

GAD65-reactive T-cells have been postulated to recognize the peptide derived by coxsackie B4 virus, leading to autoimmune type 1 diabetes (4). Furthermore, sequence homology between GAD65 and cytomegalovirus might participate in the onset of type 1 diabetes and stiff-man syndrome (5). Interestingly, HHV-6 is closely related to cytomegalovirus genomically and antigenically, and GAD65-reactive T-cells also recognize an epitope derived by HHV-6 (5), suggesting that reactivation of HHV-6 might contribute to the onset of autoimmune type 1 diabetes by the molecular mimicry.

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Favorable Effects of Early Insulin Secretion by Nateglinide on Postprandial Hyperlipidemia in Patients With Type 2 Diabetes

Severe postprandial hyperlipidemia is observed in and substantially contributes to the progression of atherosclerosis in type 2 diabetic patients, especially those with insulin resistance and compensatory hyperinsulinemia (1–4). As with postprandial hyperglycemia, increased lipid levels in type 2 diabetic patients peak late, and the magnitude of the increase is greater than that seen in healthy people (2,4). To determine whether early insulin secretion by nateglinide can suppress postprandial hyperlipidemia in type 2 diabetic patients, 20 Japanese patients (10 men and 10 women, [means \pm SE] aged 56.4 ± 2.5 years, with BMI and HbA_{1c} 25.6 ± 1.2 kg/m² and $5.7 \pm 0.1\%$, respectively) with newly diagnosed type 2 diabetes performed a 75-g oral glucose tolerance test and oral fat tolerance test (OFTT) twice. A 90-mg dose of nateglinide was administered immediately before fat loading in one of the two OFTTs. In the OFTT, each subject ingested 17 g fat/m² surface area (OFTT cream; Jomo Food Industry, Takasaki, Japan) (2). Plasma glucose and serum insulin, triglycerides, and remnant-like particles cholesterol (RLPC) concentrations were determined before and 30 min and 1, 2, and 4 h after fat loading.

When nateglinide was not administered (Nate–), triglycerides and RLPC continued to increase during OFTT, while no significant changes in plasma glucose or insulin were noted. In OFTT with nateglinide administration (Nate+), increases in triglycerides and RLPC after fat loading were significantly lower than in Nate– by ANOVA ($P < 0.001$). The average increments of triglycerides and RLPC from baseline to 4 h were 1.1 mmol/l and 0.31 mmol/l in Nate– and 0.46 mmol/l (-58% , $P < 0.01$) and 0.05 mmol/l (-84% , $P < 0.01$) in Nate+, respectively. Plasma glucose levels in Nate+ were gradually decreased by 1.6 mmol/l on average after 2 h. Insulin levels in Nate+ peaked after 30 min and then

decreased to below baseline level by 4 h. Furthermore, in Nate–, the regarding rates of increase for triglycerides and RLPC during OFTT had significant correlations with Σ insulin during the oral glucose tolerance test ($r = 0.63$ and 0.72 , respectively), which is a surrogate measure for insulin resistance, while in Nate+, there were no significant correlations among them.

Early insulin secretion following nateglinide administration was thus proved to inhibit postprandial hyperlipidemia in type 2 diabetic patients. Improvements in insulin resistance over a short period of time seem to exert substantial influence on lipid parameters. Insulin secretion patterns appear to play a major role in postprandial hyperlipidemia as well as hyperglycemia.

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