Should Insulin be First Line Therapy for Type 2 Diabetes Mellitus?

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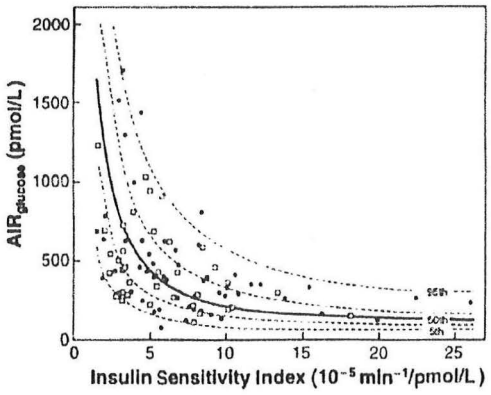
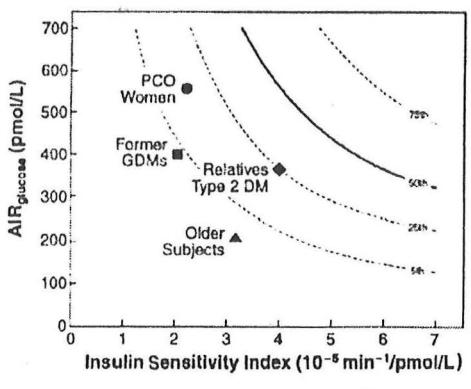
I Rationale for insulin therapy in Type 2 Diabetes

Type 2 diabetes is a progressive disease with a relentless decline in insulin secretion. Over recent years the therapeutic armamentarium for the management of Type 2 diabetes has widely expanded with multiple oral agents but with limited blood glucose lowering potency. Insulin therapy should no longer be viewed as a "last resort" to be used after long term oral agent combinations have failed, but rather, as an earlier therapeutic tool for achieving glycemic targets. Simple strategies for starting insulin therapy such as evening basal insulin replacement in combination with oral agents have been shown to be effective and follow well the basal/bolus insulin concept. Once patients on combination oral therapy are initiated on basal insulin replacement, a structured titration regimen may suffice to accomplish glycemic targets. Eventually, the need to intensify the regimen with the addition of premeal short-acting insulin therapy, to address postprandial hyperglycemia, will depend on whether target HbA_{1c} levels are achieved.

Hyperglycemia results from two fundamental pathogenic defects: impaired insulin secretion (or β-cell dysfunction) and insulin resistance (manifested by increased hepatic glucose production and reduced peripheral glucose uptake). These defects are believed to be both genetically determined and influenced by environmental factors, such as physical inactivity, obesity, and high-fat diets. The ability of the pancreas to maintain adequate hyperinsulinemia to compensate for the insulin resistance has emerged as the pivotal point in determining whether a patient progresses to type 2 diabetes. Consequently, studies of insulin secretion must be interpreted in light of a patient's insulin sensitivity. Steve Kahn and colleagues performed such studies in a young and apparently healthy Caucasian population with NGT and varying degrees of obesity. Their research showed that individual values for insulin sensitivity showed wide variation, and that β-cell function varied quantitatively with these differences in insulin sensitivity (1). Reciprocal relationships were found between insulin sensitivity and measures of β-cell function, including fasting insulin levels, the glucose-induced first-phase insulin response, and β-cell secretory capacity. By using these relationships to derive a percentile score, one can estimate the adequacy of β-cell function based on the prevailing degree of insulin sensitivity. These studies were then extended to evaluate groups at high risk for type 2 diabetes who were insulin resistant(2-4). Although these subjects still secrete insulin, their β-cell function is reduced as their insulin sensitivity falls into the lower percentiles (indicating increasing insulin resistance). This reduction in β-cell function then raises the question: Why is insulin not part of the initial therapy in all type 2 diabetic patients?

Figure 1. The relationship between Insulin Sensitivity and Insulin Secretion





Studies characterizing the nature of this β-cell dysfunction in first degree relatives of patients with type 2 diabetes have shown that the insulin secretion defects are present prior to the progression to hyperglycemia and can in fact predict progression from normal (NGT) to impaired glucose tolerance (IGT) to diabetes (DM) (5-16). This progression has been extensively studied in the Pima Indians of Arizona where an extremely high percentage of the adult population develops type 2 diabetes by age 40. Weyer et al performed a longitudinal study in which 48 adult Pima Indians with normal glucose tolerance (NGT) were monitored at yearly intervals to determine predictors of progression to diabetes (17). They found that in 17 of the 48 subjects, glucose tolerance deteriorated from NGT to IGT to diabetic over 5.1 ± 1.4 years. Transition from NGT to IGT was associated with an increase in body weight, a decline in insulin-stimulated glucose disposal, a decline in the acute insulin secretory response (AIR) to intravenous glucose, and with no change in endogenous glucose output (EGO). Progression from IGT to diabetes was accompanied by a further increase in body weight, further decreases in insulin-stimulated glucose disposal and AIR, and an increase in basal EGO. The 31 subjects who retained NGT over a similar period also gained weight, but their AIR increased in proportion to decreasing insulin-stimulated glucose disposal. Thus, defects in insulin secretion and insulin action occur early in the pathogenesis of diabetes. Weyer and colleagues have also studied adult offspring of people with early onset type 2 diabetes in this population and found that the acute insulin secretory response to a glucose challenge was lower despite having NGT (18). Similar results have been found by Steve Haffner in the 7-year follow-up of the San Antonio Heart Study, in which 195 of 1734 subjects converted to type 2 diabetes(7). Although insulin resistance, most commonly due to obesity, plays a role in the development of diabetes, the progression to hyperglycemia requires a significant loss in insulin secretory ability.

The importance of the ability of the β-cell to compensate for insulin resistance has actually been demonstrated in the identification and management of women with gestational diabetes. Although gestational diabetes (GDM) is defined as any diabetes first identified during pregnancy, the majority of "GDM" women are those who become hyperglycemic in the third trimester when a physiologic decrease in insulin sensitivity occurs. The etiology of this sudden load of insulin resistance is not known but it has been demonstrated to occur at the beginning of the third trimester, even in women with type 1 diabetes(19). The women who develop GDM are similar to those studied in the Pima population in that they are not able to adequately increase insulin levels to compensate for the insulin resistance(20). In fact, their inability to mount a hyperinsulinemic response suggests that they do not have adequate β-cell reserve. Treatment of these women has traditionally been with diet and exercise and, when that fails, insulin monotherapy which is able to normalize pre- and postprandial glycemia. Many of these women do revert to normal glucose tolerance immediately after the pregnancy is completed however they still have a risk of progressing to type 2 diabetes in their lifetime. Thus the pregnancy has revealed the fact that if they encounter similar levels of insulin resistance (i.e. obesity) in the future they will not be able to respond with sufficient insulin production and will become hyperglycemic. In fact Tom Buchanan's studies of women who have had a history of gestational diabetes show that the progression to type 2 DM is correlated with the extent of impairment of insulin secretion (21). Women who had GDM and still have

IGT or IFG at their postpartum OGG (performed 6-12 weeks postpartum) are more likely to progress type 2 diabetes than those who have a normal postpartum OGTT (21). Interestingly, because not all pregnant women develop hyperglycemia, the groups that are recommended to undergo screening for GDM are the same as those that are considered high risk for diabetes in the general population: family history of diabetes (i.e., parents or siblings with diabetes). overweight, people of certain race/ethnicity (e.g., African-Americans, Hispanic-Americans, Native Americans, Asian-Americans, and Pacific Islanders), previously identified IFG or IGT, history of GDM or delivery of a baby weighing ≥9 lbs or polycystic ovary syndrome.

The role of insulin secretory ability also becomes apparent when studying newly diagnosed type 2 diabetics. Beta cell function, as measured by the Homeostasis Model Assessment method (HOMA), can be stabilized acutely with diet and lifestyle changes, but then an inexorable decline in β-cell function occurs, necessitating insulin therapy in all people with type 2 diabetes (22,23). Although individuals in the UKPDS receiving sulfonylurea therapy demonstrated an early increase in β-cell function from 45% to 78% in year 1 of the study (consistent with a secretagogue effect of the sulfonylurea agent) β-cell function subsequently decreased along the same slope as the diet treated group. This inevitable decline in β-cell function also occurred in the metformin group, in which β-cell function initially increased (similar to that in the sulfonylurea group), then declined from 66% to 38% by year 6. The fact that significant loss of insulin secretory ability is necessary for hyperglycemia to develop suggests that replacing the missing endogenous insulin with exogenous insulin therapy will be necessary for control of type 2 diabetes.

The etiology of the loss of β-cell function has been a matter of intense research with two major leading theories: lipotoxicity and glucotoxicity. The role of genetics in the β-cell response to the environment remains to be established. The most likely etiology is lipotoxicity which has been discussed in recent Internal Medicine Grand Rounds by Roger Unger, Moshe Levi and Bob Dobbins so it will not be addressed here.

The other theory is that of "glucotoxicity" which has developed several meanings over the last twenty years. The concept of glucotoxicity arose from animal studies where diabetes was induced through partial pancreatectomy or neonatal exposure to streptozotocin which resulted in some residual β-cell function(24,25). Unexpectedly, these animals had impaired glucose-induced insulin secretion along with the fasting and postprandial hyperglycemia. The theory then emerged that hyperglycemia itself might be toxic to pancreatic islets because the defect in insulin secretion in the rats was greater than expected on the basis of mass of the remaining islet beta cells. Subsequent tissue culture studies of rat pancreatic islets have shown that elevated glucose levels in the media cause deficient insulin secretion, depleted insulin content, an increased proportion of insulin precursor molecules, a lack of augmentation of insulin mRNA, and a progressive increase of DNA fragmentation and apoptosis(26). Subsequently short-term severe (48-hour) hyperglycemia in normal rats was found to impair acute glucose-induced insulin release(27). Prolonged mild hyperglycemia, induced in rats that had undergone partial pancreatectomy by administering glucose in tap water, impaired glucose-induced insulin secretion while short-term mild hyperglycemia enhanced this response(28,29). Further studies have suggested that chronic hyperglycemia has sequential effects on the β-cell that are ultimately detrimental to glucose homeostasis(30-33). These have been characterized as three distinct phenomena: glucose desensitization,

β-cell exhaustion, and glucotoxicity. Glucose desensitization refers to the rapid and reversible refractoriness of the β-cell exocytotic machinery that occurs after a short exposure to elevated glucose and is a physiological adaptive mechanism that occurs even when insulin secretion is inhibited, thus differentiating it from β-cell exhaustion. β-cell exhaustion refers to depletion of the readily releasable pool of intracellular insulin following prolonged exposure to a secretagogue. In contrast, the term glucotoxicity describes the slow and progressively irreversible effects of chronic hyperglycemia on pancreatic β-cell function, which occur after prolonged exposure to elevated glucose. The fact that these associated β-cell defects are reversible up until a certain point in time and become irreversible thereafter suggests a continuum between β-cell exhaustion and glucotoxicity. The concept of glucotoxicity has subsequently been expanded to include the resistance of liver and muscle to insulin in the presence of high plasma glucose. For example, studies of subjects with type 1 diabetes have shown that infusion with glucose at high levels for 24 hours prior to undergoing hyperinsulinemic clamp were more insulin resistant than those preinfused with saline based on glucose utilization rates during the clamp(33). Thus when the term is used the context will indicate whether the person is referring to death of β-cells or resistance to insulin that is believed to be due to the hyperglycemia superimposed on the underlying insulin resistance. The question of whether glucotoxicity and lipotoxicity are mutually exclusive or actually work together to facilitate the demise of the β-cell will be left for a future Grand Rounds speaker to address.

Insulin Therapy for Insulin Resistance

The fact that the initial response to decreasing insulin-stimulated glucose disposal is to increase AIR, as evidenced by the Pima subjects who retained NGT throughout the longitudinal study, raises the possibility of using intensive insulin therapy to treat insulin resistance. However, insulin can cause weight gain that is also associated with increasing insulin resistance. This is consistent with epidemiologic studies that have demonstrated insulin dosage correlates with increasing insulin resistance(42) Consequently, the concern has been raised that treatment with insulin may worsen insulin resistance. This concern has been shown to be unfounded by three short term studies done with similar methods to directly test this possibility (34-36). Each study examined the insulin sensitivity of peripheral tissues -- mainly muscle -- using the glucose-insulin clamp method, before and after restoration of good glycemic control with aggressive insulin treatment in type 2 diabetes patients. In each case the treatment period was short (2 to 4 weeks), and relatively high insulin dosage was required (>100 U daily). Figure 1 shows the insulin sensitivity of tissues before and after treatment, expressed as a percentage of the mean value for insulin sensitivity of a nondiabetic control group that was matched in age, gender, and weight to the diabetic subjects. The three studies had remarkably similar results, with insulin sensitivity before treatment reduced by half, compared to the nondiabetic values, indicating marked insulin resistance. After treatment, insulin sensitivity improved toward the nondiabetic values, though some insulin resistance persisted, as would be expected. This improvement is presumably due to reduced "glucotoxicity" accompanying improved control of plasma glucose. Whether the improvement of insulin sensitivity persists when insulin treatment is continued was not tested in these studies. However, these data show that, at least in the short term, successful insulin treatment reduces rather than worsens insulin resistance.

A recent study by DeFronzo and colleagues evaluated insulin resistance after 12 weeks of aggressive glucose lowering with insulin monotherapy resulting in near-normalization of the mean day-long plasma glucose concentration(37). Their goal was to produce tight glucose control in type 2 diabetic subjects using a mixed-split insulin treatment regimen to in an attempt to determine the biochemical mechanisms responsible for impaired insulin stimulated glucose disposal in skeletal muscle. On average, the diabetic subjects took 32±5 units of NPH insulin and 9±1 units of regular insulin in the morning, 14±2 units of regular insulin with dinner, and 24±2 units of NPH insulin at bedtime. They performed hyperinsulinemic-euglycemic clamps with indirect calorimetry and vastus lateralis muscle biopsies in eight type 2 diabetic patients who had poor glycemic control (HbA_{1c} 10.1%) and again after 3 months of intensive insulin therapy designed to produce near normoglycemia (HbA_{1c} 6.6%). Improved glycemic control increased insulin-stimulated glucose disposal by ~50%, nonoxidative glucose disposal, which primarily reflects glycogen synthesis, and glycogen synthase fractional velocity. There was no improvement in insulin-stimulated glucose oxidation, hexokinase II mRNA expression, or hexokinase II enzymatic activity. The increase in insulin-stimulated glucose disposal could be completely accounted for by increased glycogen synthesis, which is likely attributable to increased activation of glycogen synthase by insulin. The authors believe these results suggest that, after achieving good metabolic control, obese patients with type 2 diabetes are inherently no more insulin resistant than obese nondiabetic subjects, and that the additional insulin resistance of the diabetic subjects when they had poor glycemic control was caused by hyperglycemia "or other alterations in the metabolic milieu". Insulin therapy did improve fasting and insulin-suppressed plasma FFA concentrations. It is possible, therefore, that some of the improvement in whole body glucose disposal, nonoxidative glucose disposal, and glycogen synthase activity was attributable to amelioration of the adverse effects of high plasma FFA concentrations. Infusion of a triglyceride emulsion to increase plasma FFAs induces insulin resistance in glucose disposal and the glycogen synthetic pathway (20–22). Therefore, it is reasonable to expect that a decrease in elevated plasma FFA levels might improve insulin sensitivity in the nonoxidative/glycogen synthase pathway. However, despite the reduction in plasma FFAs with insulin therapy, there was no improvement in glucose oxidation or HKII activity. The authors further state that this result is consistent with their hypothesis that the addition of type 2 diabetes to obesity confers little or no further reduction in insulin sensitivity. This hypothesis is based on their prior observation that obese nondiabetic subjects also have a profound defect in insulin stimulation of HKII mRNA expression. The irreversibility of these defects could be consistent with an underlying hereditary cause, an acquired defect that is not reversible by achieving near-normoglycemia and does not have an etiology secondary to obesity. It would be interesting to know if the defect in insulin stimulation of HKII mRNA expression in obese subjects could be improved with weight loss. Nonetheless, DeFronzo and colleagues have elegantly demonstrated that insulin therapy can dramatically lower and almost normalize HbA_{1c} in type 2 diabetic patients in just 12 weeks with insulin monotherapy. Treatment with secretagogues, such as sulphonylureas, as evidenced in the UKPDS has not been able to attain normal HbA_{1c} in most patients which is likely due to the inadequacy of β-cell reserve (23). The UKPDS investigators have recently reported that they added insulin to approximately 50% of the subjects taking either

chlorpropamide or glipizide to maintain fasting plasma glucose < 108mg/dl(38). The number would have been higher except that subjects were allowed to refuse initiation of insulin therapy.

Cardiovascular benefit

A common objection to insulin therapy for type 2 diabetic patients is the belief, based on the epidemiologic association of hyperinsulinemia and atherosclerosis, that the risk of cardiovascular disease will be increased due to hyperinsulinemia, hypoglycemia, or other metabolic effects of insulin that might provoke or worsen the outcome of major cardiovascular events. Although the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial did not show a short term decrease in mortality post-MI they were able to demonstrate one in the long term followup(39-41). This Swedish trial studied the short-term and long-term effects of intensive insulin treatment of patients with diabetes who were enrolled in the trial at the time of a myocardial infarction. The subjects were immediately randomized to continued management according to the judgment of their physicians, or to intravenous infusion of insulin and glucose for 48 hours followed by a four-injection regimen subsequently for as long as 5 years. Other aspects of management of the infarction included treatment with β-blockers, angiotensin-converting enzyme inhibitors, fibrinolytic agents, and aspirin in high proportions of both groups. The rationale underlying the study was the old observation that, in animal experiments and studies of small numbers of humans, infarct size and outcome are improved by insulin-glucose infusion, in part because of suppression of otherwise elevated free fatty acid levels in plasma . The figure shows the cumulative total mortality rates in the whole population of 620 subjects randomized to the two treatments, as well as the rates for a predefined subgroup of subjects who were judged likely to survive the initial hospitalization and were not previously using insulin. The whole population showed an 11% actual and a 28% relative risk reduction in mortality with intensive insulin treatment after 5 years, and the subgroup not previously using insulin showed a 15% actual and a 51% relative risk reduction. Most of the benefit was apparent in the first month of treatment and presumably was partly due to immediate intravenous infusion of insulin; however, the survival curves tended to separate further over time, suggesting an ongoing benefit from intensive treatment. This study suggests that insulin is an entirely appropriate treatment for patients with type 2 diabetes and high cardiovascular risk, especially at the time of myocardial infarction.

II Issues in decision Making

Barriers to Insulin Therapy

The major barriers for some physicians to use insulin in the treatment of type 2 diabetes are the misconception that insulin therapy may increase the risk of cardiovascular (CV) disease, excessive concerns with weight gain, the potential risk of hypoglycemia and having to take injections. Insulin therapy has been considered a therapy of last resort in type 2 diabetics for many years due to these concerns about the risks.

Epidemiological studies have shown an association between hyperinsulinemia and atherosclerosis thus physicians have been concerned that initiating insulin therapy would be harmful. Insulin resistance and the consequent endogenous hyperinsulinemia are strongly associated with central obesity, hypertension and dyslipidemia, all factors

that contribute substantially to CV risk and in fact characterize the Metabolic Syndrome which is also called the Insulin Resistance Syndrome. However, to date no animal or human study has provided any evidence that exogenous hyperinsulinemia causes atherosclerosis. In fact the UKPDS demonstrated that the insulin treated patients had exogenous hyperinsulinemia without increased atherosclerotic related events (42,43).

Moreover, in the 5-year DIGAMI trial, patients receiving insulin infusion therapy during acute MI followed by intensive MDI therapy exhibited a relative mortality risk reduction of 28% as compared to control (conventional therapy) after 5 years of treatment. These results suggest that insulin may very well be the most appropriate treatment for patient with type 2 diabetes with high CV risk.

Initiation of insulin therapy is typically associated with weight gain. The weight gain is most rapid in the first 3 months of therapy and is correlated with improvements in glycemia. The initial weight gain has been thought to reflect restoration of consequences of insulin deficiency. Improvement in glycemia favors weight gain by decreasing the energy lost in the urine as glucose and by decreasing basal metabolic rate (BMR). Weight gain itself increases energy expenditure by increasing the BMR. Insulin therapy is also known to noticeably lower plasma non-esterified fatty acid concentrations, a change which is associated with a lowering of gluconeogenesis (44). A decrease in non-esterified fatty acid concentrations may also lower heat production by decreasing mitochondrial uncoupling, i.e. the ratio between heat and ATP production . The addition of metformin to the insulin therapy will attenuate the weight gain through an effect on total energy intake per day (45). This effect emphasizes the importance of increasing daily activity and decreasing dietary intake to minimize weight gain. Of note, studies in obese patients with type 2 diabetes treated with insulin therapy have shown that, despite weight gain, CV risks factors such as blood pressure remained unchanged, and lipid patterns (triglycerides, lipoproteins) were generally improved. These findings challenge the notion that insulin therapy negatively affects blood pressure and lipid profiles through weight gain. Importantly, intensive insulin therapy has been shown to improve rather than worsen insulin sensitivity in peripheral tissue by virtue of improving glycemic control, thus reducing and to some degree reversing the toxic effects of hyperglycemia (glucotoxicity)

In the UK Prospective Diabetes Study, patients in both the main study and the metformin substudy gained weight. In the main study, patients assigned to treatment with a sulfonylurea gained more weight than the conventional group, and those assigned insulin gained more weight than those on a sulfonylurea(42). In the cohort at 10 years, those assigned to glyburide gained 1.7 kg ($P < .001$) more, and those on insulin gained 4.0 kg ($P < .001$) more, than patients on conventional therapy. In the metformin substudy, which included the more obese subjects in the trial (mean BMI ~31 kg/m^2), the changes of body weight were similar to those in the main study except that the group randomized to metformin showed weight changes more like the conventionally treated group than the groups treated with insulin or a sulfonylurea(43).

Since metformin used alone does not lead to weight gain, a natural question would be whether combining metformin with insulin might minimize the gain of weight seen with insulin. In the FINFAT study, 96 patients previously not well controlled by sulfonylurea therapy were randomized to start bedtime NPH insulin in combination with metformin, continue sulfonylurea, both oral agents, or start bedtime NPH insulin in

combination with metformin plus a second injection of insulin in the morning(46). Only the data comparing the effects of bedtime insulin plus metformin with those of twice-daily NPH insulin are shown here. The 43 subjects in the study by Avilés-Santa et al had been taking insulin previously but, after enrollment, intensified their insulin treatment using two to four injections daily while taking metformin or placebo(47). In the study by Bergenstal et al, 42 patients who had previously taken insulin intensified their treatment with a three-injection regimen for 2 months, then were randomized to continue intensified treatment for 4 more months while taking either metformin or placebo(48). The subjects with complete data available are described in the table. Although the three studies used different protocols, all showed similar good glycemic control at the end with, on average, no weight gain while taking metformin plus insulin in contrast to the usual weight gain with insulin plus placebo.

Fear of hypoglycemia, both on the part of doctors and patients, limits the amount of insulin that is prescribed. The actual incidence of hypoglycemia in type 2 DM patients is very low and should not limit therapy. The risk of mild to severe hypoglycemia, generally increased with intensive insulin therapy, depends on a number of factors including age, weight, degree of insulin resistance, duration of disease, duration of insulin therapy, targeted degree of glycemic control and history of hypoglycemic episodes. Additional causal factors in hypoglycemia include overinsulinization, underfeeding, strenuous unplanned exercise, excessive alcohol intake, and unawareness of hypoglycemia. The UK Prospective Diabetes Study is the largest long-term treatment study using insulin for type 2 diabetes. Hypoglycemic episodes were monitored as a measure of outcome during the 10 years of treatment. Both nonobese and obese subjects randomized to begin with diet and exercise treatment had very little hypoglycemia, as was the case with subjects in the more obese subgroup treated with metformin. Those assigned to sulfonylurea treatment had more hypoglycemia, but very few cases were severe. The groups treated with insulin from the start showed more hypoglycemia, as might be expected, with little difference between the nonobese and the obese groups. Most of the hypoglycemia was mild or moderate in severity. Severe hypoglycemic events occurred in 2% to 3% of subjects in this group each year, on average. This rate is certainly not trivial, but it is far less than the rate seen with intensive treatment of type 1 diabetes patients in the Diabetes Control and Complications Trial (DCCT). In fact, clinical trials attempting to achieve near normalization of glucose concentrations in patients with type 2 diabetes have found that remarkably few hypoglycemic events occur, even in patients managed exclusively with insulin. Two factors are relevant to this observation: First, because these major studies failed to achieve full normalization of HbA_{1c}, whether hypoglycemia would have become more common if the patients had completely attained normoglycemia remains to be seen. Second, and likely more important, the average patient with type 2 diabetes is insulin resistant, and the endogenous insulin secretory responses are left intact. Under these circumstances, the patient with type 2 diabetes and modest hyperglycemia exuberantly increases endogenous insulin release to compensate for insulin resistance. If insulin is given exogenously, the subsequent fall in glucose concentration into the normal range or slightly below leads to a feedback decrease in endogenous insulin release from the beta cells which will help to decrease hypoglycemia. (49). Additionally, type 2 diabetic patients typically have intact counterregulatory systems with less hypoglycemia unawareness than is seen with type 1

patients. In fact, type 2 diabetic patients are have been demonstrated to have subjective symptoms of hypoglycemia at elevated glucose levels (49).

The DCCT demonstrated that most severe insulin reactions occur during the night With respect to nighttime reactions two questions should be considered: (1) How does one produce a portal insulin concentration that suppresses hepatic glucose production on awakening (8 hours after the last opportunity to inject insulin unless the patient is using an insulin infusion pump)?; and (2) How does one prevent nocturnal hypoglycemia when insulin concentrations in excess of metabolic needs arise during the early hours of sleep as a consequence of currently available crystal insulin preparations? The answer is the same for both questions, given the fact that all available intermediate and long-acting insulin preparations overinsulinize the patient during the early hours of sleep so that sufficient insulin is available on awakening: The prevention of hypoglycemia becomes entirely dependent on the prescription of nighttime snacks.

The success of diabetes management often depends on the patient's level of education about the disease process and motivation to adopt complex therapies, including insulin administration. However, the initiation of insulin therapy is often hindered by the patient's fear of taking insulin injections. Among the barriers to the use of insulin are the need to mix and inject insulin, the complexity of arriving at the best insulin regimen, and the practical limitations of the products themselves. Several methods have been devised to guide the initiation of insulin therapy in patients with type 2 diabetes. For example, Henry et al developed a stepwise approach that incorporates three clinical goals (50). Even the simplest plans may seem complex to many patients, and the need for four or more injections daily is daunting to many patients. Moreover, conventional insulin preparations have proven to have significant limitations, New delivery systems accompanied by smaller and finer needles have made delivery of insulin less painful. The ability to administer insulin using a device that has a preloaded cartridge of insulin and merely requires dialing to the desired dose has made insulin therapy much more reliable and safer in the visually impaired patients. The advent of recombinant insulin analogues has decreased the need for refrigeration and increased the flexibility in dosing insulin. Technological advances in continuous subcutaneous insulin pump therapy have made pumps feasible for all ages. The pumps now have the ability to provide more boluses per hour and increased the precision of the boluses. However, education of both patients and health care professionals remains a large barrier to initiation of insulin therapy. Increased understanding of the natural history and the progressive nature of type 2 diabetes, coupled with the growing awareness of the need for more effective treatment strategies and the significant improvements in insulin therapy merit the reassessment of the role of insulin in the treatment of type 2 diabetes.

III Types of regimens

Insulin has been used therapeutically for more than 75 years and remains the most powerful diabetes agent with almost unlimited potential to lower plasma glucose levels. Insulin therapy is capable of restoring near-normoglycemia in most patients with Type 1 and Type 2 diabetes. Hyperglycemia in early Type 2 diabetes is characterized by excessive postprandial glucose peaks related to meals along with elevated basal glycemia. This pattern consists of a fasting elevation of plasma glucose, with a superimposed additional elevation after each meal throughout the day, a nadir at approximately 0300, and, in some cases, an increase from the nadir prior to breakfast. Basal hyperglycemia

contributes more to total daytime hyperglycemia than the elevation after meals. In addition, the greater the basal hyperglycemia, the more this elevation dominates the total glycemic abnormality. The need for carefully timed overnight delivery of insulin is suggested by the presence of fasting hyperglycemia and the occurrence of the dawn phenomenon in many patients with type 2 diabetes.

Ideally, insulin replacement therapy should be modeled with insulin preparations that can reproduce the physiologic patterns of insulin secretion in response to the 24-hour postabsorptive and postprandial glucose profiles. The basal/bolus insulin concept is a physiologically sound regimen that attempts to mimic the normal insulin patterns to control glucose levels. The role of basal insulin is to suppress hepatic glucose production, so that the glucose levels remain constantly regulated overnight and also during prolonged periods between meals. Basal insulin meets about half of the patient's daily need for insulin and may be sufficient when considerable endogenous insulin remains. Bolus insulin (10% to 20% of the total daily insulin requirement given at each meal) limits hyperglycemia after meals. Administration of short acting (bolus) insulin tends to smooth the peaks of glucose that occur in response to these meals. Frequent glucose monitoring aids in optimizing the basal or mealtime regimens. Ideally, each component of insulin replacement therapy should come from a different type of insulin with a specific profile to fit the patient's needs. The basal/bolus insulin concept has long been used in the management of patients with Type 1 diabetes but can also apply to Type 2 diabetes. In fact, since both fasting and postprandial glucose levels are abnormal in type 2 diabetes and the underlying insulin deficiency typically progresses, most patients will need both basal insulin and mealtime insulin if excellent glucose control is to be maintained.

Continuous subcutaneous insulin infusion pumps are also an option for delivery of insulin. Despite the improvements in insulin kinetics with the new insulin analogs, the need to mix and inject insulin remains a barrier to patients' acceptance and compliance. Inhaled insulin preparations now under investigation are clearly very attractive, in that insulin is delivered in a non-invasive fashion removing the ultimate barrier of insulin injections. Pharmacokinetic studies have shown rapid peaks of action for inhaled insulin similar to lispro insulin but with slightly longer duration. Ongoing phase III studies in Type 1 and Type 2 diabetes, testing the efficacy and safety of inhaled insulin in different therapeutic scenarios are awaited with great interest. Oral insulins are in development, but none of these are yet commercially available.

Insulin Preparations

Over the years, multiple insulin preparations have been developed with recombinant DNA technology resulting in major improvements in purity but still with significant limitations in pharmacokinetics and pharmacodynamics after subcutaneous injections. Regular human insulin has a slow onset of action with delayed peak concentrations, as seen in Table 2, requiring patients to administer their injection 20-40 minutes prior to the meal in an attempt to improve the mismatch with the postprandial hyperglycemic peaks. This is inconvenient, is infrequently achieved, and poses the risk of premeal hypoglycemia if the meal is inadvertently delayed. Furthermore, the duration of action of regular insulin is much longer than the normal insulin peak following meals, typically at least 6 hours and up to 12 hours when large doses are injected. This

persistence of high insulin levels leads to risk of hypoglycemia, which is often countered by between-meal snacks that foster weight gain in type 2 diabetes patients.

Two short-acting insulin analogs, insulin lispro and insulin aspart, have absorption profiles that more closely match normal mealtime patterns(51,52). Small alterations in their amino acid structure relative to human insulin reduce their tendency to aggregate into pairs (dimers) or groups of six (hexamers) molecules, thus speeding their absorption after subcutaneous injection. Lispro and aspart have very desirable action profiles at mealtime because they have a rapid onset of action ranging from 5 to 15 minutes; the peak of action occurs 1 hour after injection, and the insulin effect practically vanishes 4 to 5 hours after administration. Their quick onset of action matches normal mealtime peaks of plasma insulin better than does human regular insulin. Clinical studies have shown that these properties lead to less prominent peaks of glucose after meals and less late postprandial hypoglycemia. However, rapid waning of the effects of mealtime lispro and aspart leads to greater dependency on adequate basal insulin levels between meals and overnight.

Table 1
- COMPARISON OF HUMAN INSULINS AND INSULIN ANALOGUES

Insulin Preparations	Onset of Action	Peak Action	Duration of Action *
Lispro/Aspart	5-15 minutes	1-2 hours	4-6 hours
Human Regular	30-60 minutes	2-4 hours	6-10 hours
Human NPH/Lente	1-2 hours	4-8 hours	10-20 hours
Ultralente	2-4 hours	Unpredictable	16-20 hours
Glargine	1-2 hours	Flat	24 hours

*The time course of action of any insulin may vary in different individuals, or at different times in the same individual. Because of this variation, time periods indicated are considered general guidelines only.

The intermediate-acting insulins, NPH and lente, have gradual onset and the peak effects is usually between 4 and 8 hours, with a total duration of 10 to 16 hours. Human ultralente insulin is somewhat longer acting, but still usually falls short of a 24-hour effect. NPH and lente have pronounced peaks of action, and ultralente is thought to have substantial day-to-day variation with erratic peaks. These limitations cause variations of glucose levels and unpredictable hypoglycemia, which are the leading factors limiting glycemic control at the present time. Recurrent hypoglycemia with insulin therapy of type 2 diabetes may be one factor in weight gain. Indeed, the lack of reproducibility in glucose-lowering effects of conventional basal insulin preparations, including NPH and ultralente, has been a major limitation for most insulin regimens. Consequently, development of insulin analogues has focused for many years on creating a long-acting 24-hour basal insulin replacement that would mimic normal pancreatic basal insulin secretion, to control hepatic glucose production in the postabsorptive state. Additionally. clinical use of insulin lispro, a better mealtime insulin than human regular, has directed attention to the properties of extended-release human insulins that have been used to provide basal insulin replacement. Human NPH, lente, and ultralente insulin all have mean durations of action of less than 24 hours, precluding them from providing adequate

basal insulin replacement for many patients. All three, but especially NPH and lente, have pronounced peaks of action. Ultralente is thought to have substantial day-to-day variation of action. These limitations cause variations of glucose levels and unpredictable hypoglycemia, which are the leading factors limiting glycemic control at the present time.

The first insulin analogue with a prolonged duration of action to be approved for clinical use is insulin glargine. Insulin glargine results from two modifications of human insulin: a substitution of glycine at position A21 and the addition of two positive charges (two arginine molecules) at the C terminal of the B chain(53). Changes in amino acid content shift the isoelectric point, reducing the aqueous solubility of insulin glargine at physiologic pH and stabilizing the hexamer, delaying its dissociation into monomers. In order to maintain insulin glargine in solution it is formulated at pH 4.0. It is released gradually from the injection site and because of the delay in absorption its action is prolonged, allowing a relatively constant basal insulin supply congruent with the basal insulin secreted by nondiabetic subjects. However, because insulin glargine is formulated as a clear acidic solution, it cannot be mixed with insulin formulated at a neutral pH, such as regular insulin. Lepore et al conducted pharmacokinetic studies of insulin glargine in 20 type 1 diabetes patients(53). Patients were studied in a two-way crossover clamp design after subcutaneous injection. Onset of action was more delayed with insulin glargine (median 1.1 vs. 0.7 hours, respectively) and more prolonged (median 22.8 vs. 13.8 hours, respectively) compared with NPH. Glucose-insulin clamp studies have compared the actions of insulin glargine with those of NPH and ultralente. In general, these studies have found that insulin glargine, compared with the other insulins provides an essentially flat profile with a longer duration for about 24-hours. Studies have demonstrated no variation in absorption rates at various injection sites (arm, leg, abdomen). Clinical trials have shown improvements in glycemic control similar to NPH, with significantly lower frequency of nocturnal hypoglycemia. Treatment to target has been shown to be feasible in a US study comparing evening basal insulin supplementation with insulin glargine vs. NPH following a structured insulin titration regimen in Type 2 diabetes patients on combination oral therapy. Use of the flat or peakless insulin glargine profile resulted in a 35% lower frequency of nocturnal hypoglycemia which now allows for a more vigorous titration regimen and more patients reaching target HbA1c of <7%. Insulin Detemir (NN304) is another long acting analogue that is undergoing clinical trials(54-57). Insulin detemir [LysB29(*N*_-tetradecanoyl) des(B30) human insulin] is a soluble insulin analog developed to ensure appropriate basal insulin supply. This analog exists in the presence of zinc and phenol, like native insulins, predominantly in the hexameric state. The fatty acid sidechain contributes to provide aggregation of hexamers, which can contribute to delay hexamer dissociation and absorption. In the monomeric state, the 14-C fatty acid chain attached to position B29 binds to binding sites on albumin. Because only the free fraction of insulin detemir is biologically active, albumin binding and the ensuing slow dissociation of the analog from the albumin further prolong the blood glucose–lowering action. The soluble formulation ensures a homogenous concentration, with no need for agitation before administration. Type 1 diabetics receiving detemir instead of NPH have not shown deterioration in glucose control in a pilot study (58). Detemir will have an additional advantage in that it will be soluble at comparable pHs so that it may be mixed with other currently available insulins thus not requiring an additional injection each day.

Patients who no longer respond adequately to oral agents will benefit from combination therapy that consists of maintaining the use of oral antidiabetic agents together with insulin therapy(59-77). The advantages of adding basal insulin to prior treatment with oral agents include the following: (1) only one insulin injection may be required each day, with no need for mixing different types of insulin; (2) the use of insulin pens can enhance patient acceptance of the treatment; (3) titration can be accomplished in a slow, safe, simple fashion; and (4) eventually combination therapy requires a lower total dose of insulin. The result is effective improvement in glycemic control while causing only limited weight gain.

Insulin Treatment Strategies

Bedtime NPH

A variety of strategies have been developed for initiating insulin therapy in patients with type 2 DM ranging from adding bedtime intermediate or long acting insulin to the pre-existing regimen or changing the patient's secretagogue to multiple shots per day of premixed or self-mixed insulin. One advantage of adding bedtime insulin is that the patient eases slowly into the idea of insulin therapy. Physiologically the rationale for this approach is that the high levels of insulin suppress the nocturnal hepatic glucose production thereby decreasing morning fasting hyperglycemia. Studies have show that this approach improves $HgbA_{1c}$ (46,77). Cusi and Cunningham examined the safety and clinical effects of using bedtime NPH insulin alone for 16 weeks to normalize the fasting plasma glucose in 12 obese male patients with type 2 diabetes who were poorly controlled with maximal sulfonylurea doses (78). The fasting plasma glucose (FPG) was normalized within 6 weeks and remained at target levels until the end of the study. Improved glycemic control was confirmed by a reduction in HbA_{1c} ($10.9\% \pm 0.05\%$ vs. $7.2\% \pm 0.2\%$, $p < .001$). The final mean insulin dose at week 16 was 80 ± 9 U/d (range 28-120 U). Treatment with bedtime NPH insulin did not cause excessive or severe hypoglycemia, as shown by the low incidence of mild or moderate hypoglycemic episodes. Bedtime NPH insulin significantly improved total cholesterol, LDL cholesterol, VLDL cholesterol, and triglyceride levels ($P < .01$). Weight gain was 2.4 ± 0.7 kg, and blood pressure was unchanged. Bedtime insulin was also accompanied by improved endogenous insulin secretion and insulin sensitivity.

Another strategy would be to add a long acting insulin in the form of insulin-glargine at bedtime. Insulin-glargine has been shown to decrease nocturnal hypoglycemia in patients with type 2 DM (79). Changes in $HgbA_{1c}$ were similar in one study comparing bedtime NPH and insulin-glargine in patients with type 2 DM (79). However, although studies are ongoing, there is no available data on the use of glargine bedtime monotherapy or in combination with oral agents

Bedtime dosing of insulin assumes that the patient still has adequate endogenous insulin production to respond to meals (perhaps with the help of a secretagogue). Frequently this is not the case and the patient must be changed from the secretagogue to a combination of long and short-acting insulin. There are a variety of premixed formulations which are often appropriate for use in type 2 DM. If the patient is able to monitor capillary blood glucoses (CBG) closely and mix their insulin then different combinations of shortacting and longacting insulin may be tailored to the individual's needs.

Twice-daily mixtures of NPH and regular insulins have been widely used for type 2 diabetes for many years. In some cases, premixed 70/30 insulin is used for this purpose. Patient profiles of insulin levels resulting from this method do not come close to matching the normal endogenous secretory pattern, shown in the shaded background. Patients with type 1 diabetes using this "split-mixed" regimen rarely achieve reasonably good glycemic control by present standards, since they lack endogenous insulin to supplement the partially adequate profile of injected insulin. Type 2 diabetes patients who have substantial endogenous insulin may fare much better with this regimen, but may experience late morning or nocturnal hypoglycemia because of excessive levels of insulin at these times.

Intermediate Plus Shortacting Insulin

Multiple daily doses of short acting insulin can be added when patients do not attain adequate control on oral agents plus bedtime insulin. Lindstrom and colleagues showed that this strategy may be effective in normalizing HbA$_{1c}$ but was best accomplished with 4 injection of regular per day(62). They performed a randomized crossover study of 8 weeks of oral hypoglycemic agents followed by 8 weeks of 2- or 4-dose insulin regimens. Mean blood glucose and free-insulin profiles show that patients taking the oral agents had higher blood glucose and lower postprandial insulin concentrations than those receiving insulin. When patients received the daily 4-dose regimen of preprandial regular insulin and intermediate-acting NPH insulin at 10:00 PM, glycemic control improved. The mean HbA$_{1c}$ was 8.8% during treatment with oral therapy compared with 5.6% on the 4-dose insulin regimen. Henry et al studied a group of 14 patients with type 2 diabetes to determine whether tight glycemic control can be obtained using conventional split-dose insulin therapy in an outpatient setting by aggressively titrating insulin therapy(50). Patients received conventional subcutaneous NPH and regular insulin before breakfast and supper for 6 months, with dose adjustments based on an algorithm built on frequent blood glucose measurements (4-6 times a day). The total dose of required exogenous insulin was 86 ± 13 U at 1 month and 100 ± 24 U at 6 months. One month after initiating intensive insulin therapy, day-long glycemia had improved to within normal range and remained at this level through month 6 of therapy. The HbA$_{1c}$, which was 7.7% ± 0.3% at baseline, decreased to 5.1% ± 0.2% at 6 months.

Combination Oral Agents + Insulin

Traditionally, it has been taught that most patients with type 2 diabetes require insulin – used as a "last resort" after maximal combination therapy has failed – 10 to 15 years after diagnosis of the disease. However, understanding of the natural history of type 2 diabetes suggests that insulin therapy should be started sooner rather than later and that insulin should be viewed as an essential therapeutic tool for achieving disease management goals, at an earlier stage in the natural progression of the disease, rather than a sign of failure on the part of the physician or patient. The fundamental issue is which regimen will achieve the target HbA$_{1c}$ of <7%. The oral agents can be divided into two general categories: those augmenting the supply of insulin by increasing the secretion of insulin into the portal circulation and those enhancing the effectiveness of insulin. Injected insulin, in turn, increases insulin in the systemic circulation. Because the mechanisms of action for these classes of oral agents differ, they may have complementary or additive effects and can help meet the individualized needs of patients. The sulfonylureas are oral agents that augment the supply of portal insulin. They increase

hepatic levels of endogenous insulin and enhance meal-mediated insulin release. Metformin and the thiazolidinediones are oral agents that enhance the effectiveness of insulin. Metformin improves insulin sensitivity at the liver and reduces hepatic glucose production. The thiazolidinediones improve insulin action in peripheral tissues and enhance glucose uptake. The α-glucosidase inhibitors have a different mechanism of action, decreasing postprandial glucose absorption by inhibiting digestion of complex carbohydrates and disaccharides, thereby retarding gastrointestinal glucose absorption. Several studies have demonstrated the success of a combination sulfonylurea and insulin regimen in patients with type 2 diabetes who do not respond to maximal sulfonylurea therapy. The combination of sulfonylurea and insulin has consistently shown an improvement in HbA1c as compared to continuation of usual care. The decrease in HbA1c when adding SU to insulin ranges from 0.8-2.6%, however most studies enrolled patients with initial HbA1c of 9.6-11.5%. This level of hyperglycemia suggests that the 'sulfonylurea failure' indicated very little residual beta cell function. If the insulin had been added to the therapy before the HbA1c rose to such a level perhaps the combination could have been more successful at bringing HbA1c s closer to the normal range. Specific strategies will be reviewed to address the efficacy of the different insulins in such combinations.

Ultralente Added to Sulfonylurea

A study by Holman et al involved 15 symptomatic, sulfonylurea-treated type 2 diabetic patients in a randomized crossover study of consecutive 8-week periods(80). The overnight mean basal plasma glucose level on sulfonylurea therapy was reduced to normal by adding ultralente insulin. Compared to ultralente insulin therapy alone, combining sulfonylurea with ultralente insulin therapy did not show significant differences in glucose control, but it did significantly lower the required insulin dose for restoring fasting normoglycemia. The study authors concluded that in type 2 diabetic patients who continue to have fasting hyperglycemia on maximal sulfonylurea therapy, the addition of a basal insulin supplement can easily result in normoglycemia. This regimen has not been widely utilized due to the intrasubject variability of ultralente. A similar study has been completed using insulin-glargine although the oral agents utilized were not specified. The protocol allowed continuation of the subjects prior regimen of oral antidiabetic agents (OADs) but the actual usage is not reported in the paper. Yki-Jarvinen et al showed that bedtime insulin-glargine was at least comparable to bedtime NPH in terms of lowering A1c when added to the patient's current OAD regimen (79). HgbA1cs decreased over 12 months from 9.1 and 8.9 to 8.34 ± 0.09% and 8.24 ± 0.09%, respectively, The use of insulin glargine compared with NPH was associated with less nocturnal hypoglycemia and lower post-dinner glucose levels.

Sulfonylurea Plus Bedtime NPH

Combining a sulfonylurea with bedtime insulin is an effective strategy to improve glucose control and to overcome secondary sulfonylurea failure. The rationale of combination therapy with sulfonylureas and insulin is based on the assumption that, if evening insulin lowers the fasting glucose concentration to normal, then daytime sulfonylureas will be more effective in controlling postprandial hyperglycemia and maintaining euglycemia throughout the day. Metabolic profiles of type 2 diabetics have clearly demonstrated that fasting blood glucose contributes more to daytime hyperglycemia than do postprandial changes. In addition, the fasting blood glucose

concentration is highly correlated with the degree of hepatic glucose production during the early morning hours. The initiation of insulin at bedtime while continuing the daytime sulfonylurea has been shown to result in significant decreases, although rarely normalizations, of HbA_{1c}.

Shank et al studied 30 subjects with type 2 diabetes in whom sulfonylurea (S) therapy had failed by switching them to the various combinations of bedtime insulin/daytime sulfonylurea (BI/DS) therapy in a double-blind fashion(81). To confirm sulfonylurea failure, subjects were switched to glipizide for 2 months (phase I) and then randomly assigned BI/DS, BI alone, and DS alone. During phase II, which lasted for 3 months, the BI dose was fixed (20 U/1.732 m^3, low dose). During phase III, which also lasted for 3 months, BI was titrated up (high dose) to achieve good control or until further dose increases were prevented by hypoglycemic symptoms. During phase IV, which lasted for 6 months, 25 of the original 30 subjects received open-labeled, high-dose BI/DS. Unlike low-dose BI alone or DS alone, low-dose BI/DS (phase II) markedly reduced FPG, mean 24-hour glucose, (8.9% ± 0.7% to 7.6% ± 0.3%), and basal hepatic glucose production. High-dose BI/DS (phase III) further reduced the HbA_{1c} to 7.1% ± 0.3%. During low-dose BI/DS therapy, glycemic control improved and all patients gained weight (2.1 ± 0.7 kg). In contrast, subjects who received the same dose of insulin without sulfonylurea had no improvement in glycemic control or weight gain. The study showed that combined BI/DS can achieve good long-term glycemic control for up to 1 year.

Similar results were obtained in an elderly population randomized to treatment with a two-injection scheme (regimen A) or a combination of glibenclamide with one injection of NPH insulin, administered either at bedtime (regimen B) or before breakfast (regimen C)(82). After 6 months of insulin treatment, fasting blood glucose of the total patient population had decreased from an average of 14.1 +/- 2.2 to 8.3 +/- 2.0 mmol/L ($P < 0.001$), and HbA_{1c} fell from 11.0 +/- 1.3 to 8.3 +/- 1.2% ($P < 0.001$); 34 patients reached HbA_{1c} levels below 8.0%, 25 of them even below 7.5%. With two insulin injections daily, HbA_{1c} decreased from 11.2 +/- 1.3 to 8.2 +/- 1.2%, while during combined treatment, HbA_{1c} fell from 10.5 +/- 1.2 to 8.1 +/- 1.1% (regimen B) and from 11.1 +/- 1.3 to 8.5 +/- 1.1% (regimen C).

Suppertime 70/30 Added to Glimepiride

Combination oral agents/insulin therapy has been shown to improve glycemic control. It also simplifies the insulin regimen, allows the use of lower doses of exogenous insulin, provides greater convenience, and potentially enhances compliance. These advantages were confirmed in a recent clinical trial involving severely hyperglycemic patients who had failed to respond to oral sulfonylureas (83). A total of 145 patients were randomized to receive either glimepiride or placebo in combination with insulin (70/30 at supper). Glimepiride produced a much more rapid decrease in FPG levels compared with placebo. A 2% reduction in mean HbA_{1c} values was comparable in the two treatment groups after 24 weeks (9.7% to 7.6%, glimepiride plus insulin; 9.9% to 7.9%, placebo plus insulin); however, glimepiride demonstrated a significant insulin-sparing effect, with a 38% reduction of insulin requirements allowing for more patients to use only one injection of insulin 70/30 at supper. In addition, glycemic control was restored more rapidly and with less injected insulin when glimepiride was continued.

Shortacting Insulin plus Sulfonylurea

Most combination therapy studies have addressed adding long acting insulin to secretagogue therapy with the goal of reducing overnight hepatic glucose production and fasting blood glucose resulting in improvement but not normalization of the HbA1c. Recognition of the impact of postprandial glycemia on the HbA1c raises the possibility that augmenting the postprandial insulin levels with shortacting insulin may further decrease HbA1c. Bastyr et al addressed this possibility by comparing the addition of Lispro or NPH insulin or metformin to glyburide therapy(84). A total of 135 patients were randomly assigned for 3 months to one to three combination regimens. All participants received glyburide (G) and in addition received Lispro (L) insulin to address postprandial blood glucose (the L+G group); bedtime NPH insulin to target FPG (the NPH+G group); or metformin, to target mainly overnight FBG (the M+G group). At the end of 3 months, as expected, FBG was significantly lower for the NPH+G group (153 ± 41 mg/dL) than for either the L+G group (190 ± 36 mg/dL) or the M+G group (175 ± 52 mg/dL), and the mean 2-hour postprandial glucose level after a test meal was significantly lower for the L+G group (195 ± 52 mg/dL) than for the NPH+G group (220 ± 56 mg/dL) or the M+G group (228 ± 59 mg/dL). The HbA1c, however, was significantly lower for the L+G group (7.68 ± 0.88%) than for either the NPH+G group (8.51 ± 1.38%, $P = 0.003$) or the M+G group (8.31 ± 1.31%, $P = 0.025$). The overall rate of hypoglycemia was low, and the difference among groups was not statistically significant, but, as expected, all the insulin-treatment groups had weight gain. Thus, antihyperglycemic therapy with Lispro insulin, focusing on postprandial glucose control, has a greater impact on overall metabolic control than do the more traditional approaches of NPH insulin at bedtime or metformin. Lispro insulin remains a treatment option in this patient population. The data from this study raises the question of whether short acting mealtime insulin, instead of basal insulin, should be used in combination with oral agents.

Combination Oral Agents + Mealtime Insulin

An alternative concept for starting insulin therapy is to use mealtime insulin therapy to improve the postprandial hyperglycemic peak and to leave the oral agent (sulfonylureas with or without sensitizing agents, such as metformin or a thiazolidinedione) to provide the endogenous basal insulin. Following persistent hyperglycemia despite the use of an oral agent, premeal bolus insulin can be started as part of combination treatment with oral agents. For example, short-acting lispro insulin, which is taken immediately before a meal, can be combined with an oral agent. Browdos et al examined the glycemic effect of adding preprandial lispro or metformin or bedtime NPH regimens to existing sulfonylurea therapy in 131 patients with chronic hyperglycemia (HbA1c > 8.5%)(85). At 3 months, HbA1c was lower in all three groups, but greater reductions occurred in the 41 patients who received the mealtime lispro regimen in addition to the sulfonylurea. As expected, however, this improvement in glycemic control was associated with the greatest weight gain.

Glyburide/Metformin ± Insulin

Several studies have included triple drug therapy with a secretagogue, metformin and insulin (46,86,87). In each case the insulin was added to treat "failure" of pre-existing oral therapy. To evaluate the optimal regimen of insulin treatment in patients with type 2 diabetes who do not respond to oral agents, Yki-Jarvinen et al conducted a large study in Finland with 153 patients who had had type 2 diabetes for more than 3 years, with a body-mass index (BMI) above 35 kg/m^2, and who had not responded to maximum-dose

sulfonylurea alone or with metformin. These patients were randomly allocated to one of five groups. The morning-NPH group continued oral hypoglycemic (usual) therapy and received NPH insulin before breakfast. The evening-NPH group continued usual therapy and received NPH insulin at 2100 hours. The two-insulin-injection group discontinued usual therapy and took insulin (NPH and regular insulin in a ratio of 70/30 two times/day). The multiple-injection group took NPH insulin at 2100 hours and regular insulin before all meals. Control patients continued usual medications. Insulin doses were adjusted to maintain normoglycemia. hypoglycemic drug therapy (the control group). The mean (+/- SE) value for glycosylated hemoglobin decreased similarly in all four insulin-treatment groups (1.7 +/- 0.3, 1.9 +/- 0.2, 1.8 +/- 0.3, and 1.6 +/- 0.3 percent, respectively). The decrease was significantly greater in these four groups than in the control group (0.5 +/- 0.2 percent; $P < 0.001$ vs. all insulin-treated groups). Weight gain was significantly less (1.2 +/- 0.5 kg) in the evening-NPH group than in the other insulin-treatment groups (2.2 +/- 0.5 kg in the morning-NPH group, 1.8 +/- 0.5 kg in the two-insulin-injection group, and 2.9 +/- 0.5 kg in the multiple-injection group; $P < 0.05$). There was no evidence of severe hypoglycemia with combination therapy, and patient acceptance was excellent. Thus, in patients with type 2 diabetes who do not respond to oral hypoglycemic drug therapy, the addition of NPH insulin in the evening improves glycemic control in a manner similar to combination therapy with NPH insulin in the morning, a two insulin-injection regimen, or a multiple-insulin-injection regimen but induces less weight gain and hyperinsulinemia.

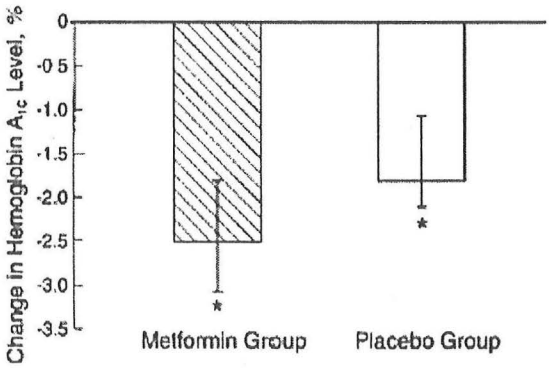
The possibility of adding once or twice daily NPH insulin without short acting insulin was further explored by Yki-Jarvinen et al in the FINFAT study which was conducted in four centers in Finland(46). Ninety-six patients with type 2 diabetes who were inadequately controlled with sulfonylurea therapy alone were randomly assigned to receive four different regimens in addition to bedtime NPH insulin: glyburide, metformin, glyburide + metformin, or a second injection of NPH insulin in the morning. Insulin therapy was started if FPG levels exceeded 144 mg/dL. The patients were instructed to self-adjust the evening insulin dose if their FPG level was elevated. The adjustments were made in increments of 4 IU/d if FPG exceeded 144 mg/dL or by 2 IU/d if FPG exceeded 108 mg/dL on 3 consecutive days. HbA_{1c} values were similar among the groups at 6 weeks before therapy and at 0 weeks. The goal was to decrease FPG levels to <108 mg/dL (<6 mmol/L, which was predicted to decrease the HbA_{1c} value to <7.5%). After 12 months of therapy, patients were evaluated to determine the effects of these regimens on glycemic control, weight, and frequency of hypoglycemic episodes. Unlike the other patients, patients receiving bedtime insulin plus metformin showed a progressive decrease in glycosylated hemoglobin values over time. At 12 months, glycosylated hemoglobin values in this group averaged $7.2\% \pm 0.2\%$; this change and the absolute change (-2.5 ± 0.4 percentage points) differed significantly from that seen in the other groups. Analysis of this study suggested that self-adjustment of the insulin dose and the addition of metformin produced slightly better overall glucose control, less weight gain, and the lowest frequency of hypoglycemic episodes. However, the group receiving metformin alone in addition to the insulin had the highest dropout rate, with 21% of patients not completing the trial. The investigators of this study attributed the improved glycemic control seen across treatment groups to successful patient education regarding adjustment of insulin doses. Although it was expected that patients receiving only one

oral drug in addition to bedtime insulin would require greater increases in the insulin doses than those receiving both oral drugs, this was not the case. Patients who received metformin had greater insulin requirements than those who received the sulfonylurea, who had a higher frequency of symptomatic, mild hypoglycemic episodes.

Metformin + insulin

Metformin has been included in a number of combination therapy studies either as part of the oral regimen that is "failing" or as the add-on therapy as compared to an insulin regimen. There are several studies that have taken a different approach in using metformin as the 'add-on' therapy with significant improvements in HbA1c(46-48,88-90). The addition of metformin to pre-existing insulin therapy was first shown to have efficacy beyond that of continuing insulin alone in a study by Giugliano et al in 1993. Subsequently, several studies have addressed this strategy with decreases in HbA1c between 1-2.5%. The largest drop occurred when Aviles-Santa et al treated 43 T2DM patients with intensive insulin therapy plus placebo or metformin. The goal of this study was to maximally decrease HbA1c instead of the traditional goal of minimizing insulin dose. In fact, insulin dose could be increased if necessary to further lower HbA1c. Hemoglobin A1c levels decreased by 2.5 percentage points (95% CI, 1.8 to 3.1 percentage points) in the metformin group, a significantly greater change (p=0.04) than the decrease of 1.6 percentage points in the placebo group. Average final HbA1c levels were 6.5% in the metformin group and 7.6% in the placebo group (difference, 11%). For patients who received placebo, the insulin dose increased 22.8 units (CI, 11 to 44 units) or 29% more than did the dose for patients who received metformin (p=0.002); for these patients, the insulin dose decreased slightly. The strategy of adding metformin to insulin can result in significant improvements in HbA1c, especially when insulin dose is not decreased.

Figure 2 Change in Hemoglobin A1c from baseline to 24 weeks



Thiazolidinedione + insulin

The clinical availability of the thiazolidinediones in 1997 introduced the possibility of improving of insulin sensitivity in the muscle, liver and adipose tissue while also providing high levels of exogenous insulin which can now be effective in the sensitized tissues. The first study to demonstrate the efficacy of this combination was utilizing troglitazone which is no longer available in the United States due to idiosyncratic hepatotoxicity (91). Subsequently, the addition of rosiglitazone to insulin in

poorly controlled, insulin-treated type 2 diabetes showed a dose related decrease in A1cs over the 24 weeks of the study(92). Glycemic control was unchanged in the patients who continued on their insulin plus placebo. By intent-to-treat analysis, treatment with rosiglitazone (8 mg) plus insulin resulted in a mean reduction from baseline in HbA_{1c} of 1.2% ($P < 0.0001$), despite a 12% mean reduction of insulin dosage. Over 50% of subjects treated daily with high dose rosiglitazone (8 mg) plus insulin had a reduction of $HbA_{1c} \geq 1.0\%$. These initial studies show that this combination will be of clinical use but further studies are needed to determine the optimal way to initiate this combination and whether it should be used along with other agents to maximally decrease HbA_{1c}.

Acarbose plus Insulin

Several studies have added acarbose to pre-existing insulin therapy with modest reductions in A1cs. The first two studies allowed reduction in insulin dose which may have minimized the effectiveness of the combination (93,94). However, Kelley et al performed a 24 week multicenter randomized double-blind placebo-controlled parallel-group comparison study(95). The dosage of insulin was to remain stable with forced titration of acarbose from 25 mg t.i.d. to 50 mg t.i.d. after 4 weeks, and titration of 50 mg t.i.d. to 100 mg t.i.d. after 12 weeks based on glucose control. Acarbose treated patients had a mean insulin dosage of 62.0 U/day, and placebo treated patients had a mean insulin dosage of 60.2 U/day. A principal goal of the study was to keep insulin doses constant throughout, and visits that followed changes in insulin dosages were judged invalid for the efficacy analyses. In the placebo-treated group, 77 of 96 patients maintained precisely the same dosages of insulin throughout the study as did 78 of 96 acarbose-treated patients. Among the placebo-treated patients, 8% had increases and 12% had decreases in the daily insulin dosage. In comparison, among the acarbose-treated patients, 7% had increases and 12% had decreases in the daily insulin dosage. Thus, insulin changes were comparable between the treatment groups. The addition of acarbose to the treatment of patients receiving background insulin and diet therapy resulted in a statistically significant reduction in mean HbA_{1c} of 0.69% compared with placebo. The addition of acarbose to previous insulin therapy produced a slight but nonsignificant reduction in fasting plasma glucose compared with placebo ($P = 0.4221$). Acarbose did significantly lower postprandial hyperglycemia compared with placebo, and this effect was evident at 60 min ($P = 0.0178$), 90 min ($P = 0.0004$), and 120 min ($P = 0.0001$) after standardized meal challenges. This study demonstrates how two agents with different but complementary modes of action can facilitate improvement in HbA_{1c}.

Of note, most the study designs in the combination therapy trials have been based on the addition of an oral agent to patients already treated with insulin, a strategy that is fundamentally different from that used in clinical practice and in the glimepiride study. The addition of insulin 70/30 to pre-existing oral therapy, glimepiride, eases the transition from oral sulfonylurea treatment to insulin. Adding insulin in the evening is a simple and effective strategy that can be regarded as "bridge therapy." It allows patients to overcome their initial resistance to start using insulin, especially when administered with an insulin pen, facilitating long-term acceptance and compliance.

When an oral agent is combined with insulin, a few management guidelines should be kept in mind. The oral agent(s) should be continued in the same combination regimen, along with consistent blood glucose self-monitoring. NPH or glargine insulin at bedtime, or alternatively insulin 70/30 at the evening meal, can be given. The initial

insulin dose should be determined according to the patient's weight and blood glucose levels, but the average safe starting dose is usually around 8 to 10 units at PM with subsequent adjustments according to blood glucose monitoring. An easy and conservative algorithm that can be adapted according to the individual circumstance is to adjust the insulin dose if the FBG level is >180 mg/dL; the dose may be increased by 4 U/week, and if the level is between 140 and 180 mg/dL, the dose may be increased by 2 U/week. It is very important that patients continue the oral agents at the same dosage and eventually reduce this dose when appropriate. Conservatively, a single insulin dose of around 10 U of NPH given at bedtime or 70/30 insulin given at the evening meal is a standard initial approach to treatment. Basal insulin glargine has the potential to facilitate and extend the use of this insulin strategy because of its long duration of action, peakless flat profile, more predictable response, and reduced risk of hypoglycemia. Insulin glargine is given once daily at bedtime, but based on its insulin kinetics, it could theoretically be given at any time. The insulin dose should be adjusted according to the fasting SMBG level. The insulin dose can be increased on a weekly basis as needed. It should be increased by 4 U if the fasting blood glucose (FBG) is greater than 140 mg/dL, and by 2 U if the FBG is 120 to 140 mg/dL. The treat-to-target level is usually an FBG < 120 mg/dL.

Clinical judgment should prevail when determining whether an advance to a basal/bolus insulin regimen is indicated, especially when the fasting blood glucose is acceptable, but this should be considered when the HbA_{1c} is >7% or >7.5% suggesting postprandial hyperglycemia, and/or the SMBG before dinner is >180 mg/dL. There are three main insulin options. The first option is to add morning NPH and mealtime regular or lispro to the initial regimen of bedtime NPH insulin. The second option is to add morning 70/30 to suppertime 70/30 insulin. The third option is to add mealtime regular or lispro to bedtime insulin glargine. In terms of options for the oral agent, the sulfonylurea may be stopped, but some patients may develop wide fluctuations in blood glucose levels that require resumption of the sulfonylurea or the addition of short acting insulin. For some patients, metformin can be continued to provide weight control, or glitazone can be continued to achieve glycemic stability.

Future Therapies

A number of treatment approaches involving combination therapy with new insulin preparations may prove viable in the future. Such approaches include the use of combination oral agents + basal insulin glargine, combination oral agents + bolus inhaled insulin, and basal insulin glargine + bolus inhaled insulin. The combination oral agents may consist of a sulfonylurea plus metformin and/or a thiazolidinedione. Basal insulin glargine has the advantage of providing prolonged action that may last up to 24 hours, with the relatively constant supply of basal insulin resulting from the continuous release of insulin from the injection site. Compared to injections, bolus inhaled insulin may provide mealtime insulin in a less invasive route of administration, which most patients would probably prefer. The combination of a long-acting insulin, such as glargine, and prandial inhaled insulin may mimics physiologic insulin effects in response to meals and allow normalization of HbA_{1c} without unacceptable incidence of hypoglycemia.

The concept of inhaled insulin has been explored for those patients with type 2 diabetes who resist initiating insulin therapy because it requires injections. As a response to this resistance, a dry powder aerosol delivery system of human insulin has been

developed. Weiss et al examined the ability of mealtime inhaled insulin to improve glycemic control in 69 subjects(96). Patients were randomized to a 3-month treatment period of either continued oral agents alone (sulfonylurea and/or metformin) or in combination with 1 or 2 puffs of inhaled insulin before meals. The inhaled insulin doses were titrated based on glucose testing 4 times daily. Patients continuing on oral agents alone had a 0.13% decrease in HbA_{1c} at 12 weeks, while those receiving the inhaled insulin in addition to the oral agents improved their HbA1c (-2.28%).

Who Should Receive Insulin?

There are certain patients with hyperglycemia who must be treated with insulin from the time of diagnosis. While it is obvious that type 1 diabetics require insulin, patients do not always present with a clinical picture that is clearly insulin deficient or insulin resistant. Therefore, if a patient has any amount of ketosis at presentation one should initiate insulin therapy. Diabetic ketoacidosis (DKA) is no longer pathognomonic of type 1 diabetes. Idiopathic type 1 diabetes, as recently described by Pinero et al based on our experience here at Parkland Memorial Hospital, typically presents in an obese subject who has lost significant amounts of weight and has mild ketosis but may have frank DKA(97). These patients have dramatic decreases in their insulin requirements in the subsequent months from diagnosis then often get switched to oral agents. However, they do not do well on oral agents, based on increasing HbA_{1c} and lack of weight regain, thus should be treated with insulin as part of their regimen to replace their inability to produce adequate amounts of insulin. Insulin therapy should also be used in surgical patients to facilitate wound healing in addition to preventing mortality, as recently demonstrated in undiagnosed type 2 diabetics in Surgical ICUs in Belgium (99).

However, the failure of the β-cell to be able to compensate for decreasing insulin sensitivity plays a critical role in the development of hyperglycemia. Historically physicians have attempted to compensate by treating patients with secretagogues with poor success as evidenced by the increasing trend in HbA_{1c} (>9.0% in the NHANES III) along with the increasing death rate and the prevelance of complications. This lack of success in controlling hyperglycemia suggests that we have not provided adequate levels of insulin to the insulin resistant tissues thus raising the question of what is the role of secretagogues in managing type 2 diabetes?

The inability of metformin to control HbA_{1c} in the UKPDS further supports the concept that sufficient circulating insulin is needed to maintain normoglycemia. Whether the thiazolidinediones will have any better success at preventing the rise in HbA_{1c} is under study at this time. However, the thiazolidinediones do need insulin to be effective so very few patients will be able to normalize their HbA_{1c} with such monotherapy.

Type 2 diabetes is a chronic, progressive disease. As hyperglycemia worsens, it is associated with an increasing prevalence of serious complications (98). The UKPDS trial has clearly demonstrated that the risk of complications can be reduced by improved glycemic control through early, combination therapy. The increased emphasis on early, aggressive treatment, coupled with the expanding arsenal of oral agents, has led to an emphasis on treating type 2 diabetes with oral agents that improve insulin resistance. We must not lose sight of the fact that the body's inability to produce adequate amounts of insulin is one of the major reasons the hyperglycemia develops. Intensive therapy to improve control of type 2 diabetes and prevent its complications will greatly enhancing the quality of life for patients with this disease.

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