Diabetes Mellitus Type 2 Evidence-Based Drivers

**Driver One:** Reducing blood glucose levels and HbA1c levels reduces the risk of diabetic complications. Intensive therapy has been shown to be superior to conventional therapy in terms of reducing glycemia and diabetic complications.

**Driver Two:** When monotherapy with an oral agent is no longer adequate, combination therapy with 2 or more oral agents has been shown to significantly improve glycemic control.

**Driver Three:** When combination oral therapy is no longer adequate, insulin can be added to the regimen to significantly improve glycemic control.

**Driver Four:** Benefits of insulin therapy, such as improved outcomes and glycemic control, outweigh risks such as the potential for inducing hypoglycemia.

**Driver Five:** Type 2 diabetes mellitus is a disease consisting of two components insulin resistance and insulin deficiency.

Combination Oral Therapy in Treatment of Type 2 Diabetes

**Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus.**

Authors and/or Affiliation: DeFronzo RA, Goodman AM, and The Multicenter Metformin Study Group. Diabetes Division, University of Texas Health Science Center.


Endpoint: Plasma glucose, lactate, lipids, insulin, and glycosylated hemoglobin were measured before, during, and at the end of the studies.

Study design: Randomized, double-blind, parallel-group, controlled. Two trials were completed: protocol 1, metformin vs. placebo; and protocol 2, metformin vs. glyburide vs. metformin and glyburide.

Summary

Combination oral therapy is effective in treating type 2 diabetes since:

- Patients with a poor response to maximal doses of a sulfonylurea received combination metformin and glyburide, the combination lowered plasma glucose and glycosylated hemoglobin (HbA1c) levels.
- 22% of patients on combination therapy had fasting plasma glucose (FPG) = 140 mg/dl after 29 weeks, while only 3% of patients in the metformin group had FPG = 140 mg/dl.
and only 2% in the glyburide group achieved FPG = 140 mg/dl.

· Metformin and glyburide together is superior to either drug as monotherapy in lowering HbA1c and FPG.

Diabetes is the Result of Insulin Resistance and Insulin Deficiency

Impaired glucose tolerance as a disorder of insulin action. Longitudinal and cross-sectional studies in Pima Indians.

Authors and/or Affiliation: Lillioja S, Mott DM, Howard BV, et al.


Endpoints: Insulin action and secretion from normal to after the development of impaired glucose tolerance.

Study design: Longitudinal, cross-sectional of Pima Indians.

Summary

This study helps demonstrates that diabetes mellitus type 2 has a dual pathogenesis, insulin deficiency and insulin resistance:

· Individuals with impaired glucose tolerance (IGT) are at an increased risk for developing diabetes mellitus type 2.
· Subjects with IGT are insulin resistant (have impaired insulin action), but have normal pancreatic function (no secretory deficiency).
· Subjects with diabetes mellitus type 2 are both insulin resistant and have pancreatic secretory deficiency because:
   o As glucose concentrations increase, plasma insulin concentrations decrease; this suggests insulin deficiency.
   o During hyperinsulinemia, subjects with IGT are less likely to suppress hepatic insulin production than normal subjects suggesting insulin resistance.

The Importance of Glucose Control in Diabetes

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33).

Authors and/or Affiliation: UK Prospective Diabetes Study (UKPDS) Group.


Endpoints: Any diabetes-related endpoint (sudden death, death from hyper- or hypoglycemia, fatal or non-fatal MI, angina, heart failure, stroke, renal failure,
amputation of at least 1 digit, vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in 1 eye, cataract extraction), diabetes-related death (MI, stroke, peripheral vascular disease, renal disease, hyper- or hypoglycemia, sudden death), all-cause mortality.

Study design: Randomized, intent to treat, controlled trial.

Summary

Intensive glucose control is an important aspect of managing patients with diabetes because:

· Treating 19.6 patients for 10 years will prevent one patient from developing any of the single (adverse) endpoints.
· The follow-up point at which at least 50% of patients had at least one diabetes-related endpoint is 14.0 years in the intensively treated group (sulfonylurea or insulin) versus 12.7 years in the conventionally treated group (diet).
· Patients on intensive treatment had a 25% risk reduction in microvascular endpoints when compared to conventional treatment. Most of the reduction was due to fewer cases of retinal photocoagulation.
· At six-years of follow-up, a smaller proportion of intensively treated patients had two-step deterioration in retinopathy than conventionally treated patients.
· An 11% reduction in median HbA1c over the first 10 years of the study decreased the frequency of some complications of type 2 diabetes.


Authors and/or Affiliation: American Diabetes Association.


Endpoint: N/A.

Study design: Position/consensus statement

Summary

The American Diabetes Association (ADA) recognizes the importance of intensive glucose control. The following statements are evidence for preferentially using intensive therapy in diabetes:

· A primary treatment goal in type 1 diabetes is to achieve blood glucose control at least equal to that of the intensively treated group in the DCCT (Diabetes Control and Complications Trial). In the intensive treatment group, mean glucose values were approximately >40% above normal limits.
· Over the 7 years of the DCCT, there was approximately a 60% reduction in risk of
diabetic retinopathy, nephropathy, and neuropathy in the intensive versus conventionally treated group.
· Intensive therapy resulted in a delayed onset and slowed progression of retinopathy, nephropathy, and neuropathy.
· To achieve tight control in type 1 diabetes, multiple daily injections of insulin or an insulin pump can be employed. The choice is dependent on the patient and the healthcare team.

Relation of glycemic control to diabetic complications and health outcomes.

Authors and/or Affiliation: Klein R, Klein BE.


Endpoints: Relationship of HbA1c to quality of life.

Study design: Multicenter, patient questionnaire and HbA1c measurements.

Summary
Control of blood glucose is important in diabetes because:

· Greater than half of the risk of common complications of diabetes was attributable to high HbA1c in both younger-onset and older-onset patients, regardless of whether they use insulin.
· The preliminary results of this study strongly suggest a relationship between increased HbA1c and decreased quality-of-life.
· Decreased quality-of-life may be due to increased glycemia or the complications of diabetes.

Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study.


Endpoint: The primary clinical outcomes are any endpoint or deaths related to diabetes and all cause mortality. Secondary outcomes are myocardial infarction, stroke, amputation, and microvascular disease. Single endpoints are non-fatal heart failure and cataract extraction.

Study design: Prospective observational

Summary
Glucose control is essential in managing diabetes because:

- This study demonstrates that the risk of complications of diabetes is directly related to glycemia levels over time.
- For every 1% reduction in HbA1c, there is a 37% decrease in risk of microvascular complications and a 21% decrease in the risk of any endpoint or death related to diabetes.
- The adjusted rate of diabetes related complications in patients with HbA1c <6% is 35.9 per 1000 person years, however as HbA1c levels increase, the adjusted rate of complications increases to 124.9 per 1000 person years in patients with an HbA1c =10%.
- The lower the level of glycemia, the lower the risk of complications. However, for all clinical outcomes that were evaluated, there was no threshold of glycemia, which substantially altered the risk of complication.
- Hyperglycemia is associated with an increase in the rate of microvascular as well as macrovascular disease.

**Oral Hypoglycemic Agent Plus Insulin Improves Glucose Levels**

**Efficacy of insulin and sulfonylurea combination therapy in type II diabetes.**

Authors and/or Affiliation: Johnson JL, Wolf SL, Kabadi UM.


Endpoints: Efficacy of sulfonylurea and insulin combination in type 2 diabetes.

Study design: Meta-analysis of randomized placebo controlled trials.

Summary

Combination therapy with insulin and a sulfonylurea:

- Improved metabolic control and significantly lowered fasting serum glucose and HbA1c concentrations when compared to insulin monotherapy.
- Improved metabolic control and resulted in lower daily insulin doses.
- Increase the fasting C-peptide concentration, which suggests enhanced insulin secretion.
- Reduced daily insulin doses and improved metabolic control without significant weight alterations. This suggests that insulin action at the receptor may be improved (an established effect of sulfonylureas).

Insulin lispro in the treatment of patients with type 2 diabetes mellitus after oral agent failure.

Authors and/or Affiliation: Bastyr EJ III, Johnson ME, Trautmann ME, et al and the IOCE Study Group.

Endpoint: Safety and efficacy of insulin lispro plus a sulfonylurea.

Study design: Randomized, open-label, clinical trial.

Summary

When pre-meal insulin lispro (L) is combined with sulfonylurea therapy, the combination improves glycemic control as evidenced by the fact that:

- Preprandial (pre-meal) lispro plus a sulfonylurea or bedtime NPH lowered post-meal blood glucose levels compared to patients on bedtime NPH plus sulfonylurea.
- Patients receiving preprandial lispro and a sulfonylurea had the lowest rate of nocturnal hypoglycemia and, when compared to baseline, the greatest mean improvement in HbA1c at the final visit.
- The mean blood glucose excursion was significantly lower for preprandial lispro plus sulfonylurea or bedtime NPH versus bedtime NPH plus sulfonylurea.
- However, fasting blood glucose levels were higher in patients receiving preprandial lispro plus sulfonylurea or bedtime NPH than in subjects on bedtime NPH plus sulfonylurea.

Comparison of insulin with or without continuation of oral hypoglycemic agents in the treatment of secondary failure in NIDDM patients.

Authors and/or Affiliation: Chow CC, Tsang LW, Sorensen JP, Cockram CS.


Endpoint: Insulin dose, body weight, glycemic control, and quality of life.

Study design: Randomized, controlled clinical trial.

Summary

Patients with uncontrolled glucose levels on a maximum dose of sulfonylurea and/or metformin can be controlled with insulin as evidenced by the fact that:

- Addition of NPH insulin 30 minutes before bed (or by 11 PM) or replacement of oral hypoglycemic agents (OHAs) with insulin alone improves fasting plasma glucose at 3 and 6 months.
- Addition of NPH at bedtime or replacement of OHAs with insulin significantly improves HbA1c at 3 and 6 months.
- Insulin alone may provide a more rapid effect on improving fructosamine levels at 3 months.
· However, about 26% of patients did not respond at 6 months. HbA1c of 8.9% or fructosamine =375 µmol/l at 6 months indicated no response.

Benefits Versus Risks of Intensive Therapy in Type 2 Diabetes

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33).

Authors and/or Affiliation: UK Prospective Diabetes Study (UKPDS) Group.


Endpoints: Any diabetes-related endpoint (sudden death, death from hyper- or hypoglycemia, fatal or non-fatal MI, angina, heart failure, stroke, renal failure, amputation of at least 1 digit, vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in 1 eye, cataract extraction), diabetes-related death (MI, stroke, peripheral vascular disease, renal disease, hyper- or hypoglycemia, sudden death), all-cause mortality.

Study design: Randomized, intent to treat, controlled trial.

Summary

The benefits of intensive blood-glucose control with either insulin or sulfonylureas in type 2 diabetes are proven to outweigh the risk of weight gain because:

· Treating 19.6 patients for 10 years will prevent one patient from developing any of the single endpoints.
· The follow-up point at which at least 50% of patients had at least one diabetes-related endpoint is 14.0 years in the intensively treated group versus 12.7 years in the conventionally treated group (diet).
· Patients on intensive treatment had a 25% risk reduction in microvascular endpoints when compared to conventional treatment.
· At six-years of follow-up, a smaller proportion of intensively treated patients had two-step deterioration in retinopathy than conventionally treated patients.
· An 11% reduction in median HbA1c over the first 10 years of the study decreased the frequency of some complications.