use of long-acting insulin secretagogues like glyburide, especially with GFR < 60, should be avoided; there are changes in pharmacokinetics and dynamics of

sulfonylureas with the concomitant use of aspirin, fibrates, warfarin, trimethoprim, allopurinol, and probenecid [36].

2. **Metformin** is an inexpensive and commonly used medication, with low risk of hypoglycemia. The main side effects are gastrointestinal such as diarrhea, and there is a restriction regarding its use in patients with GFR < 30.
3. **Incretins**: Given that the **incretin** system is maintained with aging, combining basal insulin with GLP-1 agonists is effective in advanced type 2 diabetes with a low incidence of hypoglycemia; therefore, in a relatively healthy elderly patient with high $A_{1c}$ and some support for injections, this might be a reasonable option, especially given some newer weekly formulations. Regarding the use of GLP-1 agonists, the ELIXA trial, which used liraglutide in older patients with DM, showed that $A_{1c}$ was decreased by 1.3% in >65-year-old patients. There was no hypoglycemia; there was some weight loss (data not available regarding lean body mass vs. fat) [31]. Dipeptidyl peptidase 4 inhibitors are effective in the elderly, with no significant hypoglycemia. There are decreases of 0.7% $HgbA_{1c}$. There have been recent cardiovascular safety studies with this class of medications. TECOS used sitagliptin [29] and showed no increases in cardiovascular events. This contrasted with the SAVOR-TIMI study [30] using saxagliptin, which showed a small signal regarding CHF admissions. There was a small but statistically significant increase in pancreatitis. No pancreatic cancer increase has been seen.
4. **Sodium glucose cotransporter 2** (**SGLT2**) **inhibitor glycosuric agents**: These medications cannot be used if GFR < 45; they can cause dehydration; they cause an increased incidence of urinary tract yeast/fungal infections; they can cause weight loss, presumably through additional glycosuria; and they tend to decrease BP, presumably through the diuretic effect, so that there may be a need to change antihypertensive medications. There is an additive effect with furosemide. Notably, the EMPA-REG study [32] showed decreased CV risk with a hazard ratio for empagliflozin of 0.86 (0.74–0.99), including in the greater than 65-year-old subset. This benefit was greater than that shown in the less than 65-year-old group and felt to be possibly related to decreased BP (decreased systolic of 4–5 mmHg).
5. **Insulin** is sometimes necessary to improve glucose levels, especially in patients with long-standing diabetes and presumably more significant beta cell dysfunction. Injections necessarily add an additional level of complexity to care: there are considerations of vision, of manual dexterity, of tremor, and of cognitive function and a need for caretaker, including prefilled syringes [33]. It has been shown that the use of glargine insulin, a basal insulin, in patients with mean age 69 years achieved $A_{1c}$ goals without excess hypoglycemia [33].

The **avoidance of hypoglycemia** is an important caution. According to a study using continuous glucose monitoring sensors (CGMS) in elderly patients (>69 years old), 65% had at least one episode of hypoglycemia in 24 h; 93% of these were unrecognized, often >1 h in duration; 95% were nocturnal. Correlation of CGMS with simultaneous Holter monitoring showed episodes of ventricular tachycardia and prolonged QT intervals associated with hypoglycemia [34, 35]. Medications in the elderly most associated with emergency room visits were: (1) warfarin, (2) insulin, (3) antiplatelet agents, and (4) sulfonylureas.

There are many reasons for the increased risk of hypoglycemia in the elderly, such as:

1. Diminished glucagon and epinephrine release, which additionally occur at lower thresholds of glucose
2. Reduced hypoglycemic symptoms (tachycardia and sweating)
3. Altered psychometric performance (neuroglycopenia prevents acting on hypoglycemia, even if aware)

Methods to help prevent hypoglycemia involve education regarding the timing of meals with medications, especially insulin or insulin secretagogues [36]. Additionally, continuous adjustment of medical regimens is justified. A retrospective analysis of 211,667 veteran administration patients (mean age 78 years) found that very few patients on glucose-lowering drugs other than metformin who had $A_{1c}$ levels less than 6.4% had their regimens deintensified [37].

## Aging and Diabetes

Given the similarities between the microvascular and macrovascular complications of diabetes with the findings seen in the aging process itself, it is possible to look at diabetes as a model of accelerated aging. A common point involves accumulated systemic inflammation and oxidative stress with associated endothelial and other macromolecular dysfunctions. The mediator may be advanced glycosylation end products, whereby nonenzymatic glycation alters long-term structure and function at multiple molecular and cellular levels [38]. Additionally, in a related system are the sirtuins and SIRT1. These comprise an NAD+ histone deacetylase which is an important regulator of cellular stress response (via DNA repair) and energy metabolism (via mitochondrial effects). SIRT1 and its substrates, with effects on oxidative stress and inflammation via NF-κB and other nuclear, mitochondrial, and cellular proteins, are felt to underlie the phenomenon observed in multiple species of life extension related to caloric restriction and to exercise. This system is the basis for the supplement resveratrol, a polyphenol found in red wine, popularized in the lay press as a pill that mimics exercise, fasting, and protection against high-fat diets and against aging itself [39, 40].

## Summary

Multiple organizations have developed recommendations and guidelines for the management of diabetes in the older patient; virtually all describe the need for individualization, depending on the patient's current medical condition, complications, and comorbidities, as well as anticipated life expectancy and the duration of diabetes. The goals of therapy regarding Hgb $A_{1c}$ (as well as BP and lipids) can be individualized. For example, if the life expectancy is 10–15 years, then the goal is 7%; if diabetes has been present over 10 years and with comorbidity and complications, then the goal is 8%. If there are advanced comorbidities and complications, with a life expectancy of less than 5 years, then an $A_{1c}$ goal of 8–9% is reasonable [41, 42]. The ADA [23] describes seeing benefits from tighter glucose control after about 8 years and from tighter BP and lipid control in 2 years. There is little such data regarding >75-year-olds and less regarding 85-year-olds. The

minimal level of therapy should avoid acute complications and symptoms that affect quality of life. All treatments should be tailored with a mind toward avoidance of hypoglycemia [43].

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# Acute Hyperglycemic Syndromes: Diabetic Ketoacidosis and the Hyperosmolar State

**David Wing-Hang Lam, Yun Feng**

## Abstract

The patient, often a "repeat offender" who stops taking insulin, presents with increasing urination and thirst along with nausea, vomiting, abdominal pain, dehydration, weakness, and dizziness. The patient may become confused and slip into coma. The respiratory compensation that accompanies acidemia causes deep rapid (Kussmaul) breathing. The sweet smell of the volatile ketone body acetone signals the possibility of ketoacidosis. The treating physician seeks to reestablish normal physiology and restore the patient to normal function. Thankfully, treatment is remarkably straightforward and involves intravenous fluid, insulin, potassium, and vigilance.

**Keywords:** Diabetic ketoacidosis, Kussmaul, Type 1 diabetes, Type 2 diabetes, Ketosis, Hyperglycemia, Anion gap metabolic acidosis, Free fatty acids, ß-hydroxybutyrate, Acetoacetate, Cerebral edema, Hyperosmolar hyperglycemia syndrome

## Diabetic Ketoacidosis: Clinical Presentation

**A typical patient with diabetic ketoacidosis (DKA) becomes severely ill over one to several days and represents a medical emergency.**

The patient presents with increasing urination and thirst along with nausea, vomiting, abdominal pain, dehydration, weakness, and dizziness. The patient may become confused and slip into coma. The respiratory compensation that accompanies acidemia causes deep rapid (Kussmaul)

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breathing. The sweet smell of the volatile ketone body acetone signals the possibility of ketoacidosis. In an analysis of three multinational type 1 diabetes registries, factors that are associated with an increased risk for DKA include female gender, country-specific ethnic minorities, and elevated $HbA_{1c}$ [1].

Diabetes is a heterogeneous disease [2], and patients with DKA reflect this heterogeneity [3]. While commonly considered a condition associated with type 1 diabetes, patients with type 2 diabetes can also develop DKA and, in some cases, initially present to medical attention with DKA [4, 5, 6, 99]. The majority of patients with DKA have type 1 diabetes. Consistent with this type 1 predominance, patients are likely to be young, slender, Caucasian (type 1 diabetes is 2–7 times more common in whites than blacks [7]), and lack a family history of diabetes.

In youth with type 1 diabetes, the prevalence of DKA at the diagnosis of diabetes has remained relatively stable at 31% over the last decade in the United States. However, among youth with type 2 diabetes, the prevalence of DKA at diagnosis has declined in the last decade [8]. Younger age, ethnic minority, lack of health insurance, lower body mass index, preceding infection, and delayed treatment confer an increased risk for the presence of DKA at the time of diagnosis in children and young adults. On the other hand, having a first-degree relative with type 1 diabetes at the time of diagnosis, higher parental education and higher background incidence of type 1 diabetes are protective factors [9].

## Definition

**Diabetic ketoacidosis (DKA) is a state of metabolic decompensation in which insulin deficiency (relative or absolute) causes both hyperglycemia and excess production of ketoacids, resulting in metabolic acidosis** [10].

Diabetic ketoacidosis is the first manifestation of diabetes in a minority of patients and more often occurs in patients with known diabetes taking insufficient insulin. Patients may run out of insulin or not accept the necessity for insulin. Adolescents sometimes discontinue insulin as an act of rebellion. Ill patients, who are not eating well, may reduce or omit insulin doses, not realizing that stress, which is accompanied by elevation of "counterregulatory" hormones, may have higher insulin requirements.

No absolute numbers separate uncontrolled diabetes from DKA, although there is general agreement on the definition: a glucose level >250 mg/dL (13.9 mmol/L), acidemia reflected by a pH lower than 7.30, a serum bicarbonate less than 18 mEq/L, a positive test for serum ketones, and an increase in the anion gap [11]. Reasons for exceptions to this definition are discussed below:

### The Differential Diagnosis

While considering the diagnosis of DKA, it is important to recognize that many other diseases can manifest the individual components of DKA: ketosis, hyperglycemia, and an anion gap metabolic acidosis. Alcohol intake and starvation can result in ketosis. Uncontrolled diabetes mellitus (both

**Table 1. Differential diagnosis of diabetic coma.**

| A-E-I-O-U | TIPSI |
|---|---|
| Alcohol | Trauma |
| Encephalopathy | Infection |
| Infectious | Meningitis |
| Neurologic | Sepsis |
| Insulin | Psychosis |
| Hypoglycemia, DKA, hyperosmolar, alcoholic ketoacidosis | Seizure |
| Overdose, opiates | Postictal state |
| Uremia | |

type 1 and type 2), infection, and physiologic stress can result in hyperglycemia. And lastly, a wide number of disease states can result in a metabolic acidosis with an anion gap [12].

The most severe scenario for patients with DKA is the diabetic coma. Stupor and coma have many potential causes (Table 1). Alcoholic intoxication causing coma can be assessed by a history of alcohol intake and blood alcohol levels. Decreased level of consciousness without focal findings suggests encephalopathy (unilateral weakness could suggest a stroke). Furthermore, the patient may have taken an overdose; thus, a toxicology "screen" is helpful to exclude drugs that can cause coma and acidosis. Renal failure with uremic encephalopathy can be detected with blood urea nitrogen (BUN) and creatinine measurements. Evidence of trauma should be sought. Fever and confusion may indicate central nervous system infection. A history of emotional instability may suggest psychosis or a patient who is feigning illness. Witnesses can be questioned about seizure activity, which is often followed by a decreased level of alertness. The mnemonic given in Table 1 is not comprehensive; for example, the electrocardiogram may show a cardiac arrhythmia or a myocardial infarction that can cause a drop in blood pressure and change in mental status. While reviewing the differential diagnosis, the physician simultaneously obtains the finger stick (capillary) glucose measurement to exclude hypoglycemia (low blood sugar) or hyperglycemia as a cause of coma. An elevated glucose supports a diagnosis of diabetic ketoacidosis or hyperglycemic hyperosmolar coma.

## Pathophysiology

**The fed state is an insulin-sufficient state. Insulin affects the internal machinery of cells in the liver, fat (adipose tissue), and muscles to promote energy production and storage.**

Cellular work requires massive amounts of energy. Intermediary metabolism (named for the *intermediate* compounds that are generated prior to the final metabolic products), largely through the production of ATP (adenosine triphosphate), provides this energy and the energy for synthesizing macromolecules [13–16].

Glucose, the major cellular nutrient, is transported into cells where it is metabolized in the glycolytic pathway. Enzymes in this pathway are regulated by insulin (whose action is antagonized by glucagon). At the end of this pathway, the three-carbon glucose metabolite pyruvate is further broken down into small molecules that are used to produce complex cellular components or can be converted into chemical energy (the nucleotide ATP) when transported into the energy generator of the cell (the mitochondria).

**When insulin levels are adequate, energy is stored in small quantities as glycogen for immediate use or in large quantities as triglycerides for long-term use.**

Inside the hepatocyte, glucose molecules can be linked in a tightly packed branching structure to form glycogen, the polysaccharide that stores glucose. Alternatively, the two-carbon compound acetyl coenzyme A (acetyl-CoA), which is formed from glucose breakdown, can be used to manufacture larger molecules, including fatty acids for energy storage in a large fat depot (adipose tissue). Insulin acts to stimulate and maintain these storage processes.

**In DKA, insulin action is inadequate to promote glucose entry into cells. The decreased flux of glucose into cells simulates fasting.**

With the fall in intracellular glucose, intermediary metabolism of carbohydrates and lipids shifts away from glucose breakdown and storage to an exaggerated imitation of the fasting state. Metabolism shifts away from the utilization of glucose toward gluconeogenesis, which is the production of glucose from pyruvate (Fig. 1). Precursors for gluconeogenesis are obtained from fat, which is melted down into fatty acids and glycerol, and from proteins following breakdown into constituent amino acids. Glycerol, amino acids (particularly alanine), and lactate (derived from red cell metabolism) are converted into glucose.

**The counterregulatory hormones glucagon and epinephrine, along with growth hormone and cortisol, stimulated by fasting and by stress, antagonize the effects of insulin.**

Counterregulatory hormones antagonize the glucose-lowering action of insulin and act to raise the blood glucose level. Glucagon, a potent counterregulatory hormone inhibited by insulin, is secreted from pancreatic alpha cells when cells perceive low glucose. In diabetes, pancreatic insulin levels are reduced and glucagon is chronically elevated. In DKA, in addition to low insulin action, there is the cellular perception of low glucose, which further stimulates glucagon secretion. The excessive glucagon levels of DKA dominate hepatic metabolism, promoting breakdown of glycogen to glucose, stimulating gluconeogenesis, inhibiting fatty acid synthesis, and directing long-chain fatty acids into the mitochondria where they are dedicated to ketoacid formation (Fig. 2).

Catecholamines, acting on β-adrenergic receptors, are the most potent stimulators of lipolysis (breakdown of adipose tissue triglycerides with release of free fatty acids and glycerol) and also inhibits glucose uptake in adipocytes [17]. Growth hormone also stimulates lipolysis and liberates free fatty acids [18]. Cortisol contributes to elevations of blood glucose by increasing lipolysis in certain fat depots, increasing the transcription of genes that increase protein catabolism (providing precursors for gluconeogenesis), and upregulating the expression of the rate-limiting enzyme for gluconeogenesis, phosphoenolpyruvate carboxykinase (PEPCK) [19]. Glucagon and epinephrine both activate glycogen phosphorylase, which catalyzes glycogenolysis [20].

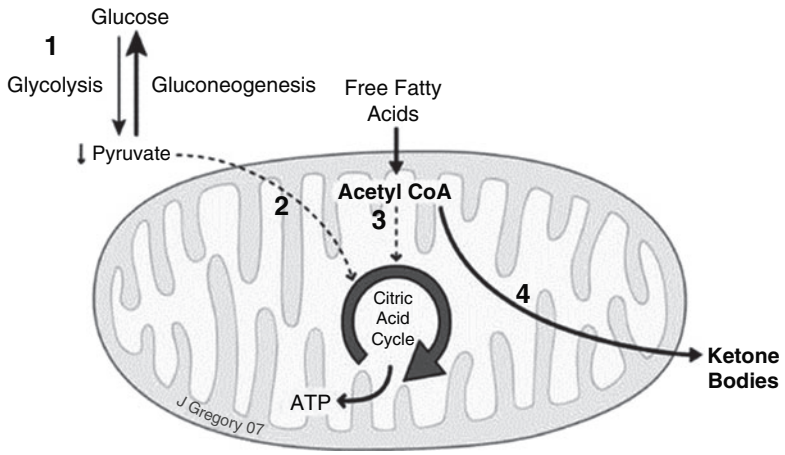


**Fig. 1.** The formation of ketone bodies is linked to increased gluconeogenesis. *1* When insulin levels fall, glycolysis decreases and gluconeogenesis increases, reducing pyruvate levels. *2* Pyruvate is not available for conversion into oxaloacetate. *3* Without oxaloacetate, acetyl-CoA cannot enter the TCA cycle. *4* Free fatty acids, converted into acetyl-CoA, are therefore diverted to mitochondrial ketone body formation.

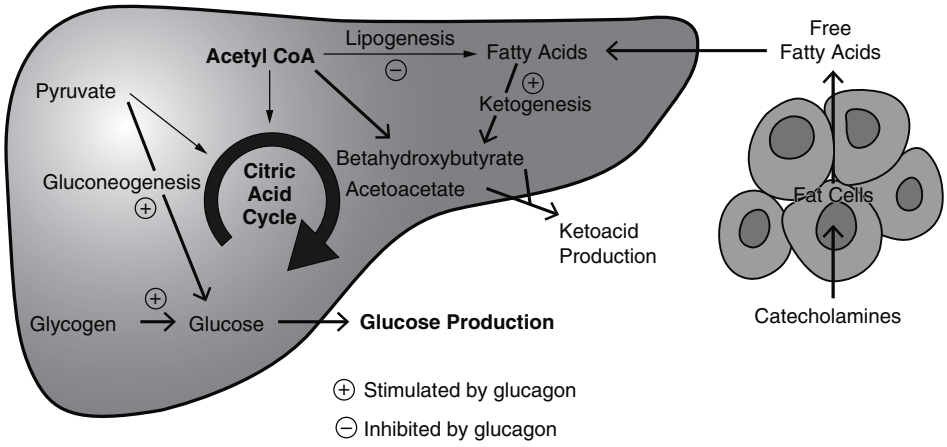


**Fig. 2.** Glucagon plays a central role in DKA. Glucagon stimulates glucose production through gluconeogenesis and glycogen breakdown. Lipogenesis is inhibited by glucagon. Free fatty acids derived from lipolysis in fat cells are transported into the mitochondria. Acetyl-CoA from fatty acid breakdown is diverted to ketoacid production.

## The Central Role of Free Fatty Acids (FFAs) in DKA

**Free fatty acids leave the fat cell and are transported to the liver.**

Without fatty acids there cannot be any ketoacids; without ketoacids there is no diabetic ketoacidosis [21]. Under the influence of insulin, free fatty acids are transported to and imprisoned inside a fat cell (adipocyte) bound as three chains to a glycerol molecule (triglyceride). The

catecholamines are ready to "spring" FFAs out of "jail," but they are unable to do so while there is adequate insulin. During starvation, when insulin levels drop, lipids stored in adipose tissue as triglycerides are released from the fat cell as the hydrocarbon long-chain fatty acids. These fatty acids are transported to the liver bound to albumin. From the viewpoint of the FFA, the scene in the liver is chaotic. The liver does not have adequate insulin levels. Glycolysis, the most ancient metabolic pathway, is at a standstill. FFAs further inhibit insulin action and stimulate gluconeogenesis and hepatic production of lipoproteins, contributing to hyperglycemia and to the marked elevation of triglycerides seen in some patients. Under fasting conditions with adequate insulin present, this process (coupled with the release of glycerol) provides sufficient calories to serve as the glucose and energy "grocery store." In DKA, this process leads to uncontrolled glucose elevations.

**Malonyl coenzyme A (CoA) levels control free fatty acid transport into the mitochondria, thereby acting as the key control of the rate of hepatic ketoacid production.**

Malonyl-CoA is a precursor molecule whose levels rise during the insulin-stimulated process of triglyceride synthesis in the cytoplasm. Malonyl-CoA then inhibits the transport of fatty acids into mitochondria, by inhibiting the fatty acid transporter carnitine palmitoyltransferase 1 (CPT1). During DKA, since insulin levels fall, malonyl-CoA levels decline, permitting a rise in fatty acid transport into mitochondria (Fig. 3).

**The fate of free fatty acids in the hepatic mitochondria is determined by the activity of the glycolytic pathway, because pyruvate is required for FFA derivatives to enter the TCA cycle** (Fig. 1).

Pyruvate formed during glycolysis is the glucose-derived metabolite that enters the tricarboxylic acid [TCA], also called the Krebs or citric acid) cycle. This pathway is oxygen requiring (oxidative) and generates large amounts of ATP. In DKA, pyruvate is diverted to gluconeogenesis, less is available to enter the TCA cycle, and the rate of oxidative metabolism of glucose declines. In addition, the fall in pyruvate alters fat metabolism in the liver. Under normal conditions of energy generation, fatty acid metabolites can enter the TCA cycle in a process that requires pyruvate. Since pyruvate is necessary for fat to enter the TCA pathway, it is said that fat burns in the flame of carbohydrate. In DKA, this energy-generating "flame" is extinguished (Fig. 1).

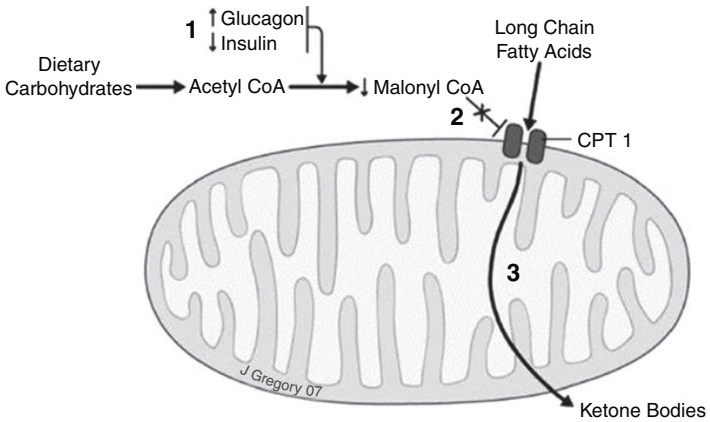


**Fig. 3.** Malonyl-CoA plays a pivotal role in the regulation of ketogenesis. In DKA, the *high* glucagon and the *low* insulin decrease malonyl-CoA production from acetyl-CoA. *1*. The fall in malonyl-CoA releases the inhibition of the transport protein (CPT1) that shuttles long-chain fatty acids into the mitochondria. *2*. Increased long-chain fatty acids are thus available for ketone body formation.

Some pyruvate is converted to lactate in a process that restores cytoplasmic $NAD^+$(nicotinamide adenine dinucleotide), necessary for minimal cellular metabolism. This can cause a lactic acidosis superimposed on top of ketoacidosis [22] (Fig. 4).

**When fatty acids cannot enter the TCA cycle in hepatic mitochondria, they are diverted to ketone body (ketoacid) formation.**

Fatty acids are broken down in the mitochondrial matrix into the two-carbon compound acetyl-CoA. Unable to enter the TCA cycle during intracellular glucose privation, acetyl-CoA in hepatic mitochondria is diverted to the production of the ketoacids β-hydroxybutyrate and acetoacetate [23].

**The "redox" (reduction–oxidation) status of the mitochondria, set by the NADH/NAD + ratio, determines the predominant species of ketoacid.**

Coenzymes cooperate with enzymes to catalyze reactions. In these reactions, the coenzymes are reversibly altered and can be cycled back and forth between two forms, creating a "pair." The coenzyme pair $NAD^+$ and NADH functions to carry electrons in oxidation–reduction reactions. An increased NADH/$NAD^+$ ratio develops in DKA during β-oxidation of fatty acids and also in states of low tissue oxygenation (such as those that occur if the patient has severe fluid loss and is hypotensive from dehydration or sepsis). NADH drives the conversion of the ketoacid acetoacetate to β-hydroxybutyrate. As will be discussed later, laboratories use the nitroprusside reaction, which does not measure β-hydroxybutyrate, to test for ketones. When β-hydroxybutyrate is the major ketoacid, a misleadingly low nitroprusside test can sway the unsuspecting physician away from the correct diagnosis.

**Since glucose is not available in DKA, alternative energy-releasing compounds must be utilized. The ketoacids function as an alternate fuel.**

Tissues are not able to utilize glucose because of inadequate insulin action. Without insulin (or without *enough* insulin), cells are left without nutrients. The ketone bodies, or ketoacids, do not require insulin for uptake into cells. If glucose is the electric power that drives the body, ketone bodies are the batteries of the brain and the heart. When the electricity fails, hepatic mitochondria

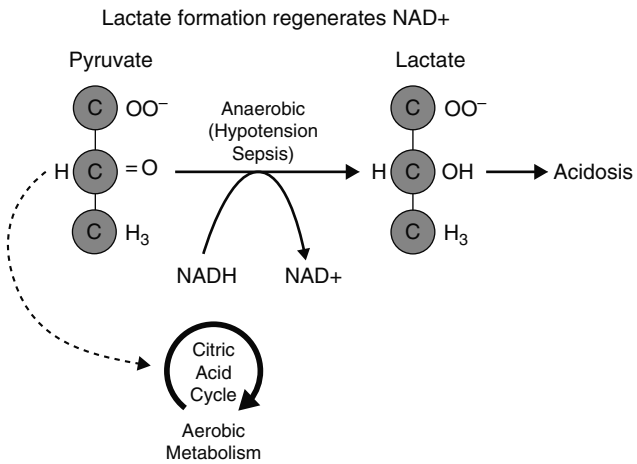


**Fig. 4.** Lactate formed from pyruvate can contribute to acidosis.

produce and export this alternate power. In the heart, skeletal muscle, brain, and kidney, ketone bodies can be converted back to acetyl-CoA, which enters the TCA cycle and provides metabolic energy through generation of ATP [24] (Fig. 5).

## Assessment of a Patient with DKA

**Among the long list of potential precipitating factors for DKA are serious conditions that require diagnosis and specific treatment.**

Although diabetic ketoacidosis often occurs in patients who run out of insulin or stop taking insulin [25, 26], there is frequently an inciting event that must be discovered. The physician's challenge is to find what went wrong, reverse the process, return the patient to health, and prevent the next episode. In considering the possibilities, it is important to remember that common things occur commonly. The patient may have stopped taking insulin or the pancreas may have gradually lost insulin secretory capacity. Counterregulatory mechanisms may be activated during any stress and may render antecedent insulin levels insufficient. Particular attention must be given to infections (with elevations of the counterregulatory hormones cortisol and catecholamines), stroke or heart attacks (extremely high epinephrine production), or pregnancy (placental lactogen or cortisol). Dehydration during gastrointestinal illness accompanied by vomiting or diarrhea may hasten the development of DKA. An alcohol binge may cause rapid decompensation in the patient with limited insulin reserve.

Very unusual causes of counterregulatory hormone elevation precipitating DKA are growth hormone elevations from acromegaly, glucocorticoid excess in Cushing's syndrome, and glucagon in the rare glucagonoma syndrome. Obscure causes of DKA, such as changing to more active pancreatic enzymes to treat chronic pancreatitis with increased absorption of nutrients or

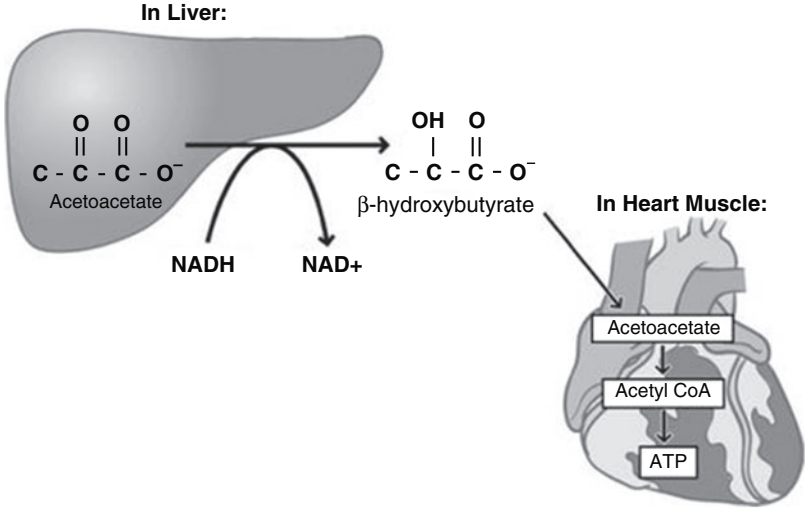


**Fig. 5.** Ketone bodies formed in the liver provide an alternate fuel for the heart, skeletal muscle, and brain.

somatostatin inhibition of insulin secretion in a somatostatinoma, have been described. In teenagers, eating disorders are a consideration, especially in recurrent DKA. Antipsychotic drugs clozapine and olanzapine are also reported to cause DKA [27, 28]. An unusual fulminant nonimmune form of type 1 diabetes can present with a rapid onset [29]. Rare cases of DKA have occurred following pancreatic destruction by a virus [30, 31].

**Infection is the most common precipitating cause of diabetic ketoacidosis; sites that hide infections should be examined carefully.**

Patients with both type 1 and type 2 diabetes are at an increased risk for infections and hospitalizations due to infections [32, 33]. Elevated glucose levels impair the ability to fight infection, [34] potentially leading to aggressive tissue destruction. Thus, it is critical to control the blood glucose and to discover and treat infections. The physician must be particularly suspicious in patients who are more likely to harbor infections. Hidden sites of infection include the teeth, sinuses, gallbladder, abscesses in the perirectal area, and pelvis (in women) and must be examined and reexamined. The nose should be carefully inspected for eschar (black necrotic tissue), which might indicate the fungus mucormycosis, classically but rarely seen in DKA.

**Measurements, tests, and calculations are used to determine the severity of acidosis, magnitude of ketonemia, and fluid and electrolyte balance.**

In order to treat DKA, the physician must measure the degree of acidosis (pH), the ability of the patient to compensate by lowering $pCO_2$, the elevation of the blood glucose level, and the serum potassium ($K^+$). Initially, an arterial sample is taken for measuring the pH, $pO_2$, and $pCO_2$ in order to know if the patient has low oxygenation (hypoxemia), a primary respiratory acidosis (indicating pulmonary disease or central hypoventilation), or a primary respiratory alkalosis (suggestive of sepsis). After the baseline arterial measurement, the calculated anion gap from chemistries (using measured – not corrected – serum sodium, chloride, and bicarbonate) and the venous pH can be used to evaluate the acid–base status (Table 2) [37]. To document or follow ketoacid production, serum ketones are typically measured. They are cleared rapidly and may be detected with greater sensitivity in urine, even when low or absent in the serum. Although it is the dominant "ketoacid" in DKA with a ratio as high as 20:1 compared to acetoacetate, β-hydroxybutyrate is not measured in the nitroprusside test for ketoacids because β-hydroxybutyrate is really an acid-alcohol. In the "redox" environment of DKA, an excess ratio of β-hydroxybutyrate to acetoacetate may result in spuriously low ketone body measurements. The astute clinician knows that DKA may occur without a markedly elevated nitroprusside reaction and is guided by the clinical presentation, pH, anion gap, and bicarbonate level [38].

## Treatment of Diabetic Ketoacidosis

### Introduction

The treating physician seeks to reestablish normal physiology and restore the patient to normal function. Treatment is remarkably straightforward and involves intravenous fluid, insulin, potassium, and vigilance.

**Table 2. Measurements useful in assessing a patient with DKA.**

| |
|---|
| Corrected serum $[Na^+]$ = measured serum $[Na^+]$ + 2 * (glucose in mg/dL – 100)/100 [35, 36] |
| The anion gap = $[Na^+]$ – ($[Cl^-]$ + $[HCO_3^-]$) |
| The normal anion gap = 8–12 |
| In pure metabolic acidosis the last two digits of the pH = $pCO_2$ |
| For example, if the pH = 7.32, the $pCO_2$ should be 32 |
| In pure metabolic acidosis the blood gas $pCO_2$ = (serum $HCO_3^-$ * 1.5) + 8 |
| The calculated effective serum osmolality = 2 ($Na^+ + K^+$) + (glucose in mg/dL/18) |
| Normal total body water (TBW) = lean body mass in kg * 60% |
| Current TBW = (normal serum osmolality * normal TBW)/current osmolality |
| Water deficit = normal TBW – current TBW |

**The osmotic diuresis of hyperglycemia causes dehydration, which exacerbates the metabolic acidosis** [15]. **The severity of dehydration determines initial rates of fluid administration.**

In the hypotensive patient, fluid resuscitation takes precedence over other concerns. A fluid "challenge" is performed with isotonic fluid given in short blocks of time (in adults, at a rate of 10–30 mL/min checking the patient every 10 min; in children, at a rate of 10–20 mL/kg over 30 min to 2 h [39, 40]). If intravascular fluid depletion is the cause of hypotension, the blood pressure responds rapidly. Failure to respond to a fluid challenge within 30 min suggests another cause for low blood pressure such as cardiac pump failure or peripheral vasodilatation in sepsis. In adults with severe dehydration, initial fluid rates of 1–2 L/h may be required. If the patient is not hypotensive, or once blood pressure is restored, a more balanced approach to fluid administration using 250–500 mL/h is desirable. These slower rates of administration avoid fluid overload with potential for pulmonary edema and hypoxemia or diuresis of potassium with resultant hypokalemia [41]. Hydration per se decreases counterregulatory hormone levels, enhances renal perfusion, and establishes a glucose diuresis, lowering the blood sugar toward the renal threshold of 180 mg/dL [42]. It is customary to choose isotonic fluid in the hypotensive, dehydrated patient; half-normal saline as the patient recovers; and dextrose-containing fluid as the blood glucose drops below 200–250 mg/dL. Fluids containing 5% or even 10% dextrose prevent the hypoglycemia that would otherwise occur with continued administration of insulin essential to restrain ketogenesis and prevent recurrence of acidosis. Dextrose containing fluids are frequently required as the duration to resolve hyperglycemia is typically shorter than the resolution of ketoacidosis. Hemodynamic monitoring, urine output, laboratory values, and clinical judgment can be used to assess the efficacy of fluid treatment in DKA.

Medical situations requiring special fluid adjustments include myocardial infarction, congestive heart failure, and acute or chronic renal failure. These situations require individualized fluid management following initial volume resuscitation [43].

**Fluid administration should be slower in pediatric patients than adults** [39, 44].

In children, the physician must be concerned about cerebral edema, which occurs in 0.5–1% of DKA episodes in children [45] and associated with a high mortality rate [46, 47]. The precise mechanism of cerebral edema is unknown. The prevailing assumption that cerebral edema is a result of organic osmoles, which accumulate in the brain to balance the cellular dehydrating effect of the hyperosmolar extracellular fluid, causing excess fluid movement into cells with hydration, is unproven [45]. Alternatively, there is suggestion that cerebral edema is a result of ischemia and subsequent reperfusion injury [48]. The risk factors identified for cerebral edema are more severe acidemia (lower $pCO_2$), greater dehydration (higher blood urea nitrogen), and the use of bicarbonate [49]. The ketone bodies themselves may increase brain microvascular permeability [50]. Even though the role of rapid fluid administration (greater than 50 mL/kg during the first 4 h of therapy) in causing brain herniation [51] is debated, fluid overload is to be avoided.

**Insulin is administered by continuous intravenous infusion using regular insulin or a rapid acting insulin analog** [52, 53].

Insulin doses are adjusted against two parameters – restoring near-normal blood glucose and reversing ketoacidosis. A loading bolus of 0.1 units/kg regular insulin is commonly administered intravenously while simultaneously beginning continuous infusion at 0.1 units/kg/h. Alternatively, using a no initial bolus but a starting infusion rate of 0.14 units/kg has been found to be equally effective in treatment [54, 55]. The glucose should fall by 50–75 mg/dL each hour. If the glucose does not fall as expected, the insulin infusion rate should be increased. Since prevention of ketoacidosis requires less insulin action than prevention of hyperglycemia, it is a paradox in the therapy of DKA that it is more difficult to stop ketone body generation than to lower serum glucose. Therefore, it is essential that the physician maintains constant insulin infusion, if only at physiologic levels of 0.5–1 unit/h, to restrain lipolysis (release of FFA from adipose tissue). The continued administration of insulin without causing hypoglycemia often requires concomitant administration of glucose-containing infusions (usually 5% or, if necessary, 10%), which should be started when the serum glucose has fallen to 200 mg/dL (11 mmol/L). Conversely, should the glucose fall at a rate greater than 75 mg/dL an hour, the insulin infusion rate should be decreased to avoid hypoglycemia. The importance of hourly glucose monitoring cannot be emphasized more while a patient is receiving intravenous insulin.

The use of subcutaneous insulin protocols in the treatment of mild DKA has been studied in small randomized trials with no significant differences found in resolution of DKA, insulin required for treatment, or length of stay. It has been proposed that this may offer a reasonable treatment alternative for mild DKA; however, this has not been recommended by any professional society for general use [56].

**Potassium repletion is necessary because $K^+$ is lost during the osmotic diuresis of DKA as the $K^+$ salt of ketoacids.**

The serum potassium level reflects both total body stores and the distribution between the intracellular (98% of total body $K^+$) and extracellular spaces. The osmotic diuresis of DKA causes huge urinary $K^+$ losses. Yet, the serum $K^+$ can be low, normal, or high at the time of presentation. Redistribution of $K^+$ out of the intracellular compartment and into the intravascular space causes a normal or high serum $K^+$ in the face of total body depletion.

Physiologic insulin levels drive $K^+$ into cells [57]. With the decreased insulin action of DKA, potassium moves out of cells into the serum. This redistribution may raise serum $K^+$. Further elevation of serum $K^+$ may occur because of redistribution related to acidosis ($K^+$ moving out of cells in exchange for $H^+$ moving in). Insulin administration during treatment moves potassium back into the cells, halts the generation of ketoacids, and reverses acidosis. Dangerous degrees of hypokalemia may then occur and are postulated to be the cause of the 30–50% DKA mortality in the 1950s [58]. The treating physician must anticipate and prevent this hypokalemia. Typically, 20–40 mEq $K^+$ is administered with each liter of fluid. If the fluid is administered more rapidly, the patient will (appropriately) receive more $K^+$ per unit time. In the event of severe hypokalemia at the initial presentation of DKA, potassium repletion with fluid resuscitation should be initiated prior to insulin therapy. Conversely, two caveats against $K^+$ administration are renal impairment, which prevents normal excretion of excess $K^+$, and dangerous hyperkalemia at the time of presentation. The physician may administer potassium as soon as urine flow is established. In addition, the physician must order an electrocardiogram (EKG) on presentation. If signs of hyperkalemia are present (tall-peaked T waves, followed by low-amplitude P wave and widening QRS complex) (Fig. 6), no potassium is given until the "stat" $K^+$ levels are back from the laboratory. In the absence of signs of hypokalemia on the EKG (low-amplitude T waves with rising amplitude U waves), some physicians do not administer $K^+$ until the laboratory measurement is available.

**More and more evidence shows that bicarbonate administration plays no role in the therapy of DKA.**

When insulin therapy reverses ketoacid formation, bicarbonate is rapidly regenerated from retained ketone body anions. To the extent that these anions were lost in the urine, the kidney takes several days to fully reclaim bicarbonate. In the past, bicarbonate was administered out of concern that severe acidosis would impair cardiac function and precipitate congestive heart failure or vascular collapse. On the other hand, administration of bicarbonate may cause fluid retention, brain edema, and unfavorable pH shifts. Current data suggest that bicarbonate administration does not favorably influence patient outcome down to a pH of 6.90 [59–61]. Below this level, there is a consensus to administer bicarbonate even if its value is unproven.

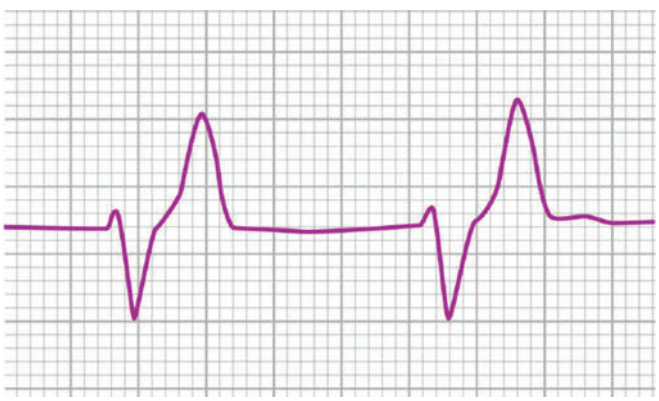

**Fig. 6.** The electrocardiogram in hyperkalemia progressively shows tall-peaked T waves followed by low-amplitude "P" wave (not even discernible in this example) and widening of the QRS.

**Complications of DKA include death, cerebral edema, pancreatitis, rhabdomyolysis, pulmonary edema, hypertriglyceridemia, and hypophosphatemia.**

Mortality in DKA is 0.25–10%, striking mostly the very young and the elderly [62–65]. Multiple organ failure (cardiac, renal, hepatic, and pulmonary) portends a high mortality in adult patients.

Cerebral edema is an uncommon but significant cause of morbidity and mortality in diabetic ketoacidosis. It occurs more frequently in the pediatric population and rarely occurs in adult patients [47]. The pathogenesis of cerebral edema in DKA is not clear. It was originally thought to be a consequence of aggressive fluid resuscitation; however, more recently, there is evidence that vasogenic and cytotoxic edema is a consequence of cerebral hypoperfusion [66]. It is the major cause of death and disability for children with diabetic ketoacidosis.

Rhabdomyolysis, the necrosis of skeletal muscle leading to the release of intracellular contents to the circulation, is a potential complication of DKA [67]. Rhabdomyolysis in the setting of DKA can have a variable clinical presentation with elevations in muscle enzymes, electrolyte disturbances, and acute kidney injury. The pathogenesis of rhabdomyolysis from DKA is unclear but is likely a result of the electrolyte and glucose disturbances in DKA.

Pulmonary symptoms may indicate pneumonia but may also occur with a "capillary leak" or interstitial edema associated with DKA [68]. Pulmonary edema, observed in association with DKA, is thought to be caused by a decrease in capillary osmotic pressure during fluid resuscitation but does not always have clinical significance [66]. However, it can lead to hypoxia and can confound treatment of DKA where volume resuscitation is a pillar of treatment.

Elevated pancreatic enzymes, such as amylase and lipase, are correlated with the degree of hyperglycemia, acidemia, and dehydration. Although not usually clinically important [69]. Dehydration with hypoperfusion of the pancreas and elevations in triglycerides may precipitate acute pancreatitis [70, 71]. Elevated triglycerides occur because insulin stimulation of endothelial lipoprotein lipase is necessary to remove lipids from the circulation, and insulin inhibition of adipose tissue lipase prevents mobilization of lipids out of the fat cell. Hypertriglyceridemia resolves following DKA unless there is an underlying defect but may contribute to pancreatitis [72]. Mild hypophosphatemia commonly occurs in DKA; there is evidence that treatment is not required unless clearly symptomatic [73–75].

**DKA costs lives and dollars; the epidemiology of DKA targets educational and preventive solutions.**

In developing countries, mortality rates for type 1 diabetic patients are high, with DKA as the leading cause of death [76]. In the U.S. children and young adults with type 1 diabetes mellitus, DKA is also the most common cause of mortality and appears to affect non-whites with greatly increased frequency compared to whites [77]. DKA, with an estimated annual incidence of 179,387 in the United States, is estimated to incur costs of nearly $90 million per year [1]. In youth, the presence of DKA is estimated to increase the predicted annual cost of medical expenditures by nearly 70% in the United States [78] and up to 3.6 fold higher diabetes-related costs in Germany [79].

Educational programs may decrease the incidence of DKA [80], although the emotional and psychological factors that stimulate knowledgeable patients to discontinue insulin are not easily addressed. Studies have shown that patients can be safely discharged following care in the emergency room if DKA is mild (pH > 7.20, $HCO_3$ > 10) [81]. Admission to a general hospital bed rather than a more expensive intensive care unit bed is also possible for less severely ill patients [82]. Specialty care may provide significant cost savings: endocrinologists treat and discharge their patients with DKA more rapidly, with fewer tests and fewer readmissions than do general internists [83].

**Patients may present with DKA with exceptions to the definition including lower glucose, higher pH, and negative nitroprusside test for ketones.**

The glucose at presentation in DKA varies widely from less than 180 to 1000 mg/dL. If a patient is not eating well prior to the onset of DKA and able to maintain adequate hydration, the glucose may be lower [84]. Young people with good kidney function or pregnant patients [85] with increased glomerular filtration rate (GFR) and lowered glucose threshold can develop DKA with normal blood sugars since they have a greater capacity to excrete glucose [86]. Patients who treat their finger stick glucose elevations with small doses of insulin may develop diabetic ketoacidosis with normal glucose levels if the stress hormones during illness stimulate sufficient lipolysis. DKA may develop unusually rapidly during fasting [87] or dehydration because these conditions increase the counterregulatory hormone glucagon and increase the pace at which acidosis occurs when insulin is withdrawn.

Patients who have excessive vomiting and develop DKA may have pH levels above the definition for DKA (pH < 7.35) because $H^+$ lost in emesis fluid superimposes metabolic alkalosis on the metabolic acidosis of DKA. Other states that cause metabolic alkalosis can have the same effect, such as DKA with Cushing's syndrome.

Patients with low tissue oxygenation, sepsis, and hypotension can present with a large predominance of β-hydroxybutyrate over acetoacetate. The test for ketoacids in these patients may be negative at presentation and become positive as the patient improves and converts β-hydroxybutyrate to acetoacetate.

**The patient with atypical diabetes mellitus is exceptional in the ability to recover normal pancreatic function** [88–90].

In the United States, perhaps 10% of black Americans who present with DKA will have a subsequent course characterized by long-term remission of diabetes mellitus. This course has been labeled "atypical diabetes mellitus," "type 1.5" diabetes, and "Flatbush" diabetes for the area of Brooklyn, New York, where it has been best characterized. Relapses occurred over a time period of months to longer than 5 years; 20% of patients were in remission beyond 6 years. Patients may have a family history of similar remissions of diabetes mellitus. This pattern is seen in younger, less obese, and more insulin-sensitive patients than the typical patient with type 2 diabetes, and in Japanese and Chinese patients with atypical diabetes mellitus who often do not require insulin after the episode. Unlike in type 1 diabetes, antibodies against glutamic acid decarboxylase (GAD) and islet cell antibodies are negative.

## Hyperosmolar Hyperglycemic Syndrome (HHS)

**Hyperosmolar hyperglycemic syndrome differs from DKA in the more dramatic degree of dehydration, higher serum glucose, lack of acidosis, advanced patient age, and much higher mortality** (Fig. 7) [91].

Hyperosmolar hyperglycemic syndrome (HHS) connotes severe hyperglycemia without (or with mild) acidemia or ketoacidosis. Diagnostic criteria include a plasma glucose level >600 mg/dl, an effective plasma osmolarity >320 mOsm/L, and an absence of significant ketoacidosis [92]. The pathogenesis of HHS bears similarities to that of DKA. In HHS, there is a relative insulin deficiency combined with increased levels of counterregulatory hormones. An increase in gluconeogenesis and glycogenolysis lead to hyperglycemia. Elevated glucose levels create an osmotic gradient leading to osmotic diuresis. HHS differs from DKA in its absence of ketoacidosis. The presence of insulin and lower levels of glucagon avoid ketoacid formation [93]. The severe dehydration and hyperglycemia often results in effective serum osmolality (Table 2) greater than 320 mOsm/L, a level at which depression of consciousness or coma can be attributed to the hyperosmolar state [94, 95]. Patients commonly have type 2 diabetes mellitus, with poor antecedent glucose control, and are older; however, HHS has been reported in those with type 1 diabetes as well as in children [96, 97].

Thrombotic complications, which may occur in DKA [98], are a feared complication of HHS. Coronary arteries may clot, and arterial clots may propagate from the periphery to include the large central vessels. Presumably, the severe dehydration results in hemoconcentration and a hypercoagulable state. Because of the typically advanced patient age, the hypercoagulability, and decreased perfusion accompanying severe dehydration, myocardial infarction must be specifically excluded as a precipitating or a complicating event. Investigations for precipitating events, similar to that in cases of DKA, should be pursued during evaluation of a patient with HHS.

Patients should be treated in an intensive care setting. Fluid management with aggressive rehydration is the critical aspect of treatment of hyperosmolar syndrome. An immediate fluid challenge should be given to guarantee continued renal perfusion and urine output. One or two

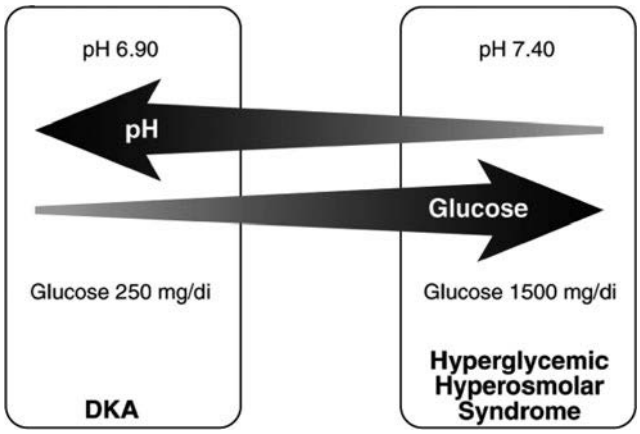


**Fig. 7.** Hyperglycemic hyperosmolar syndrome (HHS) is characterized by elevated glucose levels and increased plasma osmolality in the absence of ketoacidosis. In between, there is overlap and the clinician tailors therapy accordingly.

liters of fluid in the first hour of therapy followed by 1 L/h for the next 4 h is commonly recommended. The water deficit can be calculated from the serum osmolality (the serum sodium can be substituted for osmolality in the equation). Half the water deficit should be replaced in the first 8–12 h. Exceptions include patients with renal or congestive heart failure, who require highly individualized fluid management.

The "corrected" serum sodium (Table 2) indicates the degree of free water loss – the higher the corrected sodium, the greater the water loss. In spite of marked free water loss, initial fluid replacement is with isotonic solutions, usually normal saline (NS), to establish blood pressure and perfusion. The subsequent fluid chosen depends on hemodynamics, serum sodium, and urine output.

Insulin plays only a minor role in the treatment of HHS, since these patients are not "ketosis prone," are not acidotic, and do not require restraint of free fatty acid release. The glucose osmotic diuresis that occurs with fluid administration is the most important factor in lowering the blood glucose toward the renal threshold of 180 mg/dL.

Insulin treatment is currently recommended in the treatment of HHS if glucose levels are not declining with fluid therapy alone. The rapid blood lowering of the serum glucose with insulin is not recommended because the osmotic pull of glucose helps to maintain intravascular volume and rapid changes in osmolality could result in cerebral edema. Maintenance of glucose levels of 200–300 mg/dL is currently recommended [92].

**When it is over, the physician must educate the patient not to omit insulin at times of stress.**

Patients with type 1 diabetes must always take insulin; patients with type 2 diabetes must understand when insulin doses need to be increased. Common misconceptions have to be corrected. The patient must take insulin even when not able to eat. Ordinarily, the diabetic patient will have a basal insulin that remains active between meals or when not eating. This basal insulin can be in the form of long or intermediate acting insulin or a rapid acting insulin, continuously infused subcutaneously by an insulin pump. Patients get confused, however, when they are not eating because of illness, such as gastrointestinal "upset." At these times, counterregulatory hormones may rise resulting in increased insulin requirements. Patients must know that they need to be more vigilant with self-monitored blood glucose testing and if necessary, ketone testing.

## Conclusions

The next patient will likely be different, but the culprits – glucose, free fatty acids, and ketoacids – will be the same. The absolute or relative insulin deficiency permitting substrates (free fatty acids, amino acids and glycerol) to reach the liver and counterregulatory excesses driving hepatic gluconeogenesis and ketogenesis are important to consider when interpreting lab results and enacting a treatment plan. The reversal of controlled storage and synthetic processes resulting in hyperglycemia, systemic acidosis, osmotic diuresis, and dehydration will be pillars of the treatment plan. Therapy is straightforward, requiring insulin, fluid, and electrolyte administration. Key to a successful clinical outcome is careful monitoring of the patient, anticipation of responses, and investigation of potential precipitating factors.

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# Current Therapeutic Approaches in the Management of Hyperglycemia in Chronic Renal Disease

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## Abstract

Diabetes mellitus (DM) and chronic kidney disease (CKD) are intricately intertwined. DM is the most common cause of CKD. Adequate control of DM is necessary for prevention of progression of CKD, while careful management of the metabolic abnormalities in CKD will assist in achieving better control of DM. Two of the key organs involved in glucose production are the kidney and the liver. Furthermore, the kidney also plays a role in glucose filtration and reabsorption. In CKD, monitoring of glycemic control using traditional methods such as hemoglobin $A_{1c}$ ($HbA_{1c}$) must be done with caution secondary to associated hematological abnormalities in CKD. With regard to medication management in the care of patients with DM, CKD has significant effects. For example, the dosages of oral and non-insulin anti-hyperglycemic agents often need to be modified according to renal function. Insulin metabolism is altered in CKD, and a reduction in insulin dose is almost always needed. Dialysis also affects various aspects of glucose homeostasis, necessitating appropriate changes in therapy. Due to the aforementioned factors glycemic management in patients with DM and CKD can be quiet challenging.

**Keywords:** Diabetes mellitus, Chronic kidney disease, Dialysis, Hypoglycemia

## Introduction

Chronic kidney disease (CKD) is defined by abnormalities in kidney structure or function that are present for more than 3 months with implications for health [1]. According to the Centers for

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disease control and prevention (CDC), about 10% of adults in the United States are estimated to have CKD. Diabetes is the most common or leading single cause of CKD [2].

Diabetes mellitus consists of a group of metabolic disorders characterized by hyperglycemia [3] and is diagnosed as follows:

- Fasting plasma glucose (FPG) ≥126 mg/dl (7.0 mmol/l): Fasting is defined as no caloric intake for at least 8 h
- Two-hour plasma glucose ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT): Using a glucose load containing the equivalent of 75 g glucose
- In a patient with classic symptoms of hyperglycemia, a random plasma glucose ≥200 mg/dL (11.1 mmol/l)
- $A_{1c}$ ≥6.5%: The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the DCCT assay [4]

Prediabetes is defined as having either impaired fasting glucose or impaired glucose tolerance. It is further interesting that some recent studies have shown the 1 h post load glucose levels may identify high risk individuals not detected by standard prediabetes criteria [5, 6]. This is important from a public health perspective as it may help identify more people at risk for overt diabetes and potential diabetic nephropathy.

According to the CDC, approximately 21.3 million people in the U.S. have diabetes; at this rate, it is estimated that by the year 2050, perhaps as many as 1 in 3 adults may have diabetes [7].

Chronic kidney disease and diabetes mellitus are intricately intertwined. Certainly, adequate management of DM is paramount to prevent progression of CKD; alternatively, CKD associated abnormalities (altered glucose reabsorption, insulin metabolism, metabolic acidosis, anemia, and hyperparathyroidism) influence the goals, methods of monitoring, and management strategies needed for optimal management of DM. These patients have an increased risk of cardiovascular-related mortality and morbidity relative to those with normal renal function. Improved glycemic control in patients with DM and CKD enhances patient safety; however, anti-hyperglycemic treatment options must be carefully selected to avoid potential side effects. Therefore, successful management of DM in CKD patients represents a major challenge to clinicians. Furthermore, the presence of CKD and DM, individually or especially in combination, have a huge economic impact. DM is estimated to cost $245 billion ($176 billion in direct medical costs and $69 billion in lost productivity) [8]. In 2013, CKD is estimated to cost $50 billion in Medicare patients over the age of 65, amounting to 20% of the health expenditures of that group [9].

In this review article, we will discuss aspects of pathophysiology, with a particular focus on special management challenges and therapeutic options in the treatment of patients with DM in CKD.

## Role of the Kidney in Glucose Homeostasis

Glucose homeostasis is a vital function, as the human brain needs a constant supply of glucose. For this reason, plasma glucose is maintained within a tight range [10]. The kidney has been

increasingly recognized to play an important role in glucose homeostasis through various mechanisms: glucose production, uptake, filtration and reabsorption [11].

Endogenous glucose production occurs primarily through two different processes: glycogenolysis and gluconeogenesis. Glycogenolysis is the production of glucose from the breakdown of glycogen, whereas gluconeogenesis involves the generation of glucose from non-carbohydrate substrates [10].

Only the liver and kidney have the requisite enzymes to perform gluconeogenesis. Initially, it was thought that the liver was the only organ capable of gluconeogenesis [12]. This concept resulted from early studies showing no net change in the blood glucose between the renal artery and the vein [8]. However, it is currently accepted that gluconeogenesis occurs in the renal cortex whereas the renal medulla is an obligate user of glucose. Also, it was noted by Joseph et al. that, even after removal of the liver during transplantation, plasma glucose levels decreased by only 50%, confirming the role of the kidney in glucose homeostasis [13]. The kidney is responsible for approximately 40% of glucose produced through gluconeogenesis in the fasting state. The proximal tubule is the main site of gluconeogenesis, and the most common substrates are lactate, glutamine, glycerol and alanine [14]. Insulin suppresses renal glucose production and increases glucose uptake, whereas epinephrine augments renal glutamine gluconeogenesis. In contrast to hepatic gluconeogenesis, glucagon has minimal effect on renal gluconeogenesis.

Finally, Meyer et al. also showed that, in the post prandial state increased glucose release by the kidney results in an increase in endogenous glucose levels [15].

Glucose is freely filtered at the glomerulus and reabsorbed completely in the proximal tubule, by an insulin independent process. However once the maximal reabsorptive capacity (Tm) of the proximal tubule is reached, then glycosuria results. The Tm is dependent on the glomerular filtration rate (GFR) and glucose load. In conditions with increased GFR, as in pregnancy, glycosuria results at a lower threshold of glucose.

In patients with diabetes and normal renal function there is increased expression of the sodium dependent glucose transporter 2 (SGLT2) in the proximal tubule, due to the increased delivery of glucose to the proximal tubule. This leads to afferent arteriole constriction secondary to tubuloglomerular feedback which results in hyperfiltration [16]. Freitas et al. showed increased SGLT2 mRNA in diabetic rats which decreased to non-diabetic levels with phlorizin [17]. Also of note, Zhang et al. studied the effect of dapagliflozin in an animal model of CKD and found that dapagliflozin did not affect the decrease in GFR, hypertension or improve proteinuria [18].

## Insulin and CKD interplay

### Insulin Dynamics

Insulin is metabolized primarily in the liver and the kidney. About 40–50% of insulin clearance occurs in the kidney, primarily by two different mechanisms. Approximately, two thirds of insulin is filtered across the glomerulus and is reabsorbed by the proximal tubule cells where it is degraded. Approximately one third of insulin diffuses across the peritubular capillaries to bind to the

tubular cells of the distal nephron where it is involved in the reabsorption of sodium, phosphate and glucose [19]. In insulin-treated diabetic patients, subcutaneous-injected exogenous insulin is not metabolized by the liver, and it escapes first pass metabolism; this, therefore, increases the role of the kidney in insulin clearance. Various abnormalities in chronic kidney disease affect glucose homeostasis (Fig. 1). Further CKD also has effects on the half-life of insulin.

As GFR decreases to less than 15–20 ml/min, the clearance of insulin decreases accordingly, which leads to an effective increase in insulin duration of action [20]. Unfortunately, this often contributes to occurrences of hypoglycemic episodes. While endogenous insulin is metabolized in the liver, exogenous insulin is mainly excreted through the kidney [21]. Often, it is found that CKD patients who have a functional degree of residual beta cell function, such as those with type 2 diabetes who did not previously require large total daily doses of insulin, may not even be able to tolerate any dose of exogenous insulin therapy as CKD progresses, and this is particularly true as the patient approaches ESRD [21].

## Metabolic Abnormalities

Chronic kidney disease patients present with a myriad of metabolic abnormalities (uremia, metabolic acidosis and secondary hyperparathyroidism) all of which can affect insulin dynamics.

Uremia and metabolic acidosis contribute to the pathophysiology of insulin resistance by decreasing insulin-mediated utilization of glucose by muscles and adipose tissue and an inability of the kidney to excrete the acid load. The presence of other pro-inflammatory mediators such as IL-6, and TNF-alpha likely also contribute to insulin resistance [22, 23]. This issue is pertinent when considering that insulin resistance may decrease after hemodialysis, secondary to clearance

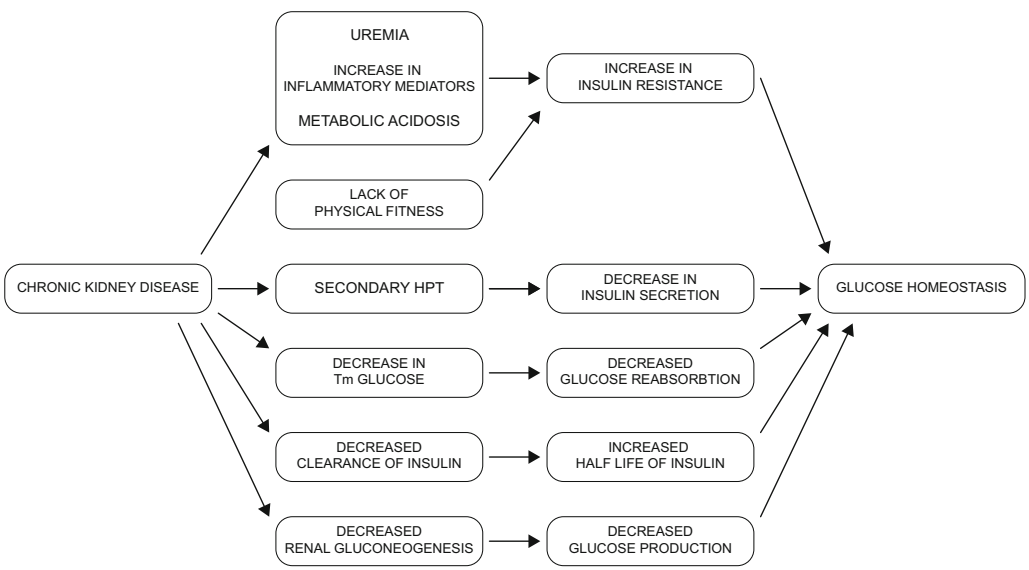


**Fig. 1.** CKD affecting glucose homeostasis.

of uremic toxins, and correction of metabolic acidosis. This may have implications on the titration of the management regimen in insulin-dependent diabetic patients.

Parathyroid hormone (PTH) increases cytosolic calcium and inhibits the ATPase-dependent potassium channels, decreasing insulin secretion [24–26]. Mak et al. showed that in adolescents with uremia and hyperparathyroidism, parathyroidectomy increased the amount of insulin secreted by 37% with no change in insulin sensitivity [27]. With regard to the molecular mechanism, Masry examined the metabolic profiles of islet cells undergoing chronic renal failure in rats. The authors noted that within 2 weeks the accumulation of islet cell cytosolic calcium depletes ATP and calcium cannot be extruded out leading to a decrease in the amount of insulin secreted [28].

Protein energy malnutrition (PEM) is also very common in dialysis patients as there is a state of a relative deficit of nutritional intake as compared to the nutritional demand. Epidemiological studies have shown an association between PEM, inflammation and poor outcomes in dialysis patients, described as the malnutrition inflammation complex syndrome (MICS). The associated inflammatory cytokines are believed to increase insulin resistance [29].

## Techniques for Assessment of Glycemic Control

While the measurement of serum glucose is considered a "gold standard", it still provides only a snapshot of the patient's overall glycemic status. In order to assess glycemic control over a longer period of time, the most common metric used is the hemoglobin $A_{1c}$ ($HbA_{1c}$). $HbA_{1c}$ constitutes approximately 4% of the total hemoglobin. $HbA_{1c}$ measures the glycosylation of hemoglobin over the life of the red blood cell, and it thus provides an estimate of glycemic control over approximately the last 3 months prior to the measurement [30].

However, the $HbA_{1c}$ measurement can be affected by analytical, biological and clinical variabilities. These may be particularly pronounced in CKD patients. Red cell life span is reduced by 30–70% in CKD [31]. Moreover, the use of erythropoietin stimulating agents can recruit more immature cells into the circulation, and these may be less prone for glycosylation [31].

Various alternative measures are also available for the monitoring of glycemic control. Fructosamine is produced via the non-enzymatic glycosylation of serum proteins, predominantly albumin. It may be useful for assessing glycemic control over the past 2–3 weeks [30]. However, Chen et al. showed that fructosamine levels were lower in CKD patients for the same level of serum glucose as compared to that of non CKD patients, thus making its reliability questionable [32].

Interindividual variability of the glucose gradient across the red blood cell membrane may affect $HbA_{1c}$ but not fructosamine which may partially explain discrepancies in their measurement assessments [33].

Glycated albumin (GA) is being increasingly recognized as an alternative to $HbA_{1c}$ in patients with CKD. Albumin is the most abundant protein in the body and is sensitive to glycation. As the half-life of albumin is approximately 20 days, it may be helpful in assessing a patient's glycemic status over the preceding 1–2 weeks. It is likely more responsive when rapid changes in glycemic status are expected [34].

Peacock et al. measured both GA and $HbA_{1c}$ in 307 patients with DM. They found that in dialysis patients, the $HbA_{1c}$ significantly underestimated glucose levels. In fact, the GA/$HbA_{1c}$ ratio was 2.77 in ESRD patients as compared to 1.98 in patients with normal renal function [35]. There are, nonetheless, still caveats in the use of GA, as it can be influenced by conditions associated with abnormal protein turnover such as catabolic states, malnutrition, peritoneal dialysis, inflammation and intravenous albumin infusions [30]. However, it has been shown that GA can predict hospitalization, and mortality in diabetic patients on dialysis. GA has also been shown to correlate with cardiovascular hospitalization and length of stay [36, 37].

As can be seen from above, despite advances, there is still a great need for better markers of glycemic control in the CKD patient.

It is worth noting that, even with all this complexity, most expert guidelines still recommend primarily the use of the $HbA_{1c}$. The NFKDOQI guidelines propose a target $HbA_{1c}$ level of less than 7% for patients with CKD who have DM [38]. This is similar to the $HbA_{1c}$ goal level recommended by the American Diabetes Association for patients without CKD, as well However, the ADA guidelines also give the option of "less stringent $HbA_{1c}$ goals (such as <8%) which may be appropriate for patients with a history of severe hypoglycemia" The latter may particularly apply to patients with ESRD, especially those with type 1 diabetes for whom hypoglycemia prevention is often most difficult [39].

## Management of Hyperglycemia

Good glycemic control is important in patients with DM and CKD however challenging it may be to safely accomplish. Glycemic control has been shown to prevent the onset and progression of nephropathy. The relationship between $HbA_{1c}$ and mortality in non-dialysis and dialysis patients has been shown to be U-shaped indicating it is potentially beneficial to keep the $HbA_{1c}$ within an optimal range [40–44].

Recently the American Association of Clinical Endocrinologists (AACE) and EAS/ADA released guidelines for the outpatient management of DM. While AACE advocated an $HbA_{1c}$ of less than 6.5, target of EAS/ADA advocated a target of less than 7. Both guidelines emphasize that in the presence of renal failure the $HbA_{1c}$ goals still need to be personalized; no specific numerical $HbA_{1c}$ target was put forth by either group specifically for patients with renal dysfunction [45, 46].

### Non-Insulin Medications for the Treatment of Patients with Type 2 DM

In the last two decades, there has been a remarkable emergence of new anti-hyperglycemic medications available for the management of type 2 DM. Guidelines from the professional societies have just begun to incorporate the newer agents, however most have not addressed the efficacy and safety of these new medications in CKD patients specifically. However, these agents are important as they must often be considered for patients with type 2 DM who have a strong predisposition against the use of insulin (Table 1).

**Table 1. Oral anti-hyperglycemic agents in CKD.**

| Drug | Common adverse effects | Risk for hypoglycemia (monotherapy) | Renal dosing |
|---|---|---|---|
| Metformin | GI (nausea, vomiting, diarrhea and abdominal pain) | No | Not for use in eGFR <30 ml/min<br>Dose reduction in eGFR <45 ml/min |
| Glipizide | Hypoglycemia<br>Weight gain<br>Skin rash, urticaria | Yes | No specific dose adjustment |
| Glyburide | Hypoglycemia<br>Weight gain<br>Skin rash, urticaria | Yes | Not recommended for a eGFR of <60 ml/min |
| Glimepiride | Hypoglycemia<br>Weight gain<br>Skin rash, urticaria | Yes | Not recommended for severe impairment |
| Gliclazide | Hypoglycemia<br>Weight gain<br>Skin rash, urticarial | Yes | Not recommended for severe impairment |
| Repaglinide | Hypoglycemia<br>Weight gain | Yes | No dose adjustment for Cr cl >40 ml/min<br>0.5 mg for *Cr cl 20–40 ml/min |
| Nateglinide | Dizziness, elevated liver enzymes | Yes | No specific dose adjustment |
| Pioglitazone | Edema | No | No specific dose adjustment |
| Rosiglitazone | Edema | No | No specific dose adjustment |
| Acarbose | Diarrhea, flatulence and abdominal discomfort | No | Not recommended for a creatinine clearance of <25 ml/min |
| Exenatide | Nausea, vomiting, diarrhea and abdominal pain. | No | Not recommended for a Cr cl <30 ml/min |
| Exenatide LAR | Nausea, vomiting, diarrhea and abdominal pain | No | Caution if Cr clearance is 30–50 ml/min<br>Not recommended for a Cr cl <30 ml/min |
| Liraglutide | Nausea, vomiting, diarrhea and abdominal pain | No | Not recommended for moderate to severe renal impairment |
| Albiglutide | Nausea, vomiting, diarrhea and abdominal pain | No | No dosage adjustment |
| Dulaglutide | Nausea, vomiting, diarrhea and abdominal pain | No | No dosage adjustment |
| Lixisenatide | Nausea, vomiting, diarrhea and abdominal pain | No | eGFR > 15 ml/min-no dosage adjustment monitor for side effects<br>eGFR <15 ml/min-not recommeded |
| Alogliptin | Nausea, diarrhea, peripheral edema, pancreatitis | No | Cr cl > 60 ml/min-no dosage adjustment<br>Cr cl > 30 ml/min to < 60 ml/min 12.5 mg once daily<br>Cr cl > 15 ml/min to <30 ml/min 6.25 mg once daily<br>Cr cl < 15 ml/min-6.25 mg once daily<br>Dialysis- 6.25 mg once daily |

*(Cont'd.)...*

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| | | | |
|---|---|---|---|
| Vildagliptin | Nausea, diarrhea, peripheral edema, pancreatitis | No | eGFR >50 ml/min-no dosage adjustment<br>eGFR >50 ml/min-50 mg once daily |
| Sitagliptin | Nausea, diarrhea, peripheral edema, pancreatitis | No | Cr cl >50 ml/min-100 mg<br>Cr cl 30–50 ml/min-50 mg<br>Cr cl <30 ml/min-25 mg |
| Saxagliptin | Nausea, diarrhea, peripheral edema, pancreatitis | No | Cr cl >50 ml/min-5 mg<br>Cr cl <50 ml/min-2.5 mg |
| Linagliptin | Nausea, diarrhea, peripheral edema, pancreatitis | No | No dose adjustment |
| Pramlintide | Nausea, loss of appetite, headache | No | Cr cl > 15 ml/min-no dose adjustment |
| Bromocriptine | Nausea, somnolence, dizziness, psychosis, orthostatic hypotension | No | No specific dose adjustment |
| Canagliflozin | Fungal vaginosis<br>Increased urinary tract infections | No | eGFR >60 ml/min-no dose adjustment<br>eGFR 45–60 m/min-100 mg<br>eGFR 30–45 ml/min-not recommended for initiation<br>eGFR <30 ml/min-contraindicated |
| Empagliflozin | Fungal vaginosis<br>Increased urinary tract infections | No | eGFR >45 ml/min-no dose adjustment<br>eGFR 30–45 ml/min-not recommended for initiation<br>eGFR <30 ml/min-contraindicated |
| Dapagliflozin | Fungal vaginosis<br>Increased urinary tract infections | No | eGFR >60 ml/min-no dose adjustment<br>eGFR 30–60 ml/min-not recommended for initiation<br>eGFR <30 ml/min-contraindicated |

*GI* Gastrointestinal, *eGFR* Estimated glomerular filtration rate, *Cr cl* Creatinine clearance; [21, 50, 57]

## Biguanides

Metformin is the one of the most common medications prescribed for the management of DM. It has been approved in the USA since 1994. It acts primarily on the liver to reduce glucose output, and also improves insulin sensitivity and decreases intestinal absorption of glucose. Advantages of metformin include less risk of hypoglycemia, and potential weight loss [46]. Of particular interest is an important historical fact: in the UKPDS trial, metformin use was associated with reduction in cardiovascular mortality in type 2 DM patients [40]. Side effects of metformin include diarrhea, nausea, metallic taste, and the potential for lactic acidosis [46].

Traditionally, the use of metformin in CKD was strictly limited only to patients with a creatinine less than 1.5 in men and less than 1.4 in women, to reduce the risk of lactic acidosis. However, a Cochrane analysis in 2010 did not find significant evidence that metformin use was actually associated with an F risk of lactic acidosis [47]. The European Association for the Study

of Diabetes (EASD) has endorsed the use of estimated glomerular filtration rate (eGFR) as criteria for appropriateness of metformin use [46], and the United States Food and Drug Administration has recently agreed [48]. Dose reduction is recommended for an eGFR of <45 ml/min and medication discontinuation is recommended for an eGFR < 30 ml/min. Further, it is contraindicated to initiate metformin in patients with an eGFR of <30 ml/min, and also not recommended in patients with an eGFR of 30-45 ml/min [48].

## Sulfonylureas

These are among the oldest known oral medications for the management type 2 diabetes. They act via the sulfonylurea receptors on the pancreatic beta cells, causing closure of the ATP-sensitive potassium channels, which leads to insulin release [46]. Because of this mechanism, these agents are already well known for the risk of hypoglycemia. This risk is increased when used in patients with CKD, which must be done with extreme caution.

There are some available data on the differential effects of individual sulfonylureas on hypoglycemia. In a meta-analysis by Schopman et al. the incidence of mild hypoglycemia in patient using sulfonylureas was 10.1%. The authors reported that patients on gliclazide had less occurrence of mild hypoglycemia as compared to glimepiride (1.4% vs 15.5% $p < 0.001$). About 0.1% patients experienced severe hypoglycemia. Regarding severe hypoglycemic episodes, gliclazide (0.1%) was significantly better as compared to glipizide (2.1% $p < 0.01$), a trend was noted with glimepiride (0.9% $p = 0.05$) and no difference was noted when compared to glibenclamide (0.5% $p = 0.17$) [49].

It is worth noting that sulfonylureas are not removed by hemodialysis, thus making the treatment of sulfonylurea-induced hypoglycemia all the more challenging in patients with DM and ESRD [50]. However, sulfonylurea-induced hypoglycemia not responding to intravenous dextrose administration can be treated with octreotide. Octreotide is a somatostatin analogue which suppresses insulin release and raises blood glucose levels. McLaughlin et al. studied 9 patients with sulfonylurea-induced hypoglycemia who were treated with octreotide and found that hypoglycemic events were reduced as compared to before administration [51]. Still this must be done with caution as hyperkalemia secondary to octreotide inhibition of insulin in a dialysis patient has been described by Adabala et al. [52].

## Glucagon-Like Peptide (GLP)-1 Agonists

The GLP-1 agonists mimick the effects of the incretin hormone GLP-1, which is known to increase insulin secretion in a glucose-dependent manner, inhibit glucagon, increase satiety and also decrease gastric emptying time. They have also been shown to reduce weight, which is of benefit for the obese patient with type 2 DM. These agents can, however, be accompanied by side effects including nausea, vomiting and infrequently have been associated with pancreatitis. [46]. Combined basal insulin and GLP-1 agonist therapy is also a newly available therapeutic option for patients with type 2 DM however more data on its safety and efficacy in patients with DM and CKD are needed [53]. Of particular interest would be the role of albiglutide and dulaglutide which require no changes in dosage with renal function.

Leiter et al. studied albiglutide versus sitagliptin in patients with DM and CKD. The authors found that at week 26 the reduction in $HbA_{1c}$ in albiglutide group was significantly higher (−0.83 versus −0.52) [54]. In the LIRA-RENAL trial liraglutide as compared to placebo in patients with moderate renal replacement reduced $HbA_{1c}$ by 0.66% with no difference in hypoglycemic episodes [55].

The FDA has received about 78 cases of renal dysfunction associated with exenatide. Exenatide is not recommended in severe renal impairment and caution should be exercised with dose increments in moderate renal impairment (GFR 30–50 ml/min) [56].

## Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

These agents act by inhibiting DPP-4, an enzyme which deactivates the incretin hormone glucagon like peptide-1 (GLP-1) DPP-4 inhibition therefore leads to an increase in endogenous GLP-1 levels [46]. This leads to an increase in insulin secretion, decrease in glucagon secretion, increase in satiety and also decreased gastric emptying time.

Four DPP-4 inhibitors have been approved by the FDA to-date. Linagliptin is not excreted through the kidney and does not need dose modification in CKD patients. Sitagliptin**,** saxagliptin and alogliptin are all excreted through the kidney and do need dose adjustments for use in CKD patients [57].

There are emerging data on the use of these agents in patients with renal dysfunction. Fuji et al. showed that alogliptin in hemodialysis patients reduced $HbA_{1c}$ from 7.1% to 6.3% with no hypoglycemic episodes [58]. McGill et al. showed linagliptin to be efficacious (decrease of $HbA_{1c}$ by 0.76%) with no increase in severe hypoglycemia as compared to placebo (3 each [59] Nowicki et al. demonstrated that saxagliptin had a mean decrease of 0.42% in $HbA_{1c}$ as compared to placebo in patients with renal impairment [60]. Chan et al. compared sitagliptin to placebo in patients with a renal impairment and found a mean difference of −0.4% decrease in $HbA_{1c}$ in the sitagliptin group [61]. Kothny et al. studied vildagliptin in a double blinded clinical study, as compared to placebo, in patients with moderate and severe renal impairment. $HbA_{1c}$ decreased by 0.4% in the moderate and by 0.7% in the severe renal impairment groups respectively. No difference in adverse events was noted [62].

Dipeptidyl peptidase-4 is expressed in various tissues, the highest levels of which are in the kidneys. Studies have shown possible benefit of renal protection by reducing albuminuria with DPP-4 inhibitors in patients with mild to moderate renal impairment. Sitagliptin and vildagliptin reduced kidney injury and albuminuria in rat models of type 1 and type 2 [63].

## Sodium Dependent Glucose Transporter (SGLT)-2 Inhibitors

These agents act by inhibiting the SGLT-2 channels in the proximal tubule of the kidney, thus directly decreasing glucose reabsorption and thereby increasing glycosuria. Non glycemic effects include weight loss and lowering of blood pressure. Side effects include an increased incidence of urinary tract infections and genitourinary candidiasis [46].

## Thiazolidinediones

Thiazolidinediones act by increasing the sensitivity of insulin (reducing peripheral insulin resistance) in the muscle as well as adipose tissue, in addition to effects on the liver (reduced hepatic gluconeogenesis). These agents act as agonists for peroxisome proliferator-activated-receptor-gamma (PPAR-gamma). Commonly recognized medications in this class include pioglitazone and rosiglitazone. They are metabolized in the liver, and no dose adjustment is needed [46].

As known side effects of this class of agents include edema and potential worsened heart failure, these agents must be used with caution. It is also of note that they are not particularly helpful for immediate management of hyperglycemia, as these agents reach steady state after a prolonged time (at least 6 weeks) [46]. Furthermore, at least one study has found that rosiglitazone can increase mortality in patients with DM who are on dialysis [64].

Galle et al. studied the efficacy of pioglitazone versus placebo in hemodialysis patient and found a 35% decrease in the total daily insulin dose, 0.6% reduction in $HbA_{1c}$ with no increased risk of hypoglycemia or volume overload [65].

Thiazolidinediones are activators of PPAR-gamma receptors which favor transformation of pluripotent mesenchymal cells into adipocytes over osteoblasts [66]. Unfortunately there have been no studies on the effect of thiazolidinediones on renal bone disease. It is unknown whether the use of thiazolidinediones would increase the already high risk of fracture. The KDOQI clinical guidelines do advise that this concern needs to be taken into consideration if thiazolidinediones are going to be used [38].

## Amylin Analogs

Amylin is a hormone produced in the beta cells of the pancreas along with insulin; it is co-secreted with it. Pramlintide is a medication which mimics the effects of amylin. Therefore, it stimulates glucose dependent insulin secretion, reduces the secretion of glucagon, increases satiety and increases gastric emptying time [46]. No dose adjustment is needed in patients with an eGFR for 20–50 ml/min [67].

## Dopamine Agonists

Bromocriptine has been approved by the FDA for the treatment of type 2 diabetes mellitus. The mechanism of action is thought to involve resetting changes in the patient's circadian rhythm by CNS effects which result in reduction of insulin resistance. No dosage adjustments according to renal function are needed [46]. Few clinical trials with dopamine agonists in DM are available. Bahar et al. in a recent double blind trial showed that cabergoline, a long acting agonist of dopamine, significantly reduced the $A_{1c}$ level in patients with DM compared to control group [68].

Of note, there is growing body of literature on the role of prolactin in affecting insulin sensitivity and insulin secretion. This is pertinent as CKD patients may have hyperprolactinemia however further studies are needed to delineate the role of prolactin in glucose homeostasis in CKD [69].

### Alpha-Glucosidase Inhibitors

Acarbose and miglitol are alpha-glucosidase inhibitors which are available on the U.S. market. Alpha-glucosidase converts complex polysaccharides into monosaccharides. Inhibition results in carbohydrate malabsorption. Side effects include diarrhea, flatulence, and abdominal discomfort [46].

Alpha-glucosidase inhibitors are poorly absorbed from the gastrointestinal tract (1–2%) and the absorbed fraction is mostly eliminated in the urine. Peak plasma levels of alpha-glucosidase inhibitors in CKD patients were 5 times that of normal volunteers. There are no studies of alpha-glucosidase inhibitors in advanced CKD, and they are not recommended in patient with creatinine clearance of <25 ml/min [70].

### Bile Acid Sequestrants

Colesevelam has been approved by the FDA as an adjunct therapy for type 2 DM. The mechanism of action has not been completely elucidated. It is believed to act through the farnesoid X receptor, fibroblast growth factor-19 and TGR-5 affecting intestinal glucose absorption and hepatic glucose metabolism. Adverse effects include constipation, dyspepsia and hypertriglyceridemia. It is contraindicated in patients with a triglyceride level greater than >500 mg/dl. No specific renal dosing is recommended [71].

Ooi et al. in a Cochrane review noted a 0.5% reduction in $HbA_{1c}$ when colesevelam was used as an add on to diabetic therapy. There is, however, little if any evidence on the use of colesevelam in chronic kidney disease patients to-date [72].

## Insulin Therapy

The most important concept to recall when managing diabetic patients who also have CKD is insulin dose reduction. As GFR declines, the duration of action of insulin becomes prolonged and the pharmacokinetics more unpredictable.

While there is general agreement that patients with CKD need to have a significant reduction in the total daily dose of insulin, the precise amount of that reduction is often based on expert opinion. There are studies which have addressed the amount of dose reduction, sometimes with a particular focus on type of insulin used:

- Rave et al. et al. recommend a decrease in the dose of human regular insulin by 30–40% [73].
- Kulozik et al. describe a reduction in glargine and/or detemir doses of 29.7% and 27.3% in patients with an eGFR of <60 ml/min [74].
- Regarding newer agents, Kiss et al. showed that degludec demonstrated no differences in absorption, or clearance in patients with normal renal function as compared to ESRD patients, an interesting finding which will need to be confirmed as more clinical experience is accrued with this emerging basal insulin [75].

- With regard to rapid-acting insulin analogues, (aspart, lispro and glulisine), Kulozik et al. found that there was no dose reduction needed with the use of aspart insulin in CKD patients, but found a dose reduction was warranted with lispro insulin [74], whereas Rave et al. studied the use of lispro in type 1 diabetes and found no change in pharmacokinetics in patients with mean GFR 90 ml/min vs 54 ml/min [73]

A more quantitative approach to dose adjustment would potentially take into account the degree of renal impairment in order to decide what specific percent dose reduction is warranted. Barnard et al. [76] have made recommendations based on data available to the Glycemic Safety Committee of a (single) academic center (see Table 2).

Regardless of the percent dose reduction selected, the most important technique in the management of insulin for diabetic patients with CKD is to perform daily follow-up of blood glucose trends and subsequent daily dose adjustment. Despite the fact that modern day glucometers tend to have various 'memory' functions, many patients will still greatly benefit from a written "blood glucose log" of data in order to capture the blood glucose trends accurately. This type of attention to detail is required for several key reasons:

- The initial % dose reduction is only an estimate and needs to be refined based on subsequent data.
- The patient's renal function is often not static. There may be significant worsening (or improvement) in the patient's GFR from day-to-day, thus requiring further adjustments in total daily dose even if the initial % dose reduction was appropriate at the time.
- Other variables continue to affect total daily dose. Patients suffering from an illness and acute AKI may have poor renal function combined with poor appetite. As the patient recovers, not only will the GFR change, but the patient's per oral intake is likely to be variable as well, and these factors both need to be accounted for in insulin dosing.
- Written documentation helps prevent clinical inertia. Recent literature has shown that, although one would expect significant adjustments in the diabetes regimens of patients with newly diagnosed CKD, sometimes few adjustments are actually made [77].

**Table 2. Adjustment of inpatient insulin regimen in CKD.**

| Scenario | Adjustment |
|---|---|
| Stable CKD stage 1 and 2 (GFR >40 ml/min) with no hypoglycemia | None |
| CKD stage 3 (GFR 30–39 ml/min) | Decrease *TDD by 30% |
| CKD stage 4 (GFR 15–29 ml/min) | Decrease *TDD by 50% |
| CKD stage 5 (GFR 15–29 ml/min) or ESRD or acute renal injury | Decrease *TDD by 60% |

*TDD* Total daily dose, *GFR* Glomerular filtration rate, *CKD* Chronic kidney disease; [76]

## Management of Type 1 vs type 2 DM patients

As renal function declines, type 2 patients who retain some beta cell function as mentioned before may not need any exogenous insulin. However type 1 diabetic patients need to be given minimal basal insulin to prevent them from going into DKA.

## Treatment of Inpatient Hyperglycemia in Patients with CKD and DM

Safe use of insulin in the inpatient setting continues to be an enormous challenge. Even in diabetic patients without renal failure, there are many factors which complicate insulin dosing in the hospital, including unexpected discontinuation of nutrition, uncoordinated delivery of hospital meals and the timing of insulin injections, changes in level of illness, physical activity, administration of fluids with dextrose, medication effects (particularly short-term bursts of glucocorticoids), and atypical forms of nutrition (including enteral feeds and total parenteral nutrition) [78].

As above, a quantitative approach to dose adjustment can be based on which CKD stage to which the patient's status corresponds (see Table 2).

Among the most recent literature is a 2016 review by Apel and Baldwin on safe management of the hospitalized patient with renal failure [79]. Some of the key points stated by the authors include:

- Patients with GFR < 45 ml/min should aim for a total daily insulin dose no more than 0.25 units/kg/day [80]
- Patients with type 2 diabetes mellitus and ESRD on hemodialysis may only need once-daily morning doses of basal insulin (rather than twice daily basal insulin regimens)
- Patients with type 1 diabetes mellitus and ESRD on hemodialysis (who may still benefit from twice daily basal insulin doses) should have the basal doses significantly reduced
- Although the ADA recommends inpatient glycemic goals of 140-180 mg/dL [81], no specific goals have been recommended for critically ill patients with both DM and ESRD. However Apel et al. recommend a target of 160-200 mg/dL in order to prevent hypoglycemia
- Similarly no specific $HbA_{1c}$ goals exist for patients with type 2 diabetes and ESRD. A conservative recommendation has been to aim for $HbA_{1c}$ less than 8%, and to discontinue any sulfonylurea therapy to prevent hypoglycemia

When possible, inpatients with both diabetes and CKD who need to undergo operative procedures should be managed with an intravenous (IV) insulin infusion in the peri-operative setting, and also in the immediate post-operative setting when logistically feasible. Of note, many hospitals use their own center-specific protocols for the titration of IV insulin [82], but it is important to note that even the use of these protocols may not effectively prevent hypoglycemia in the patient with type 1 diabetes and ESRD as these patients are already quite insulin sensitive even prior to the development of renal dysfunction. No protocol fits every individual patient, and often case-by-case IV insulin dose adjustments will truly be necessary for safety. In the future continuous glucose monitoring (CGM) guided specific IV insulin protocols could be developed which could decrease hypoglycemia risk and improve efficacy as well [83].

## Hemodialysis

Hemodialysis can predispose to both hyperglycemia and hypoglycemia because of its multiple effects on glucose, medication clearance, and insulin dynamics (Fig. 2).

### Insulin Resistance

Insulin resistance increases in ESRD patients. This likely occurs at the level of the muscle; hepatic glucose production is not thought to be increased. The insulin resistance may result from uremic toxins and pro inflammatory mediators [84]. There has been interest in using anti-inflammatory agents (i.e. aspirin, anti TNF-alpha agents) to reduce -associated insulin resistance [85]. Jamaluddin et al. have noted a 9% increase in insulin sensitivity after hemodialysis as compared to before [86].

### Insulin Removal

It has been known that post dialysis insulin levels are lower as compared to pre dialysis insulin levels. Insulin is a small molecule with a molecular weight of 6.2 kDa. Adsorption is the most likely mechanism of removal although the exact mechanism remain to be elucidated. This process is also affected by the dialysis membrane used, with greater effect with a polysulfone membrane and lesser with a polyester-polymer alloy [87].

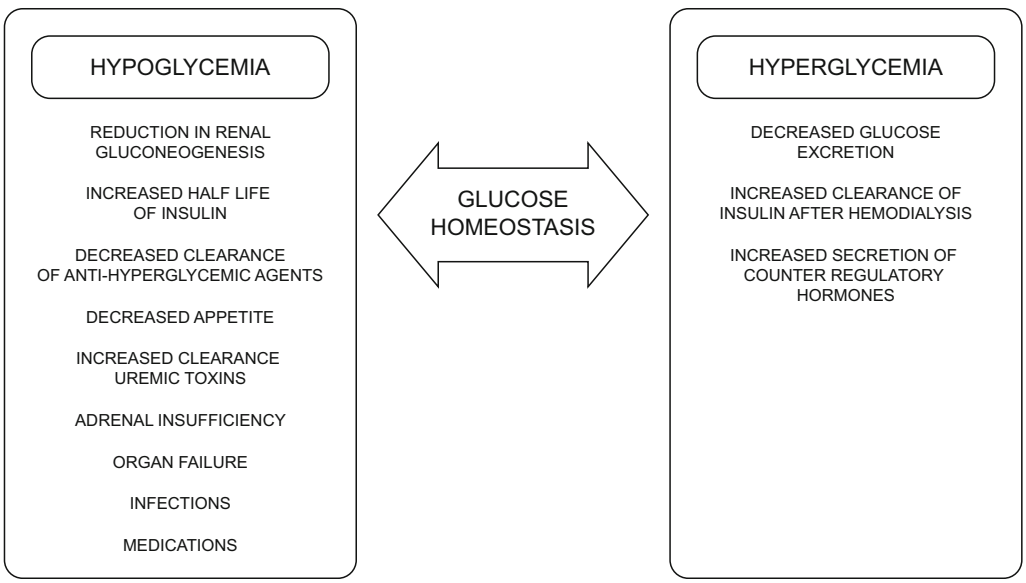


**Fig. 2.** Factors affecting glucose homeostasis in dialysis patients.

## Glucose Dynamics

Glucose levels are affected by the concentration of dextrose in the bath, which determines the diffusion gradient. Using dextrose-free dialysates can result in hypoglycemia in up to 40% of patients [87]. Therefore, most baths contain a dextrose concentration of 100–200 mg/dl to prevent frank hyper or hypoglycemia [88]. Due to changes in the cytoplasmic pH of red blood cells after hemodialysis, there is an increase in anaerobic metabolism and consequent consumption of glucose; these effects together confer a greater risk of hypoglycemia. Recurrent hypoglycemia can diminish the neuro-hormonal responses and cause hypoglycemic unawareness.

It is also of interest that, in anuric patients, the kidney does not have the capacity to excrete glucose which can contribute to hyperglycemia [87].

## Burnt-Out Diabetes

The patient with type 2 DM who develops CKD and then proceeds to develop ESRD requiring dialysis can experience what appears to be "spontaneous resolution of hyperglycemia" and a significant decrease in (or complete discontinuation of) anti-diabetic medications. This phenomenon is known as "burnt-out diabetes".

According to one study which involved 23,618 patients on dialysis, approximately 33% had a $HbA_{1c}$ of less than 6% [89]. Although there was previous enthusiasm for "tight control" in the past, most current endocrinology literature supports "optimal" rather than "tight control" and particularly emphasizes the importance of avoiding hypoglycemia, thus making a $HbA_{1c}$ of less than 6% an inappropriately low target. A U-shaped association between mortality and $HbA_{1c}$ was observed in the US Dialysis Outcomes and Practice Pattern Study. $HbA_{1c}$ less than 6% and greater than 9% were associated with increased mortality [43].

## Peritoneal Dialysis

Peritoneal dialysis (PD) can either be continuous or intermittent. A variety of techniques are employed. Cycling machines can be used to automatically perform overnight exchanges. Modalities such as continuous ambulatory peritoneal dialysis (CAPD) also involves three exchanges during the day. Although solutes are cleared more slowly in peritoneal dialysis as compared to hemodialysis, overall, the weekly removal of solutes turns out to be comparable [90].

Many issues complicate diabetic management in PD including exposure to variable amounts of dextrose in dialysate fluid, potential challenges to accurate monitoring of blood glucose, reduced accuracy of long-term glycemic control markers, and variability in peritoneal membrane kinetics.

Peritoneal dialysis fluids have typically used dextrose as the osmotic agent for ultrafiltration. However, this obviously can contribute to hyperglycemia. As an alternative, peritoneal dialysis solutions using carbohydrate polymers (icodextrin) or amino acids as the osmotic agent have been used.

Paniagua et al. showed in a randomized control trial of 60 patients that icodextrin is useful in preventing and treating hypervolemia, lowers hyperglycemia and also reduces the decline of GFR and preserve residual renal function [91].

Canbakan et al. studied 44 patient on CAPD and compared dextrose-containing peritoneal dialysis solutions with icodextrin. Insulin resistance was calculated using the Homeostasis Model Assessment Method (HOMA). The authors found that 59.25% of the patients in the dextrose group had a HOMA score > 2.5 as compared to 29.41% in the icodextrin group [92].

### "Spurious" Hyperglycemia in PD

Since approximately 2009, increased awareness has been brought to the problem of "spurious" hyperglycemia which can occur secondary to apparent hyperglycemia on point-of-care device measurements, when in fact there was no true hyperglycemia (which could be confirmed when the plasma glucose value was checked). This phenomenon is from interference, by maltose and other oligosaccharides in the icodextrin solution, with glucose assays, when measurements are performed with older meters which use the glucose dehydrogenase (GDH) enzyme of the pyrrolo-quinoline quinone (PQQ) method or glucose-dye-oxidoreductase (GDO). This interference led to apparent hyperglycemia in situations when only point-of-care devices were used (as is often the case) to guide insulin adjustments. This could result in insulin overdose, and after documented adverse events, the U.S. FDA issued a warning and held a conference on the topic. The FDA guidance stated that glucose monitoring devices using GDH-PQQ- or GDO-based methods must not be used in patients receiving icodextrin. The importance of verifying any atypical point-of-care blood glucose results with laboratory plasma glucose measurements was also emphasized to clinicians and staff throughout the country [93].

Of note, emerging literature points to the efficacy of continuous glucose monitors (CGM) in this patient population. Oei et al. showed that CGM could detect previously undetected episodes of hypoglycemia and hyperglycemia in patients on CAPD despite the patients having apparently reasonable $HbA_{1c}$ levels around 7% [94].

### Point of Caution in Transitions

The patient who is transitioning to hemodialysis from peritoneal dialysis must be monitored closely, as there is an increased risk of hypoglycemia secondary to the decreased exposure to dextrose containing peritoneal dialysis fluids. Anti-hyperglycemic therapy should be modified accordingly.

### Insulin Management in Patients with Peritoneal Dialysis

This presents a particular challenge given the variability in duration of peritoneal dialysis sessions (continuous vs intermittent) and the amount of dextrose contained in the dialysate (1.5%, 2.5%,

or 4.25%). Given these challenges, it is once again the case that much of the management plans described in the literature are based on expert opinion.

- Patients with type 1 diabetes may be able to be maintained on some version of the typical SQ twice-daily-basal and three-times-daily-bolus injection regimen, but the two basal doses may not be equal. For example, patients who use cycling machines to perform automatic overnight exchanges will often have a higher basal dose at night and a much lower basal dose in the morning.
- Patients with type 2 diabetes who use cycling machines to perform automatic overnight exchanges may only need a single SQ basal dose of insulin in the evening, and it is possible they may need only low-dose or no prandial insulin during the day.
- Patients with continuous PD may often be managed with an SQ BID NPH regimen [21, 95]
- Patients with PD do have the option of intraperitoneal (instead of SQ) insulin administration, but concern has been raised regarding bacterial contamination or other side effects which challenge its safety [96].

## Hypoglycemia in DM and CKD

Symptomatic hypoglycemia can be divided into two broad categories: neurogenic symptoms, which arise due to activation of the sympathetic nervous system (palpitations, anxiety and tremors) and neuroglycopenic symptoms, which can include fatigue, confusion, seizures, and even loss of consciousness [46]. Hypoglycemic unawareness is a phenomenon in which the patient experiences lack of the neurogenic symptoms; this is significant because without the activation of neurogenic symptoms, it is difficult for the patient to combat worsening hypoglycemia through simple methods such as increased per oral (PO) intake of carbohydrates [97]. Unawareness may be seen in as many as 25% of diabetic patients. Severe hypoglycemia is defined as an event which requires the assistance of another person to administer carbohydrates or glucagon, in order to result in neurological recovery [98].

Hypoglycemia is one of the biggest barriers to achieving good glycemic control in the management of diabetic patients. The ACCORD showed increased mortality in the intensively treated groups, indicating a negative effect of "too tight" glycemic control [99]. CKD is also an independent factor for hypoglycemia, occurring in 1–3% patients [25]. The UK hypoglycemic study group found rates of severe hypoglycemia in patients with type 2 diabetes (who has been on insulin for greater than 2 years) to be as high as 20 episodes per 100 patient years. The corresponding rates for patients with type 1 diabetes was 110 episodes per 100 patient years (<5 years duration of DM) and 320 episodes per 100 patient years (>15 years duration of DM) [100].

Many factors increase the predisposition to hypoglycemia in the CKD patient, including decreased counter-regulatory hormones, reduced renal gluconeogenesis, as well as decreased clearance of insulin (Fig. 2). Patients with type 1 diabetes may lose an effective counter- regulatory hormonal response much sooner than patients with type 2 diabetes. The glucagon response is the first to be lost, followed by the response to catecholamines [101].

Hypoglycemia in CKD could be secondary to the use of diabetic medications or due to non-diabetic related causes such as coexisting adrenal insufficiency, malnutrition, organ failure,

infections, and other medications. Indeed, hypoglycemia secondary to non-diabetic related caused is usually multifactorial. Careful assessment of the diabetic regimen, along with nutritional patterns and referral to a diabetes specialist for management may help mitigate hypoglycemia. Diabetes education is also a key component in helping patients manage their diabetes safely; however patient attendance to a diabetic education program can be a potential challenge [102, 103].

Hypoglycemia should be managed by giving carbohydrates orally or dextrose infusion intravenously when the patient is hospitalized with IV access. Intramuscular glucagon can be used if the patient is unresponsive and intravenous access cannot be obtained. Most hospitals have hypoglycemia protocols written to guide staff in emergent situations [104]. However glucagon may not be effective in malnourished patients with reduced hepatic glycogen stores as can be seen in patients with CKD [46]. Octreotide can be used in cases of sulfonylurea-induced hypoglycemia.

Management consists of judicious use of anti-diabetic medications in this hypoglycemia-prone population of patients. Medication doses should be appropriately adjusted, and agents associated with high risk of hypoglycemia such as the first generation sulfonylureas should be avoided altogether (Table 1). See the insulin therapy and inpatient management sections above for further details (Table 2).

## Conclusion

The combined effects of the two major chronic diseases, CKD and DM, lead to significant morbidity, mortality, as well as a striking economic burden. Patients with both conditions often present some of the most challenging cases for achieving adequate glycemic control. Management needs to be tailored to the specific patient's situation, with attention to the degree of CKD, or in the case of ESRD, the type of renal replacement therapy. Improved guidelines are needed regarding proper use of the new emerging anti-diabetic agent classes, safe targets of glycemic control. Developing new algorithms for titration of both subcutaneous and intravenous insulin titration in diabetic patients with CKD or requiring hemodialysis will further help in safely achieving glycemic targets. Further research is also needed to identify more reliable markers of diabetic control in this patient population. For now, the most salient point in management of these patients is attention to detail, with close follow-up of GFR and daily blood glucose trends.

**Compliance with ethical standards**

**Conflict of interest** Author Lien discloses Consulting relationships with: Eli Lilly, Sanofi, Merck, and Novo-Nordisk and a Royalty relationship with Springer, Inc.

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