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COMBATTING PATHOGENS: UNRAVELING THE ROLE OF IMMUNE SYSTEM IN INDIVIDUALS WITH OBESITY

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Abstract

Overweight and obesity are conditions that increase in prevalence as a result of the population's vulnerability to communicable diseases. Because obesity is characterized by immune dysfunction, this review looks at how this federacy comes about to promote intricate understanding of the factors involved. In normal physiology of an individual, the immune system develops a well-coordinated network to combat invading pathogens. However, in obesity, there is an alteration in immune regulation and the body acquires a constant low-grade inflammation. It has been identified that visceral adipose tissue, being an endocrine tissue, releases pro-inflammatory cytokines including TNF-α, adiponectin and leptin, which negatively affect immune cell function and homoeostasis. These alterations of immune cell populations lead to accumulation of pro-inflammatory Th1 cells and macrophages at the expense of anti-inflammatory Treg cells and M2 macrophages pushing the inflammatory process to chronicity. It also compromises the immune system and consequently the body's ability to protect itself against pathogens. The relationship between obesity and immunity is poorly comprehended; thus, assessing the interaction is critical when treating an increased risk of infections, dysregulated immunity and abnormal metabolism in obese persons. To identify new sigma-pharm treatments such as, TNF-α inhibitors, leptin modulators and adiponectin-based therapies, for this population to boost the immune system and improve overall clients' health, more studies are required.

Keywords: *Adiponectin, Immune dysfunction, Leptin, Low-grade inflammation, Obesity, Pro-inflammatory cytokines, Th1 Cells, TNF-α, Treg Cells, Visceral adipose tissue*

INTRODUCTION

Excess adipose tissue buildup closely links obesity with compromised immune function due to chronic low-grade inflammation. The extensive study explores how obesity impacts multiple immunological components, including innate immunity and the type of adaptive immunity involving T and B cell activation. It explores how excess adiposity disrupts the fine balance in immune cell activity, lowering overall immune function. The following review seeks to look at the effects of obesity as a risk factor on the immune system particularly to gain insight on which immunological alterations in obesity lead to increased risk of infections. It also expands on ideas for treatments to reverse the immune dysfunction and fight the infection threats of obesity patients. Furthermore, the focus is set to the hormone leptin, which is produced in adipose tissues and contributes to regulation of energy balance and immunomodulation (1) In orientation to the vulnerability within immunological niche it is necessary to indicate the following factors of the increased infection sensitivity of an obese individual relatively to bacteria, viruses including DNA and RNA ones, fungi, and protozoa. Knowledge of these interactions may help in designing intervention strategies that will improve immune responses in persons with obesity (2).

Since the last twenty years, the cases of obesity have raised and identified as a very sensitive global health problem. According to the current statistics more than 651 million people were reported to be suffering from obesity and more than 1.9 billion were reported to be overweight (3). It is noted that there has been a shift towards rise of obesity across the world with the developed nations being more affected. This is a common issue with variations across regions such that those countries that are developed and industrialized have higher incidences than the developing countries. The estimations of the WHO also

reveal the necessity of understanding and taking action against this issue. The relative abundance of obesity differs from region by region, population to population and is higher in the developed countries of the world while higher body mass index remains an important discriminator (4). Understanding the complex relationship of obesity and immune system is important because the population suffers from obesity and obesity related illnesses is rising rapidly all over the world (5). Now urgent help is needed to elucidate the type of immune changes which occurs in obesity as well as to inform treatment strategies according to it. A significant correlation with obesity is due to the risk of infections, reduced impact of vaccines and an increased likelihood of developing auto-immune diseases. (6). Such evidences require an understanding of the impact of obesity to the immune regulation hence the need to search for well rooted treatments for such dysfunctions. Considering the fact that obesity-induced insulin resistance exerts a considerable impact on the development of type 2 diabetes, the relationship between insulin resistance, obesity and the adaptive immunity system should be researched (7). Exploring this intricate association could provide the rationale for novel interventions targeting immunological dysfunction related to obesity that had been considered untreatable; such a discovery could undoubtedly transform the treatment of these conditions (8).

Humoral immune respondent to adaptive immunity comprises plasma cells, which release large quantities of antibodies sometimes called immunoglobulins to the blood as well as other body fluids (9). The immune system rather relies on cell-mediated immunity in which particular immune cells, or specifically the T cells, are quite conspicuous in the identification and elimination of infected or dysplastic tissues (10). Cell-mediated immunity plays a crucial role in the defense against bacterial infections (11). Advance studies have illuminated the intricate relationship between obesity and immune function. The results show that obesity is associated with chronic low-grade inflammation, which may impair the function of immune cells and compromise the body's ability to mount an effective immune response against bacterial infections. In obesity, immune cells, including macrophages, infiltrate adipose tissue, actively engaging in the immune response by engulfing and destroying bacteria (12). Unfortunately, these macrophages undergo a phenotypic shift towards a pro-inflammatory state, fostering chronic low-grade inflammation in adipose tissue. This pro-inflammatory state can compromise macrophage function, impairing their ability to clear bacteria and increasing susceptibility to infections (13).

Obesity can reduce the numbers and compromise the activity of Natural Killer (NK) cells, crucial for early defense against bacterial infections (14). Adipokines and free fatty acids derived from adipose tissue may play a role in disrupting NK cell function, thereby reducing their capacity to kill bacteria (15). Altered T cell populations and functions are linked to obesity, with adipose tissue inflammation causing an elevation in pro-inflammatory T helper 1 (Th1) cells and a reduction in regulatory T cells (Tregs). This imbalance disrupts the immune response to bacterial infections, as Th1 cells play a role in clearing intracellular bacteria, while Tregs assist in maintaining immune tolerance and preventing excessive inflammation (16).
By exploring the intricate interactions between fat mass, obesity, and immune system dynamics, the study reveals how obesity-induced excess adiposity or increased leptin levels impact immune cell activity, inflammation, and general immune system responses.

IMMUNE SYSTEM VULNERABILITY IN OBESITY

The hallmark of obesity is chronic inflammation, marked by higher pro-inflammatory molecules like cytokines and adipokines as shown in Fig. 1. This inflammatory environment disrupts immune cell functions, compromising the body's capacity to deploy an effective immune response against pathogens. Leptin, beyond its role in energy balance, regulates immune responses. Deficiencies in leptin production or desensitization of leptin receptors, common in obesity, lead to impaired immune responses and a state of leptin resistance (17). Elevated suppressor of cytokine signaling-3 (SOCS3) expression in obesity inhibits downstream keffects, contributing to immunosuppression and increased susceptibility to infections (18). Leptin's role extends to specific pathogens, influencing mucosal immune responses. Leptin enhances antibody responses in mucosal vaccines against pathogens like *Rhodococcus equi* and *Helicobacter pylori,* which leads to pneumonia, drawing attention to how leptin dysregulation linked to obesity weakens the immunity to respiratory infectious agents.

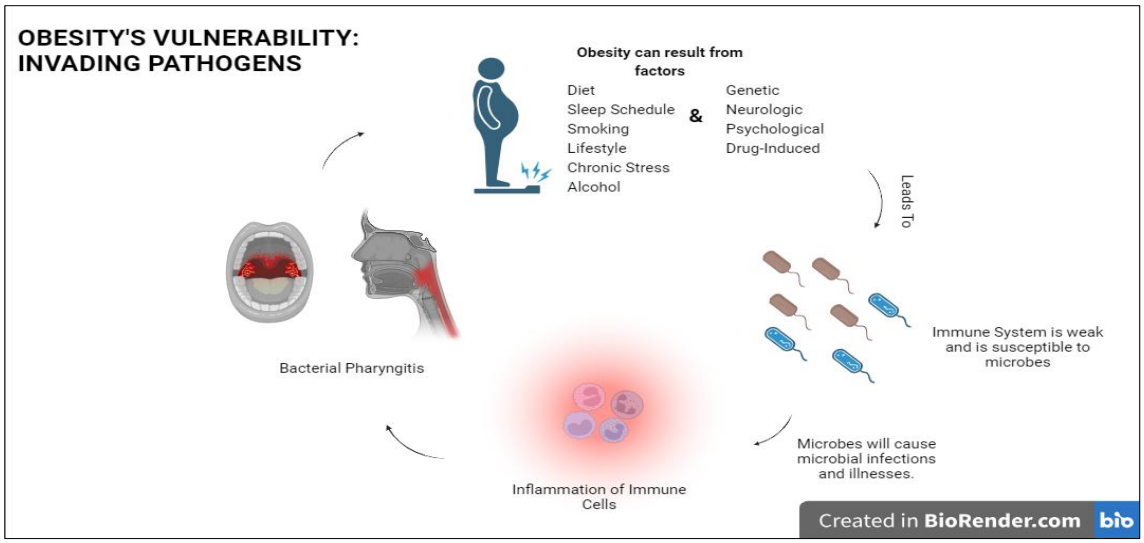

Fig. 1. Bacterial infections in obesity: overview

Additionally, leptin signaling in gut epithelial cells confers resistance against infections caused by pathogens such as *Clostridium difficile* which can lead to severe diarrhea and colitis in obese individuals whose immune systems are already compromised and *Entamoeba histolytica,* the causative agent of amoebic dysentery, which can be worsened by immunosuppression associated with obesity. Chronic low-grade inflammation in obesity, characterized by increased inframarginal cytokines like TNF-α and IL-6, disrupts the balance between pro-inflammatory and anti-inflammatory signals (19). Obesity-induced alterations impair various immune cells, including natural killer (NK), neutrophils, and macrophage cells, reducing phagocytic activity and microbial killing capacity. Changes in the gut microbiota, often marked by decrease in beneficial gut microbiota and increase in harmful microorganisms due to obesity, impaired vaccine responses, and the presence of co-morbidities such as type 2 diabetes further compromise immune system function, increasing susceptibility to infections (20).

BACTERIAL INFECTION IN OBESITY

The relationship between rapid growth of and bacterial infections is complex and challenging; this aspect raises a major risk that underscores the importance of understanding various aspects in an endeavor to design effective prevention and different approaches to therapy. It was ascertained that obesity increases doctors' patients' susceptibility to infections in all medical domains. Consequently, the body's immune system no longer has the capacity to distinguish between more beneficial and less beneficial bacteria that should be allowed and discouraged respectively. Hence being unable to maintain a balance which leads to increased endotoxin exposure which enhances the chance of bacterial infections in obese people (21). Leukocyte infiltrate obese patients' adipose tissue and secrete inframarginal cytokines and chemokines including IL6 and TNF-alpha. These molecules suppress the activities of immune cells that eliminate bacteria and initiate inflammation (22). Obesity induced inflammation of tissues reduces the immune response and invokes the convergence of immune cells to mitigate the impact of the infection. It makes people who are obese vulnerable to bacterial infections.

TARGETED PATHOGEN SUSCEPTIBILITY IN OBESITY

The immune system's response to pathogens like *Staphylococcus aureus, Streptococcus pneumoniae,* and *Escherichia coli* gets compromised in cases of obesity. This compromise is reflected in a weakened defense system, showing up as reduced phagocytic activity, a decrease in the production of antimicrobial peptides, and hindered T-cell-mediated immune responses (23).

FUNGAL INFECTIONS IN OBESITY

While not precisely defined, a concept that is gaining support, suggests a connection between obesity and fungal infections, particularly those caused by Candida. Specific body areas prone to obesity, such as skin folds and moist regions, provide an environment where various fungi, including Candida,

thrive due to increased moisture and limited air circulation (24). Obesity induces changes in the microenvironment, creating optimal conditions for fungal growth, notably with Candida emerging as a prominent pathogen. The heightened susceptibility of obese individuals to fungal infections is attributed to increased moisture and disrupted skin microflora (25). In addition, obesity modulates the gut microbiota and promotes the conditions in which fungal growth prevails. The consequences of dysbiosis in the context of obesity are considered in detail; emphasis is placed on the significance of the dysbiosis-inducing factor in increasing the risk of fungal infections. The interactions involving the gut microbiota in regulation of immune responses become essential, and disruption of this orchestration is a predisposing factor to increased susceptibility to fungal pathogens (26).

OBESITY'S FUNGAL IMPACT: ADIPOSE RESERVOIR, IMMUNE CHALLENGES, CANDIDIASIS

Technically, obese individuals have a depressed immune response because the macrophages' phagocytic activity is low. Thus there is slow clearance of fungal infection. It implies that the susceptibility rate of fungal infections is high (27). Obese people's adipose tissues are ideal for fungal camping and longevity more so for filamentous fungi. Its function it to enhance fungal infections, and this is especially the case given that individuals affected by obesity have a skewed immune response (28). Obesity in particular poses a threat to such diseases as candidiasis, which is caused by the Candida species. Obesity creates an enabling environment for fungi to infect the body due to the transformation of the immune response in such a situation. This correlation puts emphasis on the need of comprehending the interaction between weight-related risk factors and immunological response toward fungal infections (29).

VIRAL INFECTION IN OBESITY: OVERVIEW

Some of the viral infections of high risk for a person who is obese include COVID-19 and Influenza. It underlines the fact of how obesity predisposes a person to severe sickness from viruses. New American Influenza A (H1N1) virus that struck in 2009 showed for the first time that the population of obese people is especially vulnerable to this disease. That obesity has an influence over the viral infections raises this possibility for it to be contributing to influenza outcomes. (30). Weight has not only possible associations with one certain disease (influenza) but also other diseases like respiratory syncytial virus, Covid19. Other changes in T cell subsets also modulate the adaptive immune response to viral infections in obesity. SARS CoV 2 and influenza pose high risk to diabetic patients and are likely to cause severe outcomes and complications. Chronic inflammation along with a break in immune response leads to cytokine storm to further increase the risk of serious organ failure.

PROTOZOA INFECTION IN OBESITY

Some protozoa, including Plasmodium, which is responsible for malaria and Toxoplasma gondii, which is responsible for toxoplasmosis, can take advantage of obesity. Of these infections, this exploitation might have led to enhanced vulnerability and even worsened outcomes of the conditions. Immune effects of obesity on specific non-communicable disease may also impair the immune system cells such as macrophage and T cell in controlling protozoan pathogens (31). The change in the composition of microbiota presented in obesity adds confusion regarding the effect on protozoan diseases. Alterations in the gut microbiota known to occur in obesity might affect the relationships between protozoans and the host's immune response. Knowledge of these interactions is important in order to evaluate the vulnerability of obese people to protozoan diseases (32).

ANTIMICROBIAL ACTIVITY

There are myriad substances whose functions of immunomodulators can prevent or inhibit the development of microorganisms such as bacteria, viruses, and fungi. Different authors have reported that natural compounds can kill microorganisms; for instance, allicin in garlic, catechins in green tea, and curcumin in turmeric. Obesity increases susceptibility to bacterial infections because it impairs the function

of the barrier or shifts microbiota. Besides, it can reduce the number or the variation of B cells by limiting T cell-fetching activation or increasing apoptosis (39). In addition, it affects either the quality or quantity of antibodies by blocking class switching, or increasing the rate of antibody catabolism. Last, obesity leads to the change in antibodies of the affinity or avidity, either through the suppression of CSIRT1 or antibody opsonization.

Smaller amounts of the slower removal of circulating antibodies after vaccination decrease the effectiveness of the vaccination because of a decreased time of contact between vaccinated serum and possible pathogens. As a result, there is heightened interest in some immuno-enhancers with potential antimicrobial functions to offer prevention or cure to infections due to non-conventional pathogens. But more research is still needed in terms of understanding how these immune boosters play out with obesity and its effects on the immune system when it comes to infections such as COVID 19 (40).

REGULATION OF GUT MICROBIOTA

The gut microbiota, a collection of microorganisms that reside in our gastrointestinal tract, actively contribute to maintaining good health. It impacts various functions, including digestion, immunity, inflammation, and behavior. If a person is diagnosed with obesity, it indicates that they have an excessive quantity of body fat, which can significantly affect the functionality of the gut microbiota. This can lead to alterations in the gut microbiota's composition, diversity, and activity. As a result, the production of short-chain fatty acids (SCFAs) may go up, the time taken by food to pass through the colon may reduce, and there could be an emergence of chronic inflammation or oxidative stress in adipose tissue or other organs (41).

IMMUNE BOOSTERS

Being better protected by an efficient immune system is the best way to counter attack a number of pathogenic organisms in our organism. Immunostimulants commonly known by other names such as immune stimulus or immune modulators have been found to possess the capacity to enhance the immune system's ability to detect and expel diseases causing entities. These interventions activate resistant response components like cytokines, immune cells and antibodies, enhancing a body's immune response against injurious microorganisms (33). Therefore, when we start including foods that will enhance our immune system, our immune system is well-prepared to fight off all the health risks that come its way. Immunostimulants can be categorized into natural, as well as synthetic products and are allow available in numerous forms. They include vitamins, minerals and other relevant substances that are so important in the immune system. On the contrary, synthetic immunostimulants are chemical substances which are activated to stimulate the immune system (34).

Obese people immune system is boosted more by phytochemicals than how they respond to pathogens. Thus, it would be possible to contribute to the enhancement of immunity and the improvement of the treatment outcomes in obese patients when using foods containing phytochemicals in their diet (35). Besides, functional foods with probiotics are being created to combat metabolic syndrome and enhance adiposity control in obesity. Current data show that probiotics can contribute towards improvement of metabolic health and weight loss in such people. There is interest in probiotics for increasing immune strength as an alternative therapy because of its positive outcomes and therapeutic values (36).

There are numerous researches conducted for the probable benefits of DHA, omega 3 fatty acids, and EPA due to their effects of inflammation. Inflammation is chronic and low-grade, hence, such overweight is characterized by declined immune proficiency. Research based on the field of science has confirmed that it is beneficial to take Omega – 3 fatty acids, specifically for controlling inflammations (37).

MECHANISM OF ACTION OF IMMUNE BOOSTERS

Low grade inflammation (LGI) appears to be highly correlated with obesity and this condition is common in the elder population. These findings suggest that LGI may be implicated in metabolic disturbances and pathophysiology of adipose tissue. When one is obese, the adipose tissue tenderizes and is capable of producing molecules known as adipokines that cause inflammation. When chronic, inflammation

impairs the immune system, it will be harder for the body to fight pathogens, thus raising the chances of an individual getting an illness. LGI is capable of upsetting the equilibrium of immunocytes and alter their functions with the result that DM affects immunosurveillance and immune protection against pathogens. Such an impairment harms the body's ability to fight off infections and recuperate from sickness and diseases. It is also evident that NF-κB pathway is involved in LGI in obesity because this factor of activation enhances inflammatory signaling processes. Therefore other pro-inflammatory cytokines and chemokines are released which further prose chronic inflammation. B-glucans can also likely stimulate the complement system by binding to complement receptor 3. This interaction may lead to CR3-dependent cellular cytotoxicity. This process is critical in eradicating tumor cells and in the early stages improving the immune response to tumors (38).

IMMUNE BOOSTERS IN OBESITY: CHALLENGES AND POSSIBILITIES

The impact of different 'immune enhancing agents' as agents in promoting immune capacity in obesity are still under investigation. As a result of this, and despite the popularity of these supplements, there are few well done scientific trials to back it up. These earlier studies are often methodologically flawed, or report mixed findings. Studies have both painted pictures of increased efficiency and shown drastic lack of effect on the immune system. Moreover, the exact ways these supplements interact with immunity in obesity is still not well defined (42). Many metabolic disorders are linked with obesity such as; insulin resistance, chronic inflammation, change in lipid profile and oxidative stress. supplements, there exists a lack of strong scientific evidence to support their effectiveness. The available studies often suffer from methodological limitations or conflicting results. While some studies have reported benefits, others have failed to demonstrate a significant impact on immune function (43). Furthermore, the mechanisms by which these supplements modulate immune function in obesity are not fully understood. Obesity **is associated** with a range of metabolic abnormalities, including insulin resistance, chronic inflammation, altered lipid metabolism, and oxidative stress. We know that immune-boosting interventions have been of interest to prevent or treat obesity, however, is debatable whether such approach is viable and useful since a blueprint does not exist. However, newer data looking at the present show that obesity has its immune profiles and metabolic subtypes, which would mean that everyone requires different treatment. However, some foods or supplements or activities may have an unpredictable **behavior** of causing some side effects or affecting medications. This is especially so for one who has health issues which, as we all know, pose a higher risk to the COVID-19 virus. In such cases, the consumers should be very careful with supplements or some practices, getting it only on prescription from a doctor. To supplement, the risks of intake need to be evaluated constantly, always carefully making decisions about such supplements. Referral to a health care provider is crucial to this process (44).

PROMISING APPROACHES

HEALTHY DIET

Consuming a diet that contains high amounts of whole grains, vegetables, fruits, and lean protein can supply the essential nutrients needed for optimal immune function, particularly in individuals with obesity, who often experience impaired immune responses. Researchers have identified certain nutrients, such as zinc, omega-3 fatty acids, and vitamin C as particularly beneficial in this regard, as zinc deficiency is common in obese people further compromising immune system, vitamin C reduces oxidative stress and omega 3 fatty acids act against chromic low-grade inflammation which can be seen in obese people. Cells can be harmed by free radicals; however, Vitamin C serves as an antioxidant to safeguard them. Immune cells require zinc to develop and function normally. Reducing inflammation in the body is among the benefits of Omega-3 fatty acids, which can promote healthy immune function. By incorporating foods such as citrus fruits, leafy greens, nuts, seeds, and fish into our diets, we can support our immune systems and maintain optimal health. (45).

REGULAR EXERCISE

Engaging in consistent physical activity has been scientifically shown to have beneficial impacts on the immune system of the body. This includes a decrease in inflammation and the improvement of immune cell function, resulting in an enhancement of overall health. To benefit from these effects, it is recommended by the American College of Sports Medicine that individuals engage in moderate-intensity exercise for at least 150 minutes each week. The surveys indicate that physical activity decreases the chances of specific diseases including diabetes, heart diseases, some kinds of cancer, as well as some physical conditions like obesity. Also, exercise could improve the brain's capacity, mental health and quality of life. These benefits are probably because of the many bacterial and chemical changes that happen during exercise, such as the freeing of cytokines with anti-inflammatory effects, increase in immune cell activity, and enhancement of cardiovascular and metabolic health. As such, there are meaningful potential advantages of physical exercise activity standards in everyday existence for both physical and mental health. Hence regular exercise can help obese people to reduce their weight as well to prevent from harmful effects of being an overweight (46).

WEIGHT MANAGEMENT

It was also observed that obesity decreases chronic inflammation, and that weight loss has a large positive impact on immunity. Just a little consequent weight loss can bring about alterations in a person's inflammatory and immune status, for the better. To achieve a risk-free and successful weight control program it is very important to consult your health care provider. Any specific regulation pertaining to the above mentioned conditions should better be sought with the permission of a healthcare professional who will be in the position to map an individual plan for an individual as per his or her specific needs and goals. It is therefore advisable that anybody who wants to lose weight consult a physician in order to decide on the right measure of shedding weight in the right manner safely (47).

STRESS MANAGEMENT

Epidemiological research indicates that chronic stress weakens the immune system in human body. Therefore, chronic stress can cause stressors that lower immunity making an individual have poor health. This is especially worrying for people who have obesity because they show increased stress and anxiety levels, which can weaken the immune system and amplify chronic low-grade inflammation characteristic of obesity. On the immunity countenance as well as on stress management, relaxation procedures like mindfulness and meditation have been helpful. Finally, vaccination is still another effective way of avoiding infections that obese people should use to enhance their health status. People should make sure they are vaccinated in the appropriate time in a bid to minimize the risks of getting the diseases or complications that come with them. It means that there is need to have integrated plan of stress management and immunization needed. (48).

CONCLUSION

The intricate interplay between obesity and the immune system, explored in this review, has emerged as a burgeoning field within immunology with significant public health implications. These findings underscore the urgent need for targeted interventions to mitigate increased susceptibility to pathogens in individuals with obesity. Strategies aimed at reducing chronic inflammation, restoring immune cell homeostasis, and optimizing metabolic health hold immense promise. Continued efforts in this field hold immense potential to develop evidence-based strategies to strengthen the immune system and improve health outcomes for individuals living with this complex condition, ultimately yielding valuable insights for immune regulation and pathogen defense for all.

Limitations:

There are several limitations in this review. First of all, there may be some studies left about the intricate relationship between obesity and immune function uncovered, that may result in gaps in the literature. The

inconsistency of study designs means that there is variability in methodology and hence, the variation in the population samples means variability in the outcomes. Several studies contained in this review are observational or cross-sectional in design, which precludes causal inference. Also, specific use of funds or the policies of the publishing companies may also introduce biases in the conclusions made. Finally, ethnic minorities and other patients with comorbidities would be less represented, thus generalizing the results not for all the populations.

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