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Review

The weight of obesity on the human immune response to vaccination

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ABSTRACT

Despite the high success of protection against several infectious diseases through effective vaccines, some sub-populations have been observed to respond poorly to vaccines, putting them at increased risk for vaccine-preventable diseases. In particular, the limited data concerning the effect of obesity on vaccine immunogenicity and efficacy suggests that obesity is a factor that increases the likelihood of a poor vaccine-induced immune response. Obesity occurs through the deposition of excess lipids into adipose tissue through the production of adipocytes, and is defined as a body-mass index (BMI) $\geq 30\,kg/m^2$. The immune system is adversely affected by obesity, and these "immune consequences" raise concern for the lack of vaccine-induced immunity in the obese patient requiring discussion of how this sub-population might be better protected.

1. Introduction

Vaccination has played a crucial role in decreasing global infectious diseases. After almost 220 years since the creation of the first vaccine by Edward Jenner, vaccination is still considered the most feasible and effective means of protection from multiple infectious diseases [1]. However, some individuals experience vaccine-preventable illnesses and complications even after vaccination. Despite highly effective vaccine surveillance and increased vaccine use in the population, hospitalizations and deaths from vaccine-preventable illnesses continue to occur, suggesting that current immunizations do not protect all vaccinated individuals.

The efficacy of a vaccine-induced immune response relies on the initiation and amplification of the immune response. Upon an immune system challenge, innate immune pathways provide a general response to infection (or vaccination) by recruiting effector cells that release cytokines to initiate an antigen-specific adaptive immune response. Simultaneously, proper adaptive immune responses require seroconversion, the process of responding to antigens in serum with antigen-specific antibodies. Vaccines contain components (antigens) of the pathogen that activate the host's adaptive immune system to provide a rapid antigen-specific response during a subsequent infection. However, research has identified certain sub-populations that have a propensity for a diminished immune response to vaccinations. Failure to induce a protective immune response by vaccination places these groups at a higher risk for infection and vaccine-preventable complications that occur from natural exposure.

One important factor correlating with decreased vaccine-induced immune response is obesity, a condition caused by the uptake of lipids into adipocytes and the accumulation of excess adipose tissue within body fat stores and organs, such as the liver [2]. Obesity is a product of biological and environmental influences that leads to an increase of excess adipose tissue, which correlates with an increase in debilitating conditions associated with increased morbidity and mortality [2]. The pro-inflammatory hormone leptin, which has many immunologic functions, has been shown to correlate with body fat mass since it is produced and secreted from adipocytes [3]. Obesity may interfere with an obese individual's ability to mount an effective immune response to vaccination or an infection due to increased body fat and the increased production of leptin [4]. Further, there is some evidence for the involvement of leptin and leptin-related gene polymorphisms in the serum leptin concentrations [3]. The body-mass index (BMI), also referred to as the Quetelet index, is an important proxy measurement for rapid identification of patients at a heightened risk for weight-related health complications [5], such as poor vaccine-induced immune response [6]. The BMI is used by the National Institutes of Health to classify an individual as underweight (BMI $\leq 18.5\,kg/m^2$), normal weight ($18.5–24.9\,kg/m^2$), overweight ($25.0–29.9\,kg/m^2$), obese ($30.0–34.9\,kg/m^2$), or severely obese ($\geq 35\,kg/m^2$) [7]. Currently, it is estimated that over a third of the U.S. population is obese, and since this trend is predicted to continue, the percentage of obese individuals in the U.S. will most likely increase [8–10]. Data

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also suggest that the global prevalence of overweight and obesity has significantly increased (28.8% to 36.9% in men, 29.8% to 38.0% in women) over the past three decades, and no country has had a significant decrease in obesity during this same time period [11]. These data indicate that vaccines may not provide this growing subpopulation the protection they require.

The correlation between obesity and poor vaccine-induced immune response was first observed in 1985 when obese hospital employees received the hepatitis B vaccine [12]. Twenty-five years later, clinical and laboratory data published on pandemic influenza A/pH1N1 indicated that the obese population was at an increased risk for influenza-like illnesses and complications [13]. Additionally, two studies observed a significant decline in tetanus [14] and rabies [15] vaccine-induced antibody protection in the obese, furthering the concern that underlying factors related to obesity limit vaccine response, leaving many individuals vulnerable to disease-related complications. The vaccine-induced immune response discrepancy between lean and obese individuals suggests that medical and other issues related to or caused by obesity could play a significant role in suboptimal vaccine-induced seroconversion in obese persons.

While poor vaccine-induced immune responses have been observed in the obese for hepatitis B, influenza A/pH1N1, tetanus and rabies vaccines, there is a lack of depth in the data to describe the burden obesity has on vaccine-induced immunity for other vaccines. If obese persons respond poorly to current vaccines, further efforts are required to ensure this population is protected. A review that collects and examines data for vaccine-induced immune response in obese populations is needed. The effect of obesity on immune responses has been previously described [16–18]; however, this review seeks to examine the data connecting obesity to poor vaccine-related adaptive immune responses. We searched the PubMed database to identify publications that provided data of the effect of obesity on vaccine-induced immune responses. Upon further review of the search results, we included human studies that provided data on prophylactic vaccines that generate virus-specific antibody titers to protect against a subsequent immune challenge in an overweight or obese cohort. We review previously published data (Table 1) on diminished hepatitis B, influenza A/pH1N1, tetanus and rabies vaccine-induced immune responses in obese persons, and we suggest more data are required to understand the mechanisms behind the immunologic aspects of obesity (e.g., the chronic inflammatory state) that could hinder effective vaccination outcomes.

2. Hepatitis B virus (HBV)

2.1. HBV infection and obesity

Each year, there are four million new cases of HBV infection, and one million people die from chronic HBV-related complications annually. Chronic HBV infection can lead to other serious liver conditions, such as steatohepatitis, cirrhosis and hepatocellular carcinoma (HCC). HCC is the fifth most common cancer worldwide, and an estimated 620,000 people die from HBV-related causes [19]. Obesity has been correlated with non-alcoholic fatty liver disease (NAFLD), a condition of steatosis that is caused by excess lipid storage in the liver. Steatosis causes inflammation and triggers cytotoxic mechanisms that could lead to fibrosis [20]. Symptoms rarely develop in obese patients with NAFLD, but NAFLD can eventually lead to non-alcoholic steatohepatitis (NASH), which causes fibrosis and damages hepatic enzyme activity [20,21]. Viral replication of HBV occurs in the liver, also causing inflammation that could lead to fibrosis and cirrhosis. Since chronic HBV can lead to cirrhosis, obesity paired with HBV infection significantly increases the risk for chronic liver disease and HCC [22,23]. Obese individuals most likely have a pre-existing burden on liver function, and HBV-related liver disease could further increase serious complications from hepatitis infection in obese individuals with NAFLD [24,25]. This places the obese patient at a higher risk for both vaccine non-response and serious chronic HBV-related diseases, leaving obese individuals vulnerable to excess morbidity and mortality caused by HBV.

2.2. HBV vaccine-induced immune outcomes in the obese

Since the hepatitis B surface antigen (HBsAg) is crucial for infection, proper protection from HBV is identified by the induction of antibodies that detect HBsAg in circulation. Individuals with HBsAg-specific antibody (anti-HBs) titers ≥ 10 milli-international units per milliliter (mIU/mL), detected by enzyme-linked immunosorbent assay (ELISA), are considered protected against subsequent HBV infections [26,27]. Four years after the licensure of the first HBV vaccine, Weber et al. performed a study that reported a significant decline ($p = 0.002$) in protective levels (<10 mIU/mL) of anti-HBs 11 months post-vaccination in obese hepatitis B-vaccinated healthcare workers [12]. 55.7% of the subjects tested negative for protective anti-HBs titers, and a higher weight-height index ($\geq$32.88 kg/m^2) was identified as one of the greatest risk factors for HBV vaccine non-response. Only 29.5% of individuals with a gender-specific BMI greater than or equal to the 75th percentile developed protective anti-HBs titers, compared to 63.3% of individuals below the 75th percentile that achieved protective seroconversion [12]. Since all patients received the three-dose regimen from a 2.5-cm needle injection, Weber et al. speculated that the location of injection, the buttock, could play a role in the poor vaccine-induced seroconversion of the obese, and a shorter needle caused the low seroconversion by accidental injection into fat pad rather than muscle [12]. Therefore, Weber et al. conducted a follow-up study that used a longer (3.75-cm) needle for the third dose and compared deltoid and buttock HBV vaccination [28]. In the follow-up study, the authors confirmed that an inverse correlation existed between BMI > 30 kg/m^2 and significantly decreased ($p < 0.001$) positive anti-HBs titer seroconversion 17 months post-vaccination. Similar to their previous study [12], only 36% of severely obese individuals with a BMI greater than the 75th percentile had detectable anti-HBs titers compared to 66% of those with a BMI < 75th percentile [28]. However, multivariable analyses indicated that age ($p = 0.025$) and BMI ($p < 0.001$), but not injection site (deltoid and buttock location, $p = 0.43$), were significant independent predictors of poor HBV vaccine-induced anti-HBs titers [28]. Several studies indicate that HBV vaccination in the buttocks of overweight infants, adolescents and obese adults is correlated with a poor vaccine-induced immune response [29–31], and studies support deltoid injection or the use of a longer needle to decrease the risk of HBV vaccine non-response [32,33]. However, Weber et al. suggest that other systemic factors related to obesity, other than just site of injection, could influence poor anti-HBs responses [28].

By 1990, the original plasma-derived HBV vaccine was discontinued and replaced by two recombinant vaccines: Recombivax HB™ and Engerix-B™. In 1991, the Occupational Safety and Health Administration issued the blood-borne pathogens standard that required employers to provide hepatitis B vaccination for employees [34]. Due to this mandate, many previously unvaccinated adults received the HBV vaccination. Concern for low vaccine-induced anti-HBs titers grew after a study observed a high percentage of healthcare workers with non-protective (<10 mIU/mL) post HBV-vaccination anti-HBs titers [35]. 11.0–11.5% of individuals with a BMI 25–35 kg/m^2 had an inadequate response. However, protective anti-HBs titers dropped significantly as an individual's

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