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Can we achieve the goal of normoglycemia in type 2 diabetes?

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Blood glucose levels are regulated very tightly in the non diabetic individual. This is the result of a dynamic interaction between glucose absorption, insulin secretion and insulin action. It has now become clear from studies such as the DCCT, Kumamoto and UKPDS that tight glycemic control in patients with diabetes, not only prevents microvascular complications, but also slows the progression. More recently the EDIC trial in type 1 diabetes demonstrated the benefits of early tight glycemic control in slowing the development of micro and macrovascular disease even if control deteriorates later. One of the major messages of the UKPDS was that oral monotherapies fail with time and that combination treatments using two and even three oral drugs will be necessary. It is therefore important to try and treat diabetes with the goal of normalizing the blood sugar values provided the well being and safety of the patient is not threatened. One of the limiting factors in achieving and maintaining normoglycemia, especially in type 1 diabetes and also in type 2 diabetes has been the issue of iatrogenic hypoglycemia.

Based on our current understanding of the pathophysiology of type 2 diabetes, one of the earliest abnormalities is the presence of insulin resistance with compensatory hyperinsulinemia. First phase insulin secretion is lost very early and when beta cell function decreases hyperglycemia develops and over time many patients become relatively insulin deficient. The commonest causes of insulin resistance are visceral obesity, physical inactivity and ageing. Our initial goal of treatment is to reduce the peripheral insulin resistance that is present and to restore physiological insulin secretion and improve insulin action. However for those patients with longer duration disease or more advanced beta cell failure, combination oral therapies including incretin mimetics or insulin therapy will be needed.

Non-pharmacological approaches are used initially to control the glucose. Principles of medical nutrition therapy are best taught by a registered dietitian and must take into account the ethnicity of the patients, current body weight as well as socioeconomic factors. Physical activity is also important and promotes general well being, improves insulin sensitivity and helps in weight control. Failure to obtain adequate control requires drug therapy.

The American Diabetes Association goals for control are:

Biochemical index	Non diabetic	Goal
Preprandial glucose (mg/dL)	< 110	90-130
Postprandial glucose*	< 180	
Hemoglobin A1C (%)	< 6	< 7

* AACE and European Diabetes Association 2 hr goal is < 140 mg/dL

Other goals are:

- Individualized nutrition recommendations and instructions
- Preferably with a registered dietitian familiar with diabetic medical nutrition
- Recommendations for lifestyle changes e.g., exercise, smoking cessation
- Patient and family education for self management with preferably with a certified diabetes educator
- Monitoring instructions for: self blood glucose monitoring (SBGM) with appropriate recording. Urine testing for glucose and ketones where needed
- Annual eye examination

- Annual microalbumin test
- Lipid and blood pressure and weight goals

We now accept that in order to improve the care of these patients we need a team approach, setting appropriate goals and follow up care for early detection and treatment of complications.

Medical nutrition therapy is still the cornerstone in management of type 2 diabetes. Most of our patients are overweight and nutritional instruction is important despite the poor compliance. Those who do adhere to the plan can get not only better glucose control but also loose weight and thereby improve beta cell function and lessen insulin resistance. In the UKPDS, the medical nutrition therapy resulted in a 2% decrease in A1C in the first three months in both the control and intensive therapy groups. A diabetes educator teaches the other skills needed to live with diabetes, e.g. self blood glucose testing. For those patients with no major contraindication, exercising helps glucose control, weight loss and mental well-being. The usual precautions for cardiovascular risk in this high risk group apply. Because we do not achieve our goals with these non-pharmacological interventions in most patients, oral therapy is needed.

The use of oral therapies in type 2 diabetes has dramatically changed in the last 10 years. Many new drugs are available that allow us to restore the glycemic control based on our current understanding of the disease. Each class of drugs addresses a specific abnormality and the goal now is a restoration of the normal physiology and normoglycemia. Furthermore, we now have more options for those who fail a single therapy with combinations of drugs that act synergistically as well as adding incretin mimetic drugs to oral therapies. Insulin still remains the treatment of choice when true beta cell failure occurs or when the ADA goals are not met with the above options.

The major classes of therapy are:

- a. Insulin secretagogues: sulfonylureas, meglitinides
- b. Biguanides
- c. Alpha glucosidase inhibitors
- d. Thiazolidinediones
- e. Incretins
- f. Insulin

The traditional approach to therapy has been to use a monotherapy to reach the ADA A1C goal and when this was used at its maximal efficacy dose and failed to achieve or maintain control a second therapy was added or the patient switched to insulin. It is now clear that the different classes of oral medications each have a specific dose response and going above this effective dose no longer benefits the patient. With the SU and meglitinides this is 50%

of the maximum dose, with metformin it is 2000 mg/day in divided doses and with the alpha glucosidase inhibitors it is usually the tolerated dose, though the therapeutic dose is 100 mg/id. With the thiazolidinediones this will vary with the drug but appears to be the maximum dose, 8 mg/day for rosiglitazone and 45 mg/day for pioglitazone. Apart from their glucose lowering effects the TZDS may also have vascular and beta cell sparing effects that may be important. The traditional paradigm used monotherapy and if this was no longer effective a second drug was added and in some cases even a third drug. The efficacy of three oral medications is however not great in most instances and it adds to the cost and complexity of the treatment. There is more interest now in starting with 2 oral medications, usually and secretagogue and insulin sensitizer. The commonest combination is metformin and a sulfonylurea. There is no consensus on when to initiate initial combination therapy but an A1C of 8% or more can be used as a guide. Combination therapy can increase the risk of hypoglycemia so careful monitoring of blood glucose is needed. The choice of drugs is also based on the blood glucose patterns. Predominantly postprandial hyperglycemia can be treated with either drugs that increase early insulin secretion, like repaglinide or nateglinide or an alpha glucosidase inhibitor that reduces glucose absorption. For mainly fasting hyperglycemia, metformin is a good choice as well as longer acting sulfonylureas or a TZD.

The latest class of medications are the incretins. The physiological incretin is GLIP-1, secreted by the L cells of intestine. It suppresses endogenous glucagon secretion, slows gastric emptying, stimulates insulin secretion with feedback and may promote beta cell growth. The synthetic drug available for clinical use is exenatide. It is based on exendin 4, which is found in the saliva of the Hila monster, a lizard found in Arizona. The current drug is used as an injection either 5 µg or 10 µg doses bid and can be used in combination with sulfonylureas, metformin or combination oral therapies. Recent studies have demonstrated efficacy in patients poorly controlled with either combination of metformin and SU or metformin alone. The average A1C drop with combination oral therapy using 10 µg exenatide bid is about 1%. Because of the effect of suppressing glucagon secretion, postprandial glucose control is greatly improved. Hypoglycemia of mild to moderate severity has been reported, especially with higher doses of SU and the 10 µg dose of exenatide. Nausea is the main adverse effect especially in the first 8 weeks and rarely requires stopping the drug. Starting with the 5 µg dose and gradually increasing to the 10 µg dose helps reduce this. In addition there is a weight loss of up to 2 kg, which is not related to the nausea and may be from the early satiety and reduced food intake associated with the drug.

Pramlitide is also a new treatment for diabetes. It is based on the amylin molecule that is co-secreted with insulin from the beta cell and like the GLIP-1 peptide can suppress glucagon secretion, slow gastric emptying and improve postprandial glucose control. When used in type 1 diabetes it is given before meals together with the rapid insulin in a separate injection. A reduction in insulin dose is recommended and adjustments made based on the post meal glucose levels. It can also be used in type 2 diabetes in patients not controlled on SU and or metformin therapy. It has also been studied in type 2 patients treated with insulin. All these studies show improvement in glycemic control and also weight loss especially in those who are severely obese. This weight loss is most likely from increased satiety and reduced food intake.

It is important to use oral medication according to their effective doses before deciding lack of efficacy. If oral combination therapies are unable to achieve and maintain glycemic goals, then the next option is to use insulin. This can be done as bedtime insulin with an oral therapy during the day or as full insulin therapy with multiple insulin doses. When starting insulin it is best to consider a bedtime dose of intermediate acting NPH or Lente or glargine and titrating the dose based on the results of self-blood glucose testing. Recent studies have highlighted the problems with insulin therapy such as weight gain, hypoglycemia and patient reluctance to undertake intensive multiple injections programs. There may be less problems with in this regard with the newer insulin analogue glargine. In the Treat to Target Study patients with type 2 diabetes not well controlled on oral therapy were given either NPH insulin or insulin glargine at bedtime. Both insulin regimens lowered the mean A1C 1.7% but there was less hypoglycemia with the glargine insulin, especially at night.

Insulin therapy now offers us more options to replace insulin in a physiological manner. The availability of the newer short acting insulin analogues, lispro, aspart and glulisine allows us to use preprandial insulin that closely mimics normal insulin secretion and thus improves postprandial glucose control. The advent of insulin glargine now gives us a true long lasting basal insulin which can be used in combination with oral medication as well as being the basis for basal bolus therapy. The latter approach is the most physiological way to use insulin today and many patients with type 2 diabetes can benefit from this approach if they can meet the requirements for the complexities of the treatment. For those patients who have problems mixing two type of insulin we also have premixed insulin that can be used to good effect even though they are not as flexible as basal bolus therapy. There will also be some patients with type 2 diabetes who will be good candidates for CSII, which offers the best approach

for physiological insulin therapy today. Patients need to be chosen very carefully and the treatment is expensive and requires the necessary support systems for success.

In order to achieve and maintain normoglycemia in patients with type 2 diabetes we may need to rethink our treatment paradigms. It is clear that we need to get control to our goals as early as possible because of the legacy effect of excellent glycemic control. We also need to consider combination therapies much earlier in the treatment plan and also consider insulin use earlier. Our current therapies allow us to restore first phase insulin secretion, reduce glucose absorption and improve postprandial glucose, improve peripheral insulin sensitivity and reduce the increased hepatic glucose output thus controlling fasting glucose. With the incretin mimetic drugs we can now target postprandial glucose control with glucagon suppression as well as benefiting from insulin secretion with feedback. The weight loss associated with these drugs is also important because apart from metformin, none of the other treatments alone or in combination to date have been able to do control the blood sugar and still result in weight loss. In order to succeed we must continue to educate our patients on the importance diet therapy and consistent CHO intake in their meal planning. For patients who will be going on basal bolus therapy, CHO counting is an important skill as well as instruction in insulin sensitivity factors and the effects of exercise and sick days.

Self- blood glucose monitoring is crucial in all patients who are using insulin. For those on intensive therapy both pre meal and postprandial monitoring is required and goals need to be set and treatment adjusted to meet these. For patients on diet therapy or oral medication, SBGM may not be required but is desirable if done appropriately to identify specific issues, e.g. fasting or postprandial hyperglycemia that may then require modification in treatment.

Regular measurements of the A1C will also be important in not only giving our patients a goal for their treatment but it also helps us adjust our therapy. As the A1C comes closer to the goal of 7% there is a greater contribution from postprandial blood sugars, so patients must be encouraged to measure blood sugars 2 hours after meals.

Today we have many more tools that can help us develop strategies to achieve normal blood glucose levels. The goal to achieve normoglycemia in type 2 diabetes is ultimately dependent on the underlying pathophysiology and the predominant abnormality in the specific patient. Until we have better and easy ways to measure beta cell function and insulin resistance in our patients we will use surrogate markers, such as body weight, duration of diabetes and levels of fasting and postprandial glucose to make our choices of treatment. We also need to be aware that one of the problems we need to address and treat is

the increasing risk for hypoglycemia as glucose control comes into the normal range. The recent data on exenatide combination with metformin resulted in improved glycemic control, weight loss and no increase in hypoglycemia. The key in managing these patients is to remember that type 2 diabetes is a moving target and thus requires continued monitoring to assess if the goals are being met and to make adjustments to the treatment as need. We need to use all the treatments we have in an appropriate manner while being constantly aware of the socio-economic status and well being of our patients.

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