COMMENTED ARTICLES

Elevated alanine aminotransferase predicts new-onset type 2 diabetes independently of classical risk factors, metabolic syndrome, and C-reactive protein in the west of Scotland coronary prevention study.

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Sattar N, Scherbakova O, Ford I, O'Reilly DS, Stanley A, Forrest E, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J.

We examined the association of serum alanine aminotransferase (ALT) with features of the metabolic syndrome and whether it predicted incident diabetes independently of routinely measured factors in 5,974 men in the West of Scotland Coronary Prevention Study. A total of 139 men developed new diabetes over 4.9 years of follow-up. ALT, but not aspartate aminotransferase, levels increased progressively with the increasing number of metabolic syndrome abnormalities from (means SD) 20.9 7.6 units/l in those with none to 28.1 10.1 units/l in those with four or more (P < 0.001). In a univariate analysis, men with ALT in the top quartile (ALT >/=29 units/l) had an elevated risk for diabetes (hazard ratio 3.38 [95% CI 1.99-5.73]) versus those in the bottom quartile (<17 units/l). ALT remained a predictor with adjustment for age, BMI, triglycerides, HDL cholesterol, systolic blood pressure, glucose, and alcohol intake (2.04 [1.16-3.58] for the fourth versus first quartile). In stepwise regression, incorporating ALT and C-reactive protein (CRP) together with metabolic syndrome criteria, elevated ALT (>/=29 units/l), and CRP (>/=3 mg/l) predicted incident diabetes, but low HDL cholesterol and hypertension did not. Thus, elevated ALT levels within the "normal" range predict incident diabetes. The simplicity of ALT measurement and its availability in routine clinical practice suggest that this enzyme activity could be included in future diabetes prediction algorithms.

Hepatitis Monthly Editorial Board Comment ①

Egg or chicken: Which came first?

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Metabolic syndrome is the entity that changed the scientific atmosphere in the new millennium. Previously, we were focused on coronary heart disease and cerebrovascular accident as the major causes of mortality that made the world facing a real pandemic event at the end of the 20th century. As the risk factors for these diseases, physicians did stress on diabetes, hypertension, hyperlipidemia, and obesity. But now a syndrome is ever-growing: the metabolic syndrome; an “all-in-one” or better to say “do-it-all” pathogenesis engine for all risk factors and consequently cardiovascular and cerebrovascular events. As its name shows, it is still a syndrome i.e. a series of signs are gathered to form an entity with a shadow of pathophysiology, so themetabolic syndrome is still-forming and ever-changing. The metabolic syndrome is based on two main pathophysiologic states: insulin resistance and inflammation. Markers of insulin resistance are impaired glucose metabolism and hypertriglyceridemia whereas markers of inflammation are elevated CRP and leukocytosis. What is the role of liver in this scenario? Liver is a main site of glucose reuptake and also glycogenolysis. So, changing the responsiveness of liver to insulin effects i.e. hepatic insulin resistance will

interfere the whole body metabolism of glucose. On the other hand, when the process of insulin resistance and metabolic syndrome starts, it may cause increased adiposity of body and also fat deposition in liver that will itself cause hepatic enzyme increment.
An interesting finding in this article is the independent effect of ALT from CRP. C-reactive protein is a well-known feature of metabolic syndrome inflammatory background. In association with leukocytosis, CRP may predict development of diabetes and also it was shown in previous studies that ALT level and inflammatory responses are positivelycorrelated and especially when we consider interactive effect of cytokines and liver steatosis, this interaction would be more obvious. Interestingly in this study ALT increase did develop before real diabetes or impaired fasting glucose, which may lead to this conclusion that hepatic effects of metabolic syndrome develops earlier or the earlier event is the role played by liver. What would be the medical or health implications of this study? If ALT level may predict development of diabetes independently, it may be used in general population to define a real high risk group. In this group, two modalities may be used: lifestyle modification and also the drugs that will affect insulin resistance-inflammation vicious cycle to prevent probable development of metabolic syndrome.
A list of partially similar studies is presented below where gamma- glutamyltranspeptidase was the substitute for ALT in some. It seems that GGT is completely correlated with ALT. Regarding results of these studies, ALT is more important than GGT and we can omit GGT in clinical practice.

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Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B.

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Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, Lu ZM, Piratvisuth T, Germanidis G, Yurdaydin C, Diago M, Gurel S, Lai MY, Button P, Pluck N; Peginterferon Alfa-2a HBeAg-Negative Chronic Hepatitis B Study Group.

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BACKGROUND: Available treatments for hepatitis B e antigen (HBeAg)-negative chronic hepatitis B are associated with poor sustained responses. As a result, nucleoside and nucleotide analogues are typically continued indefinitely, a strategy associated with the risk of resistance and unknown long-term safety implications.

METHODS: We compared the efficacy and safety of peginterferon alfa-2a (180 microg once weekly) plus placebo, peginterferon alfa-2a plus lamivudine (100 mg daily), and lamivudine alone in 177, 179, and 181 patients with HBeAg-negative chronic hepatitis B, respectively. Patients were treated for 48 weeks and followed for an additional 24 weeks.

RESULTS: After 24 weeks of follow-up, the percentage of patients with normalization of alanine aminotransferase levels or hepatitis B virus (HBV) DNA levels below 20,000 copies per milliliter was significantly higher with peginterferon alfa-2a monotherapy (59 percent and 43 percent, respectively) and peginterferon alfa-2a plus lamivudine (60 percent and 44 percent) than with lamivudine monotherapy (44 percent, P=0.004 and P=0.003, respectively; and 29 percent, P=0.007 and P=0.003, respectively). Rates of sustained suppression of HBV DNA to below 400 copies per milliliter were 19 percent with peginterferon alfa-2a monotherapy, 20 percent with combination therapy, and 7 percent with lamivudine alone (P<0.001 for both comparisons with lamivudine alone). Loss of hepatitis B surface antigen occurred in 12 patients in the peginterferon groups, as compared with 0 patients in the group given lamivudine alone. Adverse events, including pyrexia, fatigue, myalgia, and headache, were less frequent with lamivudine monotherapy than with peginterferon alfa-2a monotherapy or combination therapy.

CONCLUSIONS: Patients with HBeAg-negative chronic hepatitis B had significantly higher rates of response, sustained for 24 weeks after the cessation of therapy, with peginterferon alfa-2a than with lamivudine. The addition of lamivudine to peginterferon alfa-2a did not improve post-therapy response rates.

Hepatitis Monthly Editorial Board Comment ②

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We read with interest the article titled" Peginterferon Alfa-2a Alone, Lamivudine Alone, and the Two in Combination in Patients with HBeAg-Negative Chronic Hepatitis B" by Marcellin et al. (N Engl J Med. 2004; 351:1206-17). It was very interesting for us to understand the efficacy of new drugs in chronic hepatitis B (CHB) patients, especially in CHB with HBeAg negative. Treatment of chronic hepatic B infection in the absence of HBe antigen is very challenging. Marcellin and his colleagues in their recent study used pegylated interferon alfa (PEG IFN) in these patients (1), but several points in their study need more clarification.
First of all, there is no comparison with standard interferon. Available data indicate prolonged course of standard interferon for ≥12 months has 20-30% sustained virologic response which is almost the same as what is reported with PEG IFN in this study with a much lower cost (1, 2, 3). It seems that we need a protocol to compare between the standard interferon alfa with pegylated interferon in HBeAg negative CHB by considering the costs. The second point is that there was one death in PEG IFN group which needs more consideration. While it was claimed that all treated patients had elevated ALT before treatment, the baseline data in table one indicate ALT level in all treatment groups included normal values!?. If this is the case then indication of treatment in these cases with normal ALT level is not clear (4). As mentioned in the article, rate of HBsAg loss and HBsAg seroconversion at week 72 occurred in seven and five patients who received peginterferon alfa-2a monotherapy respectively and; in five and three patients who received peginterferon alfa-2a plus lamivudine, respectively and in no patients in lamivudine group.

However, the authors concluded the importance of dual immunomodulatory and antiviral effects of interferon-based therapies in the treatment of HBeAg negative CHB. We think this benefit belongs to interferon alfa and not to lamivudine, which is in accordance with what the authors mentioned in another part of discussion. The results with peginterferon alfa-2a monotherapy were better than combination therapy. The best conclusion is that response rate to lamivudine is lower than that of interferon-based therapy. Several studies suggests that HBV genotypes may influence response to anti-viral therapy and genotypes A and B have been reported to be associated with higher rates of response to interferon alfa than genotypes D and C, respectively (5).There are also no data on genotypes in this article which may affect response to treatment.
By considering these points, we believe that while this is an excellent response rate with peginterferon alfa-based therapy in comparison with lamivudine, it is still a long way to conclude that peginterferon alfa is the first-line therapy for HBeAg negative CHB and it needs more studies.

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