Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 7
MISBP 2024

Analysis of Factors Attributing to Hepatitis B Vaccine Non-response

Qiqi Chen

College of international education, Shenzhen, China

s22560.Chen@stu.scie.com.cn

Abstract. Currently, 5-15% of hepatitis B vaccine recipients are non-responders despite the high global coverage 83% of the hepatitis B vaccine. The research of hepatitis B vaccine nonresponse had been going on for some time for the improvement of the vaccine and the objective to eliminate hepatitis B, this paper aims to summarize some of the factors contributing to hepatitis B vaccine nonresponse base of these previous studies after scrutiny. Factors contributing to hepatitis B vaccine nonresponse including HLA haplotypes, age, elder with comorbid condition, obesity, smoking, presence of micronutrient deficiency is involved in this paper. The understanding of these factors is important for the further progression of the vaccine, improvements like repeated vaccination, a booster dose, use of immune boosters, vaccine with a higher dosage, a different adjuvant, a more effective antigen, a different administration route of the vaccine, change of needle length when injecting the vaccine can be made considering the nonresponse factors, therefore increasing the efficacy of hepatitis B vaccine.

Keywords: Hepatitis B Vaccine; non-response; immune system.

1. Introduction

Hepatitis B infection is a widespread virus-cause infectious disease that results in liver inflammation and complications such as cirrhosis, liver cancer and even death. In 2022, it is estimated that about 250 million people were suffering from chronic hepatitis B infection over the world, and at the same year had lead to over 1 million deaths [1]. Fortunately,Vaccine against hepatitis B is available to prevent the infection, the vaccine provides up to 100% of protection after 3 doses [2]. According to the WHO, the global coverage of 3-dose hepatitis B vaccine is 83% [3].

Yet, about 5-15% of recipients of hepatitis B vaccine are non-responders. A hepatitis B vaccine “non-responder" refers to a person who does not develop protective surface antibodies after completing two full series of the hepatitis B vaccine, and more specifically, has a level of antibody to hepatitis B surface antigen (anti-HBs) of <10 mIU per mL (4-8 weeks after a booster dose, which is the 4th dose of vaccine to confirm non-responder status) [4, 5].

It is observed that HLA genotypes, age, obesity, smoking, micronutrient deficiency attributes to hepatitis B vaccine non-response, though there are still other factors with unclear relationships to non-response, therefore, to improve the efficacy of hepatitis B vaccine and a further step to eliminate hepatitis B, it is important to recognize the factors contributing to non-response of the vaccine and find the respective approaches to deal with and ameliorate the vaccine.This study aim to compile and summarize the current studies that relates factors attributing the non-response recipient of hepatitis B vaccine.

2. HLA Genotypes

Human leukocyte antigen (HLA) is a group of related cell surface proteins responsible in regulation of the immune system, it is utilized for differentiation of ‘self’ and ‘nonself’. The major histocompatibility complex (MHC) genes encode the HLAs [6].

HLA class II genes, including HLA-DR, HLA-DP, and HLA-DQ genes, their interaction between HLA molecules contributes to poor responsiveness. Some research shows that not all HLA II genotypes show hepatitis B vaccine non response, some found and advocates that HLA-DP allele and nonresponse to hepatitis B vaccine has no relationship, it is deduced that this is due to weaker linkage disequilibrium between HLA- DP alleles and the other two HLA class II haplotypes [7]. And not all DR and DQ allele shows association, for example, DRB1 01 shows increase in response to the vaccine, while DRB103 and DRB107 exhibit opposite result toward HBsAg. There are also controversial studies, displaying opposite results on the same genotype, for instance the DPB103:01 [8, 9].

Moreover, HLA genotypes between different ethnic groups demonstrates different trend, in Italian neonates, DRB10301 relates to both non-responsiveness and responsiveness to the vaccine, whereas relationship is not observed in Chinese recipients, Chinese vaccinees show non-responsiveness with other haplotype, such as DRB10401 [10].

An odd one out for both DR and DQ allele and different responses in ethnic groups is HLA-DR1 allele, it is found in Caucasians that it is associated with high responsiveness of HBsAg, and not found positive in Japanese nonresponder, which corroborates that the haplotype HLA-DR1 allele is related to positive response toward HBsAg among different population (Japanese and Caucasians) [7].

It is once hypothesized that defective antigen presentation contributes to non-response, however, this is excluded since non-responders' peripheral blood mononuclear cells (PBMC) have similar performance as good responders in presenting the HBsAg to T cells [8, 9].

It is suggested that responses to HBsAg is determines by MHC-linked immune response genes (Ir), and non-responsiveness is due to absence of an Ir gene in the haplotypes mentioned above (DRB103, DRB107) [12]. Since MHC molecules expressed by APCs present peptide of antigens to receptor of helper T cells, is greatly involved in immune response, and its polymorphism determines variations [8, 9].

Some envisagement expounds that a 'blank' in T cell antigen recognition repertoire results in non-responsiveness. There are no T cells recognizing the epitope of HBsAg that is able to associate with certain class II molecules (e.g. DR7), because they molecularly mimicked the MHC class II-associated self-peptide that they have been eliminated in the thymus, thus is unsuccessful in stimulating the helper T cell for further immune response [8, 9].

Also, despite the above reasons, the alleles may simply just be in linkage disequilibrium with other nearby polymorphic genes, for example, tumor necrosis factor, and may just be markers for linked polymorphic genes that influences immune response [8, 9].

3. Older Age

Elders are more likely to be non-responders, vaccine efficacy can be reduced due to change in humoral & cellular immune system as one ages. In immunosenescence, naive helper and killer T cell proportion decreases, while memory helper and killer T cells increase in proportion, this may result in slower immune response along with the entry of the HBsAg brought by the vaccine [10].

Co-stimulatory molecule CD28 is lost on CD8 T cells which is necessary for T cell activation, differentiation, proliferation, in this case, T cell will either die or become anergic, impairing the immune response [11].

T helper cells subsets, Th1 and Th2 cell secrete cytokines which regulates inflammation, immune response. Th1 cells produce IFN-γ, IL-2, and TNF-α, these cytokines activate macrophage and neutrophils, antigen-specific T helper and cytotoxic cells, help proliferation of B cell and production of antibodies. Th2 cells produce IL-4, IL-5 and etc which are for B cell growth, immunoglobin production [12]. Yet, compared to young people, the production of Th1and Th2cytokines is significantly reduced in the elderly after receiving the hepatitis B vaccine [13].

Also, Helper T cell conduce B cell during formation of germinal centers where processes happen to help in the production of antibodies, therefore impaired T helper cell might be the one to blame for the decreased ability for production of antibodies in elders [10].

There are other features deduced to be involved in human immunosenescence, which already is corroborated in murine studies, for example CD86 on B cell, it is critical for initiation of antibody response. Diminished CD86 expression by B cell found in senescent mice may contribute to reduced germinal center reaction which correlated with reduced antibody response [10].

Also, elders are more likely in comorbid condition at the time receiving to vaccine due to immunosenescene which make them more susceptible to diseases. This can affect vaccine response because of the concomitant diseases that impairs immune system or the treatments that interferes. For instance, vaccine recipients with diabetes mellitus can result in aberrant cytokine responses including less secretion of IL-1 which is important in triggering innate inflammation in response to PAMPs mimicked in hepatitis B vaccine, also decreased secretion of IL-6 affecting antibody production and T cell development causing weaker immune response toward vaccine. It also causes defect in ROS production, in which the ROS induces apoptosis and cellular senescence in order to prevent damaged cells from replicating, thus averting genomic instability and further damage [14]. It also affects immune cells in both innate and adaptive immunity, for instance, reduction in leukocyte recruitment, neutrophil dysfunction, neutrophil degranulation impairment, inhibition of immunoglobulin-mediated opsonization, decreased phagocytosis, Natural killer cell dysfunction due to defects in their activating receptors, and suppresses neutrophil action to produce neutrophil extracellular traps(NET formation). Which all have important contribution in immune response against HBsAg brought by the vaccine [15].

4. Obesity

Obesity is defined to be a person with a BMI $\geq$30kg/m^2. In obesity, increase influx of nutrients lead to Adipose tissue expansion, affecting the energy-storing and endocrine functions that the adipose tissue possesses.

4.1. Obesity: Inadvertent Injections

Hepatitis B vaccine intramuscularly injected in people with obesity maybe inadvertently injected into fat instead of muscle due to increase of subcutaneous tissue in obesity, which is likely to hinder absorption and mobilization of antigens as fat has poorer vascularity, they will reach the circulation slower, which therefore will result in a slower immune response, reducing the efficacy of the vaccine. It is also possible that enzyme in the site cause the HBsAg to become denatured after staying in subcutaneous fat for too long [16]. Similar effect will happen to people without obesity if intramuscular injection is inadvertently injected subcutaneously, yet people with obesity have a higher possibility of experiencing the matter,

4.2. Obesity: Immune System Impact

Obesity is associated with chronic inflammation which results from both local immune alterations and Systemic immune alterations.

This former includes immune cell dysfunction in the adipose tissue, number of M1 macrophages, Th1, Th17, CD8+ T cells that release pro-inflammatory cytokines increases and replaces M2-type macrophages, Treg, Th2, type 2 innate lymphoid cells. The latter involves elevated pro-inflammatory cytokine levels, and increased numbers of circulating inflammatory immune cells, and decreased number of Treg, while Treg help maintain glucose homeostasis and insulin sensitivity, can help in reducing adipose inflammation and a conditioning adipocyte [17, 18].

The inflammation is further enhanced by increase of leptin secretion in obesity, it prompts proliferation of monocyte and differentiation into macrophage from monocyte, also up-regulate

inflammatory cytokines production, such as TNFα, IL-6. It affects many cells of the innate immunity, as most of them they are involved in leptin signaling and possess leptin receptor isoform. Adaptive immune system is influenced by leptin as well, for the maturation and proliferation of T cells, modification expressions of helper and killer T cells [19].

Excess nutrient in obesity alters immune cell metabolism, for the case of T cells, glucose as the source of energy is required for proper proliferation and secretion. if T cell is in a condition with a high concentration of glucose, there can be reactive oxygen species generation, if in excess this can damage DNA, double stranded breaks resulting in unstable genome,

It can damage protein by oxidation of amino acids, also lipid peroxidation leading to damage of cell membrane, further damaging cell and tissue, affecting the proper functioning of immune organs. The protein responsible for glucose uptake of T cell GLUT1 may be overexpressed and may result in varying cytokine production and cell metabolism [19, 20].

The hormone adiponectin released by adipose tissue level decreases, affecting natural killer cell function and human myeloid cells in its production of cytokine. Pro-inflammatory cytokines production increases, their chronic exposure creates a persistent state of immune activation, which can lead to immune cell exhaustion and desensitize immune cells towards cytokines produced in inflammatory response in hepatitis B infection mimic by the vaccine, also reduce the ability of the adaptive immune cells, disrupting the coordination and strength of the immune response [19]. Excessive production of cytokine can also result in cell death and irreversible tissue damage as it encourages infiltration of immune cells into the adipose tissue.

5. Smoking

Both innate and adaptive immune system are affected in smoking.

Constant antigen recognition of immune cells of components or products of cigaratte (e.g. smoke particles), causes inflammation and increases cytokine production, for example, IL-2 levels, promotes activation and proliferation of CD8+ T cells, also, increase in IL-6 level stimulate antibody production, differentiation of CD8+ T cells, and reduces differentiation of Tregs, which is important in regulating inflammation. While resulting in a lower level of CD4+ T cell, specifically, decrease of naive CD4+T cells with CD38 activation marker, which shows a decreased ability to proliferate and recognition of IL-2, this result in slower immune response against the HBsAg [21]. The chronic inflammation also causes an increase of proportion of memory B cells and a decrease in plasma cells which means a decreased ability of the immune system to respond to HBsAg newly introduced into the body. Nicotine in cigarette damage pathway in T cells towards HBsAg and calcium signaling which restrains B cell response [18]. Monocyte number also decreases; it is deduced to be owing to their recruitment to the lungs by the damaged cause by the tobacco smoke [21].

Smoking generates reactive oxygen species, for example deposition of particulates into lungs by the tobacco smoke, this results in in accumulation of layer of tar which become aqueous solution, produces ROS after redox cycling. At first, ROS release brings a positive effect, it aids in repair of tissue and protection of the body against foreign substance, yet these action increases ROS secretion as well and eventually leads to oxidative stress. Oxidative stress damage proteins, nucleic acids, and other macromolecules, for example, degradation of polyunsaturated fatty acids forming malondialdehyde (MDA) able to bind to DNA forming mutagenic DNA-adducts. And specific, ROS, OH radical, can cause oxidative DNA lesions that can lead to mutation if not correctly repaired [14]. Inflammatory response is being activated by oxidative stress, and further increase generation of ROS. The components of tobacco smoke.e.g. Heavy metals, damages the tissue and cells prompt inflammatory response as well, further exacerbating the condition.

6. Micronutrient Deficiency

Micronutrient assist the proper function of immune system, lacking these essential elements causes immunosuppression, which would cause infection if one in this condition receives the vaccine as one's immune system is not able to provide complete protection allowing the hepatitis B virus to replicate.

Micronutrient involves trace elements and vitamins, for example vitamin A and zinc, their function in immune system is mentioned below.

Vitamin A is crucial in the formation of the first line defense of the immunity, which is the epithelium. It enhances the mechanical defense in the respiratory tract and intestine by its promotion of mucin secretion.

Vitamin A regulates NK cell number, function and differentiation by interferon-gamma down-regulation and IL-5 up-regulation. It activates the mTOR signaling pathway for neutrophil differentiation. It is involved in the phagocytic and oxidative burst activity of macrophage, and the transformation of M1 macrophages to M2 during inhibition of inflammatory response by inducing monocyte differentiation towards them. It regulates pre-dendritic cells differentiation into dendritic cell, promoting the release of IL-12 and 23 from dendritic cell precursors in the presence of IL-15 [22, 23].

In adaptive immunity, it is inferred that vitamin A influence of Th2 cells development and APCs can enhance production of antibodies. Retinoids are for proper growth and differentiation of B cell, it also helps Tregs in differentiation, stability and their function. T cell activation also requires vitamin A as a cofactor, and is involved in regulation of T-cell signaling by playing a role in the expression of receptors relating to the signalling [22].

Zinc deficiency shows defect in macrophage maturation and activity, and reduced NK cells.

Zinc is a important constituent for the hormone thymulin produced by thymus epithelial cells, it is involved in the maturation of pre T lymophocyte, thus Zn deficiency affect their differentiation and proliferation and cytokine production, resulting in disproportion of helper and killer T cells and also within the subsets such as the changing ratio of Th1 and Th2 cells, in which the Th1 cell decreases largely which reduced its cytokine production (interferon gamma, IL-2). B cells maturation is also impacted, which results in decrease antibody production. Zinc also reduces oxidative stress levels [23, 24].

7. Conclusion

Hepatitis B vaccine future improvement can be taking under considerations of the above factors which contributes to hepatitis B vaccine non-response, including HLA haplotypes, age along with comorbid condition, obesity, smoking and micronutrient deficiency, therefore improving protection against hepatitis B for more people over the world, and taking a step further to eliminate hepatitis B.

Improvements to increase seroconversion rate can include repeated vaccination, a booster dose, use of immune boosters, vaccine with a higher dosage, a different adjuvant, a more effective antigen, a different administration route of the vaccine, change of needle length when injecting the vaccine, therefore reducing the number of hepatitis B vaccine non-responders.

References

[1] Hepatitis B. WHO. 2024. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b.

[2] The Hepatitis B Vaccine Protect Yourself and Those You Love. https://www.hepb.org/assets/Uploads/vaccine.pdf.

[3] Immunization coverage. WHO. 2024. https://www.who.int/news-room/fact-sheets/detail/immunization-coverage.

[4] Vaccine Non-Responders. https://www.hepb.org/prevention-and-diagnosis/vaccination/vaccine-non-responders/.

[5] Non-responders to hepatitis B vaccine are recommended to receive further doses and serological testing. Australian lmmunisation Handbook. https://immunisationhandbook.health.gov.au/recommendations/non-responders-to-hepatitis-b-vaccine-are-recommended-to-receive-further-doses-and-serological-testing.

[6] https://www.carislifesciences.com/products-and-services/molecular-profiling/profiling-technologies/whole-exome-sequencing/human-leukocyte-antigen-hla/.

[7] Hatae K, Kimura A, Okubo R, Watanabe H, Erlich HA, Ueda K, Nishimura Y, Sasazuki T. Genetic control of nonresponsiveness to hepatitis B virus vaccine by an extended HLA haplotype. Eur J Immunol. 1992 Jul; 22 (7): 1899-905.

[8] Desombere I, Willems A, Leroux-Roels G. Response to hepatitis B vaccine: multiple HLA genes are involved. Tissue Antigens. 1998 Jun; 51 (6): 593-604.

[9] Ou G, Liu X, Jiang Y. HLA-DPB1 alleles in hepatitis B vaccine response: A meta-analysis. Medicine (Baltimore). 2021 Apr 9;100 (14): e24904.

[10] Rosenberg C, Bovin NV, Bram LV, Flyvbjerg E, Erlandsen M, Vorup-Jensen T, Petersen E. Age is an important determinant in humoral and T cell responses to immunization with hepatitis B surface antigen. Hum Vaccin Immunother. 2013 Jul; 9 (7): 1466-76.

[11] O'Neill RE, Cao X. Co-stimulatory and co-inhibitory pathways in cancer immunotherapy. Adv Cancer Res. 2019; 143: 145-194.

[12] Vahidian F, Duijf PHG, Safarzadeh E, Derakhshani A, Baghbanzadeh A, Baradaran B. Interactions between cancer stem cells, immune system and some environmental components: Friends or foes? Immunol Lett. 2019 Apr; 208: 19-29.

[13] Edelman R, Deming ME, Toapanta FR, Heuser MD, Chrisley L, Barnes RS, Wasserman SS, Blackwelder WC, Handwerger BS, Pasetti M, Siddiqui KM, Sztein MB. The SENIEUR protocol and the efficacy of hepatitis B vaccination in healthy elderly persons by age, gender, and vaccine route. Immun Ageing. 2020 Apr 28; 17: 9.

[14] Caliri AW, Tommasi S, Besaratinia A. Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. Mutat Res Rev Mutat Res. 2021 Jan-Jun; 787: 108365.

[15] Berbudi A, Rahmadika N, Tjahjadi AI, Ruslami R. Type 2 Diabetes and its Impact on the Immune System. Curr Diabetes Rev. 2020; 16 (5): 442-449.

[16] Ng JY. Inadvertent subcutaneous injection of COVID-19 vaccine. Postgrad Med J. 2021 Jun; 97 (1148): 400.

[17] de Frel DL, Atsma DE, Pijl H, Seidell JC, Leenen PJM, Dik WA, van Rossum EFC. The Impact of Obesity and Lifestyle on the Immune System and Susceptibility to Infections Such as COVID-19. Front Nutr. 2020 Nov 19; 7: 597600.

[18] Yang S, Tian G, Cui Y, Ding C, Deng M, Yu C, Xu K, Ren J, Yao J, Li Y, Cao Q, Chen P, Xie T, Wang C, Wang B, Mao C, Ruan B, Jiang T, Li L. Factors influencing immunologic response to hepatitis B vaccine in adults. Sci Rep. 2016 Jun 21; 6: 27251.

[19] Milner JJ, Beck MA. The impact of obesity on the immune response to infection. Proc Nutr Soc. 2012 May; 71 (2): 298-306.

[20] Shields HJ, Traa A, Van Raamsdonk JM. Beneficial and Detrimental Effects of Reactive Oxygen Species on Lifespan: A Comprehensive Review of Comparative and Experimental Studies. Front Cell Dev Biol. 2021 Feb 11; 9: 628157.

[21] Piaggeschi G, Rolla S, Rossi N, Brusa D, Naccarati A, Couvreur S, Spector TD, Roederer M, Mangino M, Cordero F, Falchi M, Visconti A. Immune Trait Shifts in Association with Tobacco Smoking: A Study in Healthy Women. Front Immunol. 2021 Mar 9; 12: 637974.

[22] Pecora F, Persico F, Argentiero A, Neglia C, Esposito S. The Role of Micronutrients in Support of the Immune Response against Viral Infections. Nutrients. 2020 Oct 20; 12 (10): 3198.

[23] Huang Z, Liu Y, Qi G, Brand D, Zheng SG. Role of Vitamin A in the Immune System. J Clin Med. 2018 Sep 6; 7 (9): 258.

[24] Weyh C, Krüger K, Peeling P, Castell L. The Role of Minerals in the Optimal Functioning of the Immune System. Nutrients. 2022 Feb 2; 14 (3): 644.