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Review Article

Role of Interleukins in Renal, Cardiac

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Abstract

Interleukins play very important role in renal, cardiac and liver functions. Among 37 interleukins. Identified so far, Interleukins 1, 5, 6, 8, 10, 12, 15, 17, 18 & 22 and their associated receptors are linked to majority of the above three organ functions. This review article highlights the recent research findings during the last three decades in this filed.

Interleukins are a group of cytokines first expressed by leukocytes and they play a prominent role as immune modulators. They modulate immune response and direct immune cells to the site of inflammations. Infections produce inflammations which in turn produces interleukins by leukocytes. The number of interleukins identified so far numbering 37 plays significant roles in many inflammatory processes. The research findings during the last two decades on the role of interleukins in renal, cardiac.

1-Introduction:

Interleukins (IL) are a type of cytokine first thought to be expressed by leukocytes alone but have later been found to be produced by many other body cells. They play essential roles in the activation and differentiation of immune cells, as well as proliferation, maturation, migration, and adhesion. They also have pro-inflammatory and anti-inflammatory properties. The primary function of interleukins is, therefore, to modulate growth, differentiation, and activation during inflammatory and immune responses. Interleukins consist of a large group of proteins that can elicit many reactions in cells and tissues by binding to high-affinity receptors in cell surfaces. They have both paracrine and autocrine function. Interleukins are also used in animal studies to investigate aspect related to clinical medicine.[1]

Cytokines coordinate both innate and adaptive immune responses, and they display pleiotropic roles in healthy and disease conditions [1]. Interleukins (ILs), a large group of cytokines, play important roles in immune cell growth, differentiation, and activation, as well as other tissue-resident cells by interacting with their receptors [2]. Acute and chronic liver diseases are characterized by liver inflammation and cell death [3,4], which are commonly associated with infiltration of different immune cells and activation of hepatic parenchymal cells to secrete ILs[5,6]. ILs as a major type of cytokines are involved in the pathogenesis and resolution of

liver diseases, such as liver inflammation (e.g., IL-35)[7], alcohol-related liver disease (e.g., IL-11)[8], non-alcoholic steatohepatitis (e.g., IL-22)[9], liver fibrosis (e.g., Il-17a)[10], and liver cancer (e.g., IL-8)[11].

Cytokines [e.g., interleukins (ILs), interferons, hematopoietic growth factors, lymphokines, monokines, and chemokines] play important roles in inflammatory and innate immune responses. They are characterized by their name or abbreviation, promoter or source cells, main biological actions, and references from the recent literature[1] Among them, Ils participate in cellular and tissue bioreactions and bind to high-affinity cell-surface receptors[12]. Ils can play proinflammatory and anti-inflammatory roles and have paracrine and autocrine functions. The primary function of ILs is to modulate inflammatory processes (growth, differentiation, and activation) and innate immune responses. In the literature, ILs account for 40 different proteins, numbered from 1 to 40. They are produced by various cells in the body, although they had been previously thought to be expressed only by leukocytes [12] Immunoassays and bioassays using antisera and antibodies have allowed the discovery of new cytokines such as IL-1, -6, and -8[13]. Yang and Zhang[14] reported the role of ILs in the pathogenesis and resolution of hepatic disorders and summarized alcohol- and virus-induced hepatitis based on a fortiori clinical studies of IL-mediated therapies pertaining to these liver dysfunctions. They suggested that preclinical and clinical studies be conducted to evaluate the efficacy of IL-mediated monotherapy and synergistic therapies. This editorial contributes to the review by Yang and Zhang [14], titled "Interleukins in liver disease treatment" and mainly focuses on IL-mediated therapies in patients with both liver disorders and potential comorbidities.[15].

2. Interleukins and Renal Diseases:

IL-1 is unlikely to be beneficial in the recovery of renal function after ischemia and may play a deleterious role [1]. Renal fibrosis is a common pathway leading to kidney failure. Infiltrating immunocytes in the end stage renal diseases (ESRD) and several related factors are involved in renal fibrogenesis. Although the B-cell count was increased ESRD, immunostaining patterns disclosed a marked increase in the number of CD3 (+) cells. The remarkable increase in IL-1 and IL-6 levels suggests that T cells in the kidneys of dogs with ESRD spontaneously express these cytokines. T lymphocytes and IL-6 play important roles in renal fibrosis [18]. Risk of cardiovascular diseases (CVD) is significantly elevated in patients with chronic kidney disease (CKD); however, this increased risk is only partially explained by traditional cardiovascular risk factors. Patients with CKD exhibit chronic inflammation, a key mechanism contributing to vascular dysfunction. [16] IL-6, the major mediator of the acute-phase response, is elevated in the plasma of ESRD patients and is a strong predictor of outcome. A number of factors prevalent in patients with ESRD, such as hypertension, adiposity, insulin resistance, fluid overload and persistent infections, could all be associated with elevated IL-6 levels. Factors associated with the dialysis procedure, such as bio incompatibility of dialyser membranes and dialysis solutions, may stimulate IL-6 production. The clinical consequences of elevated IL-6 levels and strategies to reduce IL-6 levels should be further evaluated to confirm the importance of this cytokine as a central regulator of the inflammatory response in ESRD [17].

In a multiple regression analysis serum creatinine was the sole identified determinant of IL-6 levels in a group of pre-dialysis and dialysis patients. One explanation for these findings might be the impairment of renal clearance or inactivation of IL-6. Indeed, ESRD patients have lower urinary IL-6 receptor excretion than controls 151. Links between the IL-6 system and the residual renal function, shows an association between SIL-6R and the progression rate of renal function in the pre-dialysis phase, as well as an association between changes in glomerular filtration rate and changes in IL-6 during peritoneal dialysis (PD) treatment [18], IL-6 has become a major target for clinical intervention in various autoimmune conditions and drugs including the humanized

anti-IL-6 receptor (IL-6R) antibody Tocilizumab emphasize the clinical importance of IL-6 in driving disease and poor patient outcomes [19].

Genetic deletion of IL-6 significantly reduced hypertension and key features of CKD, including renal injury and progression to renal fibrosis in angiotensin II-infused mice. Both mouse and human studies reported provide evidence that angiotensin II induces IL-6 production in the kidney, and that, in addition to its role in hypertension, increased IL-6 may play an important pathogenic role in CKD by inducing fibrotic and Endothelin genes expression. These findings suggest that IL-6 signaling is a novel therapeutic target to manage this devastating disorder affecting millions worldwide [20]

In patients on dialysis with cuprophane membranes, the synthesis and release of sgp130 "antagonistic" receptor is significantly increased. This release is seemingly due to a shedding of membrane-bound gp130 receptor. The increased sgp130 release may partially counteract the inflammatory effects caused by IL-6 191. A reduced kidney function may contribute to the increased Soluble interleukin-2 receptor (SIL-2R) levels seen in different immune diseases. Therefore, renal function should be taken into account in the interpretation of elevated plasma concentrations of SIL-2R.110] No relation was found between serum levels of IL-6 and serum levels of creatinine and complement protein factor D but SIL-2R showed a good correlation to creatinine and therefore IL-6 is not dependent upon a reduced kidney function. IL-2 induces an increase in vascular permeability causing the development of edema, sodium avidity, and prerenal azotemia as occurs during endotoxemia. IL-2 therapy induces respiratory alkalosis with the subsequent intracellular shift of phosphorous accompanied by increased renal phosphorous reabsorptions. There is no evidence of renal tubular acidosis [RTA], renal leak of glucose, phosphorous, or magnesium, [21] Serum creatinine values above 1.4 mg/dL predicted the severity of azotemia and prolonged duration of renal functional recovery and interleukin-2 therapeutic regimens induce prerenal azotemia. Careful selection of patients and early detection of adverse physiologic changes may alleviate the side effects of interleukin-2 therapy [22]

IL-2 nephrotoxicity may result from an intrarenal defect in addition to the previously described pre renal azotemia. Radionuclide studies of renal function are a reliable and reproducible noninvasive method of assessing these changes in renal function [23], Patients who produced low antibody titers also presented with enhanced IL-2 receptor expression and that an impaired antibody production following hepatitis B vaccination and an enhanced IL-2 receptor expression on T cells may already be present in early stages of chronic renal failure (CRF) [24]. Intravenous IL-2 therapy causes renal clearance perhaps because of saturation of the non-renal mechanisms of clearance. The subcutaneous route is certainly preferred if IL-2 is used in anephric patients and in those with impaired renal function, and it may be generally preferred for most purposes [25], Seven tests related to liver function viz AST, ALT, GGT, LDH, ALP, Direct and Total Bilirubin showed increases, but the test results indicated significant improvement and moved toward the baseline value five days after the end of IL-2 therapy. Serum creatinine and urea returned to normal three days after the cessation of IL-2 therapy [26], Elevated SIL-2R seen in renal failure patients are not due to an increased synthesis by circulating lymphocytes, but due to the ability of SIL-2R to bind free interleukin 2--thus making it a potential immunoregulatory molecule and high serum levels could explain some of the immunologic abnormalities observed in acute and chronic liver disease. [27]

Renal failure is an important confounder of sIL-2R levels independent of liver dysfunction and inflammation. SIL-2R is elevated in patients with liver diseases and cirrhosis, is associated with circulating inflammatory cells and is increased in concomitant renal failure. SIL-2R might be a potential marker for immune cell activation in Chronic Liver diseases (CLD), especially for proinflammatory and profibrogenic non-classical CD14 + CD16+ monocytes [28]. With decreasing renal function, the concentrations of Interleukin

18 Binding protein (IL-18BP) in the circulation are elevated as compared with subjects with a normal renal function, and these elevated levels may result in a decreased IL-18 activity. Because of the importance of IL-18 and Interferona (INF-a) in the Thi response, of IL-18 and IL-18BP are associated with immunosuppression with chronic renal failure (201, IL-15 lower the apoptotic rate in cisplatin-treated cultured respiratory epithelial cells and IL-15R-a renal cells exhibited a higher rate of cisplatin-induced apoptosis. Further, IL-15 levels negatively correlated with urea of cisplatin-treated mice, suggesting a decline in renal-derived IL-15 and it is detrimental to renal cell survival and kidney function during pathological stress [29] Suppression of IL-6 and improved iron mobilization reduces circulating IL-6 and improves haemoglobin in non-inflammatory moderate to severe CKD and is associated with changes in circulating transferrin saturation and ferritin, suggesting an improved iron release. It is hypothesized that pentoxifylline improves iron disposition, possibly through modulation of hepcidin [30]

Nutritional status in chronic hemodialysis patients is affected, at least in part, by the circulating IL-6 level. Multiple factors, such as long-term hemodialysis, aging, and the use of a regenerated cellulose membrane dialyzer was associated with this increased level of IL-6 [31] The modulation of the balance between pro- and anti-inflammatory cytokines towards the anti-inflammatory cytokine IL-10 is one salutary mechanism underlying how atorvastatin influences post-MI remodelling and thus improves Left ventricular (LV) function [32]

The feedback mechanism of IL-10 for reducing monokine synthesis seems to be intact in hemodialysis patients. The secretion of IL-10 might be regarded as a compensatory mechanism which controls monokine induction by CRF and HD treatment. Immunodeficiency patients who are unresponsive to hepatitis B vaccination seem to be unable to enhance IL-10 synthesis for control of monokine over production. This results in higher levels of IL-6 and TNF-a that might be involved in the pathogenesis of reduced immune defense. [33] Malnutrition is predicted best by hs-CRP and IL-6 levels while CVD by IL-6 level; and mortality, by S-Alb, IL-6, and fetuin A levels, but not by hs-CRP level. This comparative analysis indicates that of these biomarkers, IL-6 level may be the most reliable predictor of CVD and mortality in patients with ESRD [34]. The high frequency of Euthyroid Sick Syndrome (ESS) in patients with Non thyroid illness may be linked to IL-6 and IL-10 alterations. Perturbation of IL-6, and not IL-10, might be involved in the pathogenesis of ESS along with others in CKD 1271, Treatment of patients with IgA nephropathy with corticosteroids is followed by remission of proteinuria but still increased urinary IL-6 and Transforming Growth Factor-ß (TGF-β) excretion. This may be related to an ongoing inflammatory process within the kidney, and further research is required to estimate the value of urinary IL-6 and TGF-ß as markers of activity of the disease 1281. A relationship between II-6, TNF-a and Erythropoeitin (EPO) or GFR was not found. The existence of a circadian (mis) alignment of EPO, IGF-1, IL-6 and TNF-a was not found.[35].

The association between high Insulin like Growth Factor 1 (IGF-1) and low Hb suggests that EPO and IGF-1 have an alternating role, dependent on GFR, in stimulating erythropoiesis. These results could have consequences for the treatment of anemia [36].

Continuous Ventricular Venous Hemodialysis (CVVHD) is associated with the extraction of IL-6 and IL-8 from the circulation of patients with septic multiorgan and renal failure. The biological significance of such extraction is undetermined, but such cytokine removal highlights the complexity of the effect of continuous hemofiltration on the soluble mediators of inflammation activated during human sepsis [37], Elevated IL-6 values were associated with decreased muscle power, but not with decreased muscle fibre size. Vitamin D deficiency was not associated with muscle power. IL-6 was unchanged by high-intensity resistance training in dialysis patients. [38] Human studies reported provide evidence that angiotensin II induces IL-6

production in the kidney, and that, in addition to its role in hypertension, increased IL-6 may play an important pathogenic role in CKD by inducing fibrotic and endothelin-1 gene expression suggesting that IL-6 signaling is a novel therapeutic target to manage this devastating disorder affecting millions worldwide [39], Plasma IL-6 significantly predicted overall cardiovascular mortality and this association persisted after multiple adjustments or restricting the analysis to pre-dialysis patients. Moreover, IL-6 was a significantly better predictor of mortality than CRP, albumin or TNF-a. Hence, plasma IL-6 independently predicted overall and cardiovascular mortality in patients at different stages of chronic kidney disease; however, whether lowering plasma IL-6 will affect the outcome of chronic kidney disease will require more direct evaluation [40]. The clinical recovery from peritonitis was characterized by a rapid fall in IL-8, IL-6 and TNF-a in serum and dialysate. Hemodialysis (HD) patients showed a significant increase in serum levels of IL-8 and also IL-6 and TNF-a compared to normal individuals respectively. [41].

The profile of T cell subsets of patients with CKD with or without HD treatment was similar except for a pronounced shift to Th1 cells in HD patients. IL-7 but not IL-15 plasma concentrations were lowered in patients with ESRD as compared to healthy controls [41], Despite the elevation of B-cell growth, differentiation and survival factors of ESRD patients exhibited a diffuse reduction of B-cell sub populations. This was associated with the down-regulation of B cell activated factor receptor in transitional B cells. The latter can, in part, contribute to B-cell lymphopenia by promoting resistance to the biological actions of B cell Activating Factor (BAFF) that is a potent B-cell differentiation and survival factor [43]. Patients with detectable levels of the anti-inflammatory cytokine IL-10 in serum had significantly higher concentrations of IL-6 and the soluble TNF-R I and II in serum as compared to patients in whom IL-10 was not detectable [37]. Carriage of IL-1RN*2 and non carriage of TNF2 allele appear to be poor prognostic factors in patients suffering from various chronic renal diseases that eventually becomes ESRD [42]

Patients with peritonitis showed very high serum and Phosphodiesteras (PDE) levels of IL-8, IL-6 and TNF-a. The clinical recovery from peritonitis was characterized by a rapid fall in IL-8, IL-6 and TNF-a in serum and dialysate. HD patients showed a significant increase in serum levels of IL-8, IL-6 and TNF-a compared to normal individuals. [44] In CKD patients, neutrophils are highly activated both in the pre-dialyzed period and on regular HD. Contact with the dialysis membrane during HD causes a significant increase in blood Norepinephrine NE-a (1) PI and a(1)-PI in adults, but not in children/young adults. NE-a (1) PI seems to be a much better indicator of an inflammatory state in CKD patients than free a (1)-PI or IL-8 [45].

The human renal tubule epithelial cell may actively participate in acute inflammatory processes in the kidney, including allograft rejection, by effecting and directing leukocyte chemotaxis via the production of IL-8 [46] Although there was no difference in kidney function, structural damage was significantly aggravated in anti-IL-9 treated mice. Deceased donor grafts show a substantial IL-9 release upon reperfusion in clinical kidney transplantation. However, inhibition of IL-9 aggravated kidney damage, suggesting a regulating or minor role of IL-9 in clinical I/R injury [47].

3. Interleukins and Cardiac Diseases:

Renal IL-4 production results in matrix accumulation prior to any immunological insult, that increased circulating IL-4/TGF-ß1 ratios are associated with renal immunopathological manifestations and that upregulation of renal TGF-β1 expression following glomerular Ig deposition accelerates the sclerosis and exacerbates disease development [48] Immunomodulation by exogenous IL-4 treatment may lead to an anti-inflammatory effect by the inhibition of Thl cell phenotypic response, which may further mediate the down-regulation of Matrix Metalloproteinase (MMPs). A significant suppression of MMPs may mainly contribute to an

improvement of LV dysfunction in acute murine coxsackievirus-B3 (CVB3) induced myocarditis [49]

Worsening of fluid overload and congestive heart failure (CHF) may also contribute to increased IL-6 as renal function declines. The circulating levels of IL-6 are increased in patients with chronic heart failure and both local and systemic effects of pro-inflammatory cytokines may be involved in the pathogenesis of (CHF) [50], Increased levels of IL-6 and hs-CRP occurs mainly in patients with decompensated CHF [46]. A significant graded relationship between blood pressure and plasma levels of IL-6 were observed in apparently healthy subjects. Various persistent infections, such as Chlamydia pneumoniae, are associated with atherosclerosis, the mechanisms behind this association remain unclear. However, a recent study demonstrated that the acellular components of C. pneumoniae are potent stimuli for IL-6 production [54] One mechanism by which chlamydial infection causes atherosclerosis is due an association between serological evidence of persistent chlamydial infection, carotid atherosclerosis and elevated IL-6 levels in ESRD patients [51]. Leptin levels might actually be suppressed during inflammation. Additionally, increased serum levels of IL-6 may be associated with changes in bone remodelling in ESRD patients. Indeed, a recent study shows that calcitriol treatment has an effect on bone remodelling by influencing the levels of plasma IL-6, beyond its suppressive effect on parathyroid hormone [52] Mitochondria triggering of caspases plays a central role in ischemia-induced apoptosis intracellular IL-1R-a as a critical mechanism of the cell self-protection against ischemia-induced apoptosis and suggest that this cytokine plays an important role in the remodeling of heart by promoting the survival of cardiomyocytes in the ischemic regions [59].

Mature IL-1 ß has antiapoptotic activity when added exogenously before the onset of hypoxia, which is caused in part by its ability to downregulate the IL-1 receptor. Pro-IL-1 ß is a substrate of Interleukin Converting Enzyme (ICE) relevant to cell death, and depending on the temporal cellular commitment to apoptosis, mature IL-1 ß may function as a positive or negative mediator of cell death [60]. There are several pieces of background information that suggest that cytokines like IL-1 may play a significant role in the pathogenesis of several forms of myocardial dysfunction. Although it seems clear that IL-1 is not acting alone under circumstances of myocardial injury, but in concert with other pro-inflammatory molecules and their effectors, IL-1 is elevated in several cardiac disease states and is produced by myocardial cells themselves in response to injury. The alterations in gene expression seen in response IL-1 resemble in many ways the phenotype of the failing heart, and the co-localization of the IL-1 response to that of several previously described negative transcriptional regulators making them potential targets for therapeutic manipulation (63),Blockade of IL-1ß signalling with the IL-1 receptor antagonist reverses the phenotypes and offers a possible therapeutic approach in the management of HF [62], IL-1 induces the release of active IL-18 in the mouse that mediates the LV systolic dysfunction but not the induction of IL-6. IL-18 blockade may therefore represent a novel and more targeted therapeutic approach to treat HF 1541, T-lymphocytes are present in significant numbers in the atherosclerotic plaque, but their role in the progression and pathogenesis of coronary syndromes remains poorly understood. Mean levels of sIL-2R were significantly higher in patients with stable angina than in either patients with unstable angina or control patients. Levels of IL-2 and sIL-2R receptor are significantly elevated in patients with stable angina, but not in patients with unstable angina. The contribution of T-lymphocytes to the development of both stable and unstable angina requires further investigation [64]. T Lymphocytes are found in large numbers in human atherosclerotic plaques, indicating that immune and inflammatory mechanisms are important factors in the pathogenesis of atherosclerosis. Patients with IHD have an increase in circulating cytotoxic T lymphocytes and in IL-2 plasma levels, irrespective of their clinical presentation, compared to normal control

subjects, whereas IL-6 is elevated only in patients with Acute Ischemic Stroke [65]

Long-term IL-6 levels are associated with CHD risk about as strongly as are some major established risk factors, but causality remains uncertain, suggesting the potential relevance of IL-6-mediated pathways to CHD [66]. There is mounting evidence that inflammation plays a role in the development of coronary heart disease (CHD). Observations have been made linking the presence of infections in the vessel wall with atherosclerosis, and epidemiological data also implicate infection in remote sites in the aetiology of CHD. IL-6 is a powerful inducer of the hepatic acute phase response. Elevated concentrations of acute phase reactants, such as CRP are found in patients with acute coronary syndromes (ACS), and predict future risk in apparently healthy subjects. A role for IL-6 in the pathogenesis of CHD through a combination of autocrine, paracrine and endocrine mechanisms [67]. Tonsillar cells from patients with rheumatic heart disease produced significantly less IL-1, TNF, IL-2, and Ig than control tonsillar cells. In contrast, blood mononuclear cell cultures from rheumatic children produced more TNF and IL-2 than controls suggesting that abnormal regulation of cytokine and Ig production may contribute to the pathogenesis of acute rheumatic fever and rheumatic heart disease [69].

Serum levels of certain inflammatory markers may have some diagnostic value for ACS, and can be a useful marker reflecting diseasestability. [60] The importance of interleukins in ACS has not been clearly defined. Data concerning relations between the levels of serum interleukin-1 B, IL-2, IL -8 and TNF-a in patients with unstable angina pectoris (UAP) are lacking. High levels of IL-1B, IL-8 and TNF-a in patients with UAP during early phase has been observed Proinflammatory cytokines IL-1ß, IL-8 and TNF-a may play an important role in the development of atherosclerosis and its complications. [61] CRP is an inflammatory marker associated with increased cardiovascular risk. Production of CRP is regulated by1L-1B, IL-1 RA and IL-6. IL-1B is associated with higher CRP levels in patients with CHD, and this association is significant after adjustment for major risk factors. 162] IL-2, IL-8 and sIL-2R take part in pathogenesis of IHD. IL-2 and IL-8 levels are persistently high in angina patients while in patients with acute myocardial infarction (AMI) they are low. Low concentrations of IL-2 in the latter may be attributed to high levels of its soluble receptor [63] Persistent inflammation has been proposed to contribute to various stages in the pathogenesis of cardiovascular disease (CVD). IL-6R signalling propagates downstream inflammation cascades. Large-scale human genetic and biomarker data are consistent with a causal association between IL6R-related pathways and CHF [64], A high circulating concentration of IL-6 is associated with increased risk of CHD. Blockade of the IL6R with a monoclonal antibody (tocilizumab) licensed for treatment of rheumatoid arthritis reduces systemic and articular inflammation. Genetic studies in populations could be used more widely to help to validate and prioritise novel drug targets or to repurpose existing agents and targets for new therapeutic uses 1651

Activation of cellular immunity is frequent in patients with idiopathic dilated cardiomyopathy and may have functional consequences. T-lymphocyte activation, as reflected in elevated SIL-2R levels, is frequent in patients with dilated cardiomyopathy and is associated with more severe disease. Cellular and humoral immune activation may correlate with progression of the disease process [66], The decline in urinary output and sodium excretion during recombinant (rIL-2) was promptly counteracted by dopamine and after withdrawal of rIL-2 and dopamine, plasma protein levels were normalized. rIL-2- induced ARF in cancer patients is due to renal hypoperfusion mainly caused by a reduction in oncotic pressure 1671. There is a direct toxic interference of the interleukins and TNF-a with the contractile function of cultured cardiac myocytes [68]. The depression of myocardial function by IL-1 ß plus TNF-a is mediated, at least in part, by induction of Ca2+-independent Nitri Oxide synthase activity in the heart [69] The correlation of increased spontaneous production of IL-3 during this period

leads to postulate that IL-3 may be implicated in the activation or clonal expansion of suppressor cells, and hence may play a role in graft tolerance [70], IL-18 might contribute to immune activation and cardiac dysfunction in CHF [71],

IL-1 is elevated in several cardiac disease states, IL-1 is produced by myocardial cells themselves in response to injury, The alterations in gene expression seen in response IL-1 resemble in many ways the phenotype of the failing heart, and co-localization of the IL-1 response to that of several previously described negative transcriptional regulators (making them potential targets for therapeutic manipulation). [72].

Interleukin-18 plays a role in modulation of cardiac fibroblast function and may be an important component of the inflammation-fibrosis cascade during pathological myocardial remodeling [73], Elevated IL-18 levels have been observed in cardiac tissue and circulation after myocardial I/R and sepsis. The possible cellular and molecular mechanisms concerning IL-18-induced myocardial injury include induction of inflammation, increased apoptosis, a cardiac hypertrophy effect, modulation of mitogen activated protein kinase activation, and changes in intracellular calcium. 1741 Treatment of myocardial infarction with stem cells and IL-10 gene transfer significantly improved stem cell retention and ultimately improved overall cardiac function [75]. Treatment with recombinant human interleukin 10 (rhIL-10) significantly improved post-MI LV function. This effect was associated with a significant decrease in pro-inflammatory cytokine and chemokine levels (TNF-alpha, IL-6, MCP-1) and furthermore resulted in a reduced myocardial infiltration of macrophages [76], Correlative analysis showed that high IL-17 expression was associated with better cardiac function, as determined by LV ejection fraction and diastolic diameter values. Therefore, IL-17 expression can be a protective factor to prevent myocardial damage in human Chagas disease 1771, Either IL-1ß or TNF-a produced greater cardiac defects than IL-6 when added separately to Langendorff-perfused hearts; dysfunction was maximal with combined cytokine challenge (IL-1beta, TNF-a plus IL-6), confirming that burn trauma upregulates inflammatory cytokine secretion by cardiomyocytes and suggest that these inflammatory cytokines act in concert to produce burn-mediated cardiac contractile dysfunction [78]

Among dyspnea patients with and without acute HF, Somatostatin receptor (sST2) concentrations are associated with prevalent cardiac abnormalities on echocardiography, a more decompensated hemodynamic profile and are associated with long-term mortality, independent of echocardiographic, clinical, or other biochemical markers of risk [79], Correlations were also observed between IL-4 and TNF-a and IL-6. The urinary IL-4 level correlated with cardiac fibrosis and remodeling in patients with HF. The relationship was stronger in those with hypertensive cardiomyopathy [80]. Patients with CHF had higher IL-4 and Procollage III N-terminal peptide (PIIINP) values than the controls. Patients with hypertensive cardiomyopathy had higher concentrations of IL-4 and PIIINP. This latter finding has also been reported with markers of oxidative stress, a process linked to worsening of patients with CHF [81], Since the changes in concentrations of CRP, IL-4, and IL-6 in patients with heart failure are dynamic, the distinction between compensated and decompensated state is important when discussing the significance of acute reactive proteins or cytokines in the pathogenesis of HF 1821, IFN- a protects against the development of severe chronic myocarditis, pericarditis, and Dilated Cardiomyopathy (DCM) after CB3 infection, fibrosis and the profibrotic cytokines transforming growth factor-beta(1), IL-1 beta, and IL-4 in the heart [71]

Aging is associated with changes cytokine gene transcription, and burn plus sepsis injury further intensifies such gene responses. IL-6 deficiency does not abrogate STAT-3 phosphorylation and it may enhance expression of other inflammatory cytokines. The differential effects of IL-6 deficiency on the cardiac function in young and aging mice cannot be explained by cytokine gene expression alone, and require further studies [70]. TNF and interleukin-6 also delayed the diastolic

calcium reuptake and decay in cardiomyocytes. Through down regulation of SERCA2 gene expression, inflammatory cytokines may cause cardiac diastolic dysfunction by decreasing diastolic calcium reuptake. Novel therapeutic strategies for diastolic heart failure and critically ill patients by modulating inflammatory reactions [86]. IL-6 and TNF-a levels increase after AMI in humans. Experimental data suggest that these cytokines regulate the initiation of scar formation after AMI. IL-6 may regulate collagen formation and thus remodeling of the left ventricle after AMI. In addition, TNF- a measurement is not very useful in the assessment of infarct size or left ventricular function during the immediate post-infarction period [61].

There was an increase in cardiomyocyte TNF-a after burn plus sepsis, along with cardiac contractile dysfunction, inflammation, and apoptosis.

These changes were attenuated in the IL-6 Knock out the group, but accentuated in the Trangene group, suggesting myocardial IL-6 mediates cardiac inflammation and contractile dysfunction after burn plus sepsis .Right ventricular IL6 mRNA levels correlated inversely with cardiac index. IL6 R expression did not correlate with hemodynamic data. In advanced HF, cardiac IL6/IL6R mRNA expression is increased and may play a role in the pathophysiology of advanced HD [55]. TNF-a, leukocytes, and CRP were not increased in these patients. Immediately after surgery blood glucose was significantly increased in patients with infection. Increased IL-6 after Cardio pulmonary bypass is predictive of infection in patients with impaired LV function .The serum CRP level increased during only the most advanced phase of CVD. In addition, a high LV mass index was associated with a high IL-6 level. IL-6 and CRP serum levels could be of prognostic value in assessing Chagas disease progression because there are significant correlations between elevated levels and the deterioration of cardiac function.

Liver Diseases, Comorbidities, and Conditions:

A meta-analysis estimated that 30% of individuals worldwide are affected by nonalcoholic fatty liver disease (NAFLD). The global incidence has been estimated as 4613 new cases per 100000 person-years. Variables such as male sex, overweight status, and obesity have been significantly associated with NAFLD[5]. Regarding liver dysfunction, the study participants had significant differences in terms of sex, body mass index (BMI), geographic milieu, and study period NAFLD shares common cardiometabolic risk factors with chronic kidney disease (CKD), including metabolic syndrome (MetS), insulin resistance (IR), and type 2 diabetes mellitus (T2DM) [16]. Another meta-analysis reported a significant association between metabolic dysfunction-associated fatty liver disease (MAFLD) and the risk of CKD[1]

Hyperglycemia and hyperinsulinemia increase de nove lipogenesis by stimulating lipogenic enzymes induced by the link between protein-Ic and steroid regulatory elements, resulting in an increased endogenous production of trigly-cerides[8]. A similar effect is observed in the reduced lipolysis in adipose tissue (AT) during IR, which increases the influx of fatty acids into the liver[8]. Reciprocally, hepatic steatosis may alter hepatokine secretion, modifying fatty acid metabolism and IR in a variety of tissues, including skeletal muscle, AT, and liver. IR is reported to be the basis of the MAFLD development process, abnormal metabolic profiles in patients, and disease complications; however, more comprehensive studies are required to understand and test this hypothesis[5]. Adiponectin regulates carbohydrate metabolism, insulin homeostasis, fatty acid oxidation, and hepatic sensitivity to insulin through the phosphorylation and activation of AMP-dependent protein kinase (AMPK)[9]. In obese individuals, large amounts of free fatty acids enter the liver via the hepatic portal pathway[9]

Metabolic disorders can be defined by the condition and levels of biomarkers, such as visceral obesity, hypertension (HTA), IR, hyperglycemia, hypertriglyceridemia, and

decreased high-density lipoprotein levels. The occurrence of three of these abnormalities may characterize MetS[10]. NAFLD is a liver manifestation of MetS; this hepatic abnormality can progress to nonalcoholic hepatic steatosis (NASH), defined as the macrovesicular accumulation of triglycerides (TG) in liver cells[9,10]. NASH can progress to cardiovascular disease (CVD), T2DM, and CKD and may even evolve toward hepatocellular carcinoma (HCC) without cirrhotic episodes. Hepatitis C virus (HCV) infection and NASH significantly impact public health worldwide. Some diets, including those with saturated and trans fats, sodium, and refined and processed sugar, that promote proinflammatory cytokines are associated with a high incidence of MetS. The intake of phenclic acids (e.g., fruits, vegetables, nuts, green tea, and coffee) reduces the prevalence of IR, NAFLD, and fibrosis.

Although NASH treatment can be complicated by the comorbidities of T2DM and CVD, physical activity may slow the progression and severity of NAFLD and NASH. An appropriate lifestyle, including food, hygiene, quality, and exercise, is an essential first-line therapy for both NASH and CVD[10,11] Aspirin is recommended for secondary prevention of CVD, but not NASH, owing to the limited availability of data. Statins are recommended for patients with conditiens such as hyperlipidemia, T2DM, a 10-year atherosclerotic cardiovascular disease (ASCVD) risk, or a CVD clinical state. Statins are also suggested to be safe for patients with NAFLD/NASH, except for patients with Child-Pugh B/C cirrhosis and a Model for End-Stage Liver Disease score > 15, requiring multidisciplinary risk-to-benefit evaluations to avoid toxic cutcomes such as myositis and liver failure[10].

Yang and Zhang[] reported the role of the IL-12 family in immune response regulation and naïve T-cell differentiation in diverse pathologies, including inflammatory, autoimmune, and cardiovascular diseases. The IL-12 family, especially IL-12 and -27, can inhibit chronic hepatitis B virus and HCV infections, respectively [12] Furthermore, an animal model study using IL-12p40-deficient mice infected with human metapneumovirus (hMPV) demonstrated that IL-12 reduces lung inflammation and mucus secretion[12] Experimental mice infected with hMPV progressively experience abnormal lung function and altered cytokine responses. The authors highlighted the importance of immune modulation by the IL-12 family in viral infections, which helps reduce viral replication and regulate virus-induced inflammation. However, the authors suggested investigating the involvement of cytokines in host antiviral defense to precisely understand their mechanism of action targeting viral infections, since long-lasting anti-inflammatory responses and persistent proinflam-matory courses may not be beneficial. In addition, an imbalanced immune response may trigger irreversible tissue injury, ergan failure, and delayed viral clearance. Therefore, the challenge of developing cytokines into effective antiviral therapies requires rigorous research to provide as safe, long-lasting, and effective drug formulations for viral diseases.

IFN-13 (IL-28B) gene variants are responsible for the clinical progression of various pathologies [15]. The 'cytokine storm, ie, the release of proinflammatory cytokines, including ILs, leads to molecular pathophysiological defects and possible organ damage to the lung, heart, or liver. Potential liver injury in patients with coronavirus disease 2019 (COVID-19) has been reported, as indicated by the levels of laboratory parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and albumin[14]

COVID-19 has been associated with diverse systemic and organ failures. Alongside respiratory tract defects, potential damage to the gastrointestinal tract, liver, kidneys, and immune and neurological systems has been reported. Other disorders, such as coagulation defects and cutaneous symptoms, may also occur. The risk of COVID-19 morbidity and mortality increases in patients with specific comorbidities such as obesity, diabetes, and HTA[15] Regarding COVID-19 in patients with preexisting chronic

liver disease (CLD), apart from the above-mentioned specific comorbidities, predictors such as CLD severity, related etiologies, and COVID-19 severity with breathlessness may lead to mortality [16]. However, the authors have suggested that the comprehensive relationship between these risk factors and the outcomes requires further studies Regarding the COVID-19 pandemic, patients with fatty liver disorders (FLD) have a high risk of infection, and the incidence of FLD increases during containment periods[17]. These patients experience risk factors associated with the severity of infection, such as high BMI, metabolic comorbidities, and liver fibrosis, though FLD per se is an unconfirmed independent risk factor.

A high risk of liver defects has been reported in patients with MAFLD who are infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Monitoring of markers pertaining to heart, kidney, and liver function, muscle injury; and coagulation is required in patients with COVID-19. Due to the common polytherapy in COVID-19, such patients may experience drug-induced liver injury[18]

Silaghi-Dumitrescu et al [19] reported decreased insulin secretion, due to reduced insulin secretory granules from pancreatic beta cell, in patients with COVID-19. SARS-CoV-2 may alter the beta cells in the pancreas and trigger proinflammatory cytokine production. In AT, proinflammatory processes lead to persistent low-grade inflammation, which is involved in T2DM occurrence and IR pathogenesis Hyperglycemia and IR have been reported in patients with COVID-19 without any history of diabetes. Apoptosis in SARS-CoV-2-induced thyroid lesions has also been reported [19]. Decreased blood plasma levels of anticxidant enzymes, such as glutathione peroxidase, glutathione, superoxide dismutase (SOD), and catalase, have been observed in patients with COVID-19, in addition to increased oxidative stress parameters, which increases the severity and mortality risks of the disease. Oxidative stress is influenced by inflammatory cytokine production, innate immune response activation, and infected cell death. Similarly, a reduction in glutathione rates due to factors such as dehydration, malnutrition, high urea levels, diarrhea, and increasing cyanate levels in patients with COVID-19 may trigger cataractogenesis.

Acute liver failure (ALF) and CLD are associated with diverse neurological alterations. Brain inflammation is involved in neurological disorders in patients with hepatic encephalopathy (HE). Gut microbiota dysbiosis, accompanied by impaired intestinal permeability, triggers bacterial translocation and endotoxemia, causing systemic inflammation such as neuroinflammation in brain tissue[20]. Furthermore, metabolites from the gut microbiota may alter the central nervous system, leading to neurological complications and worsening clinical manifestations. However, factors such as the etiology, comorbidities, disease severity, and external milieu may influence neuroinflammation and the gut microbiota Hence, inhibiting neurcinflammation may be a promising strategy for HE management Available therapeutic options are somewhat effective, and new approaches with clinical practice implications have been suggested [20]

The pathogenesis of osteopenia and osteoporosis in patients with NAFLD remains poorly understood. A high prevalence of NAFLD has been reported in patients with obesity, which may lead to sarcopenia, regardless of the patient's age. Authors have hypothesized the possible occurrence of osteopenia and osteoporosis in these patients because the metabolism, biological function, and skeletal muscle are closely linked to bone health. They have suggested further research pertaining to osteopenia, osteoporosis, and sarcopenia in patients with NAFLD[21].

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