Impact of Interleukin-6 in Various Diseases Condition

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***Abstract*- Interleukins, a type of signaling protein, aid in cell-to-cell communication within the immune system. Interleukin 6 (IL-6) is a pleiotropic cytokine that has a wide range of functions, including impacts on acute phase reactant pathways, B and T lymphocytes, blood brain barrier permeability, synovial inflammation, hematopoiesis, and embryonic development. This cytokine facilitates the transition between innate and adaptive immune responses by recruiting macrophages and lymphocytes to areas of damage or infection. Diabetes, chronic kidney disease (CKD), and cardiovascular disease (CVD) are three cardiometabolic disorders that continue to be major sources of morbidity and early death. Here, we discuss current knowledge of how anti-inflammatory treatments through suppression of the pro-inflammatory yet pleiotropic cytokine interleukin (IL) 6 may assist patients suffering from these or related disorders or consequences.**

***Index Terms*- Interleukin-6, Diabetes Mellitus, Chronic Kidney Disease, Polycystic Ovary Syndrome, Cardiovascular Disease, Metabolic Syndrome, Subclinical Hypothyroidism.**

I. INTRODUCTION

IL-6 was first reported in 1973 as a protein secreted by T lymphocytes that promoted B cell development into antibody-producing cells; consequently, it was initially referred to as 'B cell stimulatory factor 2 (BSF2)'. A decade later, other proteins previously identified as hepatocyte stimulating factor, IFN-β2, and plasmacytoma growth factor were cloned and shown to be identical to IL-6, demonstrating its pleotropic action. In 1988, during a meeting titled 'Regulation of the Acute Phase and Immune Responses: A New Cytokine,' BSF2 was renamed interleukin 6 [1]. IL-6 is a short polypeptide with a molecular weight of 19-28 kDa and four α helices. It is usually found as a monomer, with 184 amino acid residues, glycosylation sites, and two disulfide linkages. IL-6 encoding gene is located on chromosome 7p and includes four introns and five exons [2]. Numerous cell types, including as T cells, B cells, monocytes, fibroblasts, endothelial cells, and adipocytes, produce IL-6 in response to inflammatory stimuli, infection, or damage [3]. IL-6 expression is primarily triggered by IL-1β and TNFα, although it can also be stimulated by TLRs, prostaglandins, adipokines, stress response, and other cytokines [4]. The pleiotropic cytokine interleukin-6 (IL-6) regulates hematopoiesis, inflammation, oncogenesis, and immune responses [5]. IL-6 is a member of the glycoprotein 130 (gp130) cytokine family structurally and communicates via two separate pathways: trans-signaling, which is mediated by soluble IL-6R, and classic signaling, which is mediated by membrane-bound IL-6 receptor (IL-6R) [6]. Classic signaling is frequently related with protective and regenerative functions, whereas trans-signaling is associated with pro-inflammatory and chronic disease processes [7]. IL-6 plays a dual role in physiology and pathology, aiding host defense during acute inflammation and simultaneously feeding chronic inflammation when dysregulated [8]. Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Crohn's disease have all been associated to elevated levels of IL-6 [2]. IL-6 also contributes to carcinogenesis by promoting cancer cell proliferation, survival, and angiogenesis [9].

IL-6 can connect to both membrane-bound IL-6 receptors (mIL-6R) and soluble IL-6 receptors. IL-6 cytokines use gp130 for signal transduction via gp130 homodimers or GP130-containing heterodimers. While IL-6R is mostly expressed on immune cells and hepatocytes, gp130 is found throughout the body, explaining IL-6's several functions. In the

conventional signal transduction pathway, IL-6 binds to the membrane-bound IL-6R. When the IL-6-IL-6R complex binds to GP130, it phosphorylates the JAK family kinases that are constitutively linked with GP130's cytoplasmic area. In the second pathway, known as trans-signaling, IL-6 binds to the soluble IL-6 receptor (sIL-6R), which is produced through alternative mRNA splicing or is shed from cells after being cleaved by ADAM17 (metalloprotease). IL-6, in combination with sIl-6R, binds to GP130. Thus, the trans-signaling pathway enables the activation of cells that do not have the IL-6R on their membranes. A third mechanism of IL-6 signal transduction has recently been characterized as 'trans-presentation.' This mechanism is exclusive to dendritic cells, which transfer the IL-6mIL-6 combination to T cells expressing gp130, priming them to become pro-inflammatory Th17 subsets [10].

II. ROLE OF IL-6 IN DIABETES MELLITUS

Diabetes mellitus (DM), one of the most common public health diseases, has a high incidence, numerous complications, a high rate of impairment, a low level of knowledge, and a considerable financial burden [11]. It affects approximately 537 million people globally between the ages of 20 and 79 (10.5% of all adults in this age range) [12]. According to the Ministry of Health and Family Welfare's (MoHFW) National Family Health Survey-V (NFHS-5) from 2019 to 2021, 10.0% of women and 11.6% of men in Uttar Pradesh have T2D [13]. Diabetes, a major hazard to human health, is a progressive metabolic disease characterized by hyperglycemia caused by a combination of environmental and genetic factors. The World Health Organization estimates that more than 400 million people worldwide have diabetes, and that number is anticipated to climb to 552 million by 2030 [14]. Diabetes is a chronic condition characterized by hyperglycemia, where blood glucose levels exceed the usual range of 70-110 mg/dl [15]. Diabetes mellitus is a common cardiometabolic condition that includes type 1 and type 2 diabetes. Insulin shortage is a common trait, although the pathophysiology of the two illnesses is highly distinct. T1D is an autoimmune illness characterized by the slow destruction of insulin-producing β cells in the pancreatic islets by an intolerant immune system. The pathophysiology of T2D comprises numerous metabolic derangements; at least eight according to the 'ominous octet' hypothesis, and inflammation is a crucial contribution [16]. These derangements contribute in complex interdependent ways to insufficient insulin secretion relative to the level of, primarily muscular and hepatic, insulin sensitivity [17]. Regardless of the source, hyperglycemia is the primary downstream inducer of various pathogenic processes that lead to micro- and macrovascular problems in both type 1 and type 2 diabetes. One of these processes is the intracellular production of reactive oxygen species, which promote and maintain pro-inflammatory pathways through epigenetic modifications. Although type 1 diabetes is according to the 'double-diabetes' hypothesis [18]. With its various functions in maintaining glucose homeostasis [19]. IL-6 is an intriguing target in diabetes. IL-6 enhances insulin-induced glucose clearance in the liver and skeletal muscle. Infusions of 5 μg/hour have been found to improve insulin-induced glucose disposal in humans [20]. Furthermore, IL-6 is released by the skeletal muscle during exercise [21]. Furthermore, IL-6 has been found in humans to supplement insulin secretion by boosting the release of glucagon-like peptide [22]. Highlighting the duality of the cytokine, however, it has long been recognized that systemic chronic inflammation mediated by pro-inflammatory cytokines such as IL-6 is crucial in the pathophysiology of T2D [23,24]. For instance, it is widely documented that chronic inflammation induces insulin resistance [25,26]. and inhibiting IL-6 with tocilizumab decreased insulin resistance [27]. Several studies have found that individuals with T2D had higher levels of IL-6 and CRP [28].and are likely associated with extra adipose tissue [29]. In such tissues, macrophages express IL-6, which enhances fatty acid oxidation and ultimately lipolysis [30]. As a result, obese individuals, including those without T2D, have higher IL-6 levels [31]. It should be noted, however, that therapy with anti-IL-6 drugs is associated with an increase in body weight, most likely due to the general catabolic effect of physiological IL-6 levels in adipose tissue. The extra IL-6 generated by macrophages in adipose tissue may also worsen insulin resistance and enhance gluconeogenesis in the liver [32].

III. ROLE OF IL-6 IN CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is becoming increasingly prevalent around the world. By 2040, this condition is expected to be the fifth most common cause of death globally. CKD is defined as the steady and permanent decline of kidney function over a three-month period based on the existence of abnormal structure or function or abnormal glomerular filtration rate (GFR), with or without evidence of kidney injury [33].The complex pathophysiology of chronic kidney disease causes dysregulation of adipokines, which are essential regulators of insulin sensitivity, adipogenesis, energy metabolism, endothelial function, and blood pressure [34].

Elevated IL-6 has consistently been documented throughout all stages of chronic renal disease: When renal function deteriorates, IL-6 levels rise [35]. More than 70% of hemodialysis patients had IL-6 levels higher than normal. IL-6 levels are 2-3 times higher in CKD patients than healthy controls, and they strongly predict cardiovascular morbidity and mortality [36].

1. Inflammation and renal injury: - IL-6 levels rise in CKD patients' plasma and kidney tissue, contributing to chronic inflammation and leukocyte recruitment. Nishimoto and Kishimoto (2006) identified IL-6 as a primary cause of chronic inflammatory diseases. Han et al. (2021) emphasized the importance of IL-6 signaling in renal disease progression via activating JAK/STAT.
2. The Renin-Angiotensin System and Fibrosis: - Angiotensin II has been demonstrated to stimulate IL-6 synthesis in the kidney, and IL-6 reduction protected mice from hypertension and renal fibrosis, emphasizing its deleterious role in CKD progression [37].
3. Cardiovascular and Metabolic Complications: -In end-stage renal disease (ESRD), IL-6 has been associated to malnutrition, atherosclerosis, and cardiovascular mortality, indicating poor outcomes due to systemic inflammation [38].
4. CKD Anemia: - The upregulation of hepatic hepcidin by IL-6 results in functional iron deficiency and anemia. This mechanism is central chronic disease anemia, which is frequent in individuals with CKD [39].
5. Prognostic Marker: - Higher levels of IL-6 predicted mortality in dialysis patients, regardless of known risk factors. Later, Kimmel et al. (2008) discovered that IL-6 levels are related to hospitalization and cardiovascular events in ESRD patients [40].

IV. ROLE OF IL-6 IN POLYCYSTIC OVARY SYNDROME (PCOS)

PCOS affects around 6-12% of women of reproductive age worldwide, with global pooled estimates varying from 9 to 10% depending on diagnostic criteria, making it one of the most frequent endocrine disorders among this age group. It is associated with a variety of conditions, including hyperandrogenism, insulin resistance, metabolic syndrome, and obesity. Thyroid problems, which can affect menstruation and reproduction, are more prevalent in women than in men [41]. Because the majority of PCOS patients are obese, metabolic disorders play a role in PCOS pathogenesis. Glucose intolerance is also associated with PCOS, and it is regarded to be the primary source of the disease's clinical symptoms. Infertility is more likely among obese PCOS patients. Obesity causes infertility in PCOS patients through a number of processes, including increased insulin resistance, altered luteinizing hormone (LH) secretion, and amplification of hyperandrogenism [42].

Women with PCOS have low-grade chronic inflammation that contributes to the development of T2DM and cardiovascular disease [43]. Interleukin-6 (IL-6), a key proinflammatory cytokine in chronic inflammation, has been found to be closely related with IR and cardiovascular problems [44]. Early in vivo studies revealed that infusion of human recombinant IL-6 could cause gluconeogenesis, hyperglycemia, and compensatory hyperinsulinemia. Obesity, a key risk factor for T2DM, was found to be related with higher IL-6 levels [45]. In contrast, IL-6 levels fell in PCOS patients after reducing their level of IR and body obesity [46]. PCOS is associated with a persistent low-grade inflammatory state in which interleukin-6 (IL-6) plays a significant role. IL-6 is secreted by adipose tissue, immune cells, and ovarian cells, and women with PCOS have significantly higher levels than controls [47]. Elevated IL-6 levels impair insulin signaling pathways and enhance the serine

phosphorylation of insulin receptor substrates, leading to insulin resistance, a significant metabolic feature of PCOS [48]. Additionally, IL-6 is found in ovarian tissue and follicular fluid, where it can affect granulosa cell activity, folliculogenesis, and local steroidogenesis, contributing to anovulation and reproductive failure [49]. Obesity promotes IL-6 production, however studies show higher IL-6 independent of BMI, indicating both obesity-dependent and intrinsic inflammatory mechanisms in PCOS [50].

V. ROLE OF IL-6 IN CARDIOVASCULAR DISEASE

Cardiovascular illnesses are currently the largest cause of death and morbidity in the globe. They endanger patients' safety and quality of life while also imposing a significant burden on society. Inflammatory has a significant role in CVD, and inflammatory indicators can predict future CVD occurrences [51]. Inflammation contributes significantly to the development of cardiovascular disease [52]. Members of the IL-6 family contribute to the emergence of cardiovascular disorders by regulating the immune system and inflammatory activities [53]. Elevated IL-6 levels are predictive of myocardial infarction and stroke in the general population. Elevation of IL-6 is favorably associated with carotid atherosclerosis development [54]. In order to control the subsequent inflammatory reactions that lead to the development of atherosclerosis, IL-6 is crucial. The establishment of atherosclerotic plaque and plaque destabilization are caused by IL-6's promotion of smooth muscle cell (SMC) migration and proliferation, endothelial dysfunction, and the recruitment and activation of inflammatory mediators [55]. Decreased cardiac function at 4 months and a bigger infarct size are linked to higher levels of IL-6 24 hours after ST-elevation myocardial infarction (STEMI). The prognosis of STEMI may be improved by targeting IL-6, which may also be a possible biomarker for the condition [56]. According to clinical studies, IL-6 is a biomarker of death from unstable coronary artery disease. Future cardiac events and CAD mortality in patients with anginal syndrome or healed myocardial infarction are strongly correlated with elevated IL-6 levels [57].

VI. ROLE OF IL-6 IN METABOLIC SYNDROME

Obesity, insulin resistance, hypertension, hyperglycemia, and dyslipidemia are among the three metabolic disorders that co-occur in metabolic syndrome (MS), a complicated illness. About 20–25% of adults worldwide suffer with multiple sclerosis (MS), a condition whose incidence is rising quickly due to factors like obesity, aging populations, and inadequate nutrition [58]. It is widely recognized that individuals with multiple sclerosis (MS) have heightened risks of cardiovascular disease (CVD), type 2 diabetes, and kidney impairment [59]. As a multifunctional cytokine, IL-6 is crucial in numerous metabolic activities through its autocrine and/or paracrine effects on adipocyte function [60]. Currently, a growing body of evidence has shown that IL-6 is significantly associated with metabolic disorders, including metabolic syndrome (MS) and type 2 diabetes. Additionally, increased levels of IL-6 have been observed in the adipose tissues of individuals with diabetes mellitus or obesity, especially in those exhibiting characteristics of MS [61]. Eckel et al suggested that the rise of IL-6 in multiple sclerosis influences several critical factors, which lead to insulin resistance, heightened glucose production in the liver, alongside the suppression of insulin-mediated glucose absorption in skeletal muscle, and the promotion of hypertension. IL-6 is a versatile cytokine mainly produced by adipose tissue, immune cells, and skeletal muscle. Persistently elevated levels of IL-6 contribute to the chronic inflammation that leads to metabolic syndrome (MetS). It disrupts insulin signaling by triggering the JAK/STAT3-SOCS3 pathway, enhances gluconeogenesis in the liver, and alters lipid metabolism, all of which further contribute to insulin resistance and abnormal lipid levels. Increased IL-6 concentrations are closely associated with inflammation related to obesity and the onset of insulin resistance, signifying its role as both a biomarker and a mediator of MetS [62].

VII. ROLE OF IL-6 IN SUBCLINICAL HYPOTHYROIDISM

SCH is characterized by elevated serum Thyroid Stimulating Hormone levels, accompanied by normal total or free T4 and T3 levels [63]. Individuals with

subclinical hypothyroidism (SCH) are divided into two categories based on the Indian Thyroid Society's guidelines: one group has a significantly high serum TSH level (>10 mUI/L), while the other group has a moderately elevated TSH level (4.5–10 mIU/L) [64]. Reviews showed that the prevalence of SCH was 9.4% and hypothyroidism was 3.9%, with women more likely to have these diseases (11.4%) than men (6.2%). Additionally, it was discovered that the prevalence of SCH rose with age. A study found that between 7% and 10% of women aged 60 and beyond suffer from SCH, the most prevalent thyroid disorder in the elderly [65]. A member of the Th2 class of cytokines, IL-6 is an early marker of inflammation and is essential for the humoral immune response. Hepatocytes are strongly influenced by interleukins, which causes them to produce a class of proteins known as acute-phase proteins. Normal and healthy people showed the baseline levels of acute phase proteins in their serum. However, when hepatic stimulation occurs, their concentrations are increased. Adipocytes secrete IL-6 in response to thyroid stimulating hormone. IL-6 serves as a regulator and plays a critical role in the early stages of inflammation [66].

Abbreviation

IL-6: Interleukin 6
CKD: Chronic Kidney Disease
CVD: Cardiovascular Disease
BSF2: B Cell Stimulatory Factor 2
TNF: Tumor Necrosis Factor
RA: Rheumatoid Arthritis
SLE: Systemic Lupus Erythematosus
DM: Diabetes Mellitus
MOHFW: Ministry Of Health And Family Welfare's
NFHS-5: National Family Health Survey-V
T1D: Type 1 Diabetes
T2D: Type 2 Diabetes
CRP: C-Reactive Protein
CKD: Chronic Kidney Disease
GFR: Glomerular Filtration Rate
PCOS: Polycystic Ovary Syndrome
BMI: Body Mass Index
CVD: Cardiovascular Disease
SMC: Smooth Muscle Cell
STEMI: St-Elevation Myocardial Infarction
METS: Metabolic Syndrome
SCH: Subclinical Hypothyroidism
TSH: Thyroid Stimulating Hormone

CONCLUSIONS

According to the evidence reviews, IL levels were significantly associated with a variety of diseases, but only a few had robust levels of supporting evidence. Further prospective studies are necessary to investigate if IL levels could be an intervention in the treatment and management of DM and related diseases, and to provide a more comprehensive and standardized analysis.

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CONFLICT OF INTERESTS

The authors declare no competing interests.

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