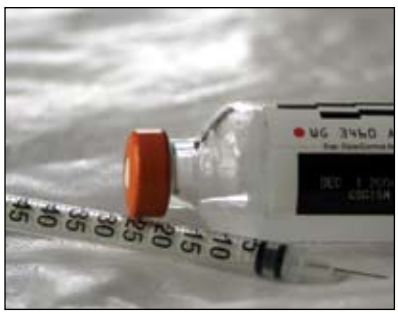
Insulin Update



Controversies Over Insulin as Initial Treatment of Type 2 Diabetes

Early insulin treatment may temporarily improve endogenous insulin secretion, which will result in better glycemic control, explained Michael Alvarsson, MD, PhD, Karolinska University Hospital, Stockholm, Sweden.

The possible benefits of early insulin treatment on insulin secretion are the effects of rapid normalization of blood glucose similar to other glucose-lowering agents ("more or less proven"), and the potential benefit of "beta cell rest" (not proven), according to Dr. Alvarsson.

Ineffective or inappropriate treatments expose patients to hyperglycemia and increase the risk of micro and macrovascular complications. The potential benefits of the early initiation of insulin are rapid glycemic control, possibly at lower insulin doses needed to achieve glycemic targets, lower risk of hypoglycemia and lower risk of weight gain due to smaller doses of insulin. The early addition of insulin when maximal sulfonylurea therapy is inadequate can significantly improve glycemic control without promoting weight gain or increased hypoglycemia (Wright A, et al. *Diab Care* 2002). One study showed that when insulin was started in patients with newly-diagnosed type 2 diabetes and then stopped after near euglycemia was achieved, about 50% of individuals required oral drugs and a few required insulin within a year (*Diab Care* 2004).

"We need to start insulin treatment earlier than we do now, initiate insulin treatment more than we do now, and realize that quality of life is not affected in a negative way by insulin treatment," stated Dr. Alvarsson.

Should insulin be the initial treatment for type 2 diabetes? Not according to Mayer B. Davidson, MD, UCLA School of Medicine, Los Angeles, CA. Dr. Mayer explained that the treatment of markedly symptomatic type 2 diabetic patients involves a number of therapeutic considerations: >90% can be successfully treated with sulfonylureas (max doses in patients <65; ½ max dose in patients >65), and insulin should be used only if oral agents do not bring patients to target (Peters AL, et al. *J Clin Endocrinal Metab* 1996).

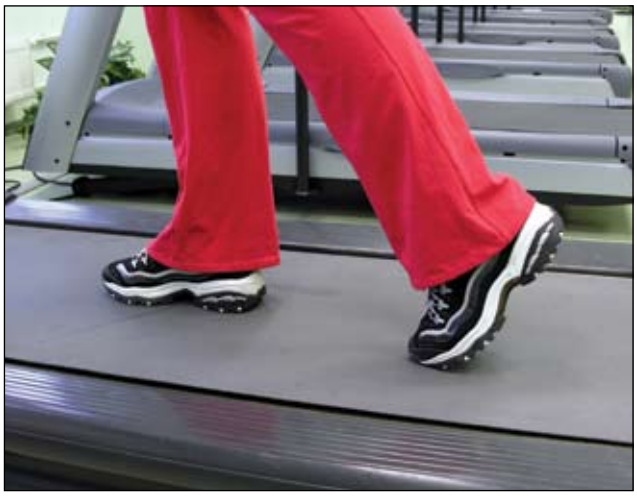
The Mechanisms of Exercise

Enhanced insulin action on glucose uptake in the leg occurs 4 to 10 hours after exercise in humans (Richter et al. J *Appl Physiology* 1989). Exercise causes a prolonged reduction of malonyl coenzyme A (COA), which may increase insulin sensitivity, explained Erik A. Richter, MD, PhD, University of Copenhagen, Copenhagen, Denmark. Even in as little as four hours after exercise, there is a decrease in malonyl coA ($p<0.05$ rested versus exercise leg). Prior exercise does not alter insulin's effect on IR activity in vitro, IRS-1 associated P13K, and aPKC Thr410 phosphorylation; however, it does increase IRS-2 associated P13K activity in the resting state and during insulin stimulation, which could lead to increased production of PIP-3 (Roepstorff et al, unpublished).

The STRRIDE study (Kraus et al. *MSSE* 2001) found that a high-dose vigorous exercise group had a greater percentage of change in body mass compared to those who exercised at a moderate level. However, those in the moderate exercise group had a larger decrease in triglycerides, a larger percentage increase in insulin sensitivity index (ISI), and a larger percent increase in homeostasis model assessment (HOMA).

Exercise can also alter where fat is deposited in the body. A study which compared women athletes and normal-weight controls between ages 18 and 70 found that visceral fat increased with age in both groups (Ryan et al. *AJP* 1996). However, there was a reduction in visceral fat and increased glucose utilization when weight loss was combined with aerobic or resistive training. Adipokines, which are inflammatory markers that may have direct effects on liver and skeletal muscle, also decrease with aerobic training.

Alice Smith Ryan, PhD, University of Maryland School of Medicine, Baltimore, MD, stated that weight loss in combination with exercise increases skeletal muscle lipoprotein lipase (LPL) activity and decreases adipose tissue LPL activity. LPL regulates the uptake and storage of triglycerides-fatty acids (TG-FA) by fat and muscle. Weight loss alone has no effect on basal skeletal muscle, nor does it change mean adipose tissue LDL activity in the abdomen or gluteal region. The combination of exercise and weight loss is vital for improving metabolic parameters.



Type 2 Diabetes — Where Do We Go From Here?

Matthew C. Riddle, MD, Ohio State University, Columbus, OH, explained that portal insulin is the main regulator of glucose production. Systemic insulin suppresses free fatty acid (FFA) production and further reduces glucose production. Subcutaneously injected insulin augments both portal and systemic insulin and suppresses basal overproduction of glucose.

Basal insulin controls basal glucose. Other favorable metabolic effects of basal insulin include reducing hypertriglyceridimia, improving high-density lipoprotein (HDL)

levels, improving vasodilatory responses, and suppressing inflammatory markers. Endothelium-dependent vasodilation improves after starting basal insulin (Yki-Jarvinen H et al. *Arterioscler Throm Vasc Biol* 2000).

The "proof of principle" for basal insulin is the "Treat to Target" trial (Riddle M et al. *Diab Care* 2003). The trial examined the use of bedtime glargine versus bedtime NPH added to 1 or 2 oral agents with a strict titration scale to lower fasting glucose levels. Fifty-eight percent of T2 patients reached the 7% A1C target (starting mean A1C 8.6%). Glargine caused less hypoglycemia than NPH. Dr. Riddle and colleagues concluded that the success of treatment was not affected by age or gender.

Dr. Riddle explained that ways to manage postprandial plasma glucose (PPG) after basal insulin titration are to switch to twice daily premixed or intermediate acting insulin; add the GLP-1 agonist exenatide, or add prandial injection in a step-wise fashion.

"Five years ago we couldn't get anyone to 7%, and now 15% of our patients reach 7%. We have to use whatever means are available to reach that," said Dr. Riddle.

Combination therapy is another alternative. Reasons to consider using combination therapy with insulin and oral agents, according to Philip Raskin, CDE, MD, University of Texas, Southwestern Medical Center, Dallas, TX, are better glycemic control (drug synergy) and better patient acceptability.

Dr. Raskin went on to explain the effect of triple therapy in type 2 diabetes. Twenty-eight subjects with T2 were treated with insulin and metformin (2000 mg daily) or insulin and troglitazone (600 mg/daily) for four months (Strowig et al. *Diab Care* 2004). Troglitazone or metformin were added to the patients' therapy and titrated to the maximum dose. The insulin dose was decreased only to prevent hypoglycemia. The group receiving insulin and troglitazone plus metformin reached glycemic target ($p<0.05$ versus dual therapies). Triple therapy helped 100% of the subjects reach a target HbA1C of <7.0%, with 83% of them reaching <6.5% and 57% reaching <6.0%.

The combination of insulin and insulin sensitizers is a very effective means of achieving glycemic goals in patients with type 2 diabetes noted Dr. Raskin. Thiazolidinediones tend to have greater insulin sensitizing effects than metformin but can result in significant weight gain, he said.

Adding exenatide to oral agents is another option. David Kendall MD and others conducted a study in which exenatide or placebo was added to maximum-effective doses of metformin and/or sulfonylurea in patients with type 2 diabetes (Kendall, Diab Care 2005). Patients who received exenatide were more likely to achieve A1C ≤7% compared with patients who received placebo ($P < 0.0001$).

Why add on exenatide? Exenatide works, explained Robert E. Ratner, MD, MedStar Research Institute, Washington, DC:

- Patients can achieve A1C goals without weight gain and in many cases with weight loss
- Exenatide is simple — >40% of patients reach goal after six months with minimum titration and no adjustments
- Exenatide is durable — providing A1C-lowering maintenance over 2 years
- Exanatide is safe — low and progressively lower GI adverse events
- Exenatide causes minimal hypoglycemia when used in combination with metformin