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Inhaled Insulin Therapy in Diabetes Mellitus

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Abstract: **Diabetes is a class of diseases characterized by elevated blood sugar in the face of inadequate insulin production or insulin action. The disease affects approximately 23.6 million Americans (8% of the population), and fully one-third of those individuals are unaware that they have the disease. There are two broad categories of diabetes – type 1 (T1DM) and type 2 diabetes (T2DM). Individuals with T1DM are dependent on insulin for survival and rely on subcutaneous administration by injection or continuous infusion. Patients with T2DM may control their disease for a time with lifestyle intervention or oral therapies. However, those who fail these strategies will require insulin to achieve adequate disease control. Delivery of insulin via inhalation is a potential alternative to subcutaneous insulin in the management of diabetes. This review will discuss the rationale for development of pulmonary delivered versions of insulin as well as discuss the role that inhaled insulin may play in improving long-term diabetes care.**

Keywords: **Diabetes, inhaled insulin, disease, blood sugar, Patients.**

1. INTRODUCTION

Therapy with insulin is effective at lowering blood glucose in patients with diabetes, but there is resistance to its use by patients and health care providers because of its need to be injected subcutaneously and because of concern regarding interference with patients' lifestyle, risk of hypoglycemia and weight gain, and perception that people treated with insulin are "sicker" . Consequently, patients with type 1 diabetes may hesitate to embrace multiple-dose injection regimens, while patients with type 2 diabetes may defer initiating insulin therapy, resulting in inadequate glycemic control. Therefore, less invasive options for insulin therapy are desirable.

Inhaled insulin represents a paradigm shift for insulin delivery, as it differs not only in route of administration but also patient eligibility (due to exclusions related to lung disease and smoking) and need for periodic testing for safety. This topic reviews the efficacy, safety, and patient acceptability of inhaled insulin therapy.

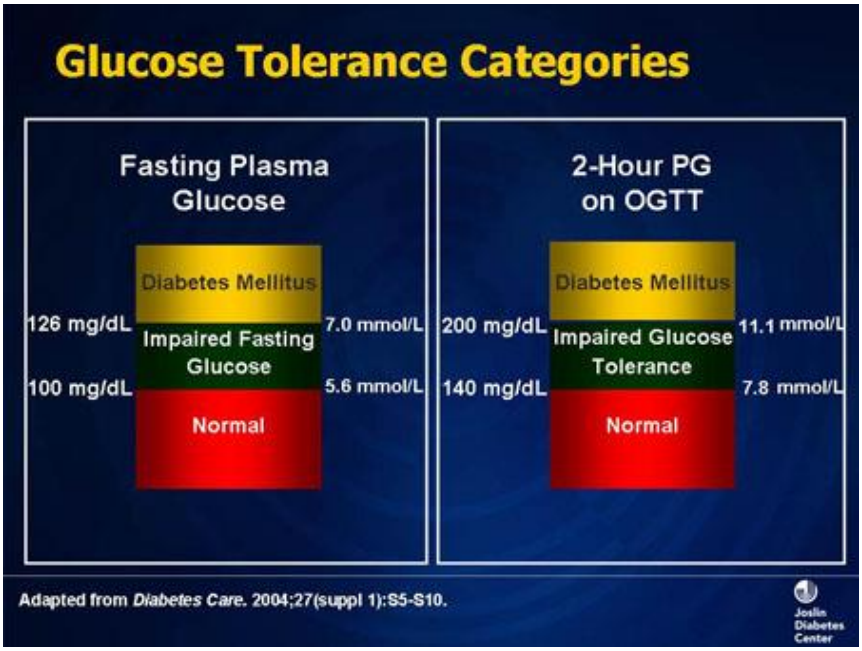
2. INSULIN THERAPY OF DIABETES

Pathophysiology:

We have all heard about the explosion in the prevalence of diabetes; and frequently the term "epidemic" is used in this context. Currently, about 10% of adults in the United States have diabetes; that is, about 20 million people. Nearly a third do not know they have diabetes; that is a lot of people, but it is better than it was about 10 years ago when it was 50%.

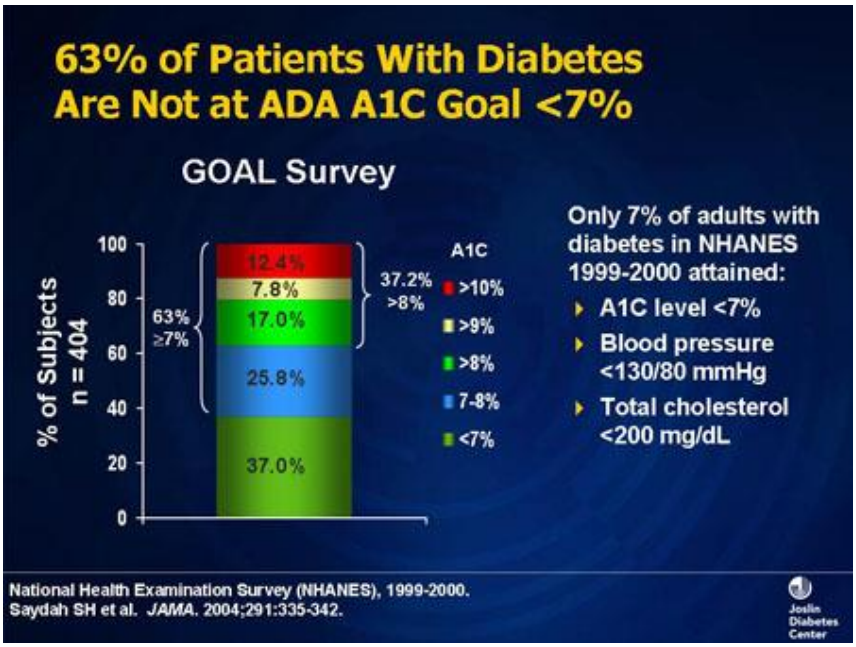
In addition, and perhaps a little bit more alarmingly, is the fact that there are 2 to 3 times that number of people who have what is now called prediabetes; they either have impaired fasting glucose or impaired glucose tolerance. This category is very important because these individuals have a 40-fold likelihood of making the transition from prediabetes to actual type 2 diabetes. Although their vascular risk is not quite as high as in DM2, the increase in macrovascular disease in these individuals is substantial.

In addition, not all of those with prediabetes actually make the move to DM2, so attention is being drawn to this category as a legitimate treatment target. Consequently, about 1 out of every 3 adults in the US has either diabetes or prediabetes, which is a substantial number of people--70 or 80 million.



Slide 1: Glucose Tolerance Categories

When talking about the prediabetic state, make sure you are familiar with these glucose criteria: Normal (normoglycemia) is fasting blood glucose of less than 100 mg/dL, and diabetes is diagnosed at levels of 126 mg/dL or above. Two-hour postprandial glucose of 140 mg/dL or less is normal and a postprandial glucose of 200 mg/dL or over constitutes diabetes. Between these parameters are the categories of either impaired fasting glucose or impaired glucose tolerance. Prediabetes is no longer a descriptive term; it actually applies to a category of individuals who have blood glucose levels that fall within certain clearly defined parameters.

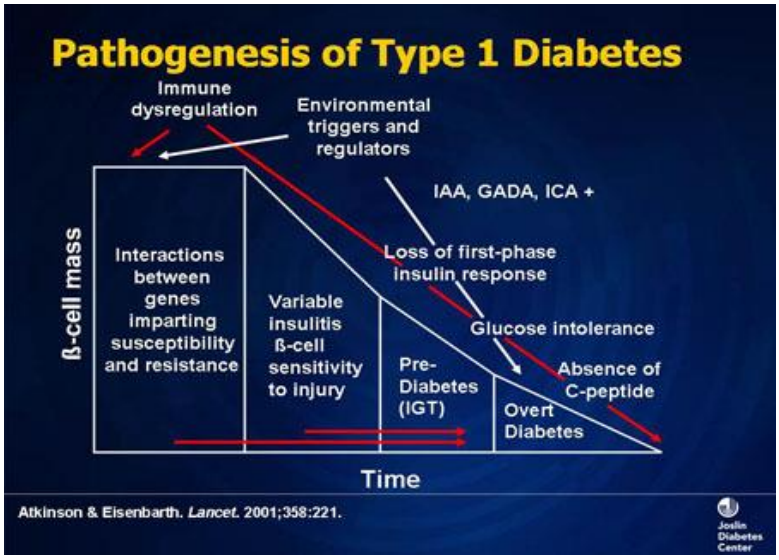


Slide 2: 63% of Patients With Diabetes Are Not at ADA A1C Goal <7%

Given the fact that we know all of this, it is surprising that we have not been able to make better penetration in terms of control of diabetes. This is information from the National Health and Nutrition Examination Survey (NHANES), which is a large, government-sponsored, population-based epidemiologic study that examined many conditions, including diabetes. This study tells us that only 37% of individuals with diabetes in the study population had hemoglobin A1C levels of less than 7%, which means that the other two thirds are above that fairly conservative American Diabetes Association (ADA) goal.

If you include other macrovascular risk factors that we are supposed to be controlling, only about 7% of adults with diabetes have an A1C less than 7%, blood pressure less than 130/80 mm Hg, and total cholesterol less than 5 mmol/L (200 mg/dL). This represents a substantial opportunity for improvement.

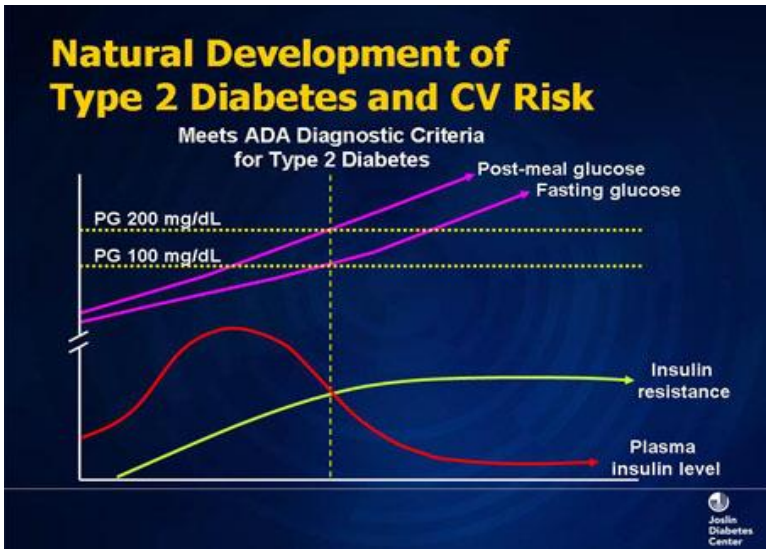
3. PATHOGENESIS AND ETIOLOGY OF TYPE 1 AND 2 DIABETES:



Slide 3: Pathogenesis of Type 1 Diabetes

The vast majority of diabetes is type 2 diabetes, but about 5% to 10% of individuals have type 1 diabetes. This is a complex condition of absolute insulin deficiency focused around immune dysregulation, immune disorders, in which autoantibodies are directed at various surface components of the beta cell, leading to diabetes. We used to think of it as childhood diabetes and as an explosive condition. But we know now, based on our ability to track autoantibodies and various circulating chemical markers, that there is a preamble to type 1 diabetes. Perhaps in the future we will be able to intervene before the beta-cell mass is decreased to the point where there is no insulin being produced.

The hallmark of type 1 diabetes from a clinical point of view is that these individuals cannot make any insulin, and therefore are dependent on external insulin for survival. Of the 95% of people with type 2 diabetes, a substantial number will eventually need insulin therapy to control their blood glucose. However, they are not absolutely insulin-deficient, meaning they do make insulin, in some cases a substantial amount. But it is not enough to overcome their insulin resistance. Although they may require insulin, they are not dependent on insulin for survival; that is a critical differential between the pathogenesis of those two conditions.



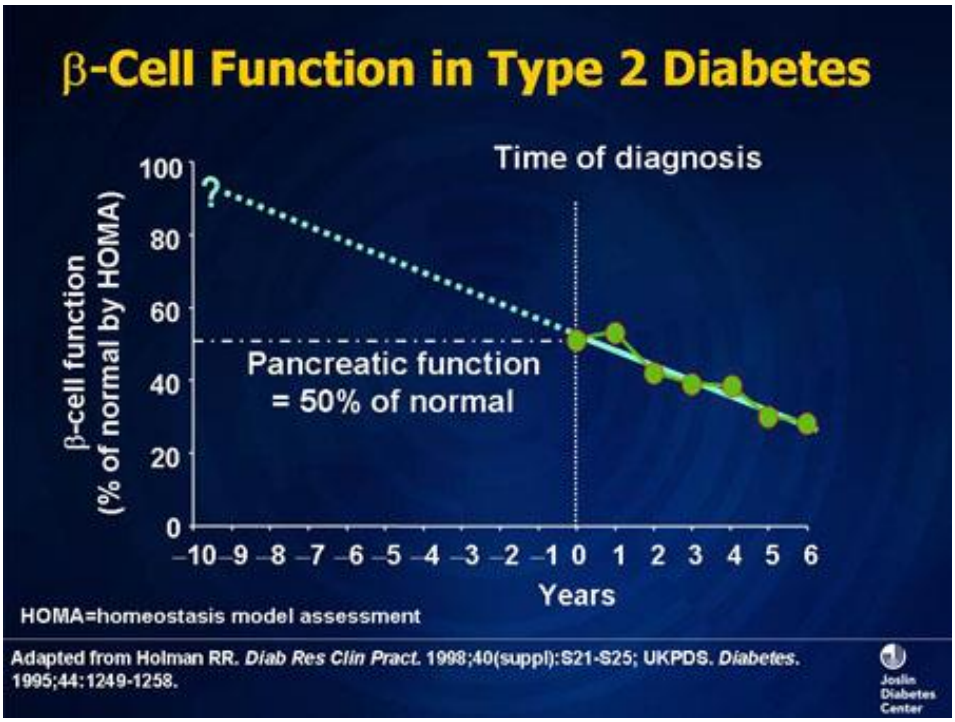
Slide 4: Natural Development of Type 2 Diabetes and CV Risk

In type 2 diabetes, the underpinning of its pathophysiology, insulin resistance, present in almost every individual with type 2 diabetes, starts early. By the time we diagnose diabetes, insulin resistance is essentially at or almost at a peak, and stays at that level for the rest of that patient's life unless we include a strategy in our therapy to reduce insulin resistance.

If you are a person with insulin resistance, meaning you are one of 70 to 80 million people, your response should be to make more insulin, to mount a compensatory hyperinsulinemia. And if you are an individual who has insulin resistance and you can make unlimited amounts of insulin, your blood glucose will remain normal. But if you are in that approximately 25% of insulin-resistant individuals who cannot continue to make insulin in unlimited amounts, your beta cells die, and as they fail, insulin levels will go down, followed by rises in postprandial and then fasting blood glucose. At that point, we will diagnose prediabetes or type 2 diabetes.

You can extract a number of things from diagrams such as this. One is that if you were able to raise the insulin level -- for example, you gave an insulin secretagogue, (e.g., a sulfonylurea) or insulin itself -- you might be able to lower or even normalize the blood glucose, but you still would not have done very much to reduce the insulin resistance. That is important, because the general feeling is that most of the macrovascular risk factors that we see clustered in these individuals are related to the insulin resistance and not necessarily to the hyperglycemia, per se.

Secondly, there is a lot going on before the diagnosis of DM2 is made. Insulin resistance has increased, and parallel to this increase is the development of macrovascular disease, which may start well before a patient is diagnosed with type 2 diabetes. The goal, then, is to intervene in the natural history of these patients much earlier, when their beta-cell mass is more substantial, because it is always easier to prevent things from happening than it is to try to reverse them after they have happened.

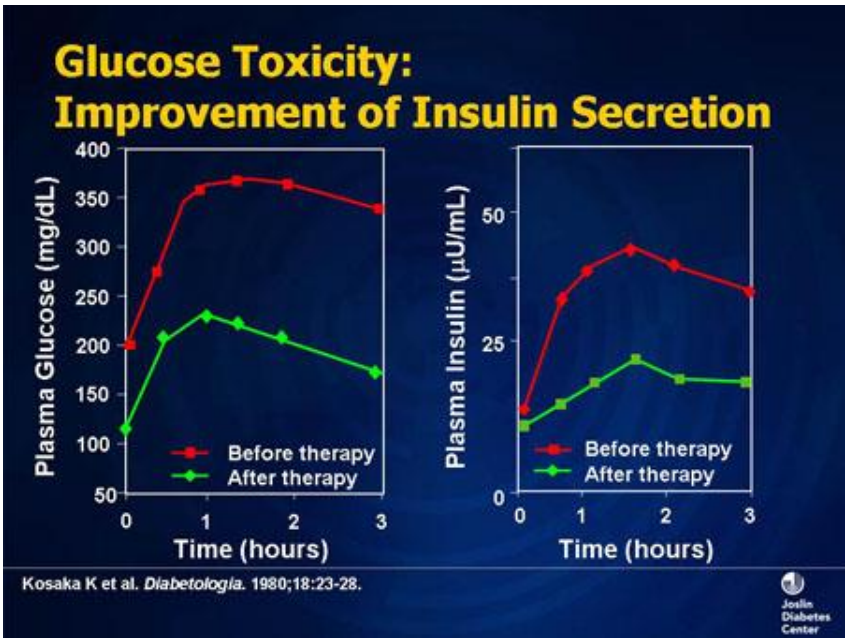


Slide 5: Beta-Cell Function in Type 2 Diabetes

Beta-cell function is the discriminating feature of people with diabetes; it is what determines blood glucose levels, because insulin resistance is at or near maximal by the time we diagnose diabetes. Consequently, the degree of dysglycemia is predominantly related to beta-cell function, and this starts to decline well before we diagnosis type 2 diabetes, possibly as long as 10 years prior to diagnosis. This is another good argument for getting involved earlier in the natural history of this condition.

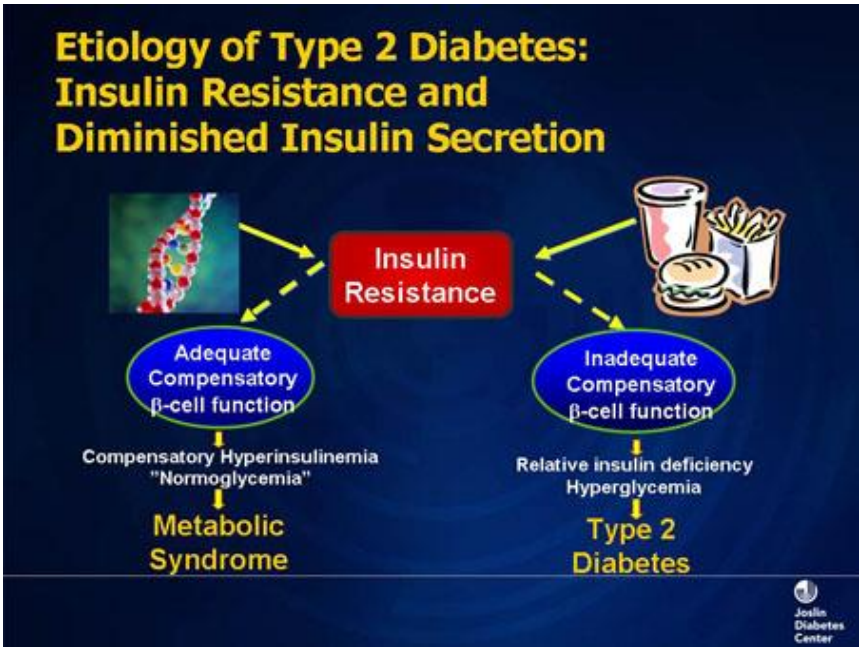
The beta cell, the insulin producer, is subject to a number of factors that can lead to progressive malfunction. Hyperglycemia itself creates glucose toxicity: If blood glucose is high, this elevation in and of itself will impair insulin production and secretion, and also will increase insulin resistance. Conversely, when you lower blood glucose by any means, you may overcome some of the associated glucose toxicity and improve beta-cell function.

There also is a lipotoxicity. Insulin is an antilipolytic hormone; it keeps fatty acids in fat cells. But when you do not produce enough insulin or when there is insulin resistance, there is less insulin action. Free fatty acids, as well as other chemical products, flow from adipose tissue, accumulating in and affecting the function of the beta cell. We are even beginning to think of the beta cell as possibly being an insulin-sensitive tissue; at the very least, it seems to be a victim of the systemic chemical environment that accompanies insulin resistance. Therefore, strategies that lower insulin resistance may also improve beta-cell function. This is a very complex set of events, but it also presents multiple treatment targets as well.



Slide 6: Glucose Toxicity: Improvement of Insulin Secretion

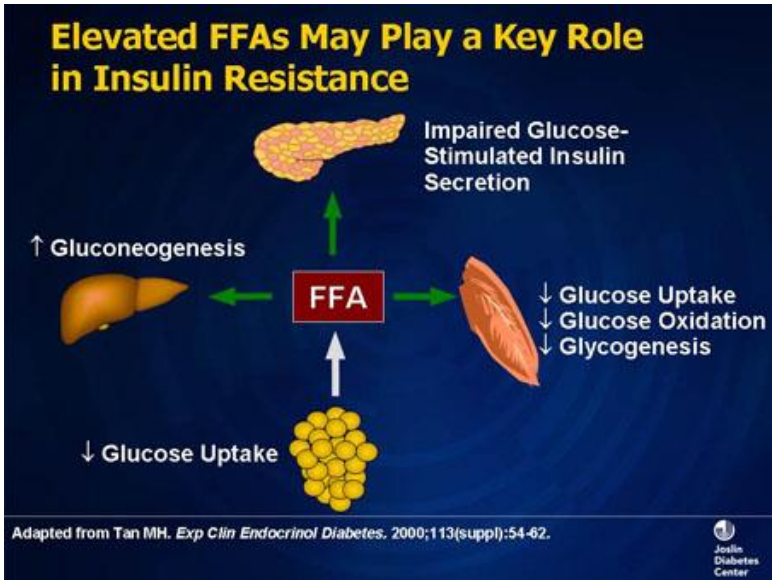
These data demonstrate glucose toxicity. If one tracks plasma glucose and plasma insulin, if you lower blood glucose (for example by giving insulin), you can improve insulin release. For example, if you have a patient who presents with a blood glucose level of 20-30 mmol/L (400 or 500 mg/dL), and you give that patient insulin at the beginning of their therapy and lower his or her blood glucose to normal, you may actually improve insulin production. Therefore, in some patients, the early administration of insulin may prevent the use of more complex regimens, or insulin altogether, at a later time.



Slide 7: Etiology of Type 2 Diabetes

4. INSULIN RESISTANCE AND DIMINISHED INSULIN SECRETION

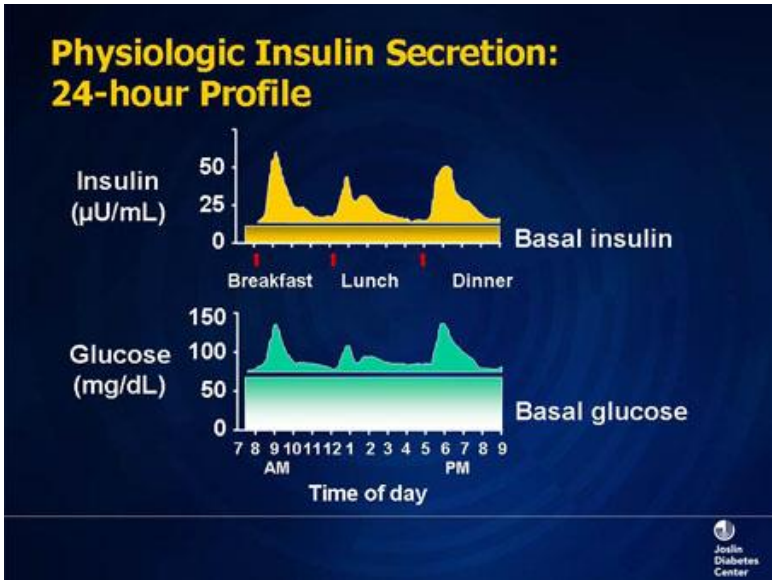
Insulin resistance occurs partially because of genetic predisposition (represented by double helix icon). Additionally, there are lifestyle issues -- eating too much, weighing too much, and not getting enough exercise -- represented by the fast food burger and fries. In that situation, if you can produce unlimited amounts of insulin, blood glucose will remain normal, but you may still have the metabolic syndrome, a cluster of risk factors related to insulin resistance. If you are in the 25% of people who cannot make enough insulin, your blood glucose will go up and you will be somebody with type 2 diabetes as part of your metabolic syndrome.



Slide 8: Elevated FFAs May Play a Key Role in Insulin Resistance

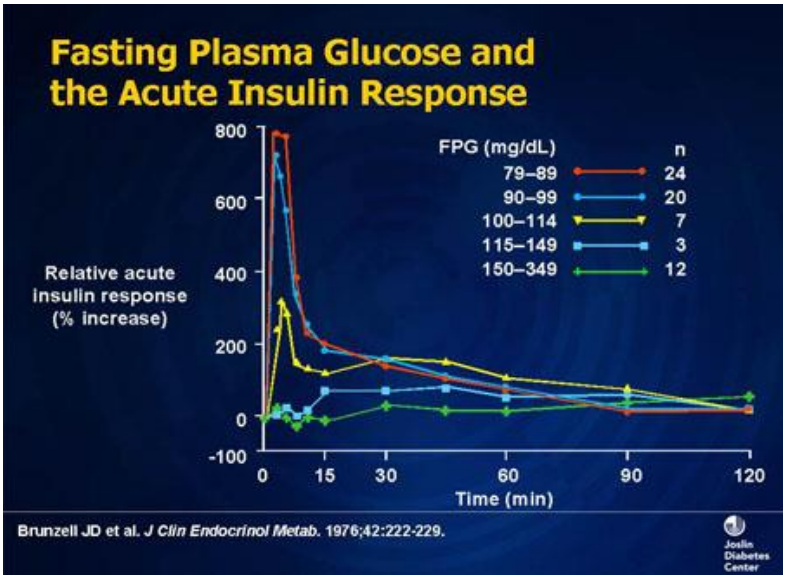
When released from adipose tissue, they end up in a number of tissues critical to the insulin resistant and dysglycemic state. In the liver, the net effect is to antagonize insulin action. We see less glucose staying in the liver and more gluconeogenesis and glycogenolysis, contributing to both fasting and postprandial hyperglycemia. But a large contribution to hyperglycemia comes from free fatty acids being deposited in muscle, since over 80% of glucose is taken up in muscle tissue. Free fatty acids can end up in the beta cell as well, where again there are structural and functional impairments of insulin synthesis and insulin release due to the lipotoxic part of beta-cell dysfunction.

5. INSULIN PHYSIOLOGY: NORMAL AND DIABETIC STATES



Slide 9: Physiologic Insulin Secretion: 24-hour Profile

The objective of insulin therapy is to recreate normal physiology. In the basal fasting state, blood glucose stays fairly constant. The level of insulin is low, but a basal amount is always present. Superimposed on the basal level will be bursts or spikes (sometimes referred to as a bolus) of insulin being released periodically into the circulatory system, to assimilate the carbohydrates that we have ingested. This concept of basal and bolus insulin as found in normal physiology is the platform upon which our insulin strategies are based.

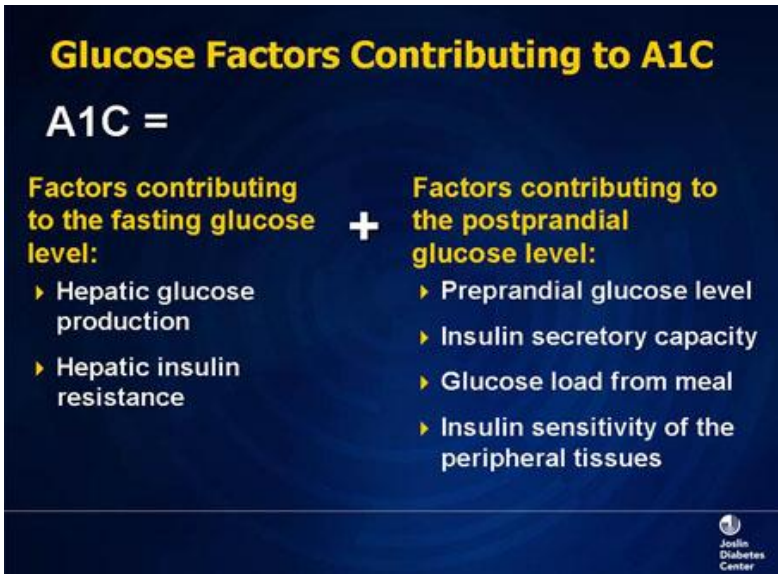


Slide 10: Fasting Plasma Glucose and the Acute Insulin Response

When people develop diabetes, they always produce insufficient amounts of insulin relative to the level of blood glucose and insulin resistance that exists. Type 1 diabetes patients have no insulin at all and type 2 diabetes patients have some insulin, but less than they need to keep their blood glucose levels normal. Shown here on the y-axis is insulin response as a percentage increase from baseline for groups of patients who have varying degrees of impaired glucose tolerance and a varying severity of diabetes.

What you see is more than an overall decrease in insulin production. The first thing to disappear is the "first-phase" or acute insulin response, during which nondiabetic individuals may have as much as an 8-fold increase in insulin production over the basal level. By the time you reach a fasting blood glucose in the highest range, there is practically no acute insulin response. When we construct insulin therapies, short-acting insulins best mimic this phase of insulin release.

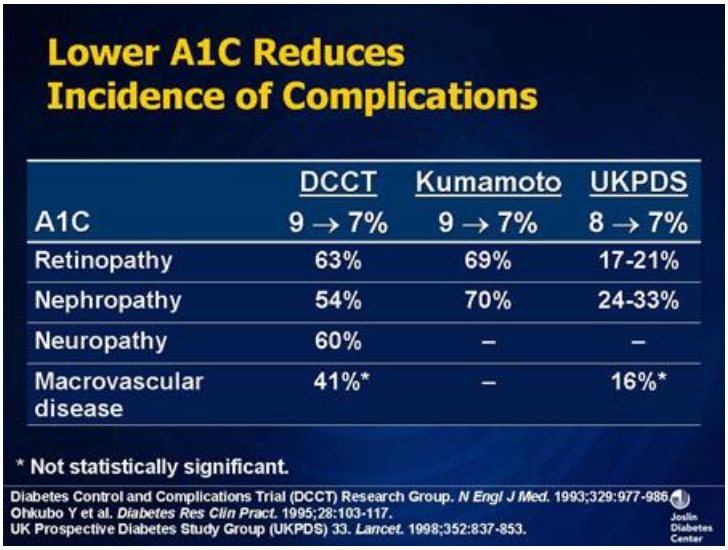
6. UNDERSTANDING A1C



Slide 11: Glucose Factors Contributing to A1C

Hemoglobin A1C, which is the surrogate for mean integrated average blood glucose over a period of roughly 8 to 12 weeks, may represent many factors. Glucose is released by the liver to prevent hypoglycemia when not eating overnight. When there is decreased insulin activity, this process is dysregulated and you release too much blood glucose.

We also have a number of factors that not only contribute to fasting glucose, but also contribute to postprandial glucose, including insulin secretory capacity, how much glucose is ingested, and the sensitivity of the tissues to insulin. It is, then, a complex set of factors and regulators that contribute to the overall glycemic burden.



Slide 12: Lower A1C Reduces Incidence of Complications

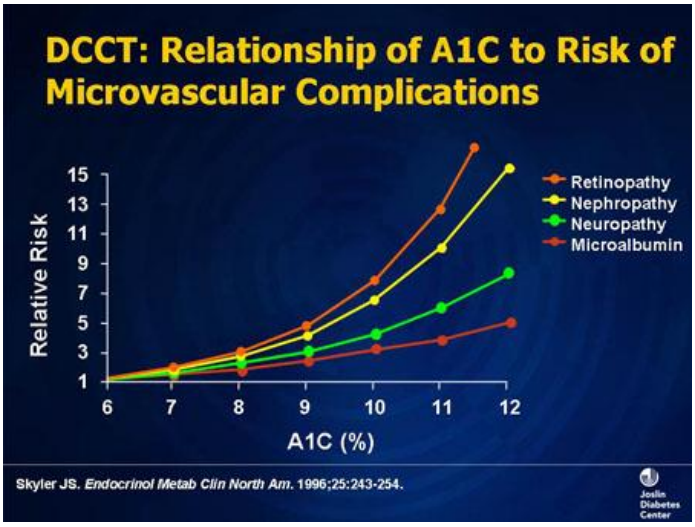
We know that lowering A1C reduces complications. This is particularly true for microvascular complications, such as retinopathy or nephropathy, but also true, to perhaps a less robust degree, for macrovascular disease.

A number of studies have demonstrated this protection. The sentinel study for type 1 diabetes is the Diabetes Control and Complications Trial (DCCT), which included type 1 patients who were getting either conventional insulin therapy or an intensified insulin regimen of multiple doses per day, with A1C targets that were more aggressive.

In that study there were substantial reductions in all of the vascular parameters that were followed.

This same intensive insulin strategy was applied to type 2 patients in the Kumamoto study, and similar results were seen.

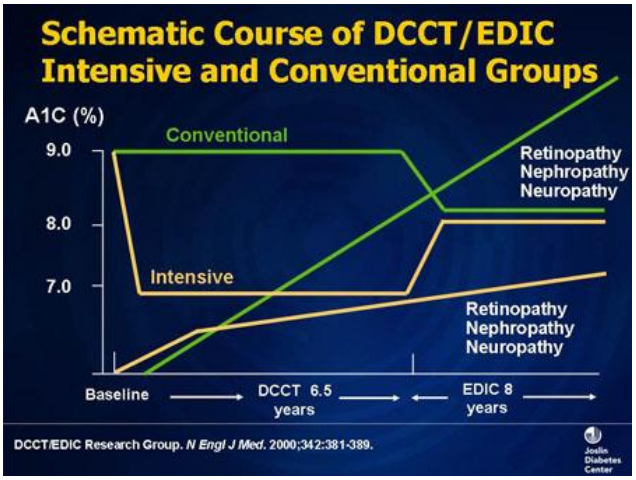
In another study of type 2 patients receiving not only insulin but also metformin (the United Kingdom Prospective Diabetes Study or UKPDS), diet and exercise, or a sulfonylurea, the same principle was reinforced; lowering A1C reduces the incidence of complications. To whatever degree that you can reduce A1C, whether it is 1% or 2%, or taking a patient from 10% to 9%, or 9% to 8%, you will convey a protective effect to their tissues.



Slide 13: DCCT: Relationship of A1C to Risk of Microvascular Complications

This is another analysis of data from the DCCT, which examines individual complications: retinopathy, nephropathy, neuropathy, and microalbuminuria. All of these would be considered microvascular complications, which are very tightly linked to blood glucose. Macrovascular disease is more complex because we have many other risk factors such as lipids and hypertension that are contributing to the macrovascular disease.

As shown, no matter what the complication, there is a significant relationship between A1C and the relative risk of developing that complication. The higher the A1C, the more the complications or, conversely, the lower the A1C, the less the complications.

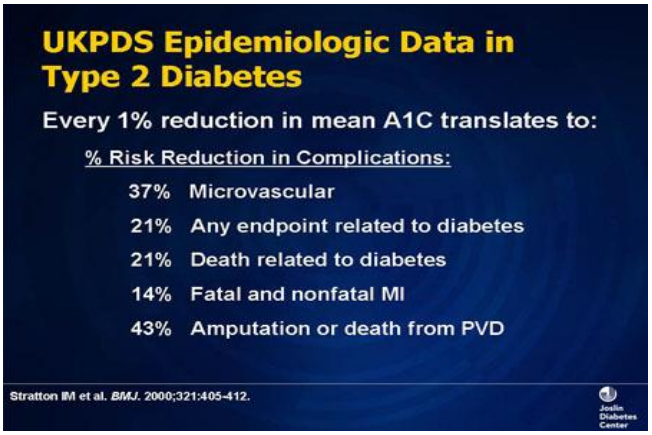


Slide 14: Schematic Course of DCCT/EDIC: Intensive and Conventional Groups

The DCCT investigators did something that was interesting. The original trial duration was 7 years. Patients were either given a conventional type of insulin regimen, perhaps 2 shots per day, or an intensive regimen where patients might get multiple subcutaneous injections and received very intensive management with a high ratio of healthcare personnel to patients. This intensive group had lower A1Cs during the study period.

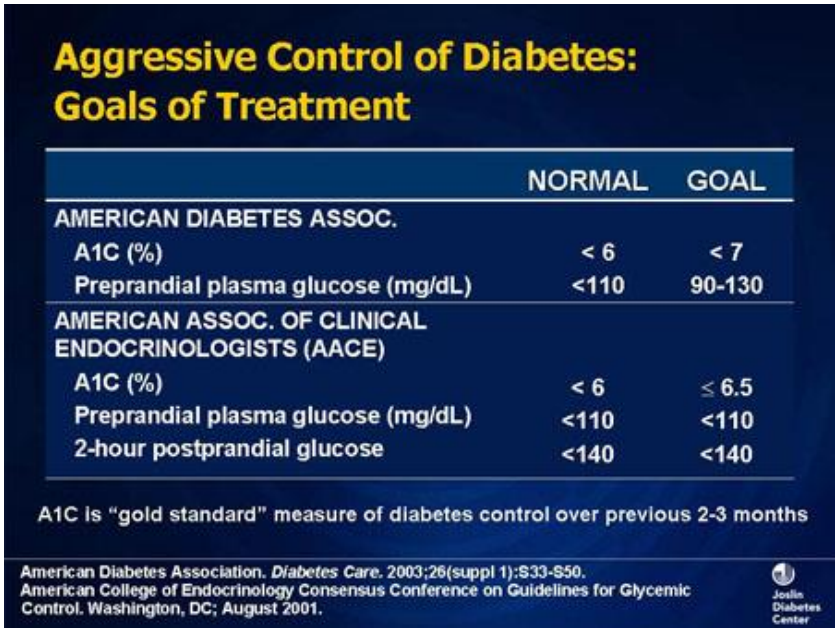
After these DCCT results were published, the investigators followed patients for another several years. Not surprisingly, when the intensity of management was relaxed, A1Cs rose. In addition, during this period of time, the notion of being more aggressive about insulin therapy took hold in the medical community, and those patients who had initially received "conventional" therapy were actually getting a little bit better therapy than previously, and the two groups met in the middle in terms of A1Cs.

The investigators also tracked complications during this extended observation period. Patients who received conventional therapy at the beginning had a progressive increase in microvascular complications, whereas patients who had the initial intensive care were able to maintain their advantage in terms of reduced rates of retinopathy, nephropathy, and neuropathy. Note that the rate of complications between groups is not parallel; complications increased as A1C went up, but not as much in the intensive therapy group during this extended period of time, as in the conventional therapy group. So it appeared that there was some memory from the period of intensive control. These same trends were also shown for macrovascular disease.



Slide 15: UKPDS Epidemiologic Data in Type 2 Diabetes

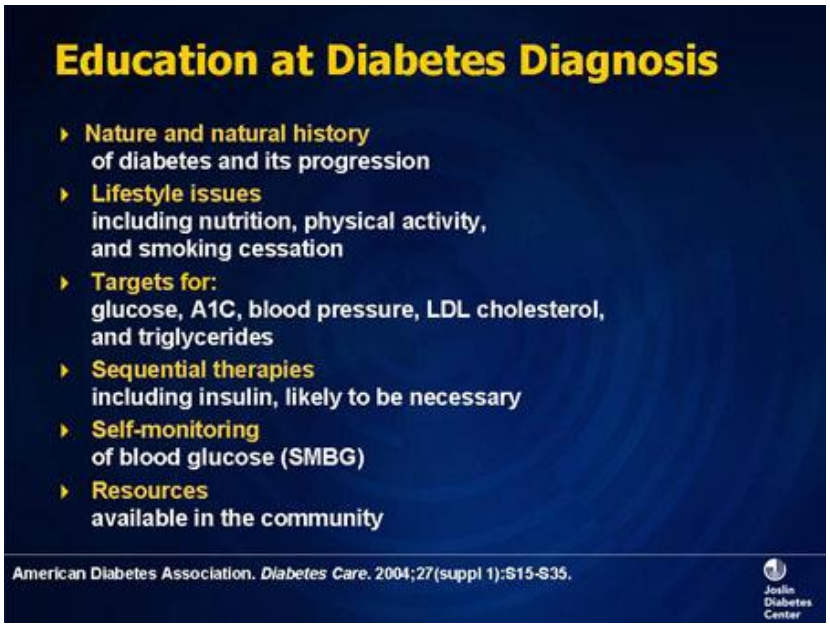
Data from the UKPDS for type 2 diabetes showed that a 1% reduction in mean A1C could result in the substantial percentage reduction shown for all of these various complication endpoints.



Slide 16: Aggressive Control of Diabetes: Goals of Treatment

There is no single agreed-upon A1C target, but most people would agree that the goal is to get A1C to normal without exposing the patient to undue risks of hypoglycemia. Organizational goals are always consensus statements; for the ADA, the A1C goal is less than 7% and for the American College of Endocrinology, it is less than/equal to 6.5%. But both groups acknowledge the fact that if you can get patients to normal, you should do so.

7. PATIENT EDUCATION AND MONITORING

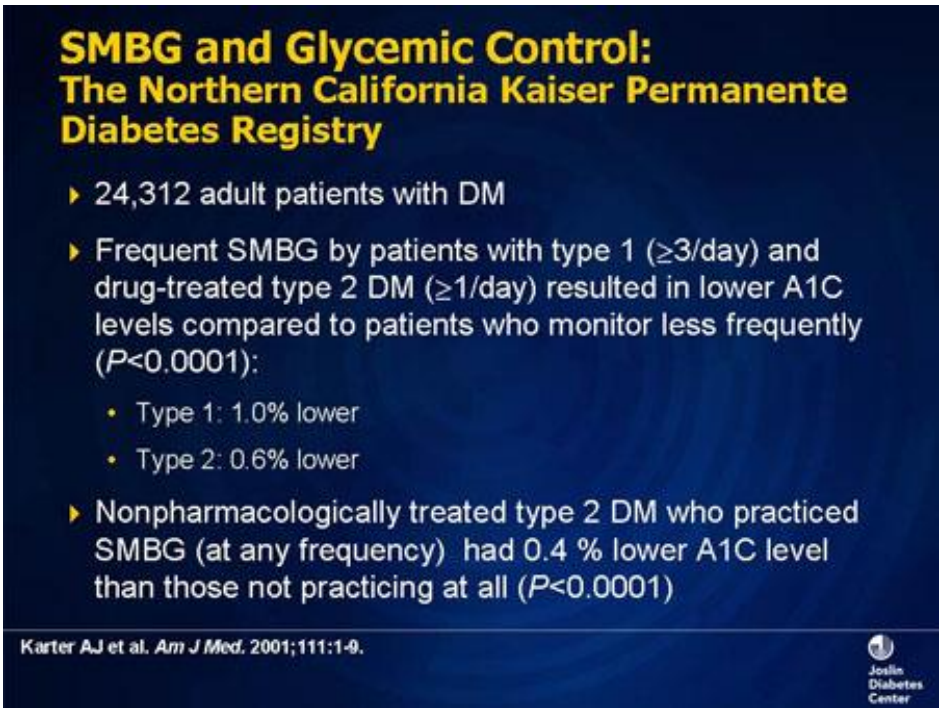


Slide 17: Education at Diabetes Diagnosis

We have a lot of therapeutic tools to offer patients. We have education. The role of Certified Diabetes Educators is inestimably important in terms of the breadth and depth of education they give in a number of areas, not only in disease education but education regarding various therapeutic modalities, explaining the nature of these therapies and getting patients involved in self-monitoring. Educators are able to devote the time and the skills necessary in terms of teaching patients about their diabetes

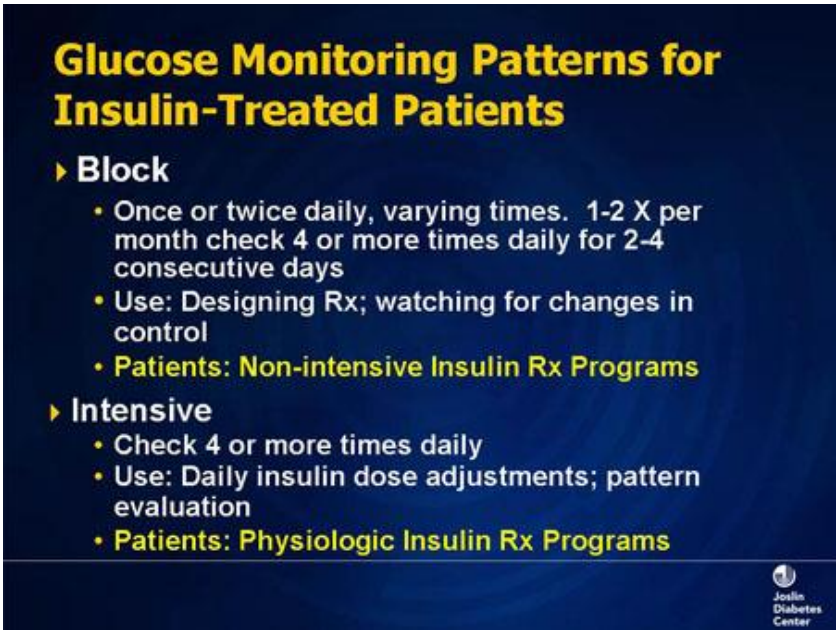
Slide 18: Principles of Medical Nutrition Therapy

Medical nutrition therapy forms a large part of this education, and there are a number of goals. Weight loss does not have to be overwhelming to reduce hyperglycemia or other macrovascular risk factors. A reduction of about 5% to 10% of body weight has substantial metabolic benefits. Patients are not always happy with a 5% weight loss; their goals are sometimes more cosmetic or social. But metabolically, even that amount of weight loss will be very beneficial.



Slide 19: SMBG and Glycemic Control: The Northern California Kaiser Permanente Diabetes Registry

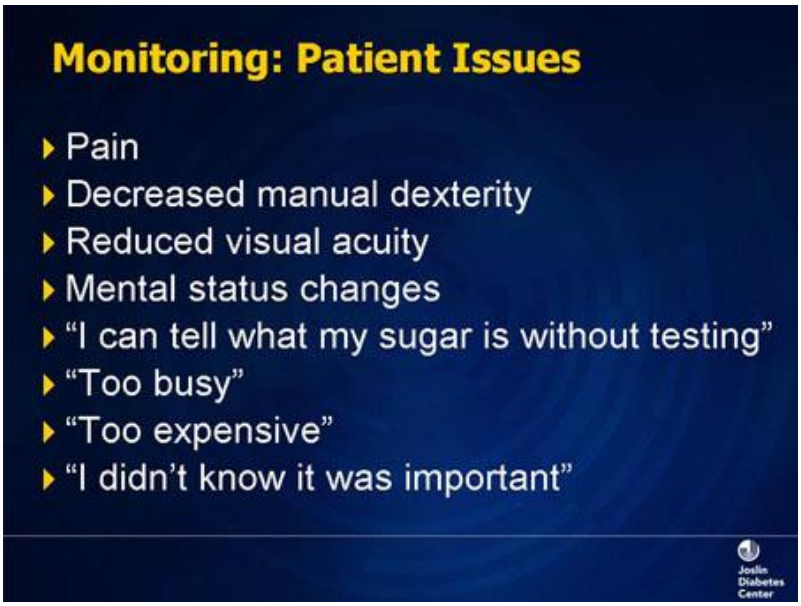
Self-monitoring of blood glucose is equally important. Not many studies have looked at this, but this was a very good study from Kaiser Permanente Health System of roughly 24,000 patients. Patients who monitored blood glucose at home had better A1Cs; in type 1 patients, it was about 1% lower and in type 2 patients, it was about 0.6% lower. Individuals who practiced self-monitoring of blood glucose with any frequency had some statistically significant lowering of A1C. Working with patients to impart the meaning of their blood glucose can make this is a very useful technique.



Slide 20: Glucose Monitoring Patterns for Insulin-Treated Patients

There are many different patterns for testing blood glucose. Patients can do "block testing" once or twice daily. If they do it once daily, sometimes we will tell them to do fasting glucose one day and postprandial the next day. Or we may rotate postprandial blood glucose in combination with fasting; a patient will be testing fasting glucose one day, 2 hours after breakfast the next day, 2 hours after lunch on the next day; and 2 hours after dinner on the next. Over a period of time you can develop a grid that yields good information while testing only once a day.

There are more intensive ways of approaching this, such as having patients check their blood glucose 4 or more times daily. This can be used to determine patterns that will help adjust patient insulin programs.

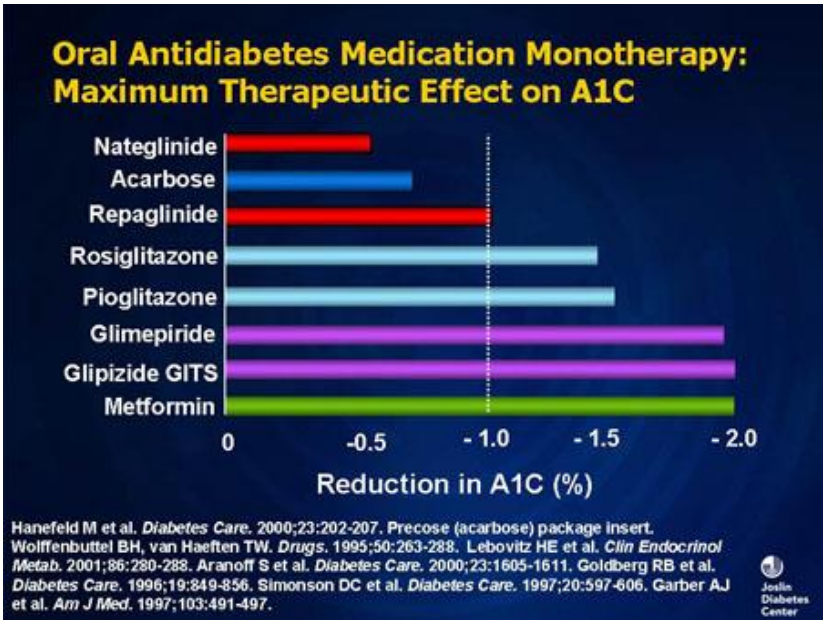


Slide 21: Monitoring: Patient Issues

There are issues with self-monitoring. It causes pain in some patients more than others. Some patients do not have the manual or visual skills to be able to accomplish self-monitoring. There may be issues with cognitive function. We have to work with those patients, and the educators do a great job. There are also a number of different meters, which tend to work better for one type of patient than the other.

Then we have the excuses that patients give us as to why they do not want to do testing, which do not have anything to do with physical issues. But they are, nonetheless, real-life issues, particularly the expense.

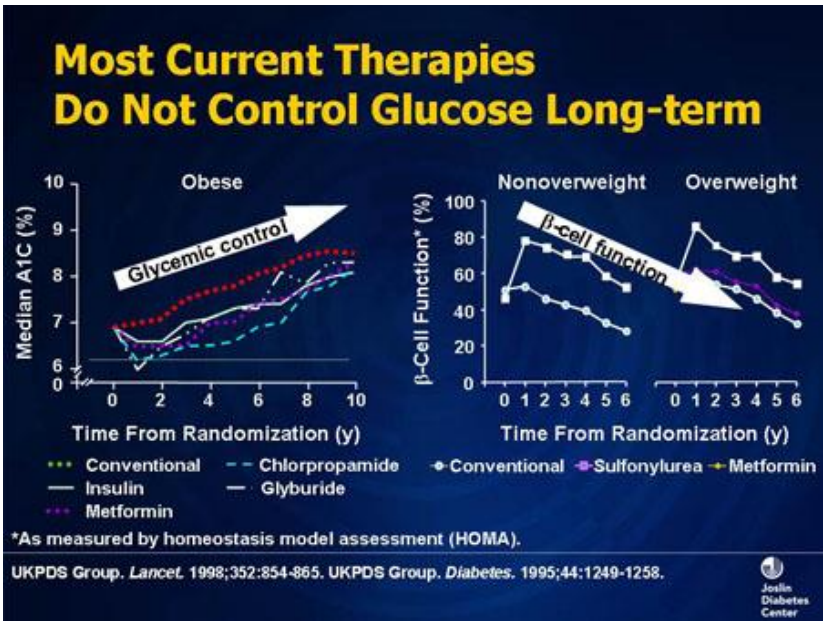
8. ORAL AGENTS FOR DIABETES TREATMENT



Slide 22: Oral Antidiabetes Medication Monotherapy:

9. MAXIMUM THERAPEUTIC EFFECT ON A1C

In terms of oral therapy, we have a number of tools. The medications we tend to use the most are the ones capable of conveying a 1% to 2% reduction in A1C, either as monotherapies or as add-on therapies. Remember that the degree of reduction in A1C is going to be conditioned by the A1C at which the patient starts treatment; the lower the A1C at baseline, the smaller the decrease in A1C that is likely to occur with the addition of a therapy. All of these medications are good as monotherapies or in combination, with the obvious exception of using 2 insulin secretagogues together or 2 thiazolidinediones (TZDs) together. But each class of drugs is effective as a mono- or combination therapy.



Slide 23: Most Current Therapies Do Not Control Glucose Long-term

During the early years of the UKPDS, all study arms were effective in lowering A1C, whether insulin, metformin, or a sulfonylurea was the treatment modality. But as time went on, there was a decline in glycemic control. Not surprisingly, this was associated with a decrease in beta-cell function. The implication is that most patients end up using combination therapy, similar to the way in which hypertension and dyslipidemia are treated.

Numerically, the rise in A1C was about 0.2% to 0.3% per year despite being on a given monotherapy, and is much the same whether the result of diet failure, sulfonylurea failure, or metformin failure. All treatment groups experienced failure at more or less the same rate, and the decline in beta-cell function was also approximately the same for all of them. As such, combination therapy is routinely needed.

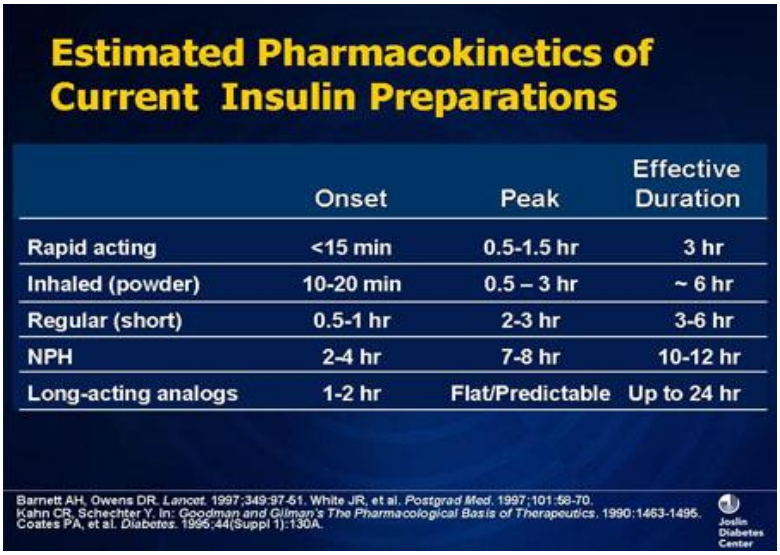
In addition, if your patient has been on combination therapy (2 agents) that is inadequate, you could add a third oral agent, exenatide or insulin. A number of insulins are available: long-acting basal insulin; premixed insulin (70/30, 75/25); and prandial insulin coverage, the latter being short- or extremely short-acting insulins that target postprandial blood glucose.

10. INSULIN THERAPY FOR DIABETES

Slide 24: Insulin Therapy of Type 2 Diabetes

Insulin therapy is not the course of last resort. Many patients view it as the end of the road for their diabetes. Of course it is not that, it is just a tool for controlling blood glucose. But many patients have heard that their parents or their grandparents got insulin just before they died, their kidneys failed, or they had an amputation. Insulin is an appropriate therapy for any patients who have not reached targets by other means.

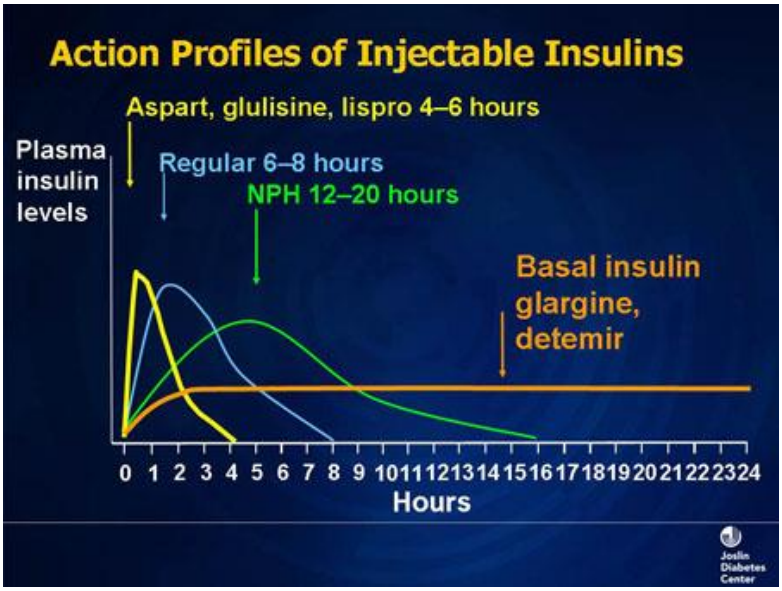
I used to think that people did not like the idea of injections. But then I realized that injecting insulin is not as uncomfortable as self-glucose monitoring. Exenatide, which is an injectable administered twice a day, comes with the promise of weight loss, and suddenly it becomes very acceptable. Although there are occasional patients who are truly phobic, the fear of injections is not as widespread as we once thought it was.



Slide 25: Estimated Pharmacokinetics of Current Insulin Preparations

What types of insulin are available? There are rapid-acting insulins that begin to work in about 15 minutes, and peak somewhere between 1 and 2 hours. Examples of such rapidly acting insulins are insulin lispro, insulin as part, or insulin glulisine. These are very appealing insulin choices because they have a quick onset of action, and their peak action tends to coincide with the time that postprandial glucose levels are at their peak.

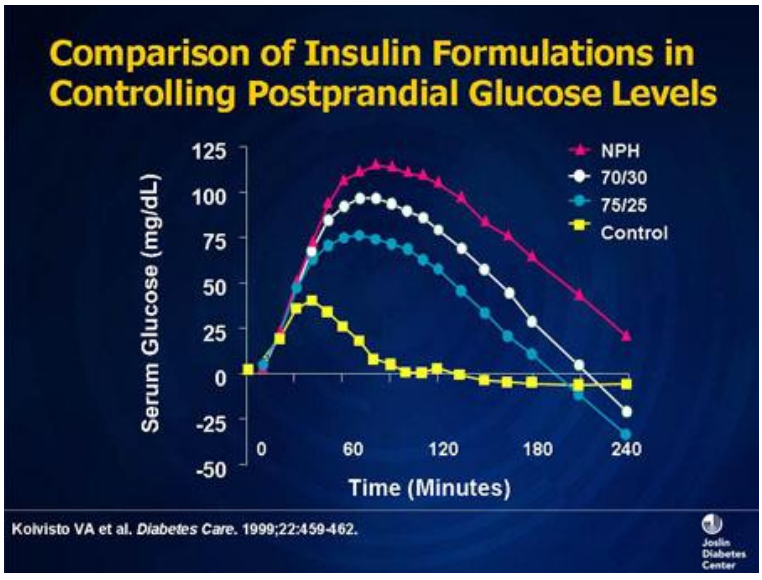
In addition, we have inhaled insulin, which is also quick-acting. Regular insulin pharmacokinetics are similar to the rapid-acting insulins, but with some significant time course differences. There are also intermediate-acting insulins, such as neutral protamine Hagedorn (NPH), which has a peak 7 to 8 hours after you take it. The longer-acting analogs, such as insulin glargine or insulin detemir, are "24-hour" insulins.



Slide 26: Action Profiles of Injectable Insulins

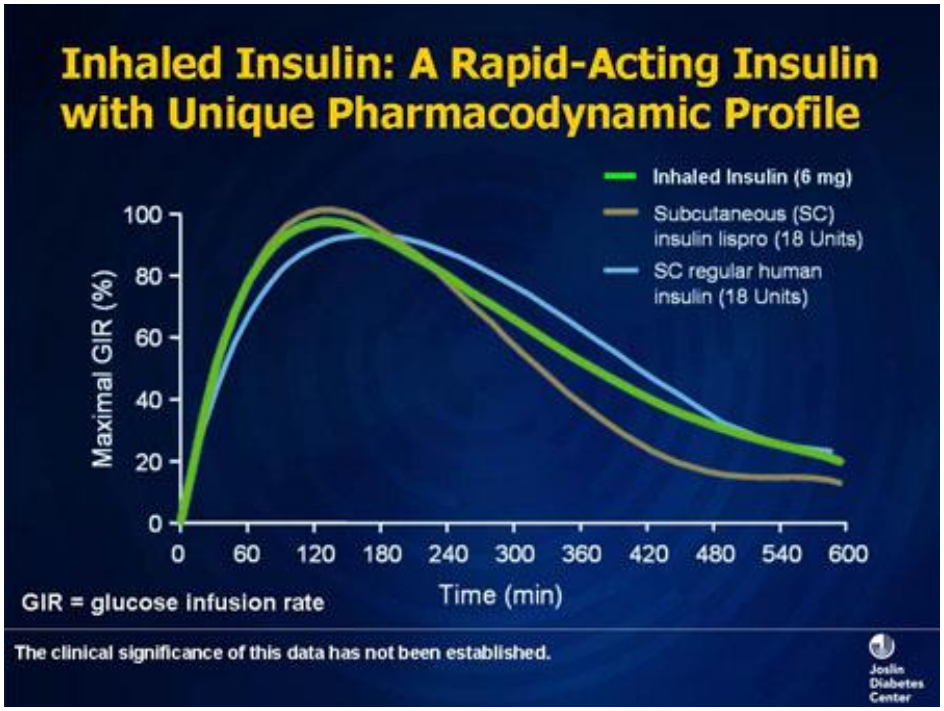
This schematic gives you the profiles for injectable insulin. The longer-acting insulins, such as glargine(Lantus) or detemir(Levemir), are theoretically 24-hour insulins; they have a duration of action of about 24 hours, and they tend to mimic basal insulin levels.

In terms of shorter-acting insulins, we have the rapid-acting ones, as part(Novorapid), glulisine(Apidra), or lispro(Humalog), which have a fairly rapid peak of onset, but their effect is dissipated fairly quickly, in a few hours. The rapid dissipation of these insulins results in less hypoglycemia but also can leave a void in insulin activity in some patients between meals. NPH has a significantly longer profile.



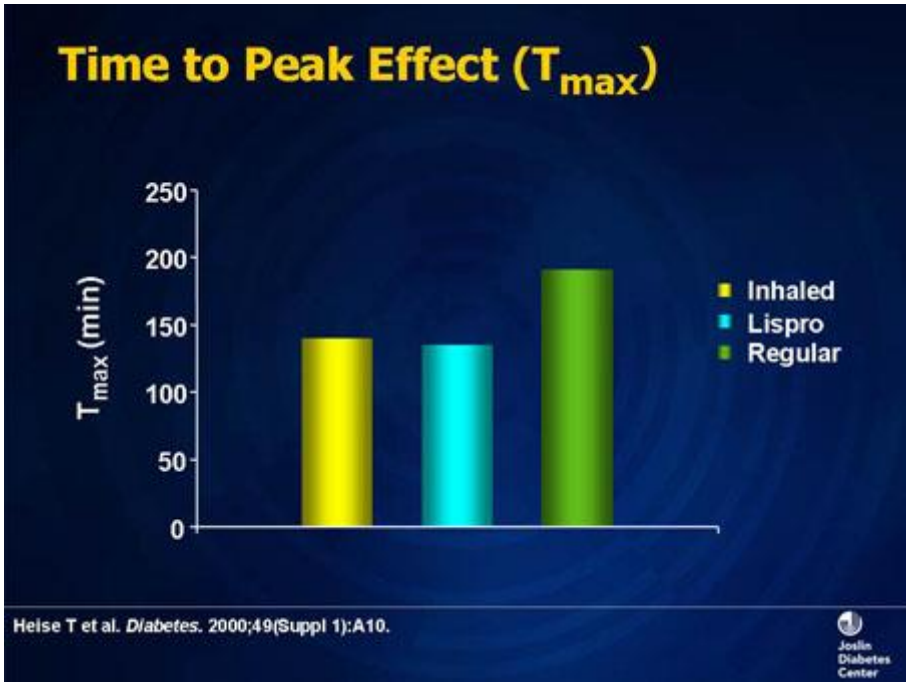
Slide 27: Comparison of Insulin Formulations in Controlling Postprandial Glucose Levels

If one examines the glucose profiles over a period of 4 hours in nondiabetic controls and in individuals given either glucose and NPH, a mixture of 70% NPH/30% regular, or 75%/25%, (a mixture of an NPH-type insulin with a short-acting insulin, either lispro or as part), the insulins that have a quicker onset tend to suppress the rise in postprandial glucose to a greater degree.



Slide 28: Inhaled Insulin: A Rapid-Acting Insulin With Unique Pharmacodynamic Profile

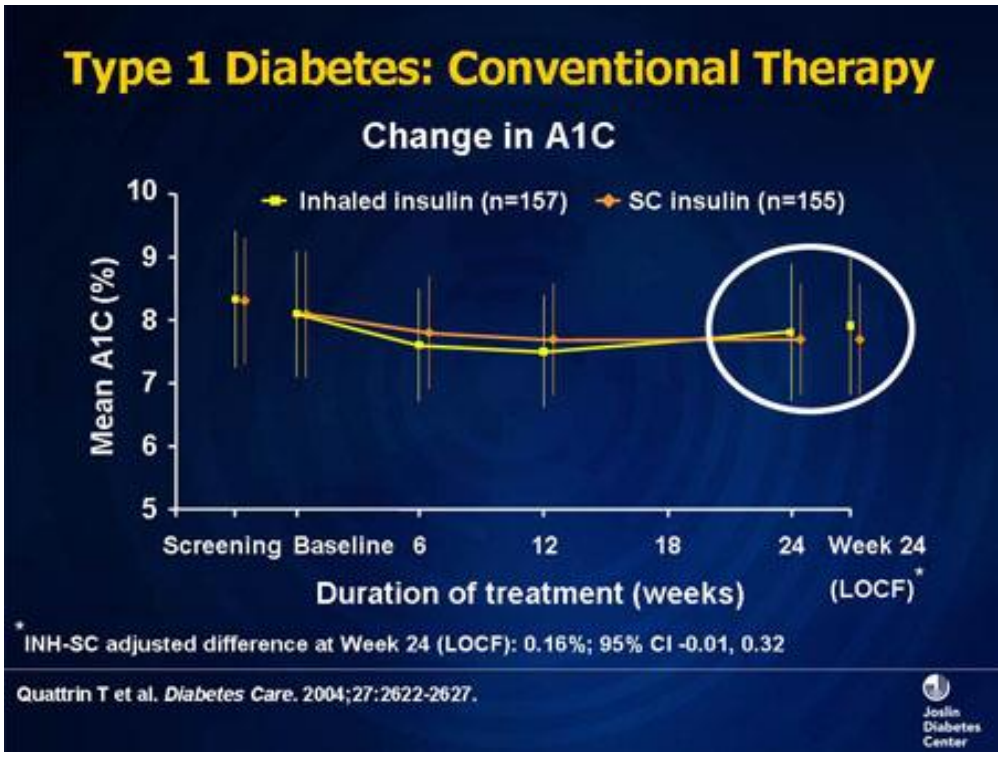
Inhaled insulin fits in between the more rapid-acting insulins, in this case lispro or regular. In terms of the onset of action, it is rapid, close to the more rapid-acting insulin, but it is not gone quite as quickly, which is more like regular. So, to a certain extent, you get some of both when using the inhaled insulin.



Slide 29: Time to Peak Effect (Tmax)

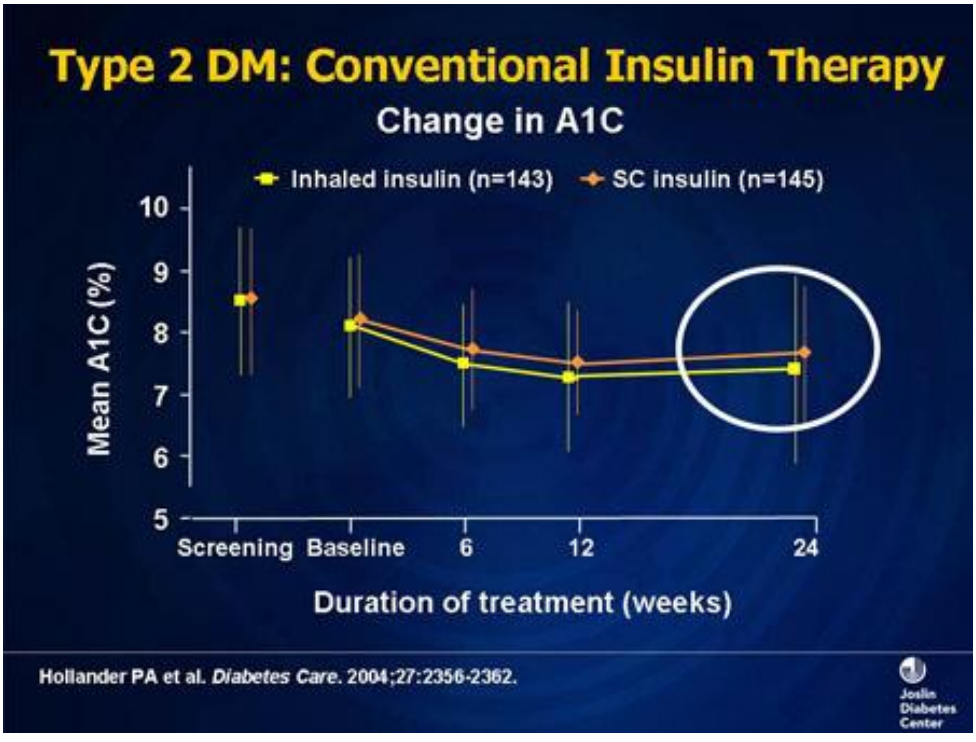
This is a more quantitative bar graph of the time to peak effect of these 3 insulins. And you can see, when viewed in this format, the inhaled insulin is more like the rapid-acting insulin, lispro, than it is like the regular insulin.

11. INSULIN EFFECTS ON A1C



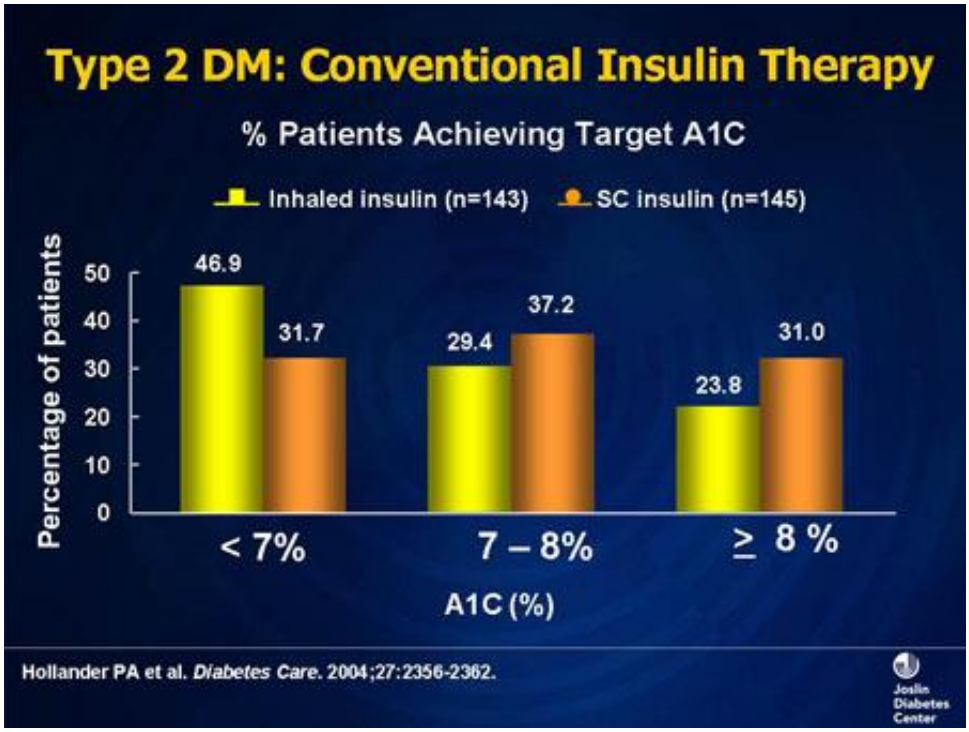
Slide 30: Type 1 Diabetes: Conventional Therapy

Many studies have compared the effect of inhaled insulin to subcutaneous insulin. This is a 6-month study in which type 1 diabetes patients either receive subcutaneous insulin or inhaled insulin as part of their program. As shown, there was essentially no difference in A1C at the end of 6 months between the two groups.



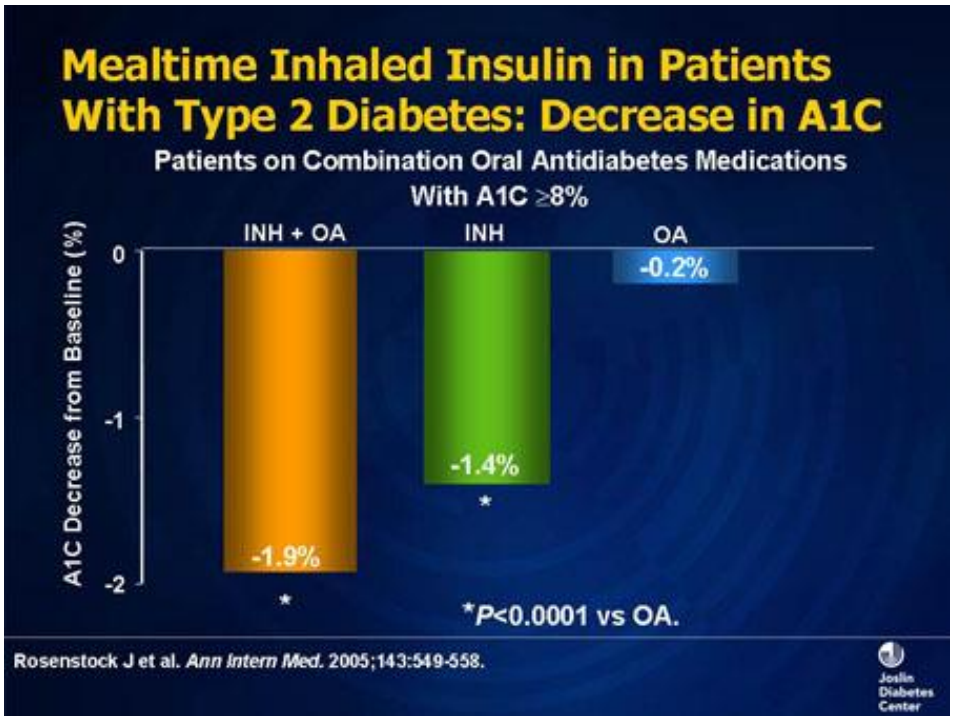
Slide 31: Type 2 DM: Conventional Insulin Therapy

This is a study of type 2 diabetes patients being treated either with subcutaneous insulin or inhaled insulin. Again, at the end of 6 months, there is essentially no difference in A1Cs.



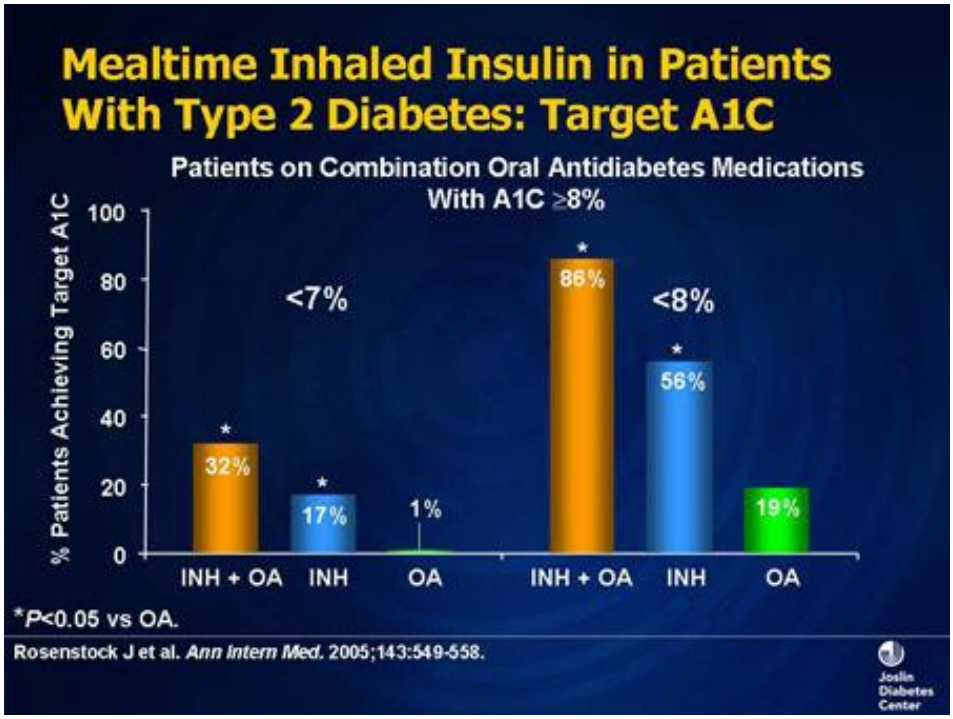
Slide 32: Type 2 DM: Conventional Insulin Therapy

If you compare inhaled insulin with subcutaneous insulin in terms of percentage of patients who reached some predetermined A1C goal, more of the patients on inhaled insulin got to a target of less than 7% than those on subcutaneous insulin.



Slide 33: Mealtime Inhaled Insulin in Patients With Type 2 Diabetes: Decrease in A1C

These data show decreases in A1C in patients who are being treated with combinations of oral agents, with inhaled insulin, or both. These patients all qualified for the study because they had been on combinations of an insulin sensitizer, either metformin or a TZD, plus a secretagogue such as a sulfonylurea. In those in whom no therapy change was made, there was no further decrease in A1C. In patients taken off the combination and started on inhaled insulin, an A1C decrease of 1.4% was seen. If left on oral agents and adding inhaled insulin, the largest decrease of 1.9% occurred.

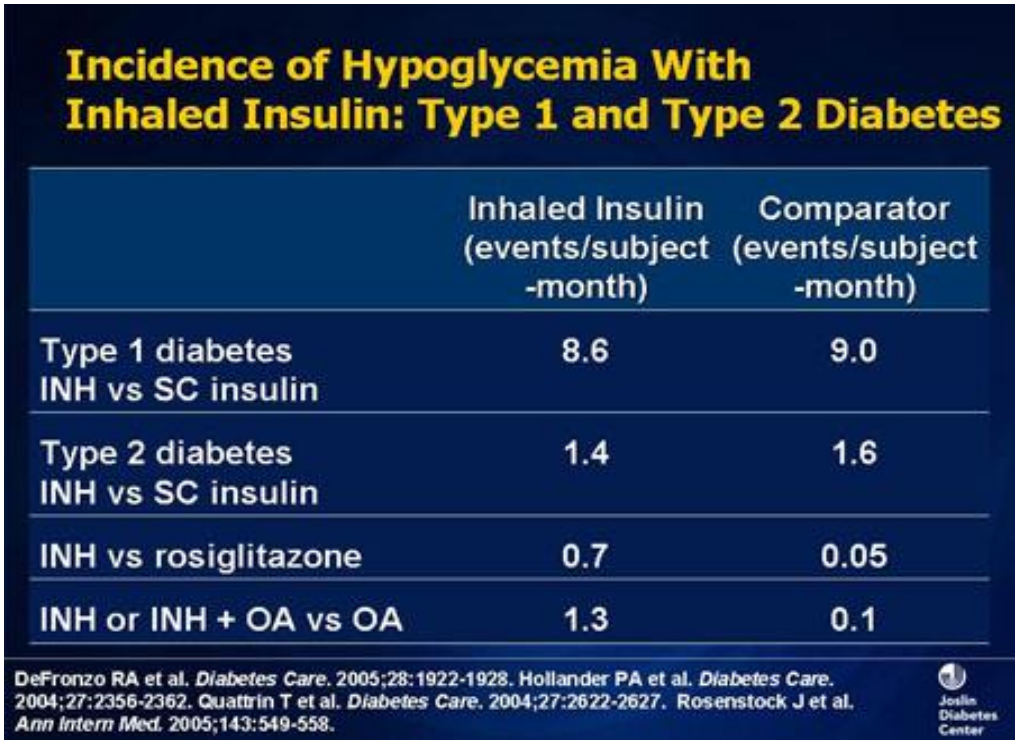


Slide 34: Mealtime Inhaled Insulin in Patients With Type 2 Diabetes:

12. TARGET A1C

This study involved stratification according to the achievement of predetermined targets for A1C in that same group of patients, i.e., patients maintained on oral agents, switched to inhaled insulin, or combining the two. A larger percentage of patients reached a target of either less than 8% or less than 7% with the combination of inhaled insulin and oral agents.

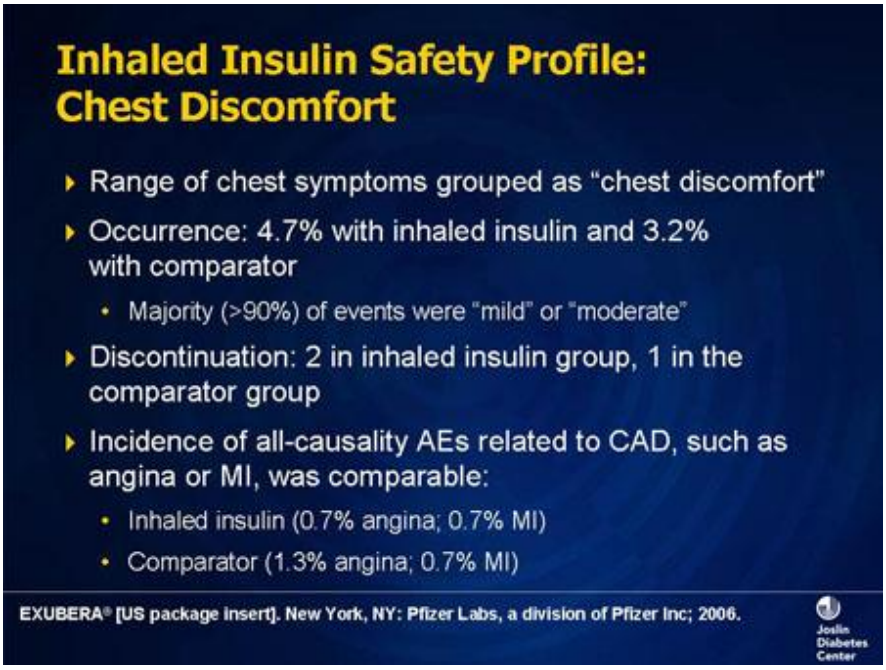
13. SAFETY WITH INHALED INSULIN: ADVERSE EVENTS AND PULMONARY SAFETY



Slide 35: Incidence of Hypoglycemia With Inhaled Insulin:

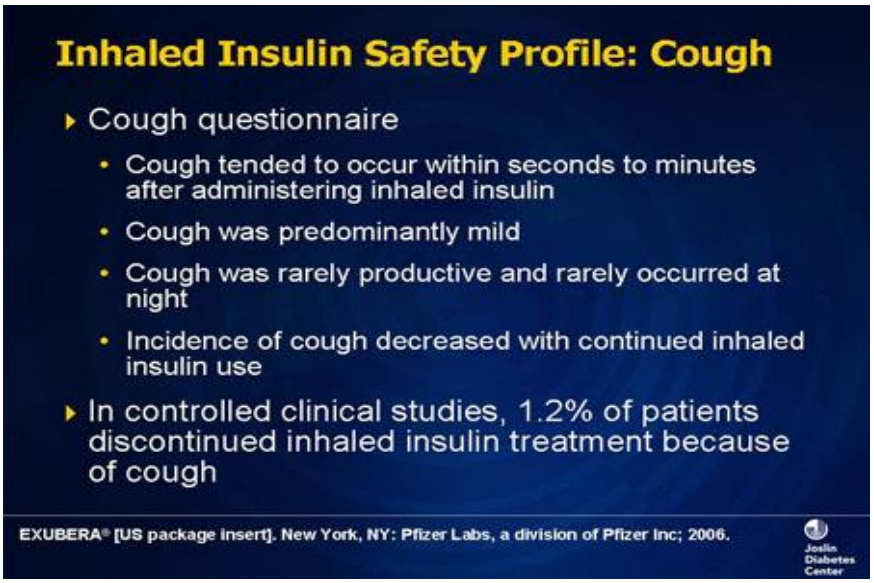
As with every type of insulin, hypoglycemia is the most frequent adverse event that is reported in trials. The incidence of hypoglycemia in trials was comparable in the inhaled and subcutaneous insulin groups. When compared with oral agents, some of which do not even cause hypoglycemia, obviously hypoglycemia was more common in the patients who took inhaled insulin.

In a numerical comparison of the incidence of hypoglycemia in patients with type 1 diabetes receiving either inhaled or subcutaneous insulin, there is roughly the same incidence in both groups; in patients with type 2 diabetes, similar results were seen. The biggest differential was in patients who were taking inhaled insulin plus oral agents vs. the oral agents alone. Remember, these patients had failed on oral agents, were therefore not as close to hypoglycemic levels, and received no additional intervention.



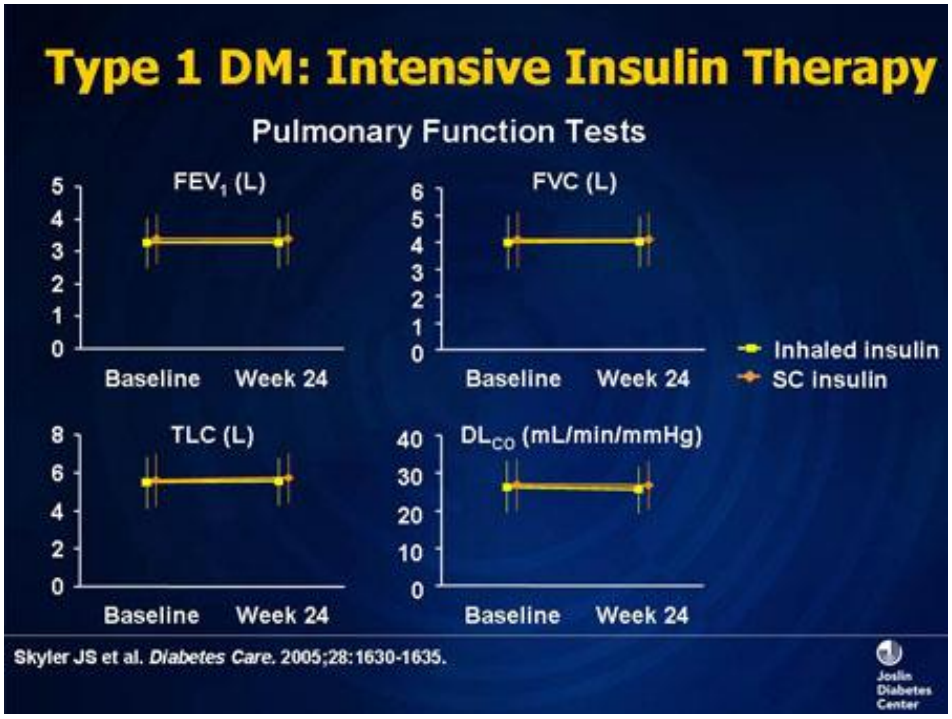
Slide 36: Inhaled Insulin Safety Profile: Chest Discomfort

Chest discomfort is a vaguely described group of symptoms that patients often report when they have taken inhaled insulin, with about 5% incidence in the trials. Most of the patients classified it as either mild or moderate. There were few patients who discontinued therapy because of this particular sensation, and there was not any increase in reported ischemic cardiac adverse events in the inhaled insulin group.



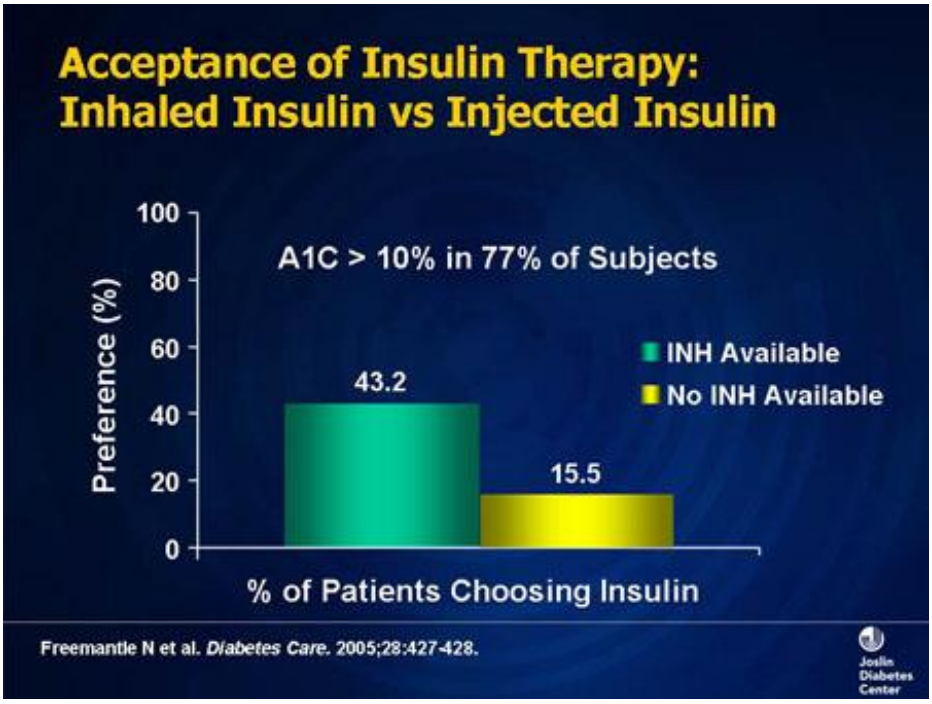
Slide 37: Inhaled Insulin Safety Profile: Cough

Cough was another symptom that occurred with enough frequency to draw attention. It tends to occur early, soon after the insulin is inhaled, is characterized as relatively mild, and is associated with some but relatively modest sputum production. There was a tendency for patients to develop some tolerance to this symptom. Overall, in the clinical trials, slightly over 1% of patients discontinued specifically because of the cough.



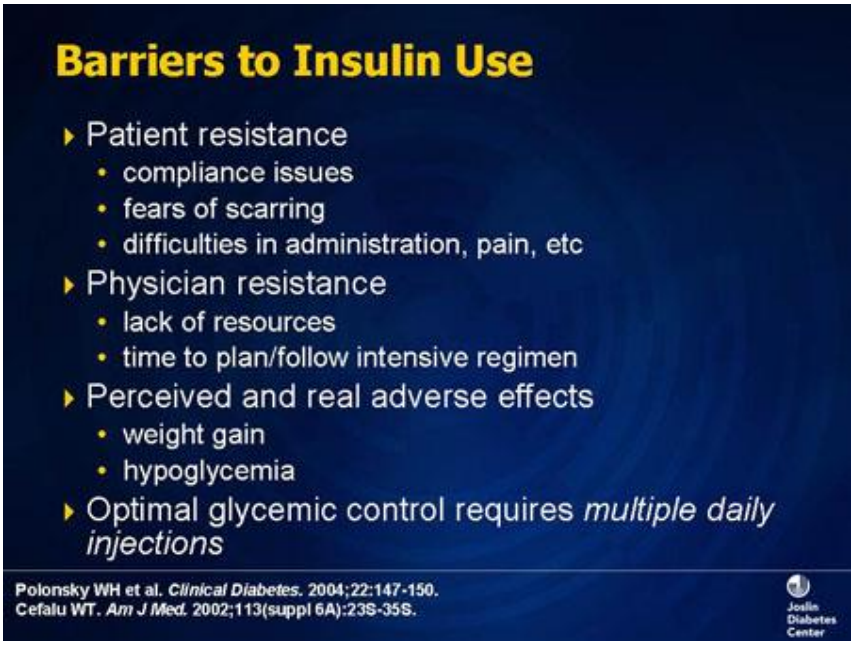
Slide 39: Type 1 DM: Intensive Insulin Therapy

These data represent pulmonary function tests in patients on inhaled vs subcutaneous insulin. In this study of these specific parameters of pulmonary function over a 6-month period, no major change was noted.



Slide 40: Acceptance of Insulin Therapy: Inhaled Insulin vs Injected Insulin

Patient acceptance of inhaled insulin is very good, since most patients who gravitate towards this modality do so because they do not like self-administered injection. It has been well received in those studies that have addressed this issue.



Slide 41: Barriers to Insulin Use

There are barriers to insulin use. There are patient issues; we call this "psychological insulin resistance." However, the needles today are very fine; self-glucose monitoring is far more painful. But patients have this idea that shots will scar them, and they are going to be painful.

Practitioners are very busy. When we use insulin therapy, we start at one point and we may end up at a very complex place, using intensive therapy, which is time-consuming, requires staff, and requires a lot of input. When you use multiple daily injections (MDI) or intensive therapy, someone has to be on call to treat these patients. Consequently, available resources sometimes determine the steps we take.

We also know that patients are very savvy. They know that insulin causes you to gain weight. Why do you think the use of GLP-1 analogs is going up so fast? They control blood glucose, and you lose weight at the same time.

Hypoglycemia is very real. If you have experienced hypoglycemia, all you can think of is food. It is not a nice feeling.

And finally, I think we recognize that for optimal control of diabetes we should be prepared to use multiple injections. One of the things we never do is to promise our patients that there will only be 1 shot a day. It is going to be as many shots as it takes.

Slide 42: Specific Considerations in Determining the Next Therapeutic Step

In terms of determining what therapeutic tool you are going to use, one of the most important assessments is glycosylated hemoglobin (A1C). If you see a patient who has had 5 or more years of type 2 diabetes, is on two drugs, and their A1C is 10% or 12%, it is not coming down to 7% with another drug; if A1C is 8%, you can probably get it down to 7%, with a third drug. So the level of A1C is very important, especially with longer-duration diabetes. Early in the disease, when it is newly diagnosed, the higher the A1C, the bigger the decrease with initial treatment but this changes with time as beta-cell insulin secretion decreases.

14. SUMMARY

Diabetes mellitus is a metabolic disease characterized by hyperglycemia and abnormal carbohydrate, fat, and protein metabolism. Diabetes has a very high prevalence worldwide. There are approximately 20.8 million (7%) people in the United States who have diabetes.1

Diabetes results from defects in insulin secretion, sensitivity, or both. Although the exact cause remains unclear, genetics and environmental factors such as obesity and lack of exercise appear to be involved.

The diagnosis of diabetes mellitus is based on one of three criteria: fasting plasma glucose (FPG), casual elevated glucose levels that occur in conjunction with symptoms, or an abnormal oral glucose tolerance test (OGTT).2 Fasting plasma glucose is defined as the glucose level taken after no caloric intake for at least 8 hours.2 Casual glucose levels are defined as the glucose level taken at any time of the day without regard to meals. In the OGTT test, blood glucose levels are measured 2 hours after drinking a glucose-rich beverage that contains 75 grams of glucose.

Most patients with diabetes mellitus are classified as having either type 1 or type 2. Type 1diabetes (previously known as juvenile diabetes) accounts for about 10% of all diabetes cases and is usually diagnosed in children and young adults.2 In these patients, insulin is not produced because of immune mediated destruction of pancreatic cells. In comparison, type 2 diabetes, which accounts for almost 90% of diabetes cases, is characterized by both insulin resistance and insufficient insulin production.2 There are other uncommon causes of diabetes which include endocrine disorders (e.g., Cushing's syndrome), gestational diabetes mellitus, disease of the pancreas (e.g., pancreatitis) and some medications (e.g., glucocorticoids, pentamidine, and interferon Alfa).

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