Hyperglycemia in people with vulnerable immune system.

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Introduction

Diabetes, as a chronic illness, raises the risk of a variety of different diseases caused by macrovascular and microvascular damage, as well as having harmful effects on organs such as the brain, kidneys, heart, and eyes. Diabetic people are also more vulnerable to infection. Several studies have found that persons with diabetes had a higher risk of lower respiratory tract infections such pulmonary TB and pneumonia, urinary tract infections, and skin and soft tissue infections [1]. Patients with diabetes have a terrible prognosis when it comes to infection therapy. Because of the high cost of therapy, the time of treatment, and accompanying problems, infection in diabetic patients increases the patient's financial burden.

Insulin resistance leading to hyperglycemia

Increased blood glucose levels after eating cause islet cells to produce and secrete insulin into the bloodstream. Insulin and insulin receptors connect to cell membranes, causing glucose transporters to translocate to the cell membrane, increasing glucose absorption by the cells and lowering blood glucose levels. Hyperglycemia is caused by the pancreas' inability to generate enough insulin, incorrect insulin activity, or both. This is linked to long-term damage and failure of many organs and tissues.

Increased levels of Tumour Necrosis Factor (TNF)- in obese mice's adipose tissue were linked to insulin resistance in those animals. In addition, the plasma of obese mice had higher levels of interleukin (IL)-6, C-reactive protein, plasminogen activator inhibitor, and other inflammatory mediators. In adipose tissue and the liver, TNF-, free fatty acids, diacylglyceride, ceramide, reactive oxygen species (ROS), hypoxia activate I kinase (IKK), and c-Jun N-Terminal Kinase I (JNK1) inhibit insulin receptor substrate (IRS-1). TNF- also causes insulin resistance by inhibiting the action of the peroxisome proliferator-activated receptor-gamma.

Insulin binds to its receptor, causing IRS-1 and -2 tyrosine phosphorylation. Insulin signalling is inhibited by IKK and JNK1, which are mediators of stress and inflammatory reactions, phosphorylating IRS substrates on serine. JNK1 and IKK also cause the transcriptional activation of many genes involved in the inflammatory response, leading to insulin resistance. In addition, with obesity, the inflow of free fatty acids and glucose stimulates the JNK1 and IKK signalling pathways [2].

Activated IKK phosphorylates I, increases ubiquitination and degradation of I in the proteasome, and causes NF to translocate into the nucleus, where it induces transcription of genes implicated in inflammation and other immune responses. IKK also suppresses insulin signalling pathways in adipocytes by phosphorylating IRS-1 serine residues. TNF-induced JNK activation suppresses insulin signalling by phosphorylating IRS-1.

Hyperglycemia and vulnerability to infections

The human body normally employs incredible processes to defend itself against millions of bacteria, viruses, fungi, poisons, and parasites. Pathogens find it difficult to penetrate this defensive mechanism under normal circumstances, but the immune system can malfunction due to a variety of situations and flaws [3]. For example, bacteria may readily penetrate an open wound and produce an infection, as seen by the presence of pus. Natural barriers (for example, undamaged skin and mucosal surfaces) as well as the generation of reactive oxygen species, cytokines, and chemokines aid human defence systems in combating pathogenic invasion.

Leukocyte recruitment inhibition: In the brains of db/db mice afflicted with West Nile virus-associated encephalitis, the infiltration of CD45+ leukocytes and CD8+T cells was considerably decreased. This study discovered that decreased expression of cell adhesion molecules (CAMs) such E-selectin and intracellular adhesion molecule (ICAM)-1 was linked to impaired recruitment of CD45+ leukocytes and CD8+ T lymphocytes. Martinez et al. confirmed this impairment in leukocyte recruitment in streptozotocin-induced diabetic mice infected with *Klebsiella pneumoniae* in an *in vivo* research. The diabetic mice's alveolar airspace included a lower number of granulocytes. They also found lower levels of cytokines such CXCL1, CXCL2, IL-1, and TNF- in lung tissue after exposure to *K. pneumoniae* LPS [4].

Defects in pathogen recognition: In diabetic mice, the expression of Toll-like receptor (TLR)-2 and Toll/IL-1R domain-containing adaptor protein (TIRAP), both of which are involved in pathogen recognition, was decreased. TLR expression was shown to be higher in neutrophils and monocytes isolated from diabetic patients in various investigations.

Macrophage dysfunction: Hyperglycemia also affects macrophage function. On isolated monocytes, chronic hyperglycemia was related with abnormalities in complement

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receptors and Fc receptors, resulting in phagocytosis impairment. Antibacterial activity and phagocytosis were decreased in macrophages generated from mice bone marrow that were treated with high glucose in an *in vitro* investigation. Diabetic mice's peritoneal macrophages showed decreased phagocytosis. This might be due to macrophages' decreased glycolytic ability and reserve as a result of long-term glucose sensitivity.

Natural killer cell dysfunction: Natural Killer (NK) cell dysfunction, which is critical for combating invading infections. T2D patients' isolated NK cells showed deficiencies in the NK cell-activating receptors NKG2D and NKp46, which were linked to functional NK degranulation problems [5].

Conclusion

Diabetes is a metabolic condition caused by inflammation in the body as a result of a complicated immunological process. Insulin resistance, which is caused by the suppression of insulin signalling, triggers a cascade of immunological responses that aggravate the inflammatory state, leading to hyperglycemia. Immune system weakness against invading pathogens in diabetic people is hypothesised to be caused by both innate immune response deficiencies (such as neutrophil and macrophage dysfunction) and adaptive immune response dysfunction (such as T cell dysfunction). A deeper knowledge of the processes through which hyperglycemia impairs host defence against pathogens is critical for the development of innovative ways to treat infections in diabetic patients and thereby improve treatment results.

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