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Inflammatory Biomarkers in Tissue Remodeling and Fibrosis Progression

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Abstract. Background; Inflammatory biomarkers play a crucial role in tissue remodeling and fibrosis progression by mediating the inflammatory response and influencing extracellular matrix deposition. Aims of the study; Investigate the role of inflammatory biomarkers in tissue remodeling and the progression of fibrosis. Methodology; A case-control study of 90 patients, conducted from November 1, 2024, to February 1, 2025, aimed to examine the role of inflammatory biomarkers in tissue remodeling and fibrosis progression. The study included 60 patients diagnosed with fibrosis and 30 healthy controls. Blood samples were collected, processed, and analyzed for biomarkers (CRP, IL-6, IFN-γ, MCP-1, adiponectin) using ELISA. Fibrosis severity was assessed using FibroScan elastography and histopathology with Masson's trichrome stain to evaluate collagen deposition. These methods helped correlate systemic inflammatory biomarker levels with fibrosis progression. Result; The study showed no significant age difference between patients with tissue fibrosis (48.6 ± 10.4 years) and controls (47.2 ± 9.8 years, $p = 0.52$). However, patients had significantly higher BMI (27.8 ± 3.5 kg/m², $p = 0.01$) and a higher smoking rate (38%, $p = 0.03$). Inflammatory markers, including CRP, IL-6, IFN-γ, and MCP-1, were significantly elevated in patients. Adiponectin levels were lower (7.8 ± 1.9 µg/mL, $p < 0.001$). Strong correlations were found between inflammatory markers and fibrosis severity, with MCP-1 showing the strongest association. Conclusions; The study concluded that elevated inflammatory markers (CRP, IL-6, IFN-γ, MCP-1) and decreased adiponectin levels are strongly associated with tissue fibrosis progression. The inflammatory response, characterized by these biomarkers, promotes fibrosis through immune activation and tissue remodeling. Adiponectin's protective role against inflammation and fibrosis underscores its potential as a therapeutic target.

Highlights:

1. Biomarker Impact: Elevated CRP, IL-6, IFN-γ, and MCP-1 levels correlate with fibrosis severity.
2. Protective Role: Lower adiponectin levels suggest its antifibrotic potential.
3. Clinical Relevance: MCP-1 shows the strongest association, making it a key fibrosis indicator.

Keywords: Inflammatory Biomarkers, Tissue Remodeling, Fibrosis Progression, CRP, Adiponectin, MCP-1

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Introduction

Tissue restructuring and scarring are intricate organic mechanisms that are vital in multiple long-term inflammatory illnesses, such as even more liver cirrhosis, lung fibrosis and also heart problems. Fibrosis is defined by an abnormal accumulation of extracellular matrix (ECM) proteins, particularly collagens, which disrupts normal tissue structure and function. Inflammatory pathways, immune cell activation, and the release of numerous cytokines and chemokines tightly regulate the progression of fibrosis. Several inflammatory biomarkers (CRP, IL-6, IFN-γ, MCP-1, and adiponectin) have been previously investigated in the context of inflammation, tissue remodeling, and fibrosis progression [1] [2]. Fibrosis is primarily driven by chronic inflammation. In the process of repairing tissue injury, immune cells at the damage site, including macrophages, neutrophils, and lymphocytes, are recruited to the area and secreting inflammatory mediators that activate fibroblast activation and ECM deposition. Chronic inflammation causes an upregulation of profibrogenic factors, ultimately leading to irreversible fibrosis and organ failure. Given this context, inflammatory biomarkers are important indicators of disease severity and progression [3] [4]. C-Reactive Protein (CRP) CRP is an acute-phase protein that is produced by the liver in response to a state of systemic inflammation. It is a candidate biomarker to assess inflammation and is associated with the severity of diseases characterized by fibrosis, such as liver fibrosis and cardiovascular disease. Increased CRP may lead to persistent inflammation, and fibroblast activation and collagen deposition. Previous studies have demonstrated that CRP levels found in patients with advanced degrees of fibrosis were significantly higher than those of healthy individuals, indicating its potential utility as a predictive biomarker of fibrosis progression [5] [6]. IL-6 is a pro-inflammatory cytokine with a critical role in immune regulation, inflammation and fibrosis. It is released by various lesional cell types including macrophages, fibroblasts, and endothelial cells following tissue injury. IL-6 encourages fibroblast proliferation and differentiation into myofibroblasts, predominant effector cells in fibrosis. Moreover, increased expression of IL-6 is associated with the severity of liver fibrosis, pulmonary fibrosis, and cardiac fibrosis, which highlights its importance as a biomarker for disease progression [7] [8]. IFN-γ is a cytokine made in large part from activated T cells and natural killer (NK) cells. Its effects are context-dependent, exuding

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both pro- and anti-fibrotic effects dependent on the given disease state. Inhibiting IFN-γ is an important means of regulating immune response and maintaining fibroblast activity. Certain studies have proposed that IFN-γ may help to obstruct excessive fibrosis through the inhibition of fibroblast proliferation22, whereas others have suggested that persistent expression of IFN-γ in a state of chronic inflammation leads to tissue damage and accrual of fibrotic tissue18. The duality of the effect of IFN-γ illustrates the complexity of the regulation of inflammation in fibrosis [9] [10]. CP-1 is a major chemokine that mediates monocyte recruitment and activation in inflammatory tissue. It is closely associated with the pathogenic mechanism of fibrotic organ injury, especially the liver, kidney and lung. MCP-1 drives fibroblast activation and ECM deposition, thus facilitating fibrotic tissue remodeling. It has been shown that higher circulating MCP-1 levels appear to be associated with increased severity of fibrosis and could be a potential biomarker for disease progression [11] [12]. Adiponectin is an anti-inflammatory adipokine released from adipose tissue. Adiponectin is an inflammatory biomarker that has protective effects against fibrosis, which is not the case for the other inflammatory BMI's. The secretion of TGF-β could inhibit the proliferation of fibroblasts, downregulate ECM deposition, and modulate inflammatory responses. In metabolic and cardiovascular disease, low adiponectin levels correlate with increased fibrosis severity. This suggests that adiponectin may be used as a biomarker in evaluating fibrosis risk and progression [13]. Activity of inflammatory macrophages is highlighted as a potential contributor to this fibrosis; cues that guide such remodeling, and translational approaches that assign a critical role to these macrophage-based signals in the progressive intertissivity of certain organ fibrosis, are also considered. Biomarkers Including CRP, IL-6, IFN-γ, MCP-1, and adiponectin are helpful to enhance the understanding of underlying mechanisms of fibrosis and have the potential to enable early diagnosis of disease, possibility of predicting the prognosis, and monitoring of treatment efficacy [14] [15]. This study aims at analyzing the correlation between these biomarkers and severity of fibrosis to enrich understanding of inflammation-driven fibrosis and to identify potential targets for therapeutic intervention.

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Methodology

A case-control study of 90 clinic patients followed from November 1, 2024, to February 1, 2025 to examine the role of inflammatory biomarkers in tissue remodeling and fibrosis progression. Included a total of 90 patients, 60 patients with a diagnosis of fibrosis and 30 healthy controls. Participants in this study were AL-Habbobi Teaching Hospital and written informed consent was obtained from all participants before sample collection. Venous blood was taken from each participant and placed in sterile vacutainer (5 mL) tubes with a minimum of hemolysis. Blood samples were centrifuged immediately for 10 minutes at 4°C, 3000 rpm, and separated serum was stored at -80°C until further analysis. Inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), interferon-gamma (IFN-γ), monocyte chemoattractant protein-1 (MCP-1), and adiponectin were measured using enzyme-linked immunosorbent assay (ELISA) kits according to the instructions from suppliers. Fibrosis severity was assessed by FibroScan elastography (measurement of hepatic tissue stiffness, results are expressed in kPa) and histopathologic examination of biopsy samples stained using Masson's trichrome stain to assess collagen deposition and structural changes. These complementary clinical and diagnostic methods allowed a thorough FSC assessment, which could be correlated with the systemic inflammatory biomarker levels.

1. Statistical Analysis

Statistical analysis was used to evaluate quantitative data, providing methods for data description and inference for both continuous and categorical variables. Data were presented as frequencies and percentages. SPSS (version 26) was employed, with dependent and independent t-tests (two-tailed) for normally distributed variables. For non-normally distributed variables, the Mann-Whitney U test, Wilcoxon test, and Chi-square test were applied. A p-value < 0.05 was considered statistically significant.

2. Ethical Approval

The study received approval from the human ethics committee of Al-Imamain Alkadhimain Medical City. All participants were informed about the study and asked

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to sign a consent form. Additionally, participants were assured that their personal information would remain confidential.

Results

A. Sociodemographic Characteristics of Study Participants

Table 1 shows that the mean age of patients with tissue fibrosis and remodeling was 48.6 ± 10.4 years, which is close to the mean age of the control group 47.2 ± 9.8 years, without statistically significant differences ($p = 0.52$). However, the body mass index (BMI) of the patients was significantly higher (27.8 ± 3.5 kg/m²) compared to the control group (24.9 ± 2.9 kg/m²) with clear statistical significance ($p = 0.01$). It was also noted that the percentage of smokers among the patients was 38%, which is higher than the control group, which was 22%, indicating an association between smoking and the occurrence of fibrosis, and this result was statistically significant ($p = 0.03$).

Table 1. Comparison of Age, BMI, and Smoking Status Between Patients and Control Groups

Parameter	Patients (n = 60)	Control (n = 30)	p-value
Gender	**Male** (n=30) / **Female** (n=30)	**Male** (n=15) / **Female** (n=15)	-
Age (years)	48.6 ± 10.4	47.2 ± 9.8	0.52
BMI (kg/m²)	27.8 ± 3.5	24.9 ± 2.9	0.01*
Smoking (%)	38%	22%	0.03*

Statistical significance: *p < 0.05

B. Inflammatory Biomarkers in Patients and Control Groups

Table 2 shows a significant increase in the levels of inflammatory markers in patients with tissue fibrosis compared to the control group. The average CRP level in the patient group was 12.8 ± 3.4 mg/L compared to 2.1 ± 0.9 mg/L in the control group, with a statistically significant difference ($p < 0.001$). The IL-6 level in patients also increased to 18.4 ± 4.1 pg/mL compared to 4.2 ± 1.3 pg/mL in the control group, indicating the role of inflammatory cytokines in the progression of fibrosis ($p < 0.001$). In addition, IFN-γ levels recorded a significant increase in the patient group (24.6 ± 5.2 pg/mL) compared to the control group (10.3 ± 3.1 pg/mL), with

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a high statistical significance ($p < 0.001$), confirming the role of the immune response in the inflammatory process associated with tissue remodeling.

Table 2. Comparison of CRP, IL-6, and IFN-γ Levels Between Study Groups

Biomarker	Patients (n = 60)	Control (n = 30)	p-value
CRP (mg/L)	12.8 ± 3.4	2.1 ± 0.9	<0.001*
IL-6 (pg/mL)	18.4 ± 4.1	4.2 ± 1.3	<0.001*
IFN-γ (pg/mL)	24.6 ± 5.2	10.3 ± 3.1	<0.001*

Statistical significance: *p < 0.05

C. Adipocytokines and Chemokine Levels in Patients and Control Groups

Table 3 shows a significant decrease in adiponectin levels in patients with tissue fibrosis (7.8 ± 1.9 µg/mL) compared to the control group (12.4 ± 2.5 µg/mL), and this decrease was highly statistically significant ($p < 0.001$). This decrease in adiponectin levels reflects its potential role in inhibiting inflammatory processes and tissue remodeling. On the other hand, a significant increase in MCP-1 levels was observed in patients (195.6 ± 34.7 pg/mL) compared to the control group (108.2 ± 18.9 pg/mL), with a clear statistical significance ($p < 0.001$). This increase suggests a role for MCP-1 in stimulating the immune cell response and promoting fibrosis via inflammatory mechanisms, supporting the association of these indicators with disease progression.

Table 3. Comparison of Adiponectin and MCP-1 Levels Between Study Groups

Biomarker	Patients (n = 60)	Control (n = 30)	p-value
Adiponectin (µg/mL)	7.8 ± 1.9	12.4 ± 2.5	<0.001*
MCP-1 (pg/mL)	195.6 ± 34.7	108.2 ± 18.9	<0.001*

Statistical significance: *p < 0.05

D. Correlation Between Biomarkers and Fibrosis Indicators

Table 4 shows a strong positive correlation between inflammatory markers and the degree of fibrosis, as CRP recorded a strong correlation with the degree of fibrosis ($r = 0.82$, $p < 0.001$) and tissue stiffness ($r = 0.76$, $p < 0.001$), indicating

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the role of inflammation in the aggravation of fibrosis. IL-6 was also closely associated with both the degree of fibrosis ($r = 0.85$, $p < 0.001$) and tissue stiffness ($r = 0.81$, $p < 0.001$), reflecting its role in stimulating inflammatory processes and contributing to fibrosis. In addition, IFN-γ showed a positive correlation with both the degree of fibrosis ($r = 0.79$, $p < 0.001$) and tissue stiffness ($r = 0.72$, $p < 0.001$), strengthening its role in immune interaction. In contrast, adiponectin had a negative correlation with fibrosis score ($r = -0.68$, $p < 0.001$) and tissue stiffness ($r = -0.64$, $p < 0.001$), suggesting its potential protective role against fibrosis. In contrast, MCP-1 was the most strongly correlated with fibrosis score ($r = 0.88$, $p < 0.001$) and tissue stiffness ($r = 0.84$, $p < 0.001$), highlighting its key role in promoting fibrosis by inducing inflammatory response and recruiting immune cells into injured tissues.

Table 4. Association of Inflammatory and Adipocytokine Markers with Fibrosis Score and Tissue Stiffness

Parameter	CRP	IL-6	IFN-γ	Adiponectin	MCP-1
Fibrosis Score	0.82*	0.85*	0.79*	-0.68*	0.88*
Tissue Stiffness (kPa)	0.76*	0.81*	0.72*	-0.64*	0.84*

Correlation values (r), *p < 0.05 indicates statistical significance

Discussion

A comparative analysis of demographic characteristics showed no significant difference in age ($p = 0.52$), therefore the patients and control groups were matched for age and hence, the potential confounding effects could be minimized. However, the BMI in the patient group (27.8 ± 3.5 kg/m²) was significantly higher than in controls (24.9 ± 2.9 kg/m²) ($p = 0.01$), which was possibly associated with fibrosis progression. This is consistent with findings like Kruszewska et al., which described how obesity induces chronic inflammation and fibrotic tissue remodeling [16]. On the contrary, some studies Zinellu al. that found no absolute correlation between BMI and fibrosis severity,

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which may be explained by differences in patient populations and related metabolic factors [17]. Moreover, the proportion of patients smoking (38%) was significantly greater than controls (22%) ($p = 0.03$), confirming results from Bellou et al., indicating that smoking in a significant RF for fibrosing progression because of the contribution that oxidative stress and pro-inflammatory cytokine activation play in the mechanism [18]. In contrast, Bae et al. proposed that the effects of smoking may be more significant in specific subgroups, including those with specific genetic predispositions. Differences in BMI and smoking effects between studies may reflect differences in other lifestyle, genetic and environmental exposures, and further research will be necessary to better understand the contributions of these exposures to fibrosis development [19]. Statistical Elucidation of Inflammation Biomarker differences in Patients and Control Groups: The patients group showed significantly higher CRP, IL-6, and IFN-γ levels compared with controls. CRP levels were 12.8 ± 3.4 mg/L in patients and 2.1 ± 0.9 mg/L in controls ($p < 0.001$), IL-6 levels were 18.4 ± 4.1 pg/mL in patients and 4.2 ± 1.3 pg/mL in controls ($p < 0.001$) and IFN-γ levels were 24.6 ± 5.2 pg/mL in patients, compared with 10.3 ± 3.1 pg/mL in controls ($p < 0.001$). These results correlate with previous results like İnaltekin et al., who found markedly raised CRP, IL-6, and IFN-γ concentrations in people with inflammatory diseases, especially those with fibrotic diseases [20]. Elevated levels of these markers reflect persistent inflammation that drives tissue remodeling to advance fibrosis. These results are in line with the literature, showing that inflammatory factors such as IL-6 and IFN-γ play a role in the development of fibrosis via pro-inflammatory signaling and tissue remodeling associated with fibrosis. But certain studies like by Wu et al., which did not observe similar differences in CRP or IL-6 levels and this may be due to differences in disease stages for the cohorts studied, methods of sampling, or population characteristics [21]. Other factors may explain these differences such as the diversity in how inflammatory makers are modulated by different underlying diseases or treatments, indicating that CRP, IL-6, and IFN-γ should be considered appropriate biomarkers to study inflammation and fibrosis progression in some patient groups, but not for other medicine populations [22] [23]. The patients had significantly different Adiponectin and MCP-1 levels compared to control groups. The levels of adiponectin were significantly lower in patients (7.8 ± 1.9 µg/mL) than those of controls

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(12.4 ± 2.5 µg/mL) with p value <0.001. Likewise, MCP-1 was elevated in patients 195.6 ± 34.7 pg/mL vs controls 108.2 ± 18.9 pg/mL; p < 0.001. These outcomes confirmed the results of multiple studies like those of Singh et al., which found decreased levels of Adiponectin and higher levels of MCP-1 in patients with chronic inflammatory diseases, especially in tandem with fibrotic processes and tissue remodeling. Adiponectin is known as an anti-inflammatory adipokine, and decreased levels may indicate a failure to mount a protective response in fibrotic disease [24]. MCP-1, however, is an inflammatory chemokine that is essential in recruiting monocytes to inflammatory sites and, subsequently driving the progression of fibrosis. These results is consistent with the research that was performed by Puukila et al., data showing that low Adiponectin and high MCP-1 levels are correlated with severity of tissue inflammatory response and fibrosis in a number of tissues [25]. However, contrasting findings were reported by some studies Pulito-Cueto et al., where certain fibrotic conditions did not significantly modify Adiponectin levels. Because this depends on differences in key population demographics, disease stage, or other mediators in the mechanism of fibrosis, we have to understand that biomarkers have to be interpreted in terms of the acute inflammatory pathways in the cohort we are studying [26]. There are strong correlations between all the fibrotic score and tissue stiffness with inflammatory and adipocytokine markers. The correlations of CRP, IL-6, IFN-γ, and MCP-1 with fibrosis score (0.79 to 0.88) and with tissue stiffness (0.72 to 0.84) were statistically significant. Conversely, Adiponectin presented positively correlated with both fibrosis score (-0.68) and tissue stiffness (-0.64), potentially indicating a protective role of this adipokine in tissue remodeling and fibrogenesis. Associations of CRP, IL-6, IFN-γ, and MCP-1 with the progression of fibrosis, albeit positive, are consistent with literature noting the involvement of these markers in areas of inflammatory signaling cascades leading to tissue damage and remodeling pathways seen in many fibrotic diseases. For example, IL-6 and MCP-1 stimulate fibroblast activation and extracellular matrix deposition, driving the fibrotic process [27] [28]. The negative associations found for Adiponectin with both fibrosis score and tissue stiffness are consistent with its known anti-inflammatory and anti-fibrotic actions [29], which indicates lower he Modest Adiponectin levels are correlated with advanced fibrosis stages in individuals diagnosed with NAFLD. These results also

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highlight the potential roles of inflammatory markers and adipocytokines in evaluating the severity of progressive fibrosis and tissue remodeling, as well as potential targets in the management of fibrotic disorders [30].

Conclusions

The study concluded that elevated levels of inflammatory biomarkers (CRP, IL-6, IFN-γ, MCP-1) and decreased adiponectin are significantly associated with the progression of tissue fibrosis. These findings suggest that inflammation plays a central role in fibrosis development by stimulating immune responses and promoting tissue remodeling. The decrease in adiponectin, a protein with anti-inflammatory properties, further supports its potential role in inhibiting fibrosis. These results highlight the importance of inflammatory markers and adiponectin in the pathophysiology of fibrosis and suggest their potential as therapeutic targets for managing fibrosis progression.

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