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Premeal insulin lispro plus bedtime NPH or twice-daily NPH in patients with type 2 diabetes: acute postprandial and chronic effects on glycemic control and cardiovascular risk factors

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Abstract

Objective: Two insulin regimens were used to explore acute and chronic postprandial changes in glycemia, lipemia, and metabolic markers associated with increased risk of cardiovascular disease. **Methods:** An open-label, randomized, two-period crossover study (12 weeks/period) compared a prandial regimen [premeal insulin lispro + bedtime neutral protamine Hagedorn (NPH)] with a basal regimen (twice-daily NPH). There were 30 patients (12 women and 18 men; mean age=61 years) with type 2 diabetes mellitus (mean duration=16 years) who were randomized after a 2-month lead-in with twice-daily NPH treatment. A standard lunch test meal developed according to each patient's caloric needs was administered at the end of each treatment period. **Results:** Insulin lispro was associated with significantly lower postprandial glucose (area under the curve$_{0-5\ h}$=43.54 vs. 57.65 mM/h; P<.001), elevated insulin concentrations, and acutely altered lipid fractions that included an early decrease followed by an increase in free fatty acids, lower triglycerides, elevated total cholesterol, elevated low-density lipoprotein cholesterol (LDL), and elevated high-density lipoprotein cholesterol. After 12 weeks of treatment, insulin lispro + bedtime NPH reduced hemoglobin A_{1c} (HbA_{1c}; mean±SE=7.6±0.2 vs. 8.2±0.2%; P<.001) without increasing hypoglycemia or insulin dose as compared with twice-daily NPH. Furthermore, treatment with the prandial insulin regimen resulted in lower total cholesterol, lower LDL cholesterol, and lower oxidized LDL. **Conclusion:** Improved postprandial glycemic control, as observed in a regimen containing both prandial insulin lispro and NPH as the basal insulin, is associated with significantly lower HbA_{1c} and acute modulation of lipid fractions after a test meal. These biochemical modifications may potentially have a favorable impact on cardiovascular risk in patients with type 2 diabetes mellitus.

Keywords: Diabetes; Lispro; NPH; Postprandial; Test meal

1. Introduction

Patients with type 2 diabetes are notably more susceptible to morbidity and mortality than the general population, with nearly 80% of patients dying of a cardiovascular event (Colwell, 1993). Recently, the contribution of postprandial hyperglycemia and hyperlipidemia to the progression of atherosclerosis has received more interest (Ceriello, 2000; Lebovitz, 2001). In particular, it has been suggested that an abnormally high flux and excess concentration of plasma glucose and lipids, characteristic of the postprandial state in patients with diabetes, creates a glucotoxic and lipotoxic environment of oxidative stress, resulting in progressive endothelial dysfunction and atherogenesis (Ceriello, 2000; Ceriello et al., 2002; Jagla & Schrezenmeir, 2001).

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Several postprandial lipid abnormalities in patients with diabetes are associated with endothelial dysfunction; these include elevated oxidized low-density lipoprotein (LDL) and free fatty acid (FFA), alterations in chylomicron remnants, and hypertriglyceridemia (Ceriello et al., 2002; Jagla & Schrezenmeir, 2001). Although oxidized LDL is increasingly recognized to play an early and important role in atherogenesis, postprandial triglycerides (TGs) and FFA may also contribute to this pathogenic process. Postprandial TGs, in particular, peak approximately 4 h after a meal and remain elevated for as long as 12 h in patients with diabetes, promoting the enrichment of lipoprotein particles and increasing atherogenic risk (Anderson et al., 2001). The postprandial hyperglycemic state directly damages the vascular endothelium via superoxide-radical generation and substantially contributes to hemoglobin A_{1c} (HbA_{1c}), an important marker of cardiovascular mortality risk (Anderson et al., 2001; Ceriello, 2003; Esposito, Nicoletti, & Giugliano, 2002).

Insulin lispro is a human insulin analog created when the amino acids at positions 28 and 29 of the insulin B chain are reversed. Pharmacokinetic and pharmacodynamic profiles, as well as clinical studies, indicate that insulin lispro is more rapid acting and thus acts as a more physiologic mealtime insulin than regular human insulin (Howey et al., 1995; Howey, Bowsher, Brunelle, & Woodworth, 1994). Clinical studies on patients with either type 1 or type 2 diabetes demonstrated that insulin lispro, compared with regular human insulin, led to lower 2-h postprandial blood glucose (BG) concentrations and similar or improved overall glycemic control. These effects were observed at dosages similar to those of regular human insulin and were associated with similar or lower risk of hypoglycemia (Anderson, Brunelle, Koivisto, et al., 1997, Anderson, Brunelle, Keohane, et al., 1997; Lalli et al., 1999). Limited information exists regarding the impact of insulin regimens on postprandial lipids in patients with type 2 diabetes. Two small test meal studies conducted in patients with type 2 diabetes have recently been published with mixed results. One study, involving 12 patients, compared biphasic insulin aspart with biphasic human insulin and demonstrated a significant reduction in postprandial TGs (Schmoelzer et al., 2005). The other study, with 21 patients with type 2 diabetes, compared insulin aspart with regular human insulin and failed to demonstrate an effect on postprandial TGs (Gallagher & Home, 2005).

The current exploratory study was designed to compare acute postprandial and chronic effects of two insulin regimens—a prandial and basal insulin regimen [premeal insulin lispro + neutral protamine Hagedorn (NPH) at bedtime] or a basal insulin only regimen (twice-daily NPH)—on markers of oxidative stress, coagulants, inflammatory markers, and metabolic markers associated with glycemic control and cardiovascular disease (CVD) in patients with type 2 diabetes.

2. Patients and methods

2.1. Patients

Thirty patients with type 2 diabetes were recruited from four clinical centers in Italy. Written informed consent for study participation was obtained from all subjects. Eligibility criteria included inadequate glycemic control (HbA_{1c}=7%–9.5%) and treatment with either oral antihyperglycemic agents (OAMs; with the exception of thiazolidinediones) or insulin (once daily with an oral agent or twice daily with or without an oral agent) for at least 30 days before the study. Exclusion criteria included: body mass index (BMI) >35 kg/m^2; TG >400 mg/dl; having had more than one episode of severe hypoglycemia within 6 months prior to study entry; pregnant or breastfeeding women; chronic use (>2 weeks) of systemic glucocorticoids; a history of drug or alcohol abuse; and any other severe disease. Patient characteristics are shown in Table 1. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee of the University of Udine in Italy.

2.2. Methods

2.2.1. Study design

This exploratory study was a 24-week, randomized, open-label, multicenter clinical trial comparing the effect of administering premeal insulin lispro three times daily + bedtime NPH with that of twice-daily NPH on acute and overall glycemic control and postprandial markers in patients with type 2 diabetes. After screening and before the start of the study, patients discontinued all OAMs and entered an 8-week lead-in period, during which they administered twice-daily NPH. During the 2 weeks before randomization, a seven-point glucose profile (measurements taken immediately premeal, 2 h after each meal, and at 3:00 AM) was performed on 3 separate days. These profiles, along with any episode of hypoglycemia, were recorded in a study diary.

After the 8-week lead-in period, patients were randomized to one of two treatment sequence groups enrolling 15 patients each. One group received 12 weeks of insulin lispro (within 5 min) before each of the three daily meals + NPH at bedtime followed by 12 weeks of twice-daily NPH

Table 1
Patient characteristics

No. of patients enrolled	30
No. of patients treated with both therapies	27
Age (years; mean±SD)	60.7±7.9
Sex [*n* (% female)]	12 (40)
Origin [*n* (% Caucasian)]	30 (100)
Body weight (kg; mean±SD)	75.4±10.4
Body mass index (kg/m^2; mean±SD)	27.1±3.1
Duration of diabetes (years; mean±SD)	16.2±9.1
HbA_{1c} (%; mean±SD)	8.37±0.94