diately after the injection of insulin and disappeared after ~20 min, while induration persisted for 3–4 days. HbA_{1c} rose from 8.0 to 10.4% in the next 3 months. The plain chest X-ray film and chest computed tomography revealed a mass with a diameter of 3 cm in the right upper lobe, which was diagnosed as adenocarcinoma of the lung.

His serum insulin level was elevated (912 pmol/l while fasting) due to a high level of IgG anti-insulin antibodies (99.7% bound, reference range <10%). Human insulin–specific IgE, as determined by a radioallergosorbent test (RAST), was also elevated (12.20 UA/ml, RAST class 3, reference range <0.34 UA/ml). Despite injection of insulin aspart before each meal, the blood glucose level increased to 23.1 mmol/l postprandially and declined to 4.9 mmol/l during the night. This daily blood glucose pattern was not improved by the administration of mitiglinide and voglibose instead of insulin. Plasma interleukin (IL)-6 was elevated to 96.4 pg/ml (reference range <4.0 pg/ml). Chemotherapy was performed with carboplatin and docetaxel. As a result, the lung tumor was remarkably reduced in size. Three weeks later, the patient's blood glucose level ranged from 5.1 to 11.9 mmol/l on therapy with mitiglinide and voglibose. Insulin IgG antibodies (percent bound), fasting serum insulin level, and human insulin-specific IgE antibodies declined to 82%, 305 pmol/l, and 4.67 UA/ml (RAST class 3), respectively. Plasma IL-6 level also fell to 8.0 pg/ml.

Increased serum levels of IL-6 have been reported in patients with lung cancer (2). IL-6 stimulates activated B-cells to induce the production of IgM, IgG, and IgA, as well as potentiates the IL-4–dependent response of IgE (3). IL-6 is also involved in the activation, growth, and differentiation of T-cells (3). In this case, multiple immune responses to insulin, including immediate allergy, delayed cutaneous hypersensitivity, and immunologic insulin resistance, were thought to have occurred as a paraneoplastic syndrome based on IL-6 secretion by lung cancer because chemotherapy resulted in a decrease of tumor size, a decline of plasma IL-6, and a reduction of insulin antibodies.

SATOMI MIZUHASHI, MD[1]
KEIGO NAKAMURA, MD, PHD[1]
YASUMICHI MORI, MD, PHD[1]
MITSUHIKO NODA, MD[1]
KOJI NAKANISHI, MD, PHD[1,2]

From the [1]Department of Endocrinology and Metabolism, Toranomon Hospital, Tokyo, Japan; and the [2]Okinaka Memorial Institute for Medical Research, Tokyo, Japan.

Address correspondence to Koji Nakanishi, MD, PhD, Department of Endocrinology and Metabolism, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105-8470, Japan. E-mail: koji01@toranomon.gr.jp.

DOI: 10.2337/dc06-0677

References

1. Ross JM, Murali MR, Delara TC, Cheron RG: Anaphylaxis and immunologic insulin resistance in a diabetic woman with ketoacidosis. *Diabetes Care* 7:276–279, 1984
2. Yanagawa H, Sone S, Takahashi Y, Haku T, Shinohara T, Ogura T: Serum levels of interleukin 6 in patients with lung cancer. *Br J Cancer* 71:1095–1098, 1995
3. Akira S, Taga T, Kishimoto T: Interleukin-6 in biology and medicine. *Adv Immunol* 54:1–7, 1993

Relapse of Diabetes After Interruption of Chronic Administration of Anti–Tumor Necrosis Factor-α Antibody Infliximab

A case observation

Tumor necrosis factor-α (TNF-α), a proinflammatory cytokine, plays a prominent role in obesity-associated insulin resistance and β-cell dysfunction (1) and, therefore, in the development of diabetes. An association between obesity and elevated TNF-α levels and, furthermore, the substantial decline of TNF-α levels with the simultaneous restoration of insulin sensitivity during weight loss was reported by Dandona et al. (2). Recently, we found evidence that prolonged administration of anti–TNF-α antibody is able to improve insulin sensitivity in insulin-resistant subjects (3); this finding has been confirmed by Kiortsis et al. (4).

Here, we report a case demonstrating the relapse of diabetes in a former type 2 diabetic patient after an interruption of prolonged treatment for psoriatic arthritis with infliximab, an anti–TNF-α antibody. The improvement in insulin sensitivity of this patient has been reported along with post hoc evidence that chronic administration of infliximab improves insulin resistance in a small sample of patients with inflammatory joint diseases (3).

The patient, a 33-year-old male with a BMI of 22.4 kg/m^2, had been treated with infliximab continuously until April 2003. From April 2003 to October 2003, infliximab was stopped due to remission of psoriatic arthritis. Readministration of infliximab was started again in October 2003 because of increased disease activity. In the interval without infliximab treatment, we observed a significant increase of fasting capillary blood glucose (monitored by self measurement) from a mean of 4.93 ± 0.18 mmol/l in the pre-interruption period to 6.77 ± 0.26 mmol/l in the infliximab-free period (Fig.

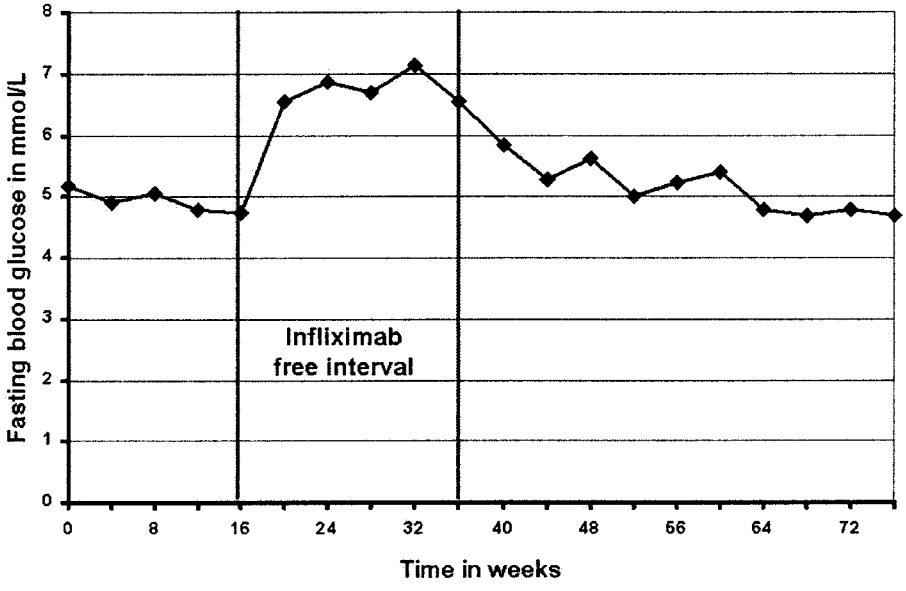

Figure 1— *Self-monitored fasting blood glucose in mmol/l. ◆, mean of a 4-week interval.*

1). Interestingly, there was a prompt decrease of fasting blood glucose (mean 4.86 ± 0.41 mmol/l, $P > 0.001$ by repeated-measures ANOVA) after 3 months of readministration of infliximab. Infliximab has been administrated in 8-week intervals, and until present, the patient has had stable fasting blood glucose in the nondiabetic range.

Our case strongly supports the hypothesis that chronic TNF-α blockade impacts glucose metabolism. First, the patient's diabetes disappeared during the chronic administration of infliximab due to active psoriatic arthritis, and then he redeveloped diabetes at the infliximab-free interval. After the readministration of the anti–TNF-α antibody, fasting blood glucose was normalized again.

Further prospective studies are strongly needed to investigate the effects of an anti–TNF-α antibody on insulin sensitivity and β-cell function in insulin resistant or diabetic patients.

Babak Yazdani-Biuki, MD[1]
Thomas Mueller, MD[1]
Hans-Peter Brezinschek, MD[1]
Josef Hermann, MD[1]
Winfried Graninger, MD[1]
Thomas C. Wascher, MD[2]

From the [1]Department of Internal Medicine, Division of Rheumatology, Medical University Graz, Styria, Austria; and the [2]Department of Internal Medicine, Metabolism and Vascular Biology Unit, Medical University Graz, Styria, Austria.

Address correspondence to Dr. Babak Yazdani-Biuki, Medizinische Universitätsklinik, Auenbruggerplatz 15, A-8036 Graz, Austria. E-mail: babak.yazdanibiuki@meduni-graz.at.

DOI: 10.2337/dc06-0636

References

1. Greenberg AS, McDaniel ML: Identifying the links between obesity, insulin resistance and beta-cell function: potential role of adipocyte-derived cytokines in the pathogenesis of type 2 diabetes. *Eur J Clin Invest* 32 (Suppl. 3):24–34, 2002
2. Dandona P, Weinstock R, Thusu K, Abdel-Rahman E, Aljada A, Wadden T: Tumor necrosis factor-α in sera of obese patients: fall with weight loss. *J Clin Endocrinol Metab* 83:2907–2910, 1998
3. Yazdani-Biuki B, Stelzl H, Brezinschek HP, Hermann J, Mueller T, Krippl P, Graninger W, Wascher TC: Improvement of insulin sensitivity in insulin resistant subjects during prolonged treatment with the anti-TNF-α antibody infliximab (Letter). *Eur J Clin Invest* 34:641–642, 2004
4. Kiortsis DN, Mavridis AK, Vasakos S, Nikas SN, Drosos AA: Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. *Ann Rheum Dis* 64:765–766, 2005

Gestational Diabetes Mellitus in Sardinia

Results from an early, universal screening procedure

The prevalence of gestational diabetes mellitus (GDM) ranges from 1 to 14% of all pregnancies, depending on the population studied and the diagnostic test and its glycemic cutoff, and it mirrors the prevalence of type 2 diabetes (1). The prevalence of GDM in Italy was reported to be 2.3–10% (2).

Sardinia has, with Finland, the highest prevalence in the world of type 1 diabetes and type 1 diabetes–related autoimmune disease (3), while the prevalence of type 2 diabetes is similar to that of other, not high-risk, populations. Its prevalence of GDM is still unknown.

Aiming to verify the prevalence of GDM in a large group of Sardinian women, we studied 1,103 pregnant volunteers of mean age 31 ± 5 years (range 16–46) and BMI 22.5 ± 3.8 kg/m^2 (12.7–47.2) who gave consent to take part in an extended, universal screening procedure, at 16–18, 24–26, and 30–32 weeks of gestations. This protocol was chosen, together with a low glycemic threshold (130 mg/dl) for the oral glucose tolerance test, to avoid undiagnosed cases of GDM. Oral glucose tolerance test and diagnosis of GDM were performed according to the American Diabetes Association (4).

We showed a very high (247/1,103; 22.3%) prevalence of GDM, of which 28.4% was diagnosed at 16–18 weeks (prevalence 6.6%), 25.9% at 24–26 weeks (5.8%; not significant vs. 16–18 weeks), and 44.5% at 30–32 weeks (9.9%; $P < 0.01$ vs. 20–24 weeks and $P < 0.02$ vs. 16–18 weeks). The 130-mg/dl threshold allowed us to detect 12.8% more GDM cases compared with the 140 mg/dl threshold. The difference in prevalence of GDM between our group and others, particularly other Italian regions, is only partially explainable by our extended screening procedure. Furthermore, it is in contrast with the prevalence of type 2 diabetes in Sardinia. Considering the genetic and immunological characteristics of the Sardinian population, we postulate that a greater proportion of our GDM cases than that reported by others (5) can have autoimmune origin and thus be associated with the high type 1 prevalence in our island. This hypothesis is strengthened by the low prevalence of obesity (4.9%) and the relatively low BMI of our patients. An autoantibody panel is currently under investigation in our laboratory.

Cinzia Murgia, MD[1]
Rachele Berria, MD[2]
Luigi Minerba, MD[3]
Barbara Malloci, MD[1]
Claudia Daniele, MD[1]
Pierina Zedda, RN[1]
M. Giovanna Ciccotto, MD[1]
Simonetta Sulis, MD[1]
Michela Murenu, MD[1]
Franco Tiddia, MD[4]
Mario Manai, MD[5]
Gian Benedetto Melis, MD[1]

From the [1]Clinica Ostetrica e Ginecologica, Università degli Studi di Cagliari, Ospedale San Giovanni di Dio, Cagliari, Italy; the [2]Department of Obstetrics and Gynecology, Case Western Reserve University, Cleveland, Ohio; the [3]Dipartimento di Sanità Pubblica, Università degli Studi di Cagliari, Italy; the [4]Laboratorio Analisi Chimico Clinche e Microbiologia, Ospedale San Giovanni di Dio, Cagliari, Italy; and the [5]Servizio di Diabetologia, Ospedale San Giovanni di Dio, Cagliari, Italy.

Address correspondence to Cinzia Murgia, MD, Clinica Ostetrica e Ginecologica, Università degli Studi di Cagliari, Ospedale San Giovanni di Dio, Via Ospedale 46, Cagliari, Italy 09100. E-mail: cinziamurgia@tiscali.it.

DOI: 10.2337/dc06-0635

References

1. King H: Epidemiology of glucose intolerance and gestational diabetes in women of childbearing age. *Diabetes Care* 21 (Suppl. 2):B9–B13, 1998
2. Di Cianni G, Volpe L, Lencioni C, Miccoli R, Cuccuru I, Ghio A, Chatzianagnostou K, Bottone P, Teti G, Del Prato S, Benzi L: Prevalence and risk factors for gestational diabetes assessed by universal screening. *Diabetes Res Clin Pract* 62:131–137, 2003
3. Songini M, Muntoni S: High incidence of type 1 diabetes in Sardinia. *Lancet* 337: 1047, 1991
4. American Diabetes Association: Gestational diabetes mellitus (Position Statement). *Diabetes Care* 26 (Suppl. 1):S103–S105, 2003
5. Weng J, Ekelund M, Lehto M, Li H, Ekberg G, Frid A, Aberg A, Group LC, Bemtorp K: Screening for MODY mutations, GAD antibodies and type 1 diabetes asso-