The Pharma Innovation Journal 2014; 3(9): 54-66

www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2014; 3(9): 54-66

www.thepharmajournal.com
Received: 08-09-2014
Accepted: 09-10-2014

Rajeswari S
Junior Technical Officer, Department of Biochemistry, Apollo Speciality Hospitals, Ayanambakkam, Chennai 600095, India

Swaminathan S
Senior Consultant and Head, Department of Biochemistry, Apollo Speciality Hospitals, Ayanambakkam, Chennai 600 095, India

Correspondence:
Swaminathan S
Senior Consultant and Head, Department of Biochemistry, Apollo Speciality Hospitals, Ayanambakkam, Chennai 600 095, India.

Role of interleukins in renal, cardiac and liver diseases: an update

Rajeswari S & Swaminathan S

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 highlight the recent research findings during the last three decades in this filed. The contents of this review article will certainly make awareness for researchers to select the appropriate interleukin assay for the diagnosis and monitoring prognosis after treatment in diseases linked to renal, cardiac and liver functions.

Keywords: Interleukins, CKD, Liver diseases, Cardiac diseases.

1. Introduction
Interleukins are a group of cytokines first expressed by leukocytes and they play a prominent role as immune modulators. They modulates immune response and direct immune cells to the site of inflammations. Infections produces 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 and liver diseases have been summarised in this review article.

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 [2]. 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. [3] 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 [4].
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 [5]. 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 [6]. 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 [7].

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 [8].

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 [9]. 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.[10] 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.[11] 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. [12] 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 [13].

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 [14]. 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) [15]. 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 [16]. 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 [17]. 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. [18]

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 [19]. 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 Interferon –α (INF-α) in the Th1 response, of IL-18 and IL-18BP are associated with immunosuppression with chronic renal failure [20]. IL-15 lower the apoptotic rate in cisplatin-treated cultured respiratory epithelial cells and IL-15R-α 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 [21]. 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 [22].

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 [23]. 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 [24].

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-α that might be involved in the pathogenesis of reduced immune defense.[25] 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 [26]. 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 [27]. Treatment of patients with IgA nephropathy with corticosteroids is followed by remission of proteinuria but still increased urinary IL-6 and Transforming Growth Factor–β (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-β as markers of activity of the disease [28]. A relationship between Il-6, TNF-α and Erythropoeitin (EPO) or GFR was not found. The existence of a circadian (mis) alignment of EPO, IGF-1, IL-6 and TNF-α was not found. 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 [29].

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 [30]. 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. [31] 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 [32]. 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-α. 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 [33]. The clinical recovery from peritonitis was characterized by a rapid fall in IL-8, IL-6 and TNF- α in serum and dialysate. Hemodialysis (HD) patients showed a significant increase in serum levels of IL-8 and also IL-6 and TNF-α compared to normal individuals respectively. [34].

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 [35]. 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 [36]. 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 [38].

Patients with peritonitis showed very high serum and Phosphodiesteras (PDE) levels of IL-8, IL-6 and TNF-α. The clinical recovery from peritonitis was characterized by a rapid fall in IL-8, IL-6 and TNF- α in serum and dialysate. HD patients showed a significant increase in serum levels of IL-8, IL-6 and TNF-α compared to normal individuals. [39] 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-α (1) PI and α(1)-PI in adults, but not in children/young adults. NE-α (1) PI seems to be a much better indicator of an inflammatory state in CKD patients than free α (1)-PI or IL-8 [40]. 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 [41]. 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 [42].

3. Interleukins and Cardiac Diseases

Renal IL-4 production results in matrix accumulation prior to any immunological insult, that increased circulating IL-4/TGF-β1 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 [43]. Immunomodulation by exogenous IL-4 treatment may lead to an anti-inflammatory effect by the inhibition of Th1 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 [44].

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) [45]. 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 [47]. 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 [48].

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 [49]. Mitochondria triggering of caspases plays a central role in ischemia-induced apoptosis intracellular IL-1R-α 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 [50]. Mature IL-1 β 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 β is a substrate of Interleukin Converting Enzyme

(ICE) relevant to cell death, and depending on the temporal cellular commitment to apoptosis, mature IL-1 β may function as a positive or negative mediator of cell death [51]. 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 [52].

Blockade of IL-1β signalling with the IL-1 receptor antagonist reverses the phenotypes and offers a possible therapeutic approach in the management of HF [53]. 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 [54]. 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 slL-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 [55]. 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 [56].

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 [57]. 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 [58]. 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 [59]. Serum levels of certain inflammatory markers may have some diagnostic value for ACS, and can be a useful marker reflecting disease stability. [60] The importance of interleukins in ACS has not been clearly defined. Data concerning relations between the levels of serum interleukin-1 β, IL-2, IL -8 and TNF- α in patients with unstable angina pectoris (UAP) are lacking. High levels of IL-1β, IL-8 and TNF- α in patients with UAP during early phase has been observed Proinflammatory cytokines IL-1β, IL-8 and TNF- α 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 byl L-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. [62] 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 [65].

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 [67]. There is a direct toxic interference of the interleukins and TNF- α with the contractile function of cultured cardiac myocytes [68]. The depression of myocardial function by IL-l β plus TNF- α 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. [74] 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 [77]. Either IL-1β or TNF- α produced greater cardiac defects than IL-6 when added separately to Langendorff-perfused hearts; dysfunction was maximal with combined cytokine challenge (IL-1beta, TNF-α 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- α 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 [82]. IFN- α 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 [83].

IL-4 and IL-13 suppress excessive neutrophil recruitment, proinflammatory cytokine production, and hepatic damage during the acute stage of S. *japonicum* infection, suggesting that neutrophils and proinflammatory cytokines are mainly responsible for hepatocyte damage during acute murine schistosomiasis japonica. However, neutrophil induction and the production of proinflammatory cytokines were not due solely to IL-17A [84].

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 [85]. 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-α 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- α measurement is not very useful in the assessment of infarct size or left ventricular function during the immediate post-infarction period [87].

There was an increase in cardiomyocyte TNF-α 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 [88]. 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 [89]. TNF-α, 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 [90]. 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 [91].

Neutrophil chemo attractant/activator IL-8 may contribute to myocyte injury after prolonged hypothermic cardiac ischemia, as occurs during human cardiac transplantation [92]. The biological effects of IL8 on MI risk may vary over time and warrant further cohort studies with repetitive IL-8 measurements. [93] Soluble form of selectin-P and interleukin-8 may be useful clinical predictors of unstable CHD. The assessment of the risk for the development of CHD requires further serial investigation [94]. IL-8 and IL-12 are involved in the process of IHD, and serum IL-12 may be a marker for differentiating AMI from Unstable Angina Pectors (UAP) [95]. Circulating IL-1 β and TNF-α concentrations were rarely detectable. Monitoring of IL-6 and IL-8 values during ventricular assist device will provide a means of early identification of high-risk patients that may allow optimization of antimicrobial therapy and selection of the appropriate time for transplantation [96]. In the major histocompatibility complex class II disparate model, heart allografts from IL-9 transgenic donors were acutely rejected, whereas grafts from wild-type donors did not develop rejection. Acute rejection of IL-9 transgenic hearts was associated with massive eosinophil infiltration and prevented by neutralization of either IL-4 or IL-5. IL-9 is critically involved in heart transplant eosinophilia in conjunction with IL-4 and IL-5 [97].

Neurohormonal activation and defective anti-inflammatory

properties are independent predictors of long-term outcome in hospitalized CHF patients with depressive symptoms [98]. Elevated circulating IL-10 levels in systolic HF patients do not have a protective counter balancing effect on mortality. Moreover, patients with elevated IL-10 and TNF-α had significantly higher mortality, suggesting that the possible interaction in the complex inflammatory and anti-inflammatory network may need further study [99]. IL-6 deletion does not block LV remodeling and dysfunction induced by pressure overload. Attenuated content of interleukin 11 appears to be a compensatory mechanism for IL-6 deletion in pressure-overloaded hearts. Limiting availability, of IL-6 alone is not sufficient to attenuate LV remodeling and dysfunction in failing hearts [100]. IL-6 induces hypertriglyceridemia by stimulating hepatic triglyceride secretion independent of endogenous catecholamines. Thus, changes in hepatic triglyceride metabolism are another acute phase response that can be induced by IL-6 [101]. There was a significant increase in IL-2 concentration with a significant decrease in CD8+ cells in patients with active Rheumatoid Heart Disease RHD in comparison with the non-active group and an increase in IL-2 and a decrease in CD8+ cells may be related to rheumatic activity. T helper (CD4+) cells did not differ significantly between groups [102].

4. Interleukins and Liver Diseases

The anti-fibrotic effects of IL-22 are mediated via the activation of STAT3 in Hematopoietic Stem Cells (HSC) and subsequent induction of suppressor of cytokine signaling 3, which induces HSC senescence. Taken together, the hepatoprotective, mitogenic, and anti-fibrotic effects of IL-22 are beneficial in ameliorating alcoholic liver injury. Importantly, due to the restricted expression of IL-22R1, IL-22 therapy is expected to have few side effects, thus making IL-22 a potential candidate for treatment of ALD [103]. IL-8 is activated in ALD, especially in alcoholic hepatitis, and is closely correlated with liver injury. IL-8 levels can reflect the stage and severity of ALD, and may serve as a predictor of survival in patients with alcoholic hepatitis. [104] Overexpression of the IL-18 binding protein, a naturally occurring, specific inhibitor of IL-18, prevents the spontaneous development of atherosclerosis in apolipoprotein E–deficient mice. From animal and human studies, one may conclude that IL-1β and IL-18 participate in fundamental inflammatory processes that increase during the aging process [105].

Local hepatic inflammatory responses inhibit liver cell proliferation and promote liver failure, presumably by affecting the functional capacity of the remnant liver [106]. Engrafted cells and their progeny was incorporated into injured livers and produced albumin and hence AF-MSCs genetically modified to over-express IL-1R-α can be implanted into the injured liver to provide a novel therapeutic approach to the treatment of Fulminant Hepatic Failure (FHF). [107] There is a detrimental effect of systemic IL-2 on liver target organ infiltration by immune T cells causing, a drop of CD4 or CD8 T cells per liver lobule in the Perivascular Epithelial cell (PEC) group to <5 in the PEC plus IL-2 group, which emphasize the importance of a better understanding of IL-2 function in vivo and of its interaction with immune cell function to improve protocols for optimal application in the clinic to achieve maximal Graft-versus-Leukemia (GvL) effects [108]. Th1/Th2 type cytokines are changed in association with progression of CLD type C and in response to therapy. [109] Reduced lymphocyte proliferation in patients with chronic hepatitis B virus infection cannot be attributed to deficient lymphokine production or to active suppression by monocytes or prostaglandins and a direct role for the hepatitis B virus or a viral product is under investigation [110].

The release of IL-2 or the induction of other factors similarly induced by IL-2 may be responsible for these findings. Tissue ultrasound and computerized hepatobiliary scans provide additional noninvasive assessments of liver function and physiology [111]. Augmented expression of IL-2 in livers of patients with chronic hepatitis C (CHC) and hepatocytes represent the principal source of the cytokine in HCV in vivo infection. Mitochondrial localization of IL-2 suggests a direct involvement of the cytokine in disturbed function of the organelles [112]. In patients with poor predictive factors of response, the addition of IL-2 to IFN ribavirin combination therapy does not exert a favourable impact on HCV treatment [113]. IL-3 may be used as an agent to enhance differentiation of Bone Marrow Derived Adult Liver Stem Cells (BALSC), both qualitatively and quantitatively. It is conceivable that stem cells may undergo IL-3 priming before their clinical application in cell transplantation or bioartificial liver systems [114]. Stem Cells Interleukin Factor-3 (SILF3) functions as a novel Liver Receptor Hormone-1(LRH-1) co-activator by acting synergistically with PRMT1 and PGC-1α, thereby promoting LRH-1-dependent gene expression [115].

There is a close correlation between hepatic IL-8 and infiltration with neutrophils. Less dramatic increases in circulating IL-8 are present in abstinent alcoholic cirrhotics and patients admitted for detoxification, suggesting a central role for IL-8 in the neutrophilia and hepatic neutrophil infiltrate characteristic of acute alcoholic hepatitis [116]. Treatment of IL-6-deficient mice with a single preoperative dose of IL-6 returned STAT3 binding, gene expression, and hepatocyte proliferation to near normal and prevented liver damage, establishing that IL-6 is a critical component of the regenerative response [117]. Restitution of normal TPO production by liver replacement seems to be of key importance for reversal of thrombocytopenia in liver disease. The early acting thrombopoietic factor IL-3 and the late acting factors IL-6 and IL-11 do not play a major role in recovery of peripheral platelet count after orthotopic liver transplantation. [118] Treatment with IL-6 for a short period prevented the susceptibility of fatty livers to warm ischemia/reperfusion injury, suggesting the therapeutic potential of IL-6 in treating human fatty liver disease [119].

Expression of IL-22 receptor 1 is up-regulated whereas IL-22 is undetectable in the livers of mice with chronic-binge ethanol feeding or patients with alcoholic hepatitis. Chronic-binge ethanol feeding may be a useful model to study the early stages of alcoholic liver injury. IL-22 treatment could be a potential therapeutic option to ameliorate ALD due to its antioxidant, antiapoptotic, anti steatotic, proliferative, and antimicrobial effects with the added benefit of potentially few side effects [120]. IL-22 treatment could be a potential therapeutic option to ameliorate ALD due to its antioxidant, antiapoptotic, anti steatotic, proliferative, and antimicrobial effects with the added benefit of potentially few side effects [121]. Synergistic effect of IL-6 and MSCs seems a favoured therapeutic option in attenuation of liver apoptosis and fibrosis accompanied by improved liver function [122]. IL-17 receptor was expressed in alcoholic liver disease by hepatic stellate cells, and these cells recruited neutrophils after IL-17 stimulation in a dose-dependent manner through IL-8 and growth related oncogene α (GRO-α) secretion *in vitro*. Human

ALD is characterized by the activation of the IL-17 pathway and alcoholic hepatitis, liver infiltration with IL-17-secreting cell infiltrates is a key feature that might contribute to liver neutrophil recruitment [123].

IL-10 synthesized during the course of liver inflammation and fibrosis may modulate KC actions, and influence subsequent progression of fibrosis. (124) -627*A allele is associated with low IL-10 expression which will favour inflammatory, immune mediated, and profibrotic mechanisms of alcohol related liver injury [125]. Localized production of IL-22 in the liver promotes hepatocyte survival and proliferation but primes the liver to be more susceptible to tumor development without significantly affecting liver inflammation [126]. An association between levels of GP73 and OSM in serum from patients with liver cirrhosis was observed, but no statistically significant correlation in HCC, suggesting that the role of the cytokines in determining circulating levels may be complex [127]. Systematic analysis of serum IL-22 in relation to morbidity and mortality of patients with advanced liver cirrhosis has not been performed so far. In patients with liver cirrhosis, elevated systemic IL-22 levels are predictive for reduced survival independently from age, liver-related complications, CRP, creatinine and the MELD score. Thus, processes that lead to a rise in systemic interleukin-22 may be relevant for prognosis of advanced liver cirrhosis [128]. In patients with hypertensive cardiomyopathy, there was a good correlation between IL-4 and PIIINP levels. Correlations were also observed between IL-4 and TNF-α 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 [129].

The low presence of IL-5 in liver and peripheral blood may represent a particular pattern of eosinophil behaviour in human liver failure, which may also involve MIP-1 α. Further *ex vivo* studies are necessary to evaluate the specific role of eosinophils in FHF [130]. Significantly higher values for cytokines were found in patients with ascites or encephalopathy in comparison to those without any features of portal hypertension and/or insufficiency of the liver cells. A high concentration of the tested cytokine is a disadvantageous prognostic factor in patients with ALD. IL-8 appears to be an important factor in liver pathology in patients with ALD, especially in the development of the inflammatory process. [131] IL-13-regulated genes have been linked to the mechanisms of wound healing and fibrosis. In addition to IL-5 polarizing the antigen-specific $CD4^{+}$Th2 cell response, and granuloma eosinophils were themselves a significant source of IL-13 [132]. In non-specific reactive hepatitis intrahepatic expression of IL-6 was minimal, while in alcoholic liver fibrosis the cytokine distribution in the lobules was similar to that of acute viral hepatitis. These results indicate that locally produced IL-6 contributes to the inflammatory process and immunological response in acute and chronic liver disease [133]. Correlations between IL-1 receptor antagonist and TNF- α soluble receptor were more significant than those of either antagonist with CRP or ESR. IL-1 receptor antagonist and TNF- α soluble receptor levels were also positively correlated with bilirubin and AST levels, and hence circulating levels of IL-1 receptor antagonist and TNF- α soluble receptor may reflect ongoing disease activity and probably modulate some effects of endogenous IL-1 and TNF- α [134].

IL-6 can function acutely to improve hepatic regeneration and repair, but that more chronic exposure not only abolishes the protective effects of IL-6, but actually sensitizes the liver to injury and death. Elevated IL-6 in certain CLD contributes to an increased likelihood of liver failure after injury. [135] Since IL-5 has been associated with cholestasis liver disease, it may contribute to liver injury through its effects on biliary secretion [136]. Obesity-driven activation of the IL-17 axis is central to the development and progression of Non-Alcoholic Fatty Liver Disease (NAFLD) to steatohepatitis and identify the IL-17 pathway as a novel therapeutic target in this condition [137]. Monocyte-derived macrophages from CLD patients, especially the non-classical $CD16^{+}$ subtype, displayed enhanced IL-8 secretion *in vitro*. IL-8 is strongly activated in CLD, thus likely contributing to hepatic inflammation. A novel role of IL-8 for recruitment and activation of hepatic macrophages via CXCR1 in human liver cirrhosis has been observed. [138] In patients with neonatal hepatitis, IL-8 levels were marginally increased. Serum IL-8 levels were significantly correlated with the histologic activity index and further studies are needed to determine the role of IL-8 in portal inflammation, the increased production of IL-8 may be a mechanism leading to the progressive portal inflammation and fibrosis in patients with CLD [139]. IL-8 elevation in patients with acetaminophen hepatotoxicity corresponds with other common clinical measures that are predictive of hepatocellular injury. Further study is warranted to evaluate possible mechanistic relationships between inflammatory cytokines and acetaminophen hepatotoxicity in children and adults. [140] IL-8 production may be associated with hepatic mitochondrial impairment during ischemia, and may contribute to new therapeutic strategies not only for hepatic ischemia reperfusion injury but also for metastatic liver tumors [141]. The severity of liver cirrhosis is an important factor for the occurrence of enhanced IL-8 levels and its does not play a role in the hyperdynamic circulation observed in patients with post-hepatitic cirrhosis [142]. Neopterin and IL-8 plasma levels are raised in patients with alcohol-induced cirrhosis, and are predictive of mortality associated with infections and upper gastrointestinal bleeding, respectively [143]. Increased IL-8 concentrations in patients with alcoholic hepatitis suggest a role for interleukin-8 in the neutrophilia and hepatic polymorphonuclear leukocyte infiltration of alcoholic hepatitis [144]. Patients with alcoholic cirrhosis and chronic alcoholic hepatitis had the highest and patients with fatty liver had the lowest serum IL-6 concentrations. In addition, IL-6 concentrations were higher in patients with hepatic encephalopathy than in those without liver failure. Furthermore, there exist a significant correlation between serum IL-6 and albumin concentrations. High IL-6 concentrations were associated with high mortality in patients with ALD [145].

Patients who continued to drink alcohol had higher serum IL-12 levels than those who abstained from alcohol in the steatosis, hepatitis and cirrhosis groups. Serum IL-12 levels reflected the different stages of ALD and can represent the status of continuous alcohol consumption. It has the potential to be a biomarker of ALD [146]. The combined assays of both serum CA 19-9 and IL-6 could be useful in diagnosing cholangiocarcinoma, particularly in populations where this cancer is prevalent [147]. *In vitro* IL-6 treatment of donor livers also markedly reduces mortality associated with fatty liver transplants from alcohol-fed rats. IL-6 induces hepatoprotection of steatotic liver isografts via preventing sinusoidal endothelial cell necrapoptosis and consequent amelioration of hepatic microcirculation, and protecting against hepatocyte death. IL-6 pre-treatment of steatotic livers

may render such allografts for clinical transplantation. [148] Atherosclerotic lesion size was decreased to levels observed in normal kidney function. Kidney function modifies arterial myeloid cell accumulation and phenotype in atherosclerosis, suggesting a central role for IL-17A in aggravation of vascular inflammation and atherosclerosis in renal impairment. [149] A dose-dependent reduction in serum levels of liver enzymes, TNF-α, and IFN-gamma corresponded with this amelioration of liver damage. No significant change in infiltrating lymphocyte populations in the liver was observed following rhIL-11 treatment. Taken together, these results indicate that rhIL-11 ameliorates T-cell-mediated hepatic injury and suggests its therapeutic potential to treat inflammatory liver disease [150].

IL-11R agonist enhanced the proliferation of hepatocytes and ameliorated oxidative stress upon acetaminophen-induced liver injury. Conversely, the effects of acetaminophen were exacerbated in mice deficient in the IL-11R α subunit and the results suggest that IL-11 provides a functional link between oxidative stress and compensatory proliferation [151]. rhIL-11 may be beneficial for patients with hepatic inflammation and advanced liver disease associated with chronic HCV infection. Larger clinical trials are warranted to further evaluate the long-term antiinflammatory and antifibrotic effects of rhIL-11 [152].

IL-13 is a critical hepatoprotective factor modulating the susceptibility to AILD and may provide hepatoprotection, in part, by down-regulating protoxicant factors and cells associated with the innate immune system [153]. The STAT pathway operates as a key negative regulator in the hepatic inflammatory ischemia-reperfusion response and it outlines requirements for Ad-IL-13 use to maximize the organ donor pool through the use of liver transplants despite prolonged ischemia [154].

IL-13-dependent fibrosis and portal hypertension and quickly succumb to the infection, and the schistosomiasis model illustrate opposing activities for IL-13 and IL-13R α2 in health and disease [155]. IL-10 and IL-15 may reflect the degree of inflammation in the liver. It is also suggested that both cytokines may be related to the development of HCC [156]. IL-6 showed inverse correlations with liver function, intensity of alcoholism, nutritional status, left arm muscle mass and short-term mortality [157]. The effect of Kupffer cells on liver triglycerides are at least partially mediated by IL-1beta, which suppresses PPAR-α expression and activity [158].

5. Conclusions

This review article has given an extensive detail about the role of interleukins in diseases associated with three major organs of human. Among the role played by various interleukins, IL-6 plays a major role and is involved in regulating the functions of the three major organ viz renal, cardiac and liver. Treatment options, with deficient interleukins is also highlighted in this review article. The contents found in this paper will certainly be useful to explore further research in the said failed.

6. Conflict Of Interest

The authors have no conflict of interests and all authors were equally involved in compiling this review article. There is no financial conflict involved in preparing and submitting this manuscript.

7. References

1. Haq M, Norman J, Saba SR, Ramirez G, Rabb H. Role of IL-1 in renal ischemic reperfusion injury. J Am Soc Nephrol. 1998; 9(4):614-9.
2. Yhee JY, Yu CH, Kim JH, Sur JH. Effects of T lymphocytes, interleukin-1, and interleukin-6 on renal fibrosis in canine end-stage renal disease. J Vet Diagn Invest. 2008; 20(5):585-92.
3. Interleukin-1 Trap to Treat Vascular Dysfunction in Chronic Kidney Disease (CKD).Clinical Trials. May 2014.
4. Roberto Pecoits-Filho, Bengt Lindholm, Jonas Axelsson and Peter Stenvinkel. Update on interleukin-6 and its role in chronic renal failure Nephrol. Dial. Transplant. 2003; 18(6):1042-1045.
5. Memoli B, Postiglione L, Cianciaruso B *et al.* Role of different dialysis membranes in the release of interleukin-6 soluble receptor in uremic patients. Kidney Int 2000; 58:417-424.
6. Pecoits-Filho R, Heimbürger O, Lindholm B, Bárány B, Stenvinkel P. Interleukin-6 system is associated with renal function in end-stage renal disease. Blood Purif 2002; 20:511.
7. Jones SA, Fraser DJ, Fielding CA, Gareth W. Jones Interleukin-6 in renal disease and therapy Nephrol Dial Transplant 2014; gfu233v1-gfu233.
8. Zhang W, Wang W, Yu H, Zhang Y, Dai Y, Ning C *et al*. Interleukin 6 Underlies Angiotensin II-Induced Hypertension and Chronic Renal Damage. Hypertension 2012; 59(1):136-144.
9. Memoli B, Grandaliano G, Postiglione MSL, Bisesti BGV, Esposito P, Procino A *et al*. *In Vivo* Modulation of Soluble "Antagonistic" IL-6 Receptor Synthesis and Release in ESRDJ. Am Soc Nephrol 2005; 16(4):1099-1107.
10. Nässberger L, Sturfelt G, Thysell H. Serum levels of the soluble interleukin-2 receptor are dependent on the kidney function. Am J Nephrol. 1992; 12(6):401-5.
11. L. Nässberger. Serum levels of interleukin-6 are not dependent on the kidney function. Mediators Inflamm. 1992; 1(3):197-199.
12. Kozeny GA, Nicolas JD, Creekmore S, Sticklin L, Hano JE, Fisher RI. Effects of interleukin-2 immunotherapy on renal function. J Clin on col. 1988; 6(7):1170-6.
13. Belldegrun A, Webb DE, Austin HA 3rd, Steinberg SM, White DE, Linehan WM, Rosenberg SA. Effects of interleukin-2 on renal function in patients receiving immunotherapy for advanced cancer. Ann Intern Med. 1987; 106(6):817-22.
14. Shalmi CL, Dutcher JP, Feinfeld DA, Chun KJ, Saleemi KR, Freeman LM, Lynn RI, Wiernik PH. Acute renal dysfunction during interleukin-2 treatment: suggestion of an intrinsic renal lesion. J Clin on col. 1990; 8(11):1839-46.
15. Dumann H, Meuer S, Meyer zum Büschenfelde KH, Köhler H. Hepatitis B vaccination and interleukin 2 receptor expression in chronic renal failure. Kidney Int. 1990; 38(6):1164-8.
16. Banks RE, Forbes MA, Hallam S, Jenkins A, Wadhwa M, Dilger P *et al*. Treatment of metastatic renal cell carcinoma with subcutaneous interleukin 2: evidence for non-renal clearance of cytokines. Br J Cancer. 1997; 75(12):1842-1848.
17. Huang CM, Elin RJ, Ruddel M, Sliva C, Lotze MT, Rosenberg SA. Changes in laboratory results for

cancer patients treated with interleukin-2. Clin Chem. 1990; 36(3):431-4.
18. Müller C, Knoflach P, Zielinski CC. Soluble interleukin 2 receptor in acute viral hepatitis and chronic liver disease. Hepatology. 1989; 10(6):928-32.
19. Seidler S, Zimmermann HW, Weiskirchen R, Trautwein C, Tacke F. Elevated circulating soluble interleukin-2 receptor in patients with chronic liver diseases is associated with non-classical monocytes. BMC Gastroenterol. 2012; 24:12-38
20. Dinarello CA, Novick D, Rubinstein M, Lonnemann G. Interleukin 18 and interleukin 18 binding protein: possible role in immunosuppression of chronic renal failure. Blood Purif. 2003; 21(3):258-70.
21. Eini H, Tejman-Yarden N, Lewis EC, Chaimovitz C, Zlotnik M, Douvdevani A. Association between renal injury and reduced interleukin-15 and interleukin-15 receptor levels in acute kidney injury. J Interferon Cytokine Res. 2010; 30(1):1-8.
22. Ferrari P, Mallon D, Trinder D, Olynyk JK. Pentoxifylline improves haemoglobin and interleukin-6 levels in chronic kidney disease. Nephrology (Carlton). 2010; 15(3):344-9.
23. Li J, Leschka S, Rutschow S, Schwimmbeck PL, Husmann L, Noutsias M *et al.* Immunomodulation by interleukin-4 suppresses matrix metalloproteinases and improves cardiac function in murine myocarditis. Eur J Pharmacol. 2007; 554(1):60-8.
24. Stumpf C, Petzi S, Seybold K, Wasmeier G, Arnold M, Raaz D *et al.* Atorvastatin enhances interleukin-10 levels and improves cardiac function in rats after acute myocardial infarction. Clin Sci (Lond). 2009; 116(1):45-52.
25. Matthias G, Hans K, Erika SW, Jörg FS, Karl-Hermann MZB, Bernhard F. Production of interleukin-6, tumor necrosis factor α and interleukin-10 *in vitro* correlates with the clinical immune defect in chronic hemodialysis patients. Kidney International (1995; 47:559-565.
26. Honda H, Qureshi AR, Heimbürger O, Barany P, Wang K, Pecoits-Filho R *et al.* Serum albumin, C-reactive protein, interleukin 6, and fetuin a as predictors of malnutrition, cardiovascular disease, and mortality in patients with ESRD. Am J Kidney Dis. 2006; 47(1):139-48.
27. Abozenah H, Shoeb S, Sabry A, Ismail H.Relation between thyroid hormone concentration and serum levels of interleukin-6 and interleukin-10 in patients with nonthyroidal illness including chronic kidney disease. Iran J Kidney Dis. 2008; 2(1):16-23.
28. Kalliakmani P, Nakopoulou L, Tsakas S, Gerolymos M, Papasotiriou M, Goumenos DS. Urinary interleukin-6 (IL-6) and transforming growth factor (TGF-β) levels in corticosteroidtreated patients with IgA nephropathy. Clin Nephrol. 2011; 76(2):144-50.
29. van der Putten K, Koch B, van Someren E, Wielders J, Ter Wee P, Nagtegaal E *et al.* The role of renal function loss on circadian misalignment of cytokines EPO, IGF-1, IL-6 and TNF-alfa in chronic renal disease. Neuro Endocrinol Lett. 2011; 32(2):148-53.
30. Bellomo R, Tipping P, Boyce N. Interleukin-6 and interleukin-8 extraction during continuous venovenous hemodiafiltration in septic acute renal failure. Ren Fail. 1995; 17(4):457-66.
31. Stig M, Pia E, Jesper L, Andersen, Inge E, Adrian P. Harrison Interleukin-6 and Vitamin D Status during High-Intensity Resistance Training in Patients with Chronic Kidney Disease. Biomed Res Int. 2014: 176190.
32. Zhang W, Wang W, Yu H, Zhang Y, Dai Y, Ning C *et al.* Interleukin 6 underlies angiotensin II-induced hypertension and chronic renal damage. Hypertension. 2012; 59(1):136-44.
33. Barreto DV, Barreto FC, Liabeuf S, Temmar M, Lemke HD, Tribouilloy C *et al.* Plasma interleukin-6 is independently associated with mortality in both hemodialysis and pre-dialysis patients with chronic kidney disease. Kidney Int. 2010; 77(6):550-6.
34. Nakanishi I, Moutabarrik A, Okada N, Kitamura E, Hayashi A, Syouji T *at al.* Interleukin-8 in chronic renal failure and dialysis patients. Nephrol Dial Transplant. 1994; 9(10):1435-42.
35. Litjens NH, van Druningen CJ, Betjes MG. Progressive loss of renal function is associated with activation and depletion of naive T lymphocytes. Clin Immunol. 2006;118(1):83-91
36. Pahl MV, Gollapudi S, Sepassi L, Gollapudi P, Elahimehr R, Vaziri ND. Effect of end-stage renal disease on B-lymphocyte subpopulations, IL-7, BAFF and BAFF receptor expression. Nephrol Dial Transplant. 2010; 25(1):205-12.
37. Jacobson SH, Lu Y, Brauner A. Soluble interleukin-6 receptor, interleukin-10 and granulocyte colony-stimulating factor in acute pyelonephritis: relationship to markers of bacterial virulence and renal function. Nephron. 1998; 80(4):401-7.
38. Shu KH, Cheng CH, Wu MJ, Chen CH, Lee WC. Interleukin 1 receptor antagonist and tumor necrosis factor-alpha gene polymorphism in patients with end-stage renal failure. Ren Fail. 2005; 27(1):53-7.
39. Nakanishi I, Moutabarrik A, Okada N, Kitamura E, Hayashi A, Syouji T *at al.* Interleukin-8 in chronic renal failure and dialysis patients. Nephrol Dial Transplant. 1994; 9(10):1435-42.
40. Polańska B, Augustyniak D, Makulska I, Niemczuk M, Zwolińska D, Jankowski A. Elastase, α1-proteinase inhibitor, and interleukin-8 in pre-dialyzed and hemodialyzed patients with chronic kidney disease. Pediatr Int. 2010; 52(5):735-43.
41. Schmouder RL, Strieter RM, Wiggins RC, Chensue SW, Kunkel SL. *In vitro* and *in vivo* interleukin-8 production in human renal cortical epithelia. Kidney Int. 1992; 41(1):191-8.
42. Kortekaas KA, de Vries DK, Reinders ME, Lievers E, Ringers J, Lindeman JH, Schaapherder AF. Interleukin-9 release from human kidney grafts and its potential protective role in renal ischemia/reperfusion injury. Inflamm Res. 2013; 62(1):53-9.
43. Kaizu Y, Kimura M, Yoneyama T, Miyaji K, Hibi I, Kumagai H. Interleukin-6 may mediate malnutrition in chronic hemodialysis patients. Am J Kidney Dis. 1998; 31(1):93-100.
44. Beate M Rüger, Qurratulain Hasan, Klaus J Erb, Paul F Davis. Progression of renal disease in interleukin-4 transgenic mice: involvement of transforming growth factor-β. Int J Exp Pathol. 1999; 80(3):113-123.
45. Wollert KC, Drexler H. The role of interleukin-6 in the failing heart. Heart Fail Rev 2001; 6:95-103
46. Sato Y, Takatsu Y, Kataoka K *et al.* Serial circulating concentrations of C-reactive protein, interleukin (IL)-4,

and IL-6 in patients with acute left heart decompensation. Clin Cardiol 1999; 22:811-813
47. Netea MG, Selzman CH, Kullberg BJ. Acellular components of Chlamydia pneumoniae stimulate cytokine production in human blood mononuclear cells. Eur J Immunol 2000; 30:541-549.
48. Stenvinkel P, Heimbürger O, Jogestrand T. Elevated interleukin-6 predicts progressive carotid artery atherosclerosis in dialysis patients: association withChlamydia pneumoniae seropositivity. Am J Kidney Dis 2002; 39:274-282.
49. Turk U, Akbulut M, Yildiz A. Comparative effect of oral pulse and intravenous calcitriol treatment in hemodialysis patients: the effect on serum IL-1 and IL-6 levels and bone mineral density. Nephron 2002; 90:188-194.
50. Vecile E, Dobrina A, Salloum FN, Van Tassell BW, Falcione A, Gustini E *et al.* Intracellular function of interleukin-1 receptor antagonist in ischemic cardiomyocytes. PLOS One. 2013; 8(1):e53265.
51. Friedlander RM, Gagliardini V, Rotello RJ, Yuan J. Functional role of interleukin 1 beta (IL-1 beta) in IL-1 beta-converting enzyme-mediated apoptosis. JEM Home. 1996; 184(2):717.
52. Carlin S. Long The Role of Interleukin-1 in the Failing Heart. Heart Failure Reviews. March 2001; 6(2):81-94
53. Bracey NA, Beck PL, Muruve DA, Hirota SA. The Nlrp3 inflammasome promotes myocardial dysfunction in structural cardiomyopathy through interleukin-1β Experimental Physiology, 2013; 98:462-472.
54. Interleukin-18 mediates interleukin-1-induced cardiac dysfunction Am. J. Physiol. Heart Circ. Physiol. April 1, 2014; 306 (7).
55. Simon AD, Yazdani S, Wang W, Schwartz A, Rabbani LE. Elevated plasma levels of interleukin-2 and soluble IL-2 receptor in ischemic heart disease. Clin Cardiol. 2001; 24(3):253-6.
56. Antonino M, Stefano DS. Plasma levels of interleukin 2, 6, 10 and phenotypic characterization of circulating T lymphocytes in ischemic heart disease. August 16, 2004
57. Danesh J, Kaptoge S, Mann AG, Sarwar N. Long-Term Interleukin-6 Levels and Subsequent Risk of Coronary Heart Disease: Two New Prospective Studies and a Systematic. PLoS Med. 2008; 5(4):e78.
58. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V.Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? Atherosclerosis. 2000; 148(2):209-14.
59. Miller LC, Gray ED, Mansour M, Abdin ZH, Kamel R, Zaher S, Regelmann WE. Cytokines and immunoglobulin in rheumatic heart disease: production by blood and tonsillar mononuclear cells. J Rheumatol. 1989; 16(11):1436-42.
60. Wang YN, Che SM, Ma AQ. Clinical significance of serum cytokines IL-1beta, sIL-2R, IL-6, TNF-alpha, and IFN-v in acute coronary syndrome. hin Med Sci J. 2004; 19(2):120-4.
61. Ozeren A, Aydin M, Tokac M, Demircan N, Unalacak M, Gurel A, Yazici M. Levels of serum IL-1beta, IL-2, IL-8 and tumor necrosis factor-alpha in patients with unstable angina pectoris. Mediators Inflamm. 2003; 12(6):361-5.
62. Latkovskis G, Licis N, Kalnins U. C-reactive protein levels and common polymorphisms of the interleukin-1 gene cluster and interleukin-6 gene in patients with coronary heart disease. Eur J Immunogenet. 2004; 31(5): 207-13.
63. Mazurov VI, Stvolov SV, Linetskaia NE, Baldueva IA. Levels of anti-inflammatory cytokines interleukin-2, interleukin-8, and soluble interleukin-2 receptor in blood of patients with various forms of ischemic heart disease. er Arkh. 2001; 73(12):14-7.
64. IL6R Genetics Consortium Emerging Risk Factors Collaboration, Sarwar N, Butterworth AS, Freitag DF, Gregson J, Willeit P, Gorman DN *at al.* Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. Lancet. 2012; 379(9822):1205-13.
65. Hingorani AD, Casas JP. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. Lancet. 2012; 379(9822):1214-24.
66. Limas CJ, Goldenberg IF, Limas C. Soluble Interleukin-2 Receptor Levels in Patients With Dilated Cardiomyopathy. Correlation With Disease Severity and Cardiac Autoantibodies. Circulation. 1995; 91:631-634.
67. Memoli B, De NL, Libetta C, Scialò A, Pacchiano G, Romano P *et al.* Interleukin-2-induced renal dysfunction in cancer patients is reversed by low-dose dopamine infusion. Am J Kidney Dis. 1995; 26(1):27-33.
68. Weisensee D, Bereiter-Hahn J, Schoeppe W, Löw-Friedrich I. Effects of cytokines on the contractility of cultured cardiac myocytes. Int J Immunopharmacol. 1993; 15(5):581-7.
69. Schulz R, Panas DL, Catena R, Moncada S, Olley PM, Lopaschuk GD. The role of nitric oxide in cardiac depression induced by interleukin-1 beta and tumour necrosis factor-alpha. Br J Pharmacol. 1995; 114(1):27-34.
70. Abbud-Filho M, Kupiec-Weglinski JW, Araujo JL, Heidecke CD, Tilney NL, Strom TB. Cyclosporine therapy of rat heart allograft recipients and release of interleukins (IL 1, IL 2, IL 3): a role for IL 3 in graft tolerance? J Immunol. 1984; 133(5):2582-6.
71. Y Naito, T Tsujino, Y Fujioka, M Ohyanagi, H Okamura, Iwasaki T. Increased circulating interleukin-18 in patients with congestive heart failure. Heart. 2002; 88(3):296-297.
72. Long CS. The role of interleukin-1 in the failing heart. Heart Fail Rev. 200; 6(2):81-94.
73. Fix C, Bingham K, Carver W. Effects of interleukin-18 on cardiac fibroblast function and gene expression. Cytokine. 2011; 53(1):19-28.
74. Wang M, Markel TA, Meldrum DR. Interleukin 18 in the heart. Shock. 2008; 30(1):3-10.
75. Holladay CA, Duffy AM, Chen X, Sefton MV, O' Brien TD, Pandit AS. Recovery of cardiac function mediated by MSC and interleukin-10 plasmid functionalised scaffold. Biomaterials. 2012; 33(5):1303-14.
76. Stumpf C, Seybold K, Petzi S, Wasmeier G, Raaz D, Yilmaz A *at al.* Interleukin-10 improves left ventricular function in rats with heart failure subsequent to myocardial infarction. Eur J Heart Fail. 2008; 10(8):733-9. doi: 10.1016/j.ejheart.2008.06.007. Epub 2008 Jul 2.
77. Magalhães LM, Villani FN, Nunes Mdo C, Gollob KJ, Rocha MO, Dutra WO. High interleukin 17 expression is correlated with better cardiac function in human Chagas disease. J Infect Dis. 2013; 207(4):661-5.
78. Maass DL, White J, Horton JW. IL-1beta and IL-6 act

synergistically with TNF-alpha to alter cardiac contractile function after burn trauma. Shock. 2002; 18(4):360-6.
79. Shah RV, Chen-Tournoux AA, Picard MH, van Kimmenade RR, Januzzi JL. Serum levels of the interleukin-1 receptor family member ST2, cardiac structure and function, and long-term mortality in patients with acute dyspnea. Circ Heart Fail. 2009; 2(4):311-9.
80. Roselló-Lletí E, Rivera M, Bertomeu V, Cortés R, Jordán A, González-Molina A. Interleukin-4 and Cardiac Fibrosis in Patients With Heart Failure. Rev Esp Cardiol. 2007; 60:777-80. -(60)07.
81. Rivera M, Roselló-Lletí E, García de Burgos F, Bertomeu V, Payá R, Cortés R, *et al.* Valores de 8-hidroxi-2'-desoxiguanosina y de peroxidación lipídica en pacientes con insuficiencia cardiaca. Rev Esp Cardiol. 2006; 59: 1140-5.
82. Sato Y, Takatsu Y, Kataoka K, Yamada T, Taniguchi R, Sasayama S, Matsumori A. Serial circulating concentrations of C-reactive protein, interleukin (IL)-4, and IL-6 in patients with acute left heart decompensation. Clin Cardiol. 1999; 22(12):811-3.
83. Fairweather D, Frisancho-Kiss S, Yusung S, Barrett M, Davis S, Gatewood S, *et al.* Interferon γ protects against chronic viral myocarditis by reducing mast cell degranulation, fibrosis, and the profibrotic cytokines transforming growth factor-ß1, inteleukin-1ß, and interleukin-4 in the heart. AJP. 2004; 165:1883-94.
84. Seki T, Kumagai T, Kwansa-Bentum B, Furushima-Shimogawara R, Anyan WK, Miyazawa Y *et al.* Interleukin-4 (IL-4) and IL-13 suppress excessive neutrophil infiltration and hepatocyte damage during acute murine schistosomiasis japonica. Infect Immun. 2012; 80(1):159-68.
85. Wang L, Quan J, Johnston WE, Maass DL, Horton JW, Thomas JA *et al.* Age-dependent differences of interleukin-6 activity in cardiac function after burn complicated by sepsis. Burns. 2010; 36(2):232-8.
86. Wu CK, Lee JK, Chiang FT, Yang CH, Huang SW, Hwang JJ *et al.* Plasma levels of tumor necrosis factor-α and interleukin-6 are associated with diastolic heart failure through downregulation of sarcoplasmic reticulum Ca2+ ATPase. Crit Care Med. 2011; 39(5):984-92.
87. Puhakka M, Magga J, Hietakorpi S, Penttilä I, Uusimaa P, Risteli J *et al.* Interleukin-6 and tumor necrosis factor alpha in relation to myocardial infarct size and collagen formation. J Card Fail. 2003; 9(4):325-32.
88. Zhang H, Wang HY, Bassel-Duby R, Maass DL, Johnston WE, Horton JW *et al.* Role of interleukin-6 in cardiac inflammation and dysfunction after burn complicated by sepsis. Am J Physiol Heart Circ Physiol. 2007; 292(5): H2408-16. Am J Physiol Heart Circ Physiol. 2008; 294(3): H1502.
89. Plenz G, Song ZF, Tjan TD, Koenig C, Baba HA, Erren M *et al.* Activation of the cardiac interleukin-6 system in advanced heart failure. Eur J Heart Fail. 2001; 3(4):415-21.
90. Sander M, von Heymann C, von Dossow V, Spaethe C, Konertz WF, Jain U *et al.* Increased interleukin-6 after cardiac surgery predicts infection. Anesth Analg. 2006; 102(6):1623-9.
91. López L, Arai K, Giménez E, Jiménez M, Pascuzo C, Rodríguez-Bonfante C *et al.* C-reactive protein and interleukin-6 serum levels increase as Chagas disease progresses towards cardiac failure. Rev Esp Cardiol. 2006; 59(1):50-6.
92. Oz MC, Liao H, Naka Y, Seldomridge A, Becker DN, Michler RE *et al.* Ischemia-induced interleukin-8 release after human heart transplantation. A potential role for endothelial cells. Circulation. 1992; 92(9):II428-32.
93. Velásquez IM, Frumento P, Johansson K, Berglund A, de Faire U, Leander K *et al.* Association of interleukin 8 with myocardial infarction: results from the Stockholm Heart Epidemiology Program. Int J Cardiol. 2014; 172(1):173-8.
94. Romuk E, Skrzep-Poloczek B, Wojciechowska C, Tomasik A, Birkner E, Wodniecki J *et al.* Selectin-P and interleukin-8 plasma levels in coronary heart disease patients. Eur J Clin Invest. 2002; 32(9):657-61.
95. Zhou RH, Shi Q, Gao HQ, Shen BJ. Changes in serum interleukin-8 and interleukin-12 levels in patients with ischemic heart disease in a Chinese population. J Atheroscler Thromb. 2001; 8(1):30-2.
96. Hummel M, Czerlinski S, Friedel N, Liebenthal C, Hasper D, von Baehr R *et al.* Interleukin-6 and interleukin-8 concentrations as predictors of outcome in ventricular assist device patients before heart transplantation. Crit Care Med. 1994; 22(3):448-54.
97. Poulin LF, Richard M, Le Moine A, Kiss R, McKenzie AN, Goldman M *et al.* Interleukin-9 promotes eosinophilic rejection of mouse heart allografts. Transplantation. 2003; 76(3):572-7.
98. Parissis JT, Farmakis D, Nikolaou M, Birmpa D, Bistola V, Paraskevaidis I *et al.* Plasma B-type natriuretic peptide and anti-inflammatory cytokine interleukin-10 levels predict adverse clinical outcome in chronic heart failure patients with depressive symptoms: a 1-year follow-up study. Eur J Heart Fail. 2009; 11(10):967-72.
99. Amir O, Rogowski O, David M, Lahat N, Wolff R, Lewis BS. Circulating interleukin-10: association with higher mortality in systolic heart failure patients with elevated tumor necrosis factor-alpha. Isr Med Assoc J. 2010; 12(3):158-62.
100. Chin Lai N, Hua Gao M. Tong Tang Pressure Overload-induced Cardiac Remodeling and Dysfunction in the Absence of Interleukin 6 in Mice. Lab invest 2012; 92(11):1518-1526.
101. Nonogaki K, Fuller GM, Fuentes NL, Moser AH, Staprans I, Grunfeld C *et al.* Interleukin-6 stimulates hepatic triglyceride secretion in rats. Endocrinology. 1995; 136(5):2143-9.
102. Zedan MM, el-Shennawy FA, Abou-Bakr HM, al-Basousy AM. Interleukin-2 in relation to T cell subpopulations in rheumatic heart disease. Arch Dis Child. 1992; 67(11):1373-5.
103. Kong X, Feng D, Mathews S, Gao B. Hepatoprotective and anti-fibrotic functions of interleukin-22: therapeutic potential for the treatment of alcoholic liver disease. J Gastroenterol Hepatol. 2013; 28(1):56-60.
104. Huang YS, Chan CY, Wu JC, Pai CH, Chao Y, Lee SD. Serum levels of interleukin-8 in alcoholic liver disease: relationship with disease stage, biochemical parameters and survival. J Hepatol. 1996; 24(4):377-84.
105. Charles A Dinarello1. Interleukin 1 and interleukin 18 as mediators of inflammation and the aging process1·2·3·4. Am J Clin Nutr February 2006 vol. 83 no. 2 447S-455S
106. Boermeester MA, Straatsburg IH, Houdijk PJA, Meyer C, Frederiks WM, Wesdorp RIC *et al.* Endotoxin and interleukin-1 related hepatic inflammatory response

promotes liver failure after partial hepatectomy. Hepatology. 1995: 22(5):1499-1506.
107. Zheng YB, Zhang XH, Huang ZL, Lin CS, Lai J, Gu YR *et al.* Amniotic-Fluid–Derived Mesenchymal Stem Cells Overexpressing Interleukin-1 Receptor Antagonist Improve Fulminant Hepatic Failure. Published: July 23, 2012.
108. Schirrmacher V, Müerköster S, Umansky V. Antagonistic effects of systemic interleukin 2 on immune Tcell-mediated graft-versus-leukemia reactivity. Clin Cancer Res. 1998; 4(11):2635-45.
109. Kitaoka S, Shiota G, Kawasaki H. Serum levels of interleukin-10, interleukin-12 and soluble interleukin-2 receptor in chronic liver disease type C. Hepatogastroenterology. 2003; 50(53):1569-74.
110. Anastassakos C, Alexander GJ, Wolstencroft RA, Dumonde DC, Eddleston AL, Williams R. Failure of exogenous interleukin 1 and interleukin 2 to correct decreased lymphocyte transformation in chronic hepatitis B virus carriers. Clin Exp Immunol. Apr 1987; 68(1):15-22.
111. Fisher B, Keenan AM, Garra BS, Steinberg SM, White DE, DiBisceglie AM *et al.* Interleukin-2 induces profound reversible cholestasis: a detailed analysis in treated cancer patients. J Clin Oncol. 1989; 7(12):1852-62.
112. Kasprzak A, Seidel J, Adamek A, Biczysko W, Wysocki J, Spachacz R, Juszczyk J *et al.* Interleukin-2 (IL-2) expression in livers of patients with chronic hepatitis C virus (HCV) infection. Folia Histochem Cytobiol. 2006; 44(2):103-10.
113. Alric L, Thebault S, Peron JM, Balard P, Metivier S, Pipy B *et al.* Pilot study of interferon-alpha-ribavirin-interleukin-2 for treatment of nonresponder patients with severe liver disease infected by hepatitis C virus genotype 1. J Viral Hepat. 2006; 13(2):139-44.
114. Inderbitzin D, Avital I, Keogh A, Beldi G, Quarta M, Gloor B *et al.* Interleukin-3 induces hepatocyte-specific metabolic activity in bone marrow-derived liver stem cells. J Gastrointest Surg. 2005; 9(1):69-74.
115. Ohno M, Komakine J, Suzuki E, Nishizuka M, Osada S, Imagawa M. Interleukin enhancer-binding factor 3 functions as a liver receptor homologue-1 co-activator in synergy with the nuclear receptor co-activators PRMT1 and PGC-1α. Biochem J. 2011; 437(3):531-40.
116. Bird G. Interleukin-8 in alcoholic liver disease. Acta Gastroenterol Belg. 1994; 57(3-4):255-9.
117. Cressman DE, Greenbaum LE, DeAngelis RA, Ciliberto G, Furth EE, Poli V *et al.* Liver failure and defective hepatocyte regeneration in interleukin-6-deficient mice. Science. 1996; 274(5291):1379-83.
118. Peck-Radosavljevic M, Zacherl J, Wichlas M, Sims P, Meng YG, Panzer S *at al.* Thrombopoietic cytokines and reversal of thrombocytopenia after liver transplantation. Eur J Gastroenterol Hepatol. 1999; 11(2):151-6.
119. Hong F, Radaeva S, Pan HN, Tian Z, Veech R, Gao B. Interleukin 6 alleviates hepatic steatosis and ischemia/reperfusion injury in mice with fatty liver disease. Hepatology. 2004; 40(4):933-41.
120. Ki SH, Park O, Zheng M, Morales-Ibanez O, Kolls JK, Bataller R *et al.* Interleukin-22 treatment ameliorates alcoholic liver injury in a murine model of chronic-binge ethanol feeding: role of signal transducer and activator of transcription 3. Hepatology. 2010; 52(4):1291-300.
121. Sung HK, Oygi P, Zheng M, Morales-Ibanez O, Kolls JK, Bataller R. Interleukin-22 treatment ameliorates alcoholic liver injury in a murine model of chronic-binge ethanol feeding: Role of STAT3Hepatology. 2010; 52(4): 1291-1300.
122. Ghazanfar Ali Nasir, Sadia Mohsin, Mohsin Khan, Sulaiman Shams, Gibran Ali, Shaheen N Khan and Sheikh Riazuddin ·Mesenchymal stem cells and Interleukin-6 attenuate liver fibrosis in mice. Journal of Translational Medicine 2013, 11:78.
123. Lemmers A, Moreno C, Gustot T, Maréchal R, Degré D, Demetter P *et al.* The interleukin-17 pathway is involved in human alcoholic liver disease. Hepatology. 2009; 49(2):646-57.
124. Thompson K, Maltby J, Fallowfield J, McAulay M, Millward-Sadler H, Sheron N. Interleukin-10 expression and function in experimental murine liver inflammation and fibrosis. Hepatology. 1998; 28(6):1597-606.
125. Grove J, Daly AK, Bassendine MF, Gilvarry E, Day CP. Interleukin 10 promoter region polymorphisms and susceptibility to advanced alcoholic liver disease. Gut. 2000; 46(4):540-5.
126. Park O, Wang H, Weng H, Feigenbaum L, Li H, Yin S *et al. In vivo* consequences of liver-specific interleukin-22 expression in mice: Implications for human liver disease progression. Hepatology. 2011; 54(1):252-61.
127. Liang H, Block TM, Wang M, Nefsky B, Long R, Hafner J, Mehta AS, Marrero J *et al.* Interleukin-6 and oncostatin M are elevated in liver disease in conjunction with candidate hepatocellular carcinoma biomarker GP73. Cancer Biomark. 2012; 11(4):161-71.
128. Kronenberger B, Rudloff I, Bachmann M, Brunner F, Kapper L, Filmann N *et al.* Interleukin-22 predicts severity and death in advanced liver cirrhosis: a prospective cohort study. BMC Medicine 2012, 10:102.
129. Roselló-Lletí E, Rivera M, Bertomeu V, Cortés R, Jordán A. Andrés González-Molina. Interleukin-4 and Cardiac Fibrosis in Patients With Heart Failure.Rev Esp Cardiol. 2007; 60:777-80. - Vol. 60 Num.07.
130. dos Santos DC, da Silva Gomes Martinho JM, Pacheco-Moreira LF, Carvalho Viana de Araújo C, Caroli-Bottino A *et al.* Eosinophils involved in fulminant hepatic failure are associated with high interleukin-6 expression and absence of interleukin-5 in liver and peripheral blood. Liver Int. 2009; 29(4):544-51.
131. Swiatkowska-Stodulska R, Bakowska A, Drobińska-Jurowiecka A. Interleukin-8 in the blood serum of patients with alcoholic liver disease. Med Sci Monit. 2006; 12(5):CR215-20.
132. Rachael MR, Robert WT, Feng CG, Hari D, Knight R, Allen WC *et al.* Interleukin-5 (IL-5) Augments the Progression of Liver Fibrosis by Regulating IL-13 Activity. Infect Immun. 2006; 74(3):1471-1479.
133. Kakumu S, Fukatsu A, Shinagawa T, Kurokawa S, Kusakabe A. Localisation of intrahepatic interleukin 6 in patients with acute and chronic liver disease. J Clin Pathol. 1992; 45(5):408-11.
134. Tilg H, Vogel W, Wiedermann CJ, Shapiro L, Herold M, Judmaier G *et al.* Circulating interleukin-1 and tumor necrosis factor antagonists in liver disease. Hepatology. 1993; 18(5):1132-8.
135. Jin X, Zimmers TA, Perez EA, Pierce RH, Zhang Z, Koniaris LG. Paradoxical effects of short- and long-

term interleukin-6 exposure on liver injury and repair. Hepatology. 2006; 43(3):474-84.
136. McGill JM, Yen MS, Cummings OW, Alpini G, LeSage G, Pollok KE *et al.* Interleukin-5 inhibition of biliary cell chloride currents and bile flow. Am J Physiol Gastrointest Liver Physiol. 2001; 280(4):G738-45.
137. Harley IT, Stankiewicz TE, Giles DA, Softic S, Flick LM, Cappelletti M *et al.* IL-17 signaling accelerates the progression of nonalcoholic fatty liver disease in mice. Hepatology. 2014; 59(5):1830-9.
138. Zimmermann HW, Seidler S, Gassler N, Nattermann J, Luedde T, Trautwein C *et al.* Interleukin-8 is activated in patients with chronic liver diseases and associated with hepatic macrophage accumulation in human liver fibrosis. PLoS One. 2011; 6(6):e21381.
139. Nobili V, Marcellini M, Giovannelli L, Girolami E, Muratori F, Giannone G *et al.* Association of serum interleukin-8 levels with the degree of fibrosis in infants with chronic liver disease. J Pediatr Gastroenterol Nutr. 2004; 39(5):540-4.
140. James LP, Farrar HC, Darville TL, Sullivan JE, Givens TG, Kearns GL *et al.* Elevation of serum interleukin 8 levels in acetaminophen overdose in children and adolescents. Clin Pharmacol Ther. 2001; 70(3):280-6.
141. Yamada T, Hisanaga M, Nakajima Y, Kanehiro H, Aomatsu Y, Ko S *et al.* The serum interleukin 8 level reflects hepatic mitochondrial redox state in hyperthermochemohypoxic isolated liver perfusion with use of a venovenous bypass. Surgery. 1999; 125(3):304-14.
142. Li CP, Lee FY, Tsai YT, Lin HC, Lu RH, Hou MC *et al.* Plasma interleukin-8 levels in patients with post-hepatitic cirrhosis: relationship to severity of liver disease, portal hypertension and hyperdynamic circulation. J Gastroenterol Hepatol. 1999; 11(7):635-40.
143. Homann C, Benfield TL, Graudal NA, Garred P. Neopterin and interleukin-8--prognosis in alcohol-induced cirrhosis. Liver. 2000; 20(6):442-9.
144. Hill DB, Marsano LS, McClain CJ. Increased plasma interleukin-8 concentrations in alcoholic hepatitis. Hepatology. 1993; 18(3):576-80.
145. Swiatkowska-Stodulska R, Bakowska A. Serum interleukin-6 concentrations in patients with alcoholic liver disease. Pol Merkur Lekarski. 2004; 17(99):255-9.
146. Tung KH, Huang YS, Yang KC, Perng CL, Lin HC, Lee SD. Serum interleukin-12 levels in alcoholic liver disease. J Chin Med Assoc. 2010; 73(2):67-71.
147. Tangkijvanich P, Thong-ngam D, Theamboonlers A, Hanvivatvong O, Kullavanijaya P, Poovorawan Y. Diagnostic role of serum interleukin 6 and CA 19-9 in patients with cholangiocarcinoma. Hepatogastroenterology. 2004; 51(55):15-9.
148. Sun Z, Klein AS, Radaeva S, Hong F, El-Assal O, Pan HN *et al. In vitro* interleukin-6 treatment prevents mortality associated with fatty liver transplants.
149. Ge S, Hertel B, Koltsova EK, Sörensen-Zender I, Kielstein JT, Ley K *et al.* Increased atherosclerotic lesion formation and vascular leukocyte accumulation in renal impairment are mediated by interleukin-17A. Circ Res. 2013; 113(8):965-74.
150. Bozza M, Bliss JL, Maylor R, Erickson J, Donnelly L, Bouchard P *et al.* Interleukin-11 reduces T-cell-dependent experimental liver injury in mice. Hepatology. 1999; 30(6):1441-7.
151. Nishina T, Komazawa-Sakon S, Yanaka S, Piao X, Zheng DM, Piao JH, *et al.* Interleukin-11 links oxidative stress and compensatory proliferation. Sci Signal. 2012 Jan 17; 5(207):ra5.
152. Lawitz EJ, Hepburn MJ, Casey TJ. A pilot study of interleukin-11 in subjects with chronic hepatitis C and advanced liver disease nonresponsive to antiviral therapy. Am J Gastroenterol. 2004; 99(12):2359-64.
153. Yee SB, Bourdi M, Masson MJ, Pohl LR. Hepatoprotective role of endogenous interleukin-13 in a murine model of acetaminophen-induced liver disease. Chem Res Toxicol. 2007; 20(5):734-44.
154. Ke B, Shen XD, Gao F, Busuttil RW, Kupiec-Weglinski JW. Interleukin 13 gene transfer in liver ischemia and reperfusion injury: role of Stat6 and TLR4 pathways in cytoprotection. Hum Gene Ther. 2004; 15(7):691-8.
155. Mentink-Kane MM, Wynn TA. Opposing roles for IL-13 and IL-13 receptor alpha 2 in health and disease. Immunol Rev. 2004; 202:191-202.
156. Kakumu S, Okumura A, Ishikawa T, Yano M, Enomoto A, Nishimura H *et al.* Serum levels of IL-10, IL-15 and soluble tumour necrosis factor-alpha (TNF-alpha) receptors in type C chronic liver disease. Clin Exp Immunol. 1997; 109(3):458-63.
157. González-Reimers E, Fernández-Rodríguez CM, Santolaria-Fernández F, de la Vega-Prieto MJ, Martín-González C, Gómez-Rodríguez MÁ, Alemán-Valls MR. Rodríguez-Gaspar MInterleukin-15 and other myokines in chronic alcoholics. Alcohol Alcohol. 2011; 46(5):529-33.
158. Stienstra R, Saudale F, Duval C, Keshtkar S, Groener JE, van Rooijen N *et al.* Kupffer cells promote hepatic steatosis via interleukin-1beta-dependent suppression of peroxisome proliferator-activated receptor alpha activity. Hepatology. 2010; 51(2):511-22.