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Glucose Abnormalities in Patients With Hepatitis C Virus Infection: Epidemiology and Pathogenesis

Response to Gentilucci et al.

We thank Gentilucci et al. (1) for their comments on our articles (2,3) regarding the pathogenic mechanisms of diabetes in patients with hepatitis C virus (HCV) infection. The authors question why an increased T-helper (Th)1 immune response can be simultaneously the major determinant of insulin resistance and responsible for a poor response to antiviral treatment. This question is based on the statement that Th1 immunoresponse favors HCV clearance. However, although a vigorous Th1 response could play an essential role in spontaneous viral clearance, this is not so evident after interferon treatment. It should be noted that in sustained responders, pretreatment intrahepatic mRNA levels of γ-interferon and tumor necrosis factor-α were lower than in nonsustained responders (4). In addition, a lower Th2 response during antiviral treatment (specifically a decrease in interleukin [IL]-10 rather than an increase of Th1) has been associated with a long-term virological response (5,6). Tsai et al. (7) and Eckels et al. (8) demonstrated that in vitro cytokine responses to recombinant HCV antigens were confined to IL-4 and IL-10 and proposed that such Th2 predominance might be conductive to viral persistence. Furthermore, Masaki et al. (9) reported that a lower Th1/Th2 ratio before interferon therapy may favor long-term virological response in patients with chronic hepatitis C. In addition, activation of naïve B-cells via CD81 has been involved in the immunological response triggered by HCV (10). Therefore, the immune mechanisms involved in the clearance of HCV after interferon therapy are complex and are far from being elucidated.

Low-grade inflammation mediated by activated innate immunity is an underlying pathogenic mechanism of insulin resistance and type 2 diabetes. Apart from the impairment of immune response, there is a cluster of alterations associated with insulin resistance such as obesity, ageing, hypertriglyceridemia, liver esteatosis, and fibrosis; these alterations are also risk factors for nonresponse to antiviral treatment. It has recently been demonstrated (11) that hyperinsulinemia blocks the inhibition of HCV virus replication by interferon. Therefore, it seems that there is a vicious circle in which insulin resistance facilitates the persistence of HCV and, alternatively, HCV favors insulin resistance.

Altogether, one can depict a complex scenario in which Th1 response is only one more of the actors. Future studies are needed to not only confirm that insulin resistance and type 2 diabetes are poor response predictors of antiviral treatment but also to unravel the mechanisms involved.

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A Clinical Screening Tool Identifies Autoimmune Diabetes in Adults

Response to Fourlanos et al.

Fourlanos et al. (1) report on a screening instrument designed to facilitate management of latent autoimmune diabetes of adults (LADA). They assert that in poorly controlled type 2 patients exhibiting two or more of five features (age <50 years, hyperglycemic symptoms, BMI <25.0 kg/m^2, and personal and family history of autoimmunity), the "logical " next step is confirmatory islet antibody testing (1).

Although the effect of routine use of the instrument on outcomes such as HbA_{1c} is unknown, the article raises important questions relating to the management of clinically diagnosed type 2 diabetes. The authors state that LADA patients can require rapid escalation of oral therapy or early commencement of insulin (1). However, patients with severely deficient β-cell function but insufficient LADA features still need insulin therapy. In addition, some LADA patients achieve reasonable initial glycemic control with oral agents (2), with insulin available should this strategy fail.

We have concerns that the LADA instrument fails to meet the necessary criteria for a valid screening tool (3). In their small study, Fourlanos et al. report a sensitivity of 90% and specificity of 71%. However, the positive predictive value is 21%, indicating that the probability of correctly diagnosing LADA is low. This, and the high false-positive rate (28%), suggest a limited ability to identify patients most in need of early insulin therapy.

The authors' apparent intention is to promote the instrument as part of usual care. Because of this, and since the American Diabetes Association does not recommend islet antibody testing in type 2 diabetes (4), why do the authors recommend serological confirmation (1)? Even in the case of children, in whom education, dietary counsel, and treatment differ markedly by diabetes type, autoantigens may be present in a substantial number with otherwise straightforward type 2 diabetes (4). One reason for antibody testing may be to characterize LADA patients fully for intervention studies (1), but this would only be appropriate in specialist centers.

We contend that the management of poorly controlled type 2 diabetes in adults should be based on detailed clinical assessment (including the LADA instrument components), review of glycemic control, implementation of strategies (including educator and dietitian input) that might improve adherence to self-management, a discussion of available therapies (including insulin), and adequate monitoring and support. The use of the LADA instrument and/or autoantibody testing appears redundant in this setting.

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A Clinical Screening Tool Identifies Autoimmune Diabetes in Adults

Response to Davis et al.

We thank Davis et al. (1) for their comments regarding the recent publication of a clinical screening tool for latent autoimmune diabetes in adults (LADA) (2). It is appreciated that the authors' routine management of "poorly controlled adult type 2 diabetes" incorporates the "LADA instrument components." However, our observations of the management of such patients by internists and diabetes nurse practitioners in the community are often contrary to the practice of the authors. Adults with suboptimal glycemic control due to declining β-cell function (often secondary to autoimmune disease) are underrecognized, leading to delays in commencing insulin therapy. The clinical screening tool was developed to aid primary care physicians and diabetes nurse practitioners to consider the pathophysiological process of autoimmune β-cell destruction. The authors cite that the positive predictive value of the clinical screening tool is low