Changes in Circulating Postprandial Proinflammatory Cytokine Concentrations in Diet-Controlled Type 2 Diabetes and the Effect of Ingested Fat

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The proinflammatory cytokines interleukin (IL)-6 and tumor necrosis factor (TNF)-α are thought to impair insulin signaling (1,2), and abnormally high levels of them are associated with insulin resistance (3,4) and type 2 diabetes (3,5). In patients with type 2 diabetes, a meal rich in fat, mainly in the form of sausages and butter, increases postprandial plasma concentrations of IL-6 and TNF-α, whereas a meal rich in carbohydrates has less effect (5). Current dietary recommendations for diabetic patients prescribe replacement of saturated fatty acids (SAFAs) with monounsaturated fatty acids (MUFAs) in the diet (6). There is little information available on the effect of ingesting MUFAs on postprandial plasma IL-6 and TNF-α concentrations in patients with type 2 diabetes. We therefore tested the effect of meals consisting of starch with or without added olive oil (MUFA) and cream (SAFA) on postprandial concentrations of plasma IL-6 and TNF-α in patients whose type 2 diabetes was controlled by diet alone.

RESEARCH DESIGN AND METHODS

— Eighteen patients (7 men and 11 women) with type 2 diabetes who had good glycemic control by diet alone, did not smoke cigarettes or use antioxidant supplements, and did not have hepatic or renal diseases or a history of cardiovascular disease were recruited. Fasted participants were fed three meals in random order and separated by weekly intervals. The meals consisted of 200 g instant mashed potatoes plus two cooked eggs alone or in combination with fat in the form of olive oil or cream (0.6 g/kg body wt) and were consumed at ~0830 h. Participants were allowed to consume water, but not other beverages or food, and remained seated during the study. Thirteen of the participants volunteered for a follow-up study to test the effect of continued fasting for 2 h instead of receiving a meal. Patients gave written and informed consent and the studies were approved by the Otago Ethics Committee.

Venous blood was taken at baseline, 1, 4, and 6 h after the meals, and serum and EDTA plasma were isolated by low-speed centrifugation at 4°C. Aliquots of serum and plasma were stored at −80°C. Glycated hemoglobin, plasma glucose, plasma insulin, and triglycerides were measured by routine methods using commercial kits (Roche Diagnostics) in the Otago Diagnostic Laboratories, Dunedin Hospital. Plasma IL-6 and TNF-α concentrations were measured in duplicate by high-sensitivity enzyme-linked immunosorbent assay methods using commercial kits (R&D Systems). Plasma free fatty acid (FFA) was measured enzymatically using a commercial kit (Roche Diagnostics). Samples from an individual were measured in the same assay to reduce the effect of interassay variation on plasma insulin, IL-6, TNF-α, and FFA.

Values are mean ± SD unless stated otherwise. Data were log transformed before statistical analysis using the STATA program. A mixed regression model that included a random effect for individuals and adjustment for order was used to analyze the data.

RESULTS

— At baseline, mean age, BMI, fasting glucose, and HbA_{1c} were 61 ± 10 years, 28.5 ± 4.4 kg/m^2, 6.8 ± 1.7 mmol/l, and 6.5 ± 0.6%, respectively. Duration of diabetes ranged from 2 to 60 months (mean 22 months).

Plasma glucose and insulin concentrations increased significantly and plasma FFA and IL-6 concentrations decreased significantly 1 h after all the meals and then returned to baseline during the following 5 h (Fig. 1). Plasma TNF-α was significantly lower than baseline at 4 and 6 h after the meals (Fig. 1). Plasma triglyceride concentration increased significantly 4 h after the fatty meals and did not vary significantly ($P = 0.19$) after the control meal. There was no significant effect of the order in which the meals were received on the IL-6 and TNF-α data.

Plasma IL-6 ($P = 0.41$), TNF-α ($P = 0.93$), glucose ($P = 0.14$), and insulin ($P = 0.72$) did not change significantly at 1 and 2 h, and plasma FFA tended to increase ($P = 0.08$) during continued 2-h fasting from 0800 h in the 13 patients (9 women and 4 men) who volunteered for the follow-up study.

CONCLUSIONS

— Our data suggest that in subjects with diet-controlled type 2 diabetes, ingestion of a meal containing potato starch plus egg with or without added MUFAs and SAFAs may have a temporary anti-inflammatory effect as in-

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Received for publication 4 July 2004 and accepted in revised form 7 July 2004.

Abbreviations: FFA, free fatty acid; IL, interleukin; MUFA, monounsaturated fatty acid; SAFA, saturated fatty acid; TNF, tumor necrosis factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

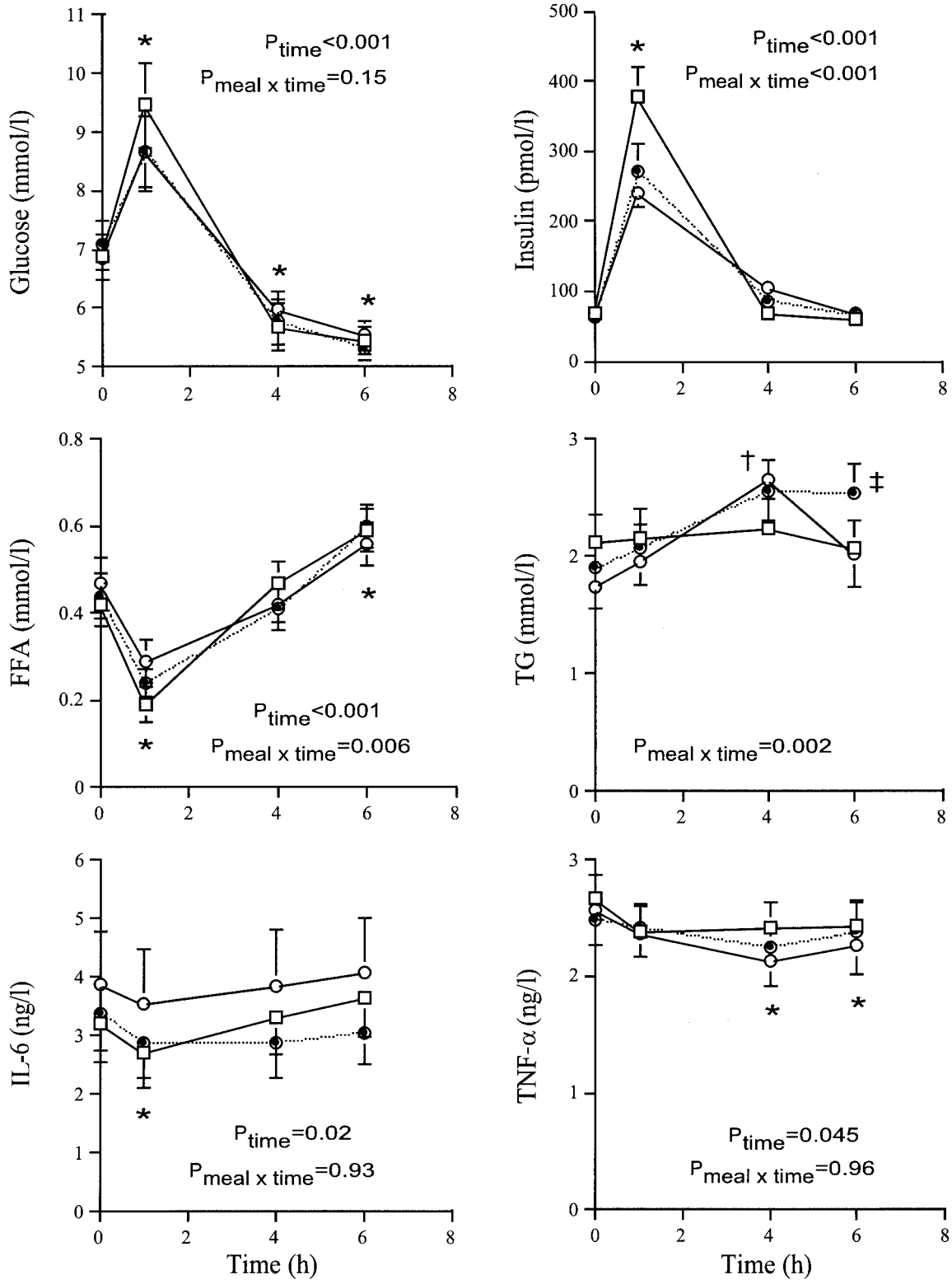

Figure 1—*Effect of the meals on plasma glucose, insulin, FFA, triglyceride (TG), IL-6, and TNF-α concentrations in the patients. Values are mean ± SE* (n = *18*). □, *control meal;* ●, *MUFA meal;* ○, *SAFA meal. Significantly different from baseline: *all meals; †SAFA and MUFA meals. ‡Significantly different from baseline and compared with other meals.*

dicated by decreases in plasma levels of both IL-6 and TNF-α in the hours after the meal. This anti-inflammatory effect may possibly be mediated by the postprandial increase in plasma insulin and the associated decrease in plasma FFA. Previous studies have reported a potent anti-inflammatory effect of insulin (7) and an inflammatory effect of raised FFA (8) in vivo. Our findings are in contrast with the previously reported increase in plasma IL-6 and TNF-α in patients with type 2 diabetes after a fatty meal (5). The factors responsible for these divergent findings are unclear. The patients we studied had less severe diabetes, as indicated by lower HbA_{1c} and fasting blood glucose, and lower plasma TNF-α concentrations. Also, the experimental meals they consumed were more standardized, with fewer components and test fats from only one source. Furthermore, the participants consumed a control meal that contained all of the components except the test fat so that the effect of the test fat alone could be assessed. Finally, it is conceivable that a postprandial decrease in plasma levels could minimize the interference of IL-6 and possibly TNF-α with insulin signaling at a time when the maximal sensitivity of tissues to insulin is important for the uptake of an increased glucose load.

Acknowledgments— This study was supported by a Novo Nordisk grant from the New Zealand Society for the Study of Diabetes.

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