The Effect of Short-Term Hyperglycemia on the Innate Immune System

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ABSTRACT

Background: Diabetes mellitus increases the susceptibility to infection by altering both the innate and the adaptive immune systems. Hyperglycemia has been associated with adverse outcomes in hospitalized patients, especially critically ill patients; these poor outcomes are explained in part by hospital-associated infections.

Materials and Methods: PubMed, EMBASE and Google Scholar were searched to identify studies published between 1970 and 2014 reporting short-term effects of hyperglycemia on the innate immune system. MeSH database search terms included hyperglycemia, immune system, inflammation, inflammation mediators, neutrophils, endothelial dysfunction, complement system proteins and diabetes. Pertinent articles reported studies in healthy volunteers and diabetic patients, using *in vitro* laboratory experiments, and with animal models.

Results: Hyperglycemia activates protein kinase C, and this inhibits neutrophil migration, phagocytosis, superoxide production and microbial killing. High glucose concentrations decrease the formation of neutrophil extracellular traps. Hyperglycemia can also induce Toll-like receptor expression and inhibit neutrophil function and apoptosis. High glucose concentrations decrease vascular dilation and increase permeability during the initial inflammatory responses, possibly through protein kinase C activation. Hyperglycemia can cause direct glycosylation of proteins and alter the tertiary structure of complement; these changes inhibit immunoglobulin-mediated opsonization of bacteria and complement fixation to bacteria and decreases phagocytosis. Hyperglycemia also stimulates the production and release of cytokines. Several trials have demonstrated that better glycemic control reduces nosocomial infections in critically ill patients and surgical site infections.

Conclusions: In summary, acute hyperglycemia can significantly alter innate immune responses to infection, and this potentially explains some of the poor outcomes in hospitalized patients who develop hyperglycemia.

Key Indexing Terms: Hyperglycemia; Host defenses; Neutrophils; Complement; Vascular endothelium. **[Am J Med Sci 2016;351(2):201–211.]**

INTRODUCTION

Infections in hospitalized patients remain a challenging and costly problem, are a major factor in prolonged hospital stays, and increase morbidity and mortality rates.[1] The Centers for Disease Control and Prevention estimates that 1.7 million hospital-associated infections from all types of microorganisms cause or contribute to 99,000 deaths each year in the United States.[2] Increased rates of infection in hospitalized patients, especially in intensive care units (ICUs), have been linked to invasive procedures, such as mechanical ventilation, urinary tract catheterization, and central venous catheters.[3,4] Infection is particularly common in burn and trauma patients who develop acute reversible immunosuppression.[5,6]

Host responses to infection are essential for control and prevention of infection. Among the known factors that undermine host defenses, diabetes mellitus increases the susceptibility of patients to viral, bacterial and fungal infections mainly through modulation of the immune system.[7,8] Acute hyperglycemia has been associated with adverse outcomes in medical and surgical patients possibly by increasing the rate of infection in these patients.[9,10] This review examines studies on the association between hyperglycemia and alterations of the immune system to provide clinicians with an overview of these associations and the rationale for glucose control during hospitalization.

METHODS

A literature search using PubMed, EMBASE and Google Scholar from 1970 to December 2014 was conducted. MeSH database search terms included hyperglycemia, immune system, inflammation, inflammation mediators, neutrophils, endothelial dysfunction, complement system proteins, surgical wound infections and diabetes. Each MeSH term was joined with hyperglycemia using the AND algorithm. Searches were restricted to English language articles and studies involving adult-aged patients and subjects. These searches were used to identify studies reporting short-term effects of hyperglycemia on the immune system. The focus was on the following types of studies: (1) studies in healthy volunteers and diabetic patients with controlled experimental increases in glucose levels, (2) *in vitro* laboratory experiments, and (3) studies involving animal models. For the purpose of this review, the duration of hyperglycemia in animal studies could not

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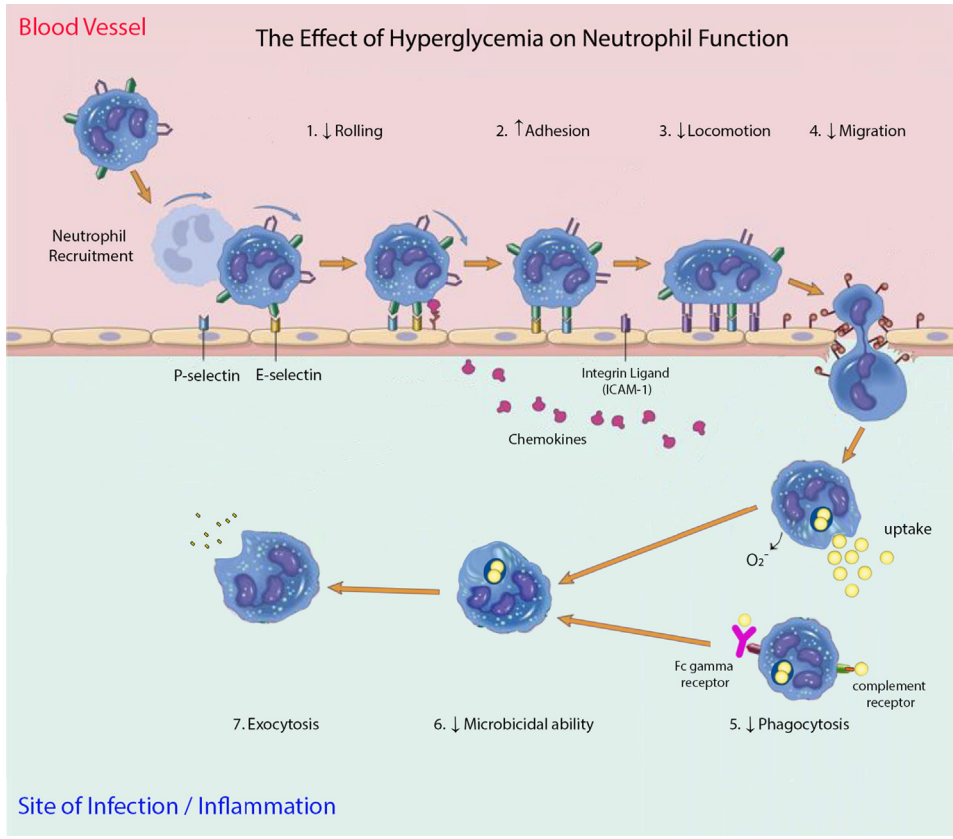

FIGURE. The effect of hyperglycemia on neutrophil function at sites of infection.

exceed 30 days, as the main interest was on the acute effects of hyperglycemia. Titles and abstracts were reviewed to identify relevant articles for more complete review. Reference lists from selected articles were carefully reviewed to identify additional articles; author names were used for additional searches in PubMed. Google Scholar was used to identify articles, which cited the articles selected for detailed review. The collected articles were used to write a narrative review.

DISCUSSION

Hyperglycemia Effects on Host Defense Responses

The host defense system includes both the innate and the adaptive immune systems. The innate immune system represents the dominant defense system against most organisms, has a fast response to infection, but has no immunological memory.[11] It includes surface barriers and their secretory exocrine glands, inflammation produced by cytokines and eicosanoids, the complement cascade system and cell barriers (neutrophils, monocytes, macrophages, mast cells, eosinophils, basophils and natural killer cells).[12] The adaptive immune system has immunological memory that promotes quick elimination of pathogens when reinfection with the same pathogen occurs. It includes T and B lymphocytes and antibodies.[13] Hyperglycemia can affect several components of the immune system, but the primary focus in this review is on the innate immune system, which includes cellular defenses, the microcirculation, complement and cytokines. Acute hyperglycemia has direct effects on each of these components. Antimicrobial substances in airway surface liquids, innate lymphoid cells and the adaptive immune system were not considered in this review.

Cellular Defenses

Neutrophils are crucial phagocytes in the innate immune response. These cells are recruited first to inflammatory sites and are essential for eliminating pathogens. Any reduction in their function contributes to increased susceptibility to infection and increased severity of infections. Human studies and animal model studies using both *in vitro* and *in vivo* methods have demonstrated defective neutrophil function in hyperglycemic states (Figure) (Table 1).

The effect of established diabetes mellitus, especially poorly controlled diabetes, on the immune system and, in particular, on neutrophil function is well known.[14] However, even transient changes in glucose levels can affect neutrophil function in diabetic patients.[15] For example, Kjersem subjected 7 patients with insulin-dependent diabetes to controlled normoglycemia and hyperglycemia using insulin infusions and measured the function of

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