Inflammation plays an important role in the development of disturbances in both glucose metabolism and CVD and is intimately related to several difficult-to-measure components of metabolic syndrome (5). In our study, concerning inflammation, IDF criteria did not give any improvement compared with the NCEP or WHO criteria. Instead, among men, the IDF definition tended to be inferior to the other two definitions of the syndrome. In addition, BMI and HOMA-IR, components not included in the IDF and NCEP definitions of metabolic syndrome, were closely associated with elevated hs-CRP. If other population studies confirm our finding about a weaker association between the IDF definition of metabolic syndrome and CRP levels, especially among men, the new criteria should be further considered by including hs-CRP or replacing waist circumference by BMI given that elevated hs-CRP levels have been shown to add to the prognostic information of the NCEP defined metabolic syndrome for cardiovascular events (5).

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Paraneoplastic Insulin Resistance Syndrome in Advanced Aggressive Fibromatosis (Desmoid Tumor) Treated by Imatinib Mesylate

A 51-year-old woman affected by advanced aggressive fibromatosis of the abdomen was admitted to the hospital because of diabetes associated with severe insulin resistance. Her medical history was notable for *1*) desmoid tumor of the abdomen at age 26 years, which had undergone 32 surgical resections (according to the patient), until the age of 44 and *2*) diabetes at age 45 years initially treated with oral agents and then by insulin, with persistent poor glucose control despite progressively increasing doses. Afterward, the patient received an intravenous insulin infusion by an external pump through a port-a-cath in the subclavian vein for severe insulin resistance. Intravenous insulin was discontinued due to sepsis, which resolved after intravenous antibiotic therapy. Family history was negative for diabetes. Physical examination revealed poor general conditions and a large mesogastric lesion (Fig. 1*A*), and BMI was 29.2 kg/m^2 and blood pressure was 140/80 mmHg. Laboratory investigations were normal, apart from features of nonketotic insulin-resistant diabetes with HbA_{1c} 14.2%, 24-h blood glucose 300–500 mg/dl, fasting insulin 144 μU/ml, proinsulin 45 pmol/l, and C-peptide 2.88 ng/ml. Autoantibodies to insulin receptor and insulin were absent, and tumor necrosis factor-α (12.5 pg/ml) and interleukin-6 (11.6 pg/ml) were elevated. Intravenous insulin (1,200 units/day) had to be resumed. The extreme insulin resistance in the absence of insulin receptor antibodies was suggestive of a paraneoplastic origin. Surgical intervention was unfeasible due to tumor diffusion and impossibility to reconstruct the abdominal wall. Immunocytochemistry on the desmoid tumor biopsies revealed the presence of α- and β-platelet–derived growth factor (PDGF) receptors.

In view of the impracticability of maintaining long-term intravenous insulin, therapy with imatinib mesylate (Gleevec) was considered (1–3). After obtaining ethical committee permission and patient's informed consent, imatinib was started at the dose of 400 mg/day orally. Insulin requirement dropped dramatically to 500 units/day s.c. within 3 days and then progressively to a nadir of 100 units/day after 2 months, accompanied by a significant decrease of tumor mass and improvement of general clinical conditions and diabetes control. After 6 months of treatment with imatinib and while still on treatment with it, partial reenlargement of the lesion and insulin resistance slowly recurred with insulin requirement increasing up to 600 units/day after 8 months of imatinib treatment (Fig. 1*B–G*). At that point, leukopenia and anemia occurred and imatinib had to be discontinued for this reason, with further worsening of severe insulin-resistant diabetes.

We hypothesize that imatinib acted positively by blocking the negative intracellular cross-talk between PDGF, tumor necrosis factor-α, interleukin-6, and insulin, either by a direct inhibition of the PDGF tyrosine kinase or by reducing the tumor mass and the related production of

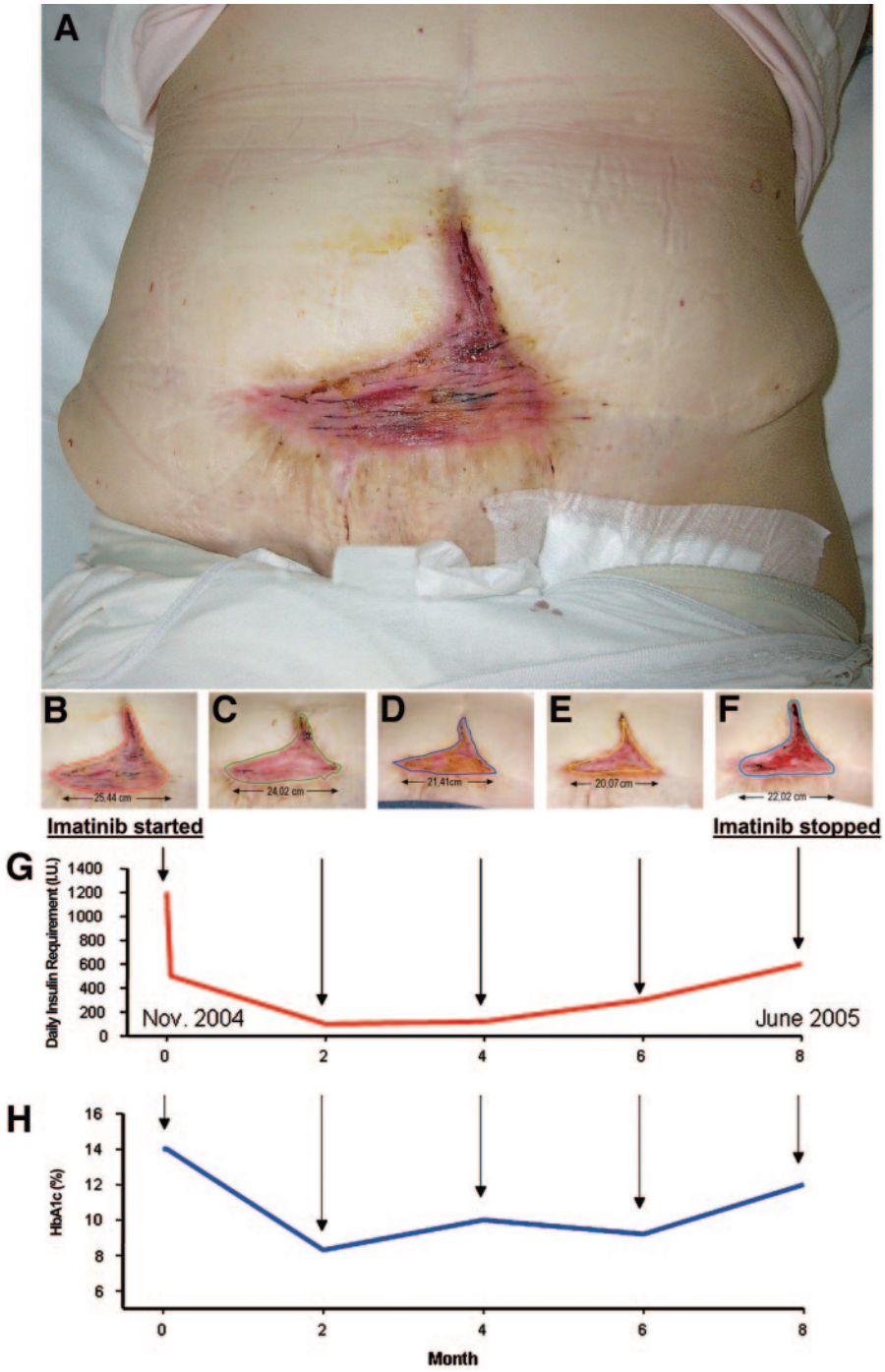

Figure 1—*The clinical and metabolic response of the patient to imatinib therapy.* A*: The desmoid tumor is a large mesogastric easily bleeding lesion.* B–F*: The lesion was measured at admission and after 2, 4, 6, and 8 months of imatinib therapy, demonstrating progressive reduction in the external size of the tumor with a partial recurrence at 8 months. Daily insulin requirements* (G) *and* HbA_{1c} *levels* (H) *demonstrate a clear-cut positive effect of the therapy with the tyrosine kinase inhibitor.*

interleukin-6, tumor necrosis factor-α, and PDGF (3–5).

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COMMENTS AND RESPONSES

Proinflammatory Cytokines, Insulin Resistance, and Insulin Secretion in Chronic Hepatitis C Patients: A Case-Control Study

Response to Lecube et al.

We read with interest the article by Lecube et al. (1), which indicated that tumor necrosis factor (TNF)-α is a mechanism by which hepatitis C virus (HCV)-infected patients are more prone to develop type 2 diabetes than patients with other chronic liver diseases. The mechanisms of the development of insulin resistance in patients with chronic HCV infection are not well understood. Insulin resistance in HCV-infected patients occurs already at an early stage in the course of HCV infection (2). Furthermore, although steatosis was more severe in patients infected with genotype 3, insulin resistance was associated with steatosis only in patients infected with genotype 1 (3).

Recently, we investigated the role of adipocytokines in HCV-related steatosis (4). Seventy-one chronic HCV patients were studied to assess the effects of adipocytokines on steatosis. We used an enzyme-linked immunosorbent assay to determine serum TNF receptors (TNF-R) I and II concentrations. Based on the findings in the study by Lecube et al. (1), we investigated whether plasma TNF-RI and TNF-RII concentrations were associated with parameters of insulin resistance in the 68 noncirrhotic subjects of this group of patients. Genotype distributions were as follows: genotype non-3, $n = 55$; genotype 3, $n = 13$.

TNF-RII and TNF-RI concentrations were correlated with homeostasis model assessment ($r = 0.26$, $P = 0.02$ and $r = 0.20$, $P = 0.09$, respectively). Homeostasis model assessment was significantly different in patients with genotype 3 than in patients with genotype non-3 (1.13 vs. 2.46; $P = 0.01$). There were no significant differences between the two groups for age, BMI, TNF-RI, and TNF-RII concentrations (genotype 3 versus non-3: TNF-RI = 1.64 vs 1.48 pg/ml, $P = 0.32$; TNF-RII = 3.79 vs. 3.41 pg/ml, $P = 0.39$).

Our results suggest that the HCV genotype must be included in further study evaluating insulin resistance in HCV-infected patients. Moreover, the lack of difference of TNF-R concentrations between subjects with HCV genotype 3 and non-3, despite a significant difference for homeostasis model assessment level, suggests that factors other than TNF-α could be implicated in the development of insulin resistance during HCV chronic infection.

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Proinflammatory Cytokines, Insulin Resistance, and Insulin Secretion in Chronic Hepatitis C Patients: A Case-Control Study

Response to Petit et al.

We thank Petit et al. (1) for their interest in our study, in which we suggest that insulin resistance mediated by proinflammatory cytokines, but not a deficit of insulin secretion, is the primary pathogenic mechanism implicated in the development of diabetes associated with hepatitis C virus (HCV) infection (2). Based on the results of our study, these authors measured tumor necrosis factor (TNF)-soluble receptors (TNF-RI and TNF-RII) and homeostasis model assessment (HOMA) in 68 noncirrhotic subjects with chronic hepatitis C. They found that HOMA was significantly lower in patients with genotype 3 ($n = 13$) than in patients with genotype non-3 ($n = 55$), and there were no significant differences between the two groups re-