

# Hepatitis B Vaccine Nonresponse: An Alarm Signal for Latent Type 1 Diabetes?

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Hepatitis B virus (HBV) infection affects more than one third of the world's population causing acute and chronic liver diseases, ranging from fulminant hepatitis to cirrhosis and eventually hepatocellular carcinoma with an incidence of 620,000 death per year [1,2]. Vaccination with the surface antigen of HBV (HbsAg) is considered as the main safe and effective strategy for protecting people from common HBV infection [1,2]. HB vaccination is routinely recommended for infants, children, and adolescents [1,2]. Moreover, it has also been suggested for high risk adults for acquiring HBV infection. Development of immune response to HbsAg is connected with the production of specific neutralizing antibodies to surface antigen of HBV (anti-HBs) [3]. Current recombinant HBV vaccines show excellent immunogenicity [3]. However, approximately 5-10% of immunized individuals are enabled to develop the minimum protective anti-Hbs titers of 10 mIU/ml after completion of primary vaccine series remaining at risk for HB infection [3]. The group of non responders patients could represent an important reservoir of HBV susceptible persons that will persist as healthy carriers, contributing significantly to the spread of the disease [1,2]. It has been estimated that there are more than 350,000 million of chronic HBV carriers in the world [3]. Thus, the problem of unresponsiveness to HBV vaccine constitutes a critical public health matter worldwide [1]. In this respect, alternative HBV vaccination schedules have been proposed to improve the responsiveness to HB vaccine in this patient category [1,2]. To date, the underlying mechanisms responsible for non response phenomenon against HbsAg in vaccinated healthy subjects are poorly understood [2-5]. The process of anti-HBs production is T cell-dependent and requires T helper (Th)-cell activation [3]. In particular, T cell type 1(Th1) immune response has been considered as a prerequisite of HBV clearance [4]. Consequently, altered Th1 immune response has been thought to account for non responsiveness to the HBV vaccine [3-5]. Anti-HBs production has been correlated with gene polymorphisms of interleukins involved in the Th1 system such as IL-18 and IFN- $\gamma$  [4-9]. On this regard, it is well recognized that IL-18 strongly enhances the secretion of interferon- $\gamma$  (IFN- $\gamma$ ) which, in turn, further skews the immune response toward a Th1 phenotype [7]. The outcome of HBV infection has been associated with IL-18 gene polymorphisms [4]. IL-18 has been reported to regulate HBV clearance and the immune response to HBV antigens during spontaneous natural infection or planned vaccination [6,8]. Interestingly, it has been demonstrated that HB core antigen is a potent inducer of IL-18 from healthy controls and patients with chronic HB or acute HB [6]. Regarding IFN- $\gamma$ , it has been verified that genetically determined differences in IFN- $\gamma$  activity could impact on the magnitude of immune response to HBV vaccination [10]. Furthermore, IFN- $\gamma$  gene polymorphism has been correlated with susceptibility to chronic HBV infection and development of intrauterine HBV infection [10,11]. Inter-individual variability in antibody response to HB vaccination has also been linked to HLA genotypes [12]. It has been advised a possible genetic predisposition to elicit protective immunity against HBV likely due to the presence of specific human leukocyte antigen (HLA) haplotypes [1,12,13]. On this regard, HLA-DRB1 gene has been directly involved in HBV vaccine non responsiveness [12]. Intriguingly, HLA-DRB1 alleles have been

described as major predictors of differential antibodies responses to HBV vaccination in youth, implying that Th cell-dependent pathways mediated through HLA Class II antigen presentation are essential to effective immune response to recombinant vaccines [13]. It has been reported a lower response to HBV vaccination in chronic conditions such as Type 1 and Type 2 diabetes than in healthy controls [1,2,14,15]. Type 1 diabetes is a chronic autoimmune disorder related to genetic, environmental and immunologic factors that ultimately leads to the destruction of the pancreatic  $\beta$  cells and insulin deficiency [16-19]. It is the most common pediatric endocrine disease that is fatal unless treated with insulin [16,18]. It has been estimated that approximately 65,000 children aged under 15 years are diagnosed worldwide every year [20]. Up to 80% of these patients present with diabetic ketoacidosis (DKA) that is linked to both short-term risks and long-term consequences [20]. It has been underlined that children with Type 1 diabetes show a higher rate of reduced seroprotection for HBV vaccination [1]. Previous studies found a reduced efficacy of HBV vaccination both in chronic diabetic adults and in children [1,14,15,21]. Recently, it has been written that older adults suffering from diabetes and obesity seem to have a greater impairment in HBV vaccine response, principally those affected by coexisting kidney diseases in comparison to the same group of high risk patients without diabetes [1,14]. In this contest, the Advisory Committee on Immunization Practices (ACIP) recommended use of HB vaccination for adults with diabetes mellitus because of the increasing incidence of diabetes, and the high prevalence of diabetes among certain groups recommended for HB vaccination as patients with end-stage renal disease [22]. The biological basis for impaired responses to HBV vaccination among individuals with diabetes still remains unclear [14]. The lower seroconversion rate in diabetic patients represents a critical problem considering that they have a number of risk factor for enhancing HBV exposure including self-monitoring of blood glucose, intravenous and subcutaneous insulin administrations [1,2]. Similarly to unresponsiveness to HBV vaccine, HLA DRB1 genotypes have been illustrated as significant predictors for latent Type 1 diabetes [23]. It has been written that HLA profile may designate the link between Type 1 diabetes and non responsiveness to HB vaccine [1,23]. What is more, it has also been advised a central role for Th1 response pattern in Type 1 diabetes development [15,16]. The inflammatory process in early diabetes is thought to be started and propagated by the effect of Th1-

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secreted cytokines [16]. Intriguingly, IL-18 and IFN- $\gamma$  among other Th1 cytokines, have been shown to play a major role in  $\beta$ -cell dysfunction [14,17,24-26]. It has been detected that serum levels of the IFN- $\gamma$ -inducing IL-18 are increased in individuals at high risk of developing Type 1 diabetes [18]. IL-18 gene promoter polymorphism has been linked to susceptibility to Type 1 diabetes [24]. IL-18 has been described as an enhancer of Th-1-type immune responses in diabetes development early in the spontaneous disease process [25]. IFN- $\gamma$  gene polymorphism has also been found to be strongly linked to Type 1 diabetes onset [14]. IFN- $\gamma$  seems to be crucially involved in  $\beta$ -cell dysfunction related to chronic pancreatitis in diabetic and non diabetic patients in comparison to controls [26]. Interestingly, it has been shown that IL-18 and IFN- $\gamma$  also play a critical role in susceptibility to obesity and Type 2 diabetes [27,28]. The prodromal phase of Type 1 diabetes is characterized by the appearance of multiple islet-cell related autoantibodies (Aab) [29]. There is general consensus that the presence of multiple Aab is associated with a high risk of developing diabetes, where the presence of a single islet-cell related Aab has usually a low predictive value [27]. Until today no treatment has been shown to prevent Type 1 diabetes in humans [18]. All these contentions led us to presume that HBV vaccine non response and Type 1 diabetes may share common immunological mechanisms in physiopathology. We hypothesize the potential pathogenic role of IL-18 and IFN- $\gamma$  gene polymorphisms in HBV vaccination failure with the possibility of long-lasting downstream effects on the pancreatic  $\beta$  cells leading to their gradual destruction and insulin deficiency. Thus, nonresponsiveness to the HBV vaccine may be an alarm signal for latent Type 1 diabetes. For that reason, post-vaccination testing for serologic response should be performed after primary series completion in children. Non-responder babies to HBV vaccination, especially those with familiarity for autoimmune disorders, should be screened for multiple islet-cell related Aab along the time. More likely, greater gains will occur with an approach that looks for identifying IL-18 and IFN- $\gamma$  gene polymorphisms to utilize as biomarkers for latent Type 1 diabetes. In this contest, administration of neutralizing antibodies against IFN- $\gamma$  and/or IL-18 might represent a future target for immunomodulatory intervention therapy to halt or even prevent islet-cell destruction. Moreover, by recognizing and treating the early symptoms of hyperglycemia, DKA can be prevented. As a final point, new vaccination strategies are needed to enhance HBV vaccine efficacy in these subjects at risk given that there is increasing incidence of Type 1 diabetes in the world, mainly among children younger than 5 years of age [30].

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