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Supplement: A CME CNE Approved Activity

Effective A1C Reduction in Type 2 Diabetes: A Closer Look at Combination Insulin Therapy

This activity is supported by an educational grant from Sanofi US

Effective A1C Reduction in Type 2 Diabetes: A Closer Look at Combination Insulin Therapy

Tom Elasy, MD, MPH

Instructions for CME/CEU: Read the monograph, answer the post test, complete the evaluation form, and send completed post test and evaluation to:

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A score of 70% must be achieved on the post test to receive continuing education credits.

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Learning Objectives:
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2. Review the most appropriate basal insulin and GLP-1 combination therapy taking into consideration the relationship of pharmacokinetics on pharmacodynamics effects on PPG and fixed vs free-dose combinations.
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Faculty Disclosure:
Dr. Elasy has no real or perceived financial relationships to disclose.

Planning Committee Disclosure
Bill Williams, MD has no real or perceived financial relationships to disclose.
Jacquelyn Smith, RN, BSN, MA, CMCN has no real or perceived financial relationships to disclose.
Katie Eads has no real or perceived financial relationships to disclose.
Will Williams has no real or perceived financial relationships to disclose.

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This activity has been approved by the American Board of Managed Care Nursing for 1.0 contact hours toward CMCN re-certification requirements.

This enduring material is valid from September 6, 2016 to December 31, 2018.

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Post Test Questions

1. There is a significant prodome phase before type 2 diabetes diagnosis marked by insulin resistance and high levels of insulin secretion.
   a. True b. False
2. Which of the following is the best explanation for why type 2 diabetes typically requires therapy escalation over time?
   a. Insulin resistance continues to increase in an exponential manner.
   b. Beta cells of the pancreas fail causing deterioration in control.
   c. Insulin secretion declines because of strain caused by medications.
   d. Insulin secretion and resistance both worsen over time in a parallel manner.
3. Per the ADA guidelines, which of the following is the medication of first choice in type 2 diabetes (assuming no contraindications)?
   a. Insulin b. Glyburide c. Alogliptin d. Metformin
4. Which of the following tests is now recommended for determining if a patient with declining kidney function can continue medication?
   a. Serum creatinine
   b. 24 hour urinary creatinine
   c. Estimated glomerular rate
   d. Albumin corrected serum creatinine
5. Which of the following is an inaccurate combination of medication and mechanism of action?
   a. Glipizide, secretion of insulin from beta cells
   b. Sitagliptin, glucose dependent secretion of insulin via GLP-1
   c. Canagliflozin, inhibition of glucose absorption in the kidney
   d. Exenatide, inhibition of glucose absorption in the gut
6. Which of the following is an adverse effect of the SGLT-2 inhibitors for which new warnings were added to package labeling?
   a. Seizures b. Severe pulmonary infections
   c. Ketoacidosis d. Pancreatitis
7. When monotherapy no longer works, addition of a second oral agent generally has an additive effect with a net decline in A1c of:
   a. 0.5 - 0.75% b. 1 - 2% c. 2 - 2.5% d. > 3%
8. When selecting an agent to add to **metformin** which of the following would be the option least likely to result in **hypoglycemia** and **weight gain**?
   a. Insulin b. Glimeperide c. Saxagliptin d. Repaglinide
9. Which of the following is a primary benefit of combining a GLP-1 agonist and long acting basal insulin compared with long acting insulin and short acting meal time insulin?
   a. Lower rates of hypoglycemia and less weight gain
   b. Lower rates of pancreatitis because lower doses of GLP-1 agonist can be used
   c. Larger reductions in hemoglobin A1C
   d. Proven cardiovascular morbidity and mortality benefit
10. A 45 year old female with type 2 diabetes is receiving metformin 1000 mg bid and glyburide 5 mg qd. She has not had any episodes of hypoglycemia or weight gain on combination. Current A1C is 7.5% but had been 7% three months ago. Has history of frequent yeast infections and would prefer not starting an injectable medication. Which of the following is the BEST next step for helping her reach her A1C goal of 7%?
    a. Add SGLT2 inhibitor
    b.Check lifestyle and medication adherence
    c. Refer for weight loss program
    d. Add DPP-IV inhibitor

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TABLE OF CONTENTS

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MANY PATIENTS WITH TYPE 2 DIABETES mellitus (T2DM) have poorly controlled glucose (i.e., hemoglobin A1C above target values). With appropriate combination therapy, they could achieve disease control. The woman described in the accompanying case study and discussed throughout is a typical example.

Why is this woman's diabetes poorly controlled? It is important when looking for the answer to begin by asking the patient what is going on in his or her life. There are likely many reasons for her lack of control. Lack of control in general can be behavioral, biologic, or both. It could be behavioral; her diet and activity are not optimal. Although she says she takes her medications, lack of adherence could be the issue. Stress, both psychological and physiological, may be contributing. Another major reason could be biological; T2DM is a progressive disease. It could be a combination of all these.

The natural history of T2DM is illustrated in Exhibit 1.[1] Note that there is a significant prodromal

Case Study

55-year-old African American woman with an 8-year history of T2DM. She is frustrated by her inability to get her glucose under control – "My sugars have been high for almost a year." Currently, she is treated with metformin 1000 mg twice daily. She also has hypertension and hyperlipidemia.

Social History: research assistant; divorced; three children; one grandchild

ROS: two yeast infections in the last year; wakes up occasionally to use bathroom (this is a change for her)

Dietary History: frequent fast food; no alcohol; carbohydrate intake is inconsistent (e.g., 60-200g at supper; 0-150g at breakfast)

Activity: None

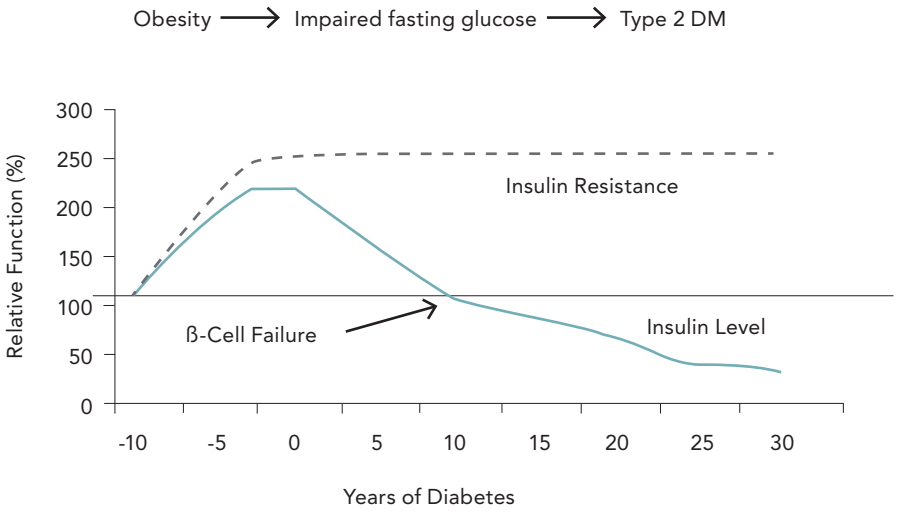
Monitoring: AM only; meter date/time not set; 14 day average = 250 mg/dl; no hypoglycemia

Medication Adherence: "I always take them."

Physical Exam: prominent acanthosis nigricans in axilla indicating insulin resistance

Labs: A1C 9.5%; microalbuminuria; LDL= 135 mg/dl; serum creatinine: 1.3

Exhibit 1: Natural History of Type 2 Diabetes[1]



phase before diagnosis (zero on Y axis). During that time, insulin resistance is increasing, but the body compensates with increasing insulin secretion. When the level of insulin resistance is closely aligned with insulin secretion, only mild elevations in glucose occur. When those two curves separate because of declining insulin secretion, the level of glucose becomes high enough for the individual to meet the criteria for diagnosis of diabetes. There is a distinction between disease diagnosis and disease onset. The disease process of T2DM starts about a decade before glucose control deteriorates to a level where diabetes is diagnosed.

Much of T2DM is related to excess body weight. Up to 70 percent of the U.S. population is either overweight or obese. Not everyone goes from obesity to T2DM, but a significant proportion will.

Exhibit 1 also illustrates the progressive nature of the disease. Left unchecked, glucose control deteriorates primarily because of beta cell dysfunction. Early on in the natural history of diabetes, the pancreas makes a lot of insulin but over time it is just not enough to overcome resistance. For some individuals, the curve of beta cell decline may be even steeper. Overall, there is progressive beta cell decline over time; as a result the gap between resistance and production increases over time. That is the rationale for combination therapy to treat T2DM. Even in the face of good behavioral therapy adherence, most patients will need additional medication as their disease progresses. This graphic also reminds us of two strategies for managing hyperglycemia – decreasing insulin resistance or increasing insulin availability.

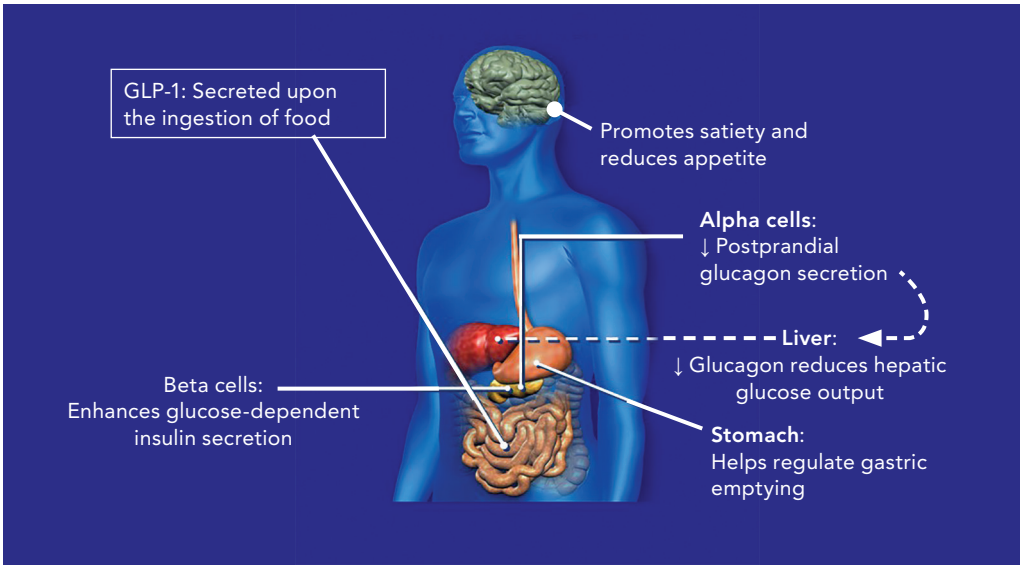
Back to the case study, the patient has had no recent stressors, such as hospitalizations or infections, and no change in diet. She does say she has gained five pounds in the last three years, but this is not an excess amount. She states she is adherent with her medications. The lack of diabetes control is making her sad, but she denies symptoms of depression.

Because patients like to please health care providers, it can be difficult to identify nonadherence. One avenue of questioning which can help patients be more honest is to open the discussion with this combination of phrases – "Many of my patients struggle with taking medications as they would like. Tell me about your struggles with taking your medications." Normalizing the behavior creates a more permissive environment for our patients to be forthright with regard to adherence. Identifying medication nonadherence before making therapy changes is especially important. If a new medication is added but the patient also begins taking the first medication correctly, hypoglycemia can occur.

No obvious reasons for the case study patient's lack of control have been identified. Although she has some areas for behavioral improvement, she likely needs an intensification of her regimen because of disease progression.

According to the American Diabetes Association guidelines, metformin is the medication of first choice unless contraindications exist.[2] There is little or no debate that metformin is the preferred first-line therapy because it is inexpensive, there is extensive data on use, it leads to few cases of hypoglycemia when used alone, and it may lead to minor

Exhibit 2: GLP-1 Modulates Numerous Functions in Humans[5-8]



weight loss. Nausea and vomiting are fairly common adverse effects but can be attenuated by giving the extended-release preparations and slow-dose titrations. Contraindications include renal insufficiency and heart failure (any degree that requires drug therapy). Metformin should be held for 48 hours before a patient receives intravenous contrast dyes. New FDA guidance now recommends using estimated glomerular filtration rates (eGFR) rather than just serum creatinine to decide whether to use or discontinue metformin; it can be used down to eGFRs of 30 ml/min.[3] Conservative use of metformin based solely on serum creatinine has led to many patients being taken off metformin with subsequent loss of glucose control. Long-term use of metformin can lead to B12 deficiency, thus B12 serum levels should be monitored annually.

After metformin, there are numerous choices for addition which have advantages and disadvantages. There is an ongoing trial (Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study) which is looking to determine what is the best second agent to add to metformin. Once the results of this trial are published, we will have more definitive data on the optimal agent to combine with metformin.

Second-line oral agents include secretagogues, insulin sensitizers, and absorption inhibitors. The secretagogues cause insulin to be released from the beta cells and thus require functioning beta cells. They can be divided into long-acting sulfonylureas (glipizide, glyburide and glimeperide), short-acting agents (repaglinide, nateglinide) and dipeptidyl peptidase 4 (DPP- 4) inhibitors. The DPP-4 inhibitors work by inhibiting the enzyme that degrades naturally occurring glucagon-like peptide-1 (GLP-1). They help the patient achieve physiologic GLP-1 levels. The DPP-4 inhibitors lead to a glucose dependent increase in insulin secretion and include sitagliptin (Januvia®), saxagliptin (Onglyza®), linagliptin (Tradjenta®), and alogliptin (Nesina®). Insulin sensitizers work either in the liver (metformin) or muscle and fat (thiazolidinedione, pioglitazone [Actos®], rosiglitazone [Avandia®]). The third mechanism of action for oral agents is inhibiting absorption of glucose either in the gastrointestinal tract with alpha-glucosidase inhibitors (acarbose [Precose®], miglitol [Glyset®]) or in the kidney with sodium-glucose co-transporter 2 (SGLT2) inhibitors (canagliflozin [Invokana®], empagliflozin [Jardiance®], dapagliflozin [Farxiga®]). The alpha-glucosidase inhibitors are not frequently used because of low patient acceptance. The SGLT2 inhibitors reduce glucose reabsorption in the proximal tubules. Postmarketing surveillance has identified two problematic adverse effects of SGLT2 inhibitors - ketoacidosis and life-threatening urinary tract infections – for which warnings have been added to the package labeling.[4]

Injectable therapies include insulins, and GLP-1 agonists are also second line in T2DM. Insulins are generally classified by their duration of action.

Exhibit 3: Pros and Cons of Various Medication Classes

Class	Pros	Cons
Sulfonylureas	• Extensive experience • Inexpensive	• Weight Gain (~ 2 - 4 kg) • Hypoglycemia - most notable with glyburide: ethanol may worsen
DPP-IV	• Well tolerated • No hyperglycemia	• More expensive than others • Less potent (less lowering of A1C)
GLP-1 Argonists	• Little to no excess hypoglycemia • Some weight loss • Good with postprandial glucose excursions	• GI adverse effects • Injectible so there is some training requirement
SGLT2 Inhibitors	• No hypoglycemia or weight gain (some weight loss) • Evidence showing decreased CVD events and mortality in patients with CVD	• Adverse Effects Urinary tract infections Polyuria, volume depletion, hypertension, diziness Ketoacidosis
Insulins	• Nearly universal response with unlimited efficacy • Experience • Precise glucose control	• Hypoglycemia • Weight gain • Injectible thereby requiring training

GLP-1 receptor agonists work by increasing glucose-dependent insulin secretion and other GLP-1 actions. GLP- 1 receptor agonists include exenatide (Byetta®), extended-release exenatide (Bydureon®), liraglutide (Victoza®), albiglutide (Tanzeum®), and dulaglutide (Trulicity®).

The development of incretin agents was as revolutionary to diabetes management as angiotensin converting enzyme inhibitors were to hypertension management. Targeting incretins does provide some great opportunities for glucose control. Incretins are gut hormones that enhance insulin secretion in response to food. This glucose-dependent insulin secretion is promoted by GLP-1, the most well-characterized incretin, which is secreted from L cells of the intestines. When someone eats, GLP-1 secretion is increased, prompting insulin secretion and lowering postprandial blood glucose; this has been called the incretin effect. GLP-1 secretion is diminished in T2DM, thus those patients typically have high postprandial glucose values.

The structure of the GLP-1 molecule looks like glucagon but functionally it has the opposite effect of glucagon. Exhibit 2 illustrates the various effects of GLP-1 secretion.[5-8] Affecting GLP-1 does provide a satiety affect and reduces appetite. This can lead to weight loss which is seen with the GLP-1 agonists but not the DPP-4 inhibitors

The medications that target the incretin system only increase insulin levels when there is glucose added to the body (i.e., after meals). When someone takes a sulfonylurea or insulin, it affects the beta cells and increases insulin levels no matter what. The incretin agent's effect is dependent on having a certain amount of glucose in the system and thus hypoglycemia is not an issue when these agents are used as monotherapy.

Exhibit 3 illustrates some of the pros and cons of the various medication classes. The classes which avoid the problems of hypoglycemia and weight gain are beneficial for patients and clinicians. The DPP-4 inhibitors are easy to use and well tolerated but are less potent than other classes. The GLP-1 agonists are good for managing postprandial glucose excursions and easier to use than mealtime insulin. Although the GLP-1 agonists are injectable, the training required for patients is less than that required for mealtime insulin. Some clinicians, including the author, do not use the SGLT2 inhibitors extensively because of the adverse effects related to excess glucose in urine, especially the urinary tract and yeast infections. A recent randomized controlled trial did show that the use of empagliflozin reduced the incidence of cardiovascular disease (CVD) events and mortality in older patients who already have CVD.[9] Insulins, although they do require significant training for optimal patient use, can be used to achieve very precise glucose control.

The efficacy of oral agents as monotherapy depends on the baseline hemoglobin A1C – the higher the baseline A1C, typically the greater the reduction. On average, oral monotherapy results in a 1 to

2% reduction in A1C. Monotherapy fails in the majority of patients, either initially to achieve an A1C less than 7% or in the long term given the progressive nature of the disease.

Normally, when an individual's glucose control deteriorates because of a lapse in behavioral therapies, glucose control declines over a period of weeks or months. For progressive disease reasons, it takes years for declining control to occur. Even if the patient does great with behavior modifications and medication adherence, glucose will begin to rise over time because of increasing decline in beta cell function. In the UK Prospective Diabetes Study, therapy had to be intensified every four to five years.[10] If clinicians see a new increase in A1C, the patient likely has a problem with medication adherence or other behavioral therapies. Slow increases in A1C are likely due to deterioration of disease. One trial using UK clinical practice research datalink data found significant delays (median 1.6 - 2.9 years) in treatment intensification in people with T2DM despite suboptimal glycemic control.[11] A substantial proportion of people remained in poor glycemic control for several years before intensification.

Remember that whether for biological or behavioral reasons (or both), combination therapy will often be needed and providers need to be comfortable with intensifying therapy. When monotherapy no longer works, the addition of a second oral agent generally has an additive effect with a net additional decline in A1C of 1 to 2%. Additional agents that target the incretin system have appeal mostly owing to less hypoglycemia and weight gain. Addition of insulin, as a second or third agent, is often done by adding long-acting insulins (NPH, glargine, detemir, or degludec) at bedtime. Normal insulin physiology is to have a nearly constant baseline amount of insulin secretion that is augmented by additional secretion in response to food intake. Physiologic basal insulin suppresses glucose production between meals and overnight and accounts for approximately 50 percent of daily needs. The long-acting insulins are used to mimic this basal insulin secretion. Long-acting insulins, added to oral therapy, are effective in reducing A1C by at least an additional 2%.

Insulin therapy should be a two-step process – initiation and intensification. This applies whether it is basal insulin or mealtime therapy with short-acting insulins. Insulin therapy is usually begun with basal insulin at 10 units at bedtime or 0.1 or 0.2 units per kilogram. The dose should be titrated up by 2 units every three to four days as long as fasting glucose is greater than 130mg/dl, but not more than 180 mg/dl. If fasting is 180 mg/dl or greater, the titration can be by 4 units. The dose should be decreased by 4 units or 10 percent (whichever is greater) if hypoglycemia (< 70mg/dl) occurs.

Returning to the case study, the patient was sent for a consultation with the registered dietician with the initial goal of achieving consistency in her dietary intake before moving on to improving the quality of her diet. It is hard to manage insulin if someone has a fluctuating carbohydrate intake. She was started on lantus insulin, with 10 units at bedtime and titrated upward by 2 units every Thursday and Sunday until her fasting level reached 130 mg/dl. Because her starting A1C was almost 10%, she would not have likely gotten to goal A1C on combination of metformin with another oral agent. She was asked to monitor her glucose at least twice daily while titrating. After titration, the intensity of monitoring would be decreased. Because she was now on insulin, she was instructed on the signs and symptoms of hypoglycemia and instructed to buy glucose tablets for management.

Three months later, her A1C was 7.8% on 58 units of basal insulin. She has several fasting values below 90, so the insulin was not increased. She is currently eating 80 to 90 carbohydrate grams at supper and 60 grams at breakfast. The next decision point is where to go with therapy to bring her A1C to goal (7%) without prompting episodes of hypoglycemia.

Typically, in a case like this, clinicians would add mealtime insulin either as a fixed dose or flexible dosing. This is highly effective but requires much more extensive training and, like all insulin additions, has the risk of weight gain and hypoglycemia. Flexible dosing is especially hard for patients to implement because it requires carbohydrate counting.

An emerging option is to add GLP-1 agonists to the basal insulin rather than adding premeal short-acting insulin. Addition of a GLP-1 agonist to basal insulin has shown comparable A1C and fasting glucose lowering to mealtime insulin combined with basal insulin. In trials, the GLP-1/basal group had less hypoglycemia and weight loss compared with weight gain in the meal time/basal group. This is a possible option under the ADA guidelines. A combination product with a fixed dose of a GLP-1 agonist and the long-acting insulin degludec (Tresiba) has been recommended for approval by the FDA.[12]

There are many barriers for insulin use. In addition to patients, physicians and nurses can have misconceptions about insulin. One barrier is fear of injections. The needles used today for injection are very tiny. Showing these to patients and having them practice injections with them will overcome many fears. Most patients will find insulin injections less painful than checking glucose. Education can go

a long way toward reducing barriers to insulin use.

Following the recommended guidelines for patient management takes significant time for primary care providers.[13] It is challenging to manage patients with diabetes. Newer combination therapies (metformin plus numerous agents, insulin/GLP-1 agonists) are simpler to give and intensify; this may help providers with their time challenges.

Conclusion

Achieving and maintaining T2DM glucose control requires attention to both behavioral and biologic reasons. Most patients will require combination therapy to achieve control, and therapy will need to be intensified every few years in order to maintain control. An emerging option is the combination of long-acting insulin and the GLP-1 agonists.

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