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JOURNAL WATCH

# Comparison of Insulin Degludec/Insulin Aspart and Biphasic Insulin Aspart 30 in Uncontrolled, Insulin-Treated Type 2 Diabetes: A Phase 3a, Randomized, Treat-to-Target Trial

**EDITOR'S VIEW**

**Rhyzodeg, which is a combination of insulin degludec and insulin aspart, is the first true analog combination. Fulcher *et al*. compared this insulin with biphasic insulin aspart 30 (Novomix 30) in type 2 diabetes. Results are very much favorable with Rhyzodeg in terms of achieving the HbA1c goal, less episodes of hypoglycemia, lower dose of daily insulin use.**

The combination of insulin degludec and insulin aspart (IDegAsp) is the first true analog premix combination of a basal insulin with an ultra-long duration of action, and a rapid-acting analog insulin. This trial have compared IDegAsp with biphasic insulin aspart 30 (BIAsp 30) in adult persons with type 2 diabetes, inadequately controlled with once- or twice-daily (OD or BID) pre- or self-mixed insulin with or without oral antidiabetic drugs in a 26-week, randomized, open-label, multinational, treat-to-target trial.

The mean age of the patients was 58.7 years, duration of diabetes 13 years, BMI 29.3 kg/m$^2$, and HbA1c 8.4% (68 mmol/mol). The patients were randomized to (1:1) BID injections of IDegAsp ($n$ = 224) or BIAsp 30 ($n$ = 222), administered with breakfast and the main evening meal. The dose was titrated to a self-measured pre-meal plasma glucose (PG) target of 4.0–5.0 mmol/L.

After 26 weeks, the mean HbA1c came down to 7.1% (54 mmol/mol) for both the groups. The group with IDegAsp achieved the prespecified noninferiority margin for mean change in HbA1c (estimated treatment difference [ETD] -0.03% points [95% CI -0.18 to 0.13]). Treatment with IDegAsp was superior in lowering fasting PG (ETD -1.14 mmol/L [95% CI -1.53 to -0.76], $p < 0.001$) and had a significantly lower final mean daily insulin dose (estimated rate ratio 0.89 [95% CI 0.83–0.96], $p$ = 0.002). The other observations were fewer incidence of confirmed, nocturnal confirmed, and severe hypoglycemic episodes reported for IDegAsp compared with BIAsp 30.

(Fulcher GR, *et al.*, *Diabetes Care* 2014;37(8):2084–90.

## Predicting Mortality in People with Type 2 Diabetes Mellitus after Major Complications: A Study Using Swedish National Diabetes Register Data

**EDITOR'S VIEW**

**Kelly *et al*. adopted this study to predict mortality risk and life expectancy for patients with type 2 diabetes after a major diabetes-related complication. Risk of death and life expectancy differs substantially among the major complications of diabetes, and factors significantly increasing risk included smoking, low estimated GFR, and albuminuria. This study will help us to concentrate on more important complications to improve the mortality and morbidity of diabetic patients.**

The study sample, taken from the Swedish National Diabetes Register, consisted of 20,836 people with type 2 diabetes who had their first major complication (myocardial infarction, stroke, heart failure, amputation, or renal failure) between January 2001 and December 2007.


Risk of death changed over time according to type of complications, with myocardial infarction initially having the highest initial risk of death, but after the first month, the risk was higher for heart failure, renal failure, and amputation. Other factors that increased the risk of death were male gender (hazard ratio 1.06, 95% CI 1.02–1.12), longer duration of diabetes (hazard ratio 1.07 per 10 years, 95% CI 1.04–1.10), smoking (hazard ratio 1.51, 95% CI 1.40–1.63), and macroalbuminuria (hazard ratio 1.14, 95% CI 1.06–1.22). Low BMI, low systolic blood pressure, and low estimated GFR also increased mortality risk. Life expectancy was highest after a stroke, myocardial infarction, or heart failure, lower after amputation and lowest after renal failure. Smoking and poor renal function were the risk factors which had the largest impact on reducing life expectancy.

(Kelly PJ, *et al. Diabet Med* 2014;31(8):954–62).

## Factors Associated with Weight Gain in People With Type 2 Diabetes Starting on Insulin

**EDITOR'S VIEW**

**Moderate weight gain is usual after starting insulin therapy. The identification and quantification of factors associated with weight gain may help target strategies for avoidance of weight gain. This study interestingly reported that by the time insulin was started, a high baseline A1C and insulin dose requirements were the independent predictors of greater weight gain, as was lower baseline BMI. Conventionally we thought that insulin is the criminal for inducing weight gain but in this study the insulin regimen per se was not a predictive factor.**

The non-interventional Cardiovascular Risk Evaluation in people with type 2 Diabetes on Insulin Therapy study (CREDIT study) included data from people with type 2 diabetes starting any insulin in 314 centers, in 12 countries. From a number of predefined candidate explanatory variables, analyses identified factors associated with weight gain 1 year after starting insulin treatment, after adjusting for investigational site as a random factor. A multivariable backward regression analysis selected a subset of these factors associated with weight gain. They studied 2,179 people with data for body weight change at 1 year and for potential predictive factors. The mean weight gain was 1.78 kg, and 24% gained ≥5.0 kg. Baseline factors associated with weight gain were BMI, A1C, insulin regimen, insulin dose, other glucose-lowering therapies, and hypertension; at 1 year, additional factors were A1C, insulin regimen, insulin dose, and use of other glucose-lowering therapies. In multivariable analysis, weight gain at 1 year was associated with a higher A1C at baseline, a higher insulin dose at baseline and at 1 year, and a lower baseline BMI.

(Balkau B, *et al*. *Diabetes Care* 2014;37(8):2108–13).

# Comparison of the Effects on Glycaemic Control and β-Cell Function in Newly Diagnosed Type 2 Diabetes Patients of Treatment With Exenatide, Insulin or Pioglitazone: A Multicentre Randomized Parallel-Group Trial (The CONFIDENCE Study)

## EDITOR'S VIEW

**Treatment of diabetes must target salvaging the β-cells side by side with lowering the blood sugar and organ protection. Progressive β-cell dysfunction is a barrier to the maintenance of glycemic control in type 2 diabetes, but comparative data on β-cell-protective therapies are lacking in the early stage of type 2 diabetes. The authors evaluated the comparative glycemic efficacy and impact on β-cell function of three antihyperglycemic agents that have a β-cell-protective effect, exenatide, insulin, and pioglitazone, in newly diagnosed type 2 diabetes patients. All three agents showed efficacy regarding glycemic control and metabolic benefits; however, exenatide showed the greatest efficacy. β-cell function improved in all treatment groups; hence early initiation of β-cell-protective therapy may halt the decline in β-cell function in type 2 diabetes. As such, when one clinician is going to choose an antidiabetic molecule, he should include any β-cell-protective molecule in the regimen.**

In a 48-week, multicenter, parallel-group study, 416 newly diagnosed type 2 diabetes patients were randomly assigned 1:1:1 to receive exenatide, insulin, or pioglitazone. The primary endpoint was the change in glycosylated hemoglobin (HbA1c) from baseline and the secondary endpoints were the effects on weight, blood pressure, lipid profiles, and β-cell function assessed by homeostasis model assessment, fasting proinsulin–insulin (PI/I), disposition index (DI), and acute insulin response (AIR).

At week 48, mean (95% confidence interval [CI]) HbA1c changes from baseline were -1.8% (-1.55% to -2.05%) with exenatide, -1.7% (-1.52% to -1.96%) with insulin, and -1.5% (-1.23% to -1.71%) with pioglitazone. Treatment differences were -0.20% (95% CI -0.46% to 0.06%) for exenatide versus insulin ($p$ = 0.185), and -0.37% (95% CI -0.63% to -0.12%) for exenatide versus pioglitazone ($p$ = 0.002). Significant improvements from baseline in AIR, PI/I, and DI were observed with all treatments, with the greatest improvements in DI, as well as weight, blood pressure, and lipid profile, observed with exenatide.

All three agents showed efficacy regarding glycemic control and metabolic benefits; however, exenatide showed the greatest efficacy. β-Cell function improved in all treatment groups, hence early initiation of β-cell-protective therapy may halt the decline in β-cell function in type 2 diabetes.

(Xu W, *et al. J Intern Med* 2014).

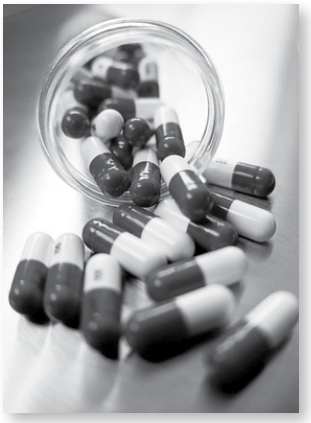
# Lean Versus Obese Diabetes Mellitus Patients in the United States Minority Population

## EDITOR'S VIEW

**This is a study to compare the profiles between the lean diabetics with the obese diabetics. The study group involved 1,784 patients with lean type 2 diabetes and 8,630 patients with obese type 2 diabetes. The lean diabetics had a significantly higher prevalence of insulin use versus those with obese diabetes (49% vs. 44%; $p$ = 0.001) and also had significantly lower TG/HDL (2.28 vs. 3.4; P < 0.001) and a significantly higher prevalence of alcoholism (5.7% vs. 2.4%; P < 0.001) and pancreatitis (3.6% vs. 0.9%; P < 0.001). Lean minority type 2 diabetes patients tended to be more insulin-dependent and had an earlier age of diagnosis. It appears that this may mean they have a higher incidence of β-cell death. The study is not self-sufficient and for final comment study of β-cell function, intra-abdominal obesity, inflammatory markers are essential.**

This study is by Coleman et al. to identify special characteristics in large group of lean diabetes minority patients in comparison to obese type 2 diabetes. Here, 1,784 lean (BMI <25) diabetes patients were identified and compared with 8,630 obese (BMI ≥30) patients. Patients with type 1 diabetes (N=523) were excluded. Patient data, including demographics, psychosocial factors, insulin use, and complications, was analyzed.

In lean compared to obese, there was male predominance (62% vs. 48%, $p$ < 0.001), higher prevalence of insulin use



(49% vs. 44%, $p = 0.001$), lower TG/HDL (2.28 vs. 3.4, $p < 0.001$), and higher prevalence of alcoholism (5.7% vs. 2.4%, $p < 0.001$), and pancreatitis (3.6% vs. 0.9%, $p < 0.001$). In both groups, African Americans and Latinos were the prevalent ethnicities (38%, 34% vs. 53%, 31%). When comparing patients within the lean group who were on insulin (49%) to those on oral medications, there were more males (65% vs. 59%, $p < 0.001$), earlier age of onset (40±14 vs. 47±12, $p < 0.001$), lower BMI (22.1±2 vs.22.6±1.7, $p < 0.001$) and lower TG/HDL (2.18 vs. 2.42, $p = 0.021$).

The study shows that a subset of diabetes patients in the United States minority population is lean and may have rapid β-cell failure. The etiology is not clear and acquired factors, genetics, and autoimmunity may be contributory.

(Coleman NJ, *et al. J Diabetes Complicat* 2014;28(4):500–5).