SURFACANT PROTEIN D LEVELS WITH OBESITY AND TYPE 2 DIABETES MELLITUS

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ABSTRACT
Surfactant protein D (SP-D) is an important component of pulmonary innate immunity. It is mainly produced by type 2 alveolar and bronchial epithelial cells, but is also found in extra pulmonary tissues and blood. It acts as a primary host defense against inhaled microorganisms. It also enhances adaptive immunity by activating T cells. SP-D deficiency can lead to upper and lower respiratory tract infections.

Obesity has reached global epidemic proportions in both adults and children and is associated with numerous co-morbidities and insulin resistance. Obesity & type 2 diabetes are highly associated with recurrent pulmonary & extra pulmonary infections.

The primary objective of this study was to determine the association of serum surfactant protein D levels with obesity and type 2 diabetes mellitus.

KEY WORDS: Surfactant Protein D; SP-D; Obesity; Type 2 Diabetes; Immunity; Innate Immunity.

INTRODUCTION
Surfactant protein D (SP-D) is collagen-containing C-type (calcium dependent) collectin predominantly produced by alveolar type II cells, calra cells and bronchiolar epithelial cells, but is also found in extra pulmonary tissues such as blood, skin, salivary glands, GIT, heart, genitourinary tract, prostate gland, blood and many other tissues.¹ ²

Structurally it is trimeric or dodecamer consisting of four trimmers cross linked by disulphide bonds, consisting of N terminal domain, coiled neck domain, collagen region and C-type carbohydrate recognition domain (CRD). First line of defense against the inhaled microorganisms and antigens is innate immunity. CRD can recognize and bind to oligosaccharides or glycoconjugates of microorganisms to promote their opsonization, aggregation and phagocytic uptake and lysis by macrophages and neutrophils.³ It also promotes clearance of apoptotic and necrotic immuno-competent cells by healthy macrophages.⁴ ⁵

Obesity has reached global epidemic proportions in both adults and children and is associated with numerous co-morbidities and insulin resistance. The simplest definition for obesity is the presence of excess amount of fat within the body of the patient. Obesity is categorized according to BMI. It is defined as weight in kg/ height in meter square. About 90% of patients who develop type 2 diabetes mellitus are obese and WHO ranks Pakistan 7th on diabetes prevalence list. In Pakistan, 6.9 million people are affected by diabetes with the International Diabetes Federation estimating that this number will grow to 11.5 million by 2025.⁶ ⁸ DM is associated with an increased risk of bacterial, viral and fungal pulmonary and extra-pulmonary infections with more severe clinical consequences of such infections. The mechanisms that lead to excess morbidity and mortality are related in part to the host immune defects associated with DM.⁹ ¹⁰

Overall immune response is impaired in diabetic patients. Several aspects of cellular immune function like chemotaxis, adherence, phagocytosis, and intracellular killing are adversely affected by hyperglycemia. Anaerobic conditions in the tissues created by vascular and inflammatory response further impair the immune response.¹¹

Diabetes mellitus can cause the development of...
pulmonary complications due to collagen and elastin changes.\textsuperscript{12,13} There are many studies which show that obesity and impaired glucose metabolism are associated with decreased level of immuno-regulator plasma surfactant protein D.\textsuperscript{14}

**Surfactant protein D levels and its relation to obesity and type 2 diabetes mellitus:**

Respiratory pathogens to which diabetic patients show particular susceptibility are known to bind and be agglutinated by SP-D. These include bacteria like *Salmonella minnesota* and *E. coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, *Respiratory syncitial virus*, *H. influenza virus*, fungi including *Candida albicans*, *Asperillus fumigatus* & *Cryptococcus neoforms*,\textsuperscript{15-17}

Glucose is one of the preferred ligand for SP-D and potential inhibitor of the SP-D function in diabetes. High concentration of the glucose can interfere with SP-D ability to interact with broad spectrum of pathogens.\textsuperscript{6,7}

Carbohydrate Recognition Domain (CRD) can be cleaved and inactivated by elastases.\textsuperscript{11} In diabetics high concentration of glucose and increased activity of elastases can inhibit the SP-D function.\textsuperscript{10,11} It has been shown in many studies that SP-D levels are significantly lowered among obese and type 2 diabetic patients. Decreased level of SP-D in pulmonary and extra-pulmonary tissues may increase susceptibility to respiratory tract infections in obese and type 2 diabetic patients than healthy non-obese subjects.

**Significance of the problem:**

Respiratory infections have a significant impact on the quality of life of affected individuals and impose a heavy burden on health care providers worldwide. The objective of our study was to determine the role of immuno-regulator surfactant protein D in pulmonary infections in obese and type 2 diabetic patients.

**Association of SP-D with diabetes:**

Obesity and type 2 diabetes are associated with reduced lung function & recurrent respiratory tract and uro-genital tract infections because of impaired immune response. There is evidence that obesity and DM are associated with decrease level of immuno-modulators surfactant protein D levels.\textsuperscript{1,8} SP-D has a key role in acting as a pulmonary host defence protein belonging to collectin family.\textsuperscript{9} It is the constituent of innate immune system that acts as a first line of defense against microbes. SP-D is trimeric or dodecamer having N terminal domain, neck, collagenous domain and CRD, which is the pattern recognition molecule binding preferentially to oligosaccharides on broad spectrum of pathogens including bacteria, viruses, fungi, and facilitating immune function that is neutralization clearance of bacteria, fungi, apoptotic and necrotic cells, modulation of allergic reactions and resolution of inflammation.\textsuperscript{5} SP-D can modulate the functions of T cells and dendritic cells of adaptive immune system.\textsuperscript{4,10} CRD can bind to oligosaccharide of pathogens, enhance their uptake by antigen presenting cells and increase surface expression of major histocompatibility complex class II proteins (MHCII) and presents MHCII-peptide complex to T cells and regulate release of IL2 and other cytokines to enhance adaptive immunity.\textsuperscript{4}

**SP-D as an immune modulator:**

SP-D has pro-inflammatory, anti-inflammatory and anti-allergic effects. In the absence of infections, it is important in limiting the inflammation, however when lungs are overwhelmed with exogenous insult, SP-D can assume pro-inflammatory role in order to complement pulmonary innate and adaptive immunity.\textsuperscript{3,16}

SP-D regulates airway function and allergic inflammation through modulation of macrophages functions. It affects allergen uptake by antigen presenting cells or prevent-IgE allergen binding and histamine release from basophils, thereby inhibiting the triggering of allergic response. Alveolar macrophages which are major resident cells in airways may play a role in SP-D regulatory effect in allergic inflammation.\textsuperscript{5,17} Evidences indicate that SP-D has protective role against asthma.

**SP-D in human health and disease:**

Most researches have shown clearly that number of the respiratory and urogenital tract pathogens to which diabetic patients show particular susceptibility are known to bind and agglutinated by SP-D.\textsuperscript{4,18,19} These include bacteria and microorganism which help in opsonization for phagocytosis. The antimicrobial effects of SP-D include aggregation, which may enhance the efficiency of neutrophil function for extracellular deceptions, cell-membrane lysis, neutralization of infectivity, or dampening of innate signaling evoked by microbe-derived ligands.\textsuperscript{20}

The subjects having low levels of SP-D have a high risk of getting pneumonia caused by these organisms. Female are more prone to get recurrent UTI and vulvo-vaginal infections.\textsuperscript{20} Glucose is the competing ligand for SP-D and potential inhibitor of SP-D function in diabetic patients.\textsuperscript{1,7} CRD of SP-D will be cleaved and inactivated by elastases.\textsuperscript{21} Many studies have suggested that the changes in elastin and collagen associated with obesity and diabetes are the cause of pulmonary dysfunction. Because of these reasons, diabetic subjects are susceptible to recurrent pulmonary and extra- pulmonary infections specially UTI.\textsuperscript{22}

**Surfactant protein D (SP-D) inversely associated with obesity:**

Obesity is a metabolic disorder in which the basic disruption is excessive fat accumulation in adipose tissue.\textsuperscript{23} Increasing evidence by recent studies suggest that surfactant protein D (SP-D) is a main controller of inflammation initiated by microbes. It is also
intricate in lipid homeostasis in mouse alveoli and blood circulation and current data have established that the body mass index is prejudiced by genes in conjoint with SP-D. Some studies propose that triglyceride accretion within adipocytes is innocuous, whereas fat insinuation in no adipose tissue such as that resulting from leptin insensitivity induces a proinflammatory response that is connected with accretion of connective tissue elements and ensuing fibrosis in various body organs, notably the respiratory and pancreas islet cells, hepatocytes, skeletal muscle, and heart.

CONCLUSION
Immuno-regulator SP-D deficiency is the cause of recurrent respiratory tract infections in obese and type 2 diabetic subjects. In high risk individuals like obese and type 2 diabetic patients, it is needed to monitor their serum levels in order to prevent recurrent infections.

Acknowledgment: We thank Mr. Zahid Balouch for administrative assistance and Dr. Naveed Iqbal for technical assistance.

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