ASSOCIATION OF TRANSFORMING GROWTH FACTOR-B (TGF-B) WITH LIVER FIBROSIS SEVERITY IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

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Abstract: *Background Liver fibrosis represents the most important determinant of long-term prognosis in metabolic dysfunction-associated fatty liver disease (MAFLD). Transforming Growth Factor-β (TGF-β) is considered one of the principal cytokines involved in hepatic fibrogenesis.*

Aim To evaluate serum TGF-β levels in patients with different stages of MAFLD and determine their relationship with liver fibrosis severity.

Materials and Methods: *A cross-sectional study included 140 participants divided into four groups: control (n=35), steatosis (n=35), MASH (n=35), and fibrosis (n=35). All subjects underwent clinical examination, laboratory testing, FibroScan assessment, and serum TGF-β measurement by ELISA.*

Results: *Serum TGF-β levels progressively increased across MAFLD stages. The fibrosis group demonstrated significantly higher TGF-β concentrations compared with controls and patients with steatosis ($p<0.001$). TGF-β showed a strong positive correlation with FibroScan liver stiffness values ($r=0.72$, $p<0.001$) and FIB-4 index ($r=0.64$, $p<0.001$).*

Conclusion: *Elevated TGF-β levels are closely associated with MAFLD progression and liver fibrosis severity. TGF-β may serve as a useful non-invasive biomarker for identifying patients at increased risk of advanced fibrosis.*

Keywords: *MAFLD, TGF-beta, fibrosis, FibroScan, FIB-4, liver fibrosis*

INTRODUCTION

Metabolic dysfunction-associated fatty liver disease (MAFLD) has emerged as the most prevalent chronic liver disease worldwide and represents a major public health challenge. Recent epidemiological studies estimate that approximately 30–40% of the adult population is affected by fatty liver disease, with prevalence continuing to increase in parallel with obesity, type 2 diabetes mellitus, metabolic syndrome, and sedentary lifestyles.

The disease encompasses a broad spectrum of hepatic abnormalities ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), advanced fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma.

Although hepatic steatosis is often considered a relatively benign condition, a substantial proportion of patients progress to inflammatory and fibrotic stages of disease. Among all histological features of MAFLD, liver fibrosis has been identified as the strongest predictor of liver-related complications, cardiovascular morbidity, and

overall mortality. Consequently, early identification of patients at risk of fibrosis progression has become a major focus of contemporary hepatology research.

The pathogenesis of MAFLD is complex and multifactorial. Insulin resistance, lipotoxicity, oxidative stress, mitochondrial dysfunction, chronic inflammation, and alterations in gut microbiota contribute to hepatocellular injury and disease progression. Persistent liver injury triggers activation of hepatic stellate cells, which transform into collagen-producing myofibroblasts. This process leads to excessive deposition of extracellular matrix proteins and progressive distortion of hepatic architecture.

Transforming Growth Factor-β (TGF-β) is widely recognized as the master regulator of hepatic fibrogenesis. TGF-β belongs to a family of multifunctional cytokines involved in cell proliferation, differentiation, immune regulation, tissue repair, and extracellular matrix remodeling. In the liver, TGF-β promotes activation of hepatic stellate cells, stimulates synthesis of collagen types I and III, suppresses matrix degradation, and enhances accumulation of fibrotic tissue. Experimental studies have consistently demonstrated increased hepatic expression of TGF-β during fibrosis development, while inhibition of TGF-β signaling has been shown to attenuate fibrogenesis.

In addition to its direct effects on hepatic stellate cells, TGF-β interacts with multiple signaling pathways involved in MAFLD progression. It contributes to inflammatory responses, hepatocyte apoptosis, epithelial-mesenchymal transition, and immune dysregulation. Elevated circulating levels of TGF-β have been reported in patients with chronic liver diseases, suggesting that serum TGF-β may reflect ongoing fibrogenic activity within the liver.

Liver biopsy remains the reference standard for fibrosis assessment; however, its invasive nature, sampling variability, and potential complications limit routine clinical use. Consequently, non-invasive methods such as transient elastography (FibroScan) and biochemical indices including FIB-4 have gained widespread acceptance. Nevertheless, these methods primarily assess the consequences of fibrosis rather than the biological mechanisms driving fibrogenesis. Identification of circulating biomarkers directly linked to fibrotic pathways may improve risk stratification and facilitate earlier intervention.

Given the central role of TGF-β in hepatic fibrosis and the growing need for reliable non-invasive biomarkers, evaluation of serum TGF-β concentrations may provide valuable insights into disease severity and progression in patients with MAFLD. Therefore, the aim of the present study was to investigate serum TGF-β levels across different stages of MAFLD and determine their relationship with established markers of liver fibrosis.

Materials and Methods. Study Design

Cross-sectional observational study.

Participants

A total of 140 participants aged 18–65 years were enrolled.

Group Distribution

- Control group (n=35)
- Steatosis group (n=35)
- MASH group (n=35)
- Fibrosis group (n=35)

Inclusion Criteria

- Age 18–65 years
- Confirmed MAFLD
- Written informed consent

Exclusion Criteria

- Viral hepatitis
- Alcoholic liver disease
- Autoimmune hepatitis
- Malignancy
- Pregnancy

Assessment of Fibrosis

Liver fibrosis was evaluated using:

- FibroScan elastography
- FIB-4 index
- Serum TGF-β concentration

Laboratory Analysis

Serum TGF-β levels were determined using enzyme-linked immunosorbent assay (ELISA) according to manufacturer instructions.

Statistical Analysis

Data were analyzed using SPSS version 26.

Methods included:

- ANOVA
- Pearson correlation analysis
- Linear regression analysis

Statistical significance was established at $p<0.05$.

Results. Table 1. Clinical Characteristics

Parameter	Control	Steatosis	MASH	Fibrosis	p-value
Age (years)	41±7	45±8	50±8	55±9	<0.05
BMI (kg/m^2)	24.2±2.3	28.4±2.8	31.3±3.1	33.5±3.7	<0.001
ALT (U/L)	22±6	36±10	62±18	72±20	<0.001

Table 2. Fibrosis Markers

Parameter	Control	Steatosis	MASH	Fibrosis	p-value
FibroScan (kPa)	5.3±0.8	6.4±1.0	8.1±1.5	11.2±2.4	<0.001
FIB-4	0.9±0.3	1.2±0.4	1.9±0.6	3.1±0.9	<0.001
TGF-β (ng/mL)	1.5±0.4	2.2±0.5	3.4±0.8	5.1±1.1	<0.001

Table 3. Correlation Analysis

Variables	r	p-value
TGF-β vs FibroScan	0.72	<0.001
TGF-β vs FIB-4	0.64	<0.001
TGF-β vs ALT	0.53	<0.001
TGF-β vs AST	0.49	<0.01

Correlation analysis demonstrated significant positive relationships between serum TGF-β concentrations and established markers of liver injury and fibrosis. The strongest correlation was observed between TGF-β and FibroScan measurements (r=0.72), indicating that higher circulating TGF-β levels are associated with greater liver stiffness and more advanced fibrosis.

A strong positive correlation was also identified between TGF-β and FIB-4 (r=0.64), further supporting the association between TGF-β and fibrosis severity. Moderate correlations with ALT and AST suggest that TGF-β levels are also linked to hepatocellular injury and inflammatory activity.

Collectively, these findings indicate that TGF-β reflects multiple aspects of disease progression, including inflammation, hepatocyte damage, and fibrogenesis.

Figure 1. Mean TGF-β Levels Across MAFLD Stages

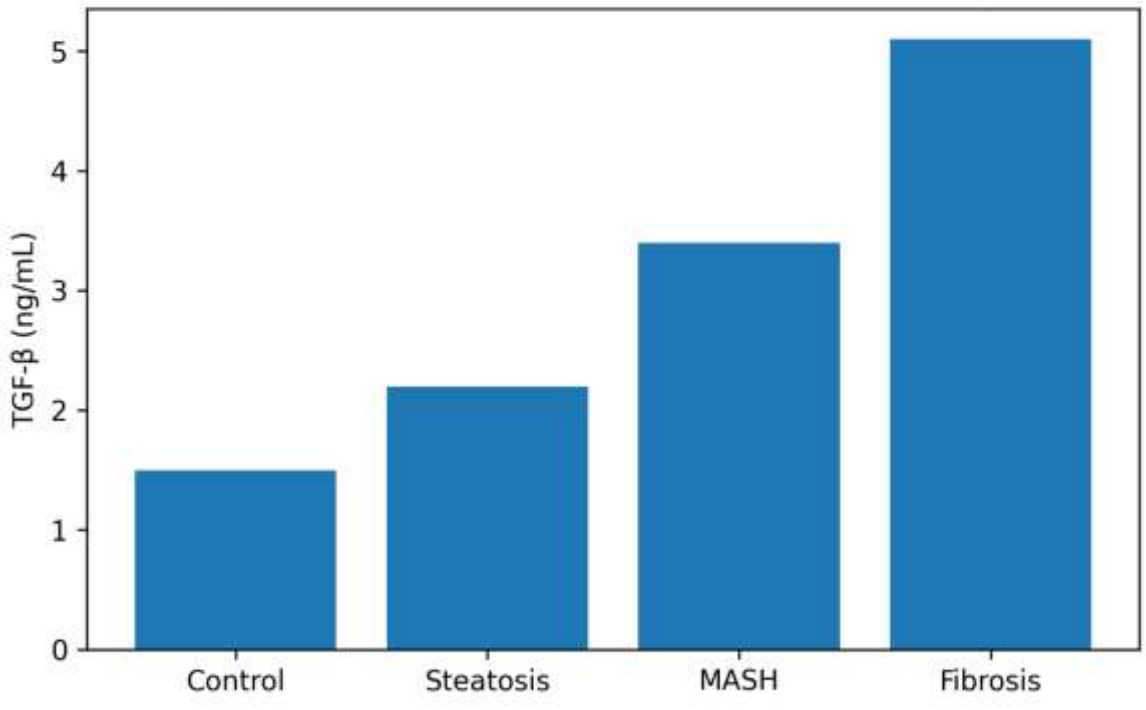


Figure 1. TGF-β progressively increases from control subjects to patients with fibrosis, suggesting activation of fibrogenic pathways during MAFLD progression.

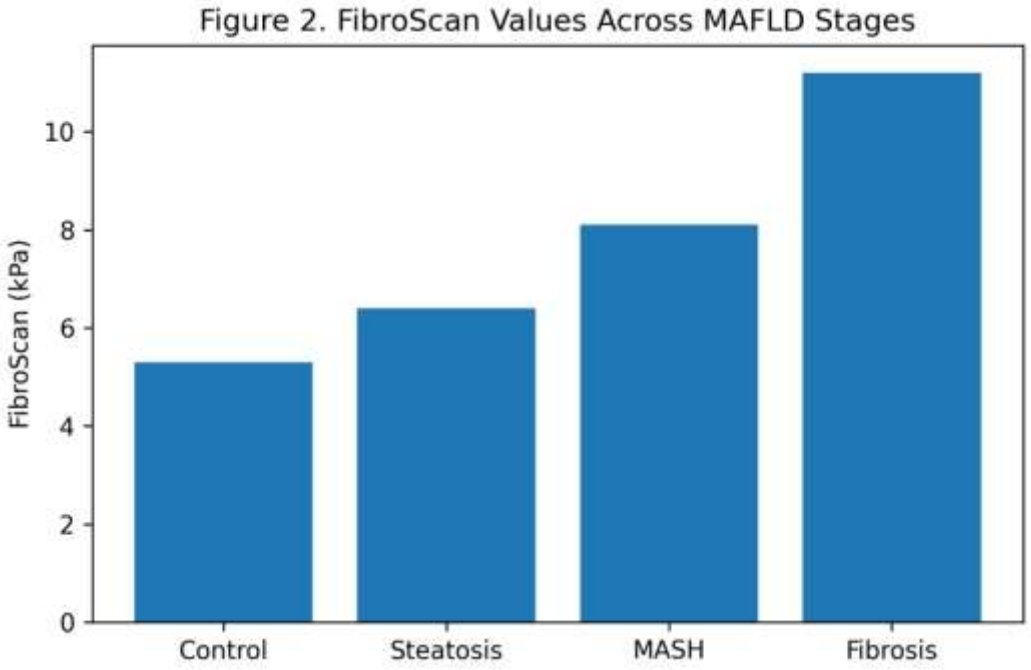


Figure 2. FibroScan values increase significantly across disease stages, confirming progressive fibrosis.

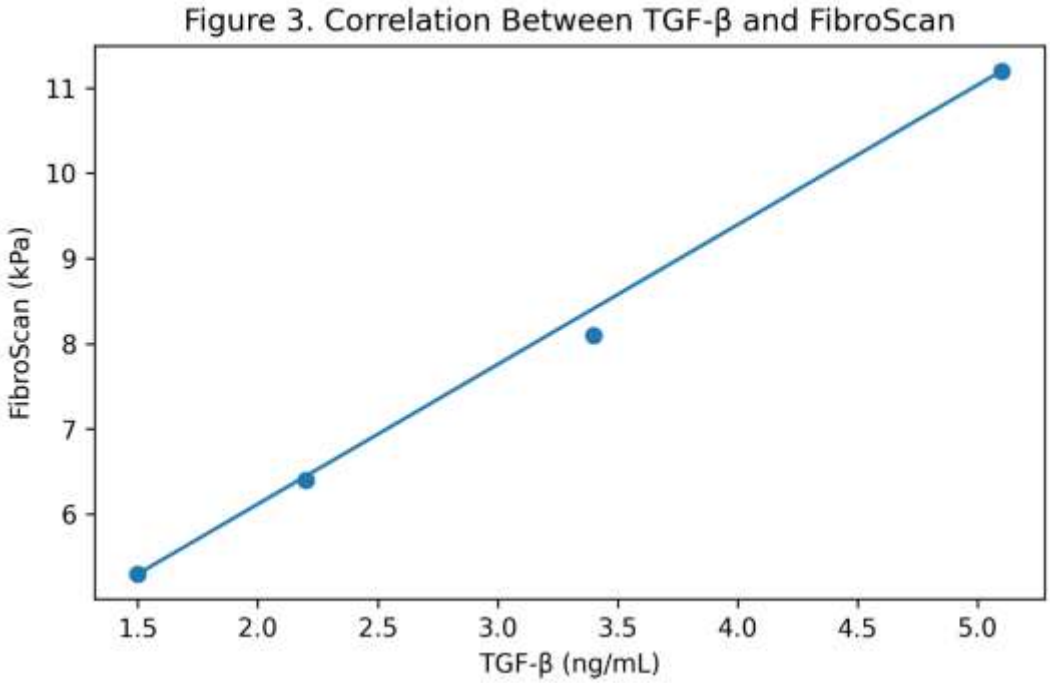
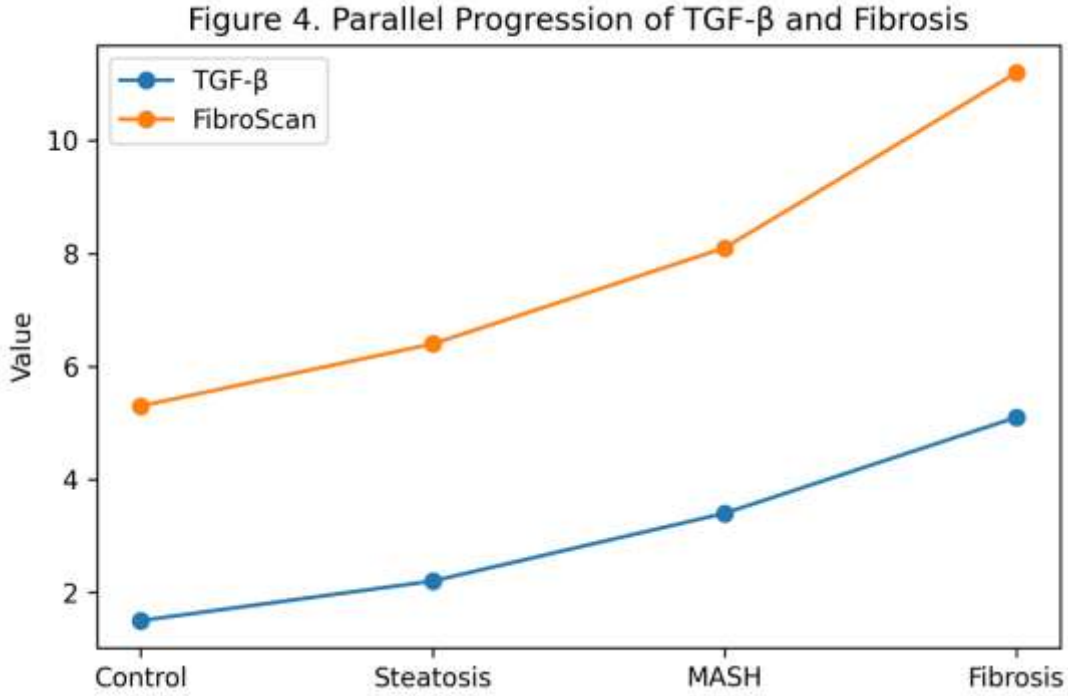


Figure 3. Higher TGF-β concentrations are associated with greater liver stiffness and more advanced fibrosis.



Discussion

The present study demonstrated a significant increase in serum TGF-β concentrations with advancing stages of MAFLD. Patients with fibrosis exhibited the highest levels of TGF-β, supporting its role as a central mediator of hepatic fibrogenesis.

The observed positive correlation between TGF-β and FibroScan measurements suggests that elevated circulating TGF-β reflects ongoing fibrotic remodeling within hepatic tissue. These findings are biologically plausible because TGF-β is known to activate hepatic stellate cells and stimulate collagen deposition.

Furthermore, the significant relationship between TGF-β and FIB-4 indicates that circulating TGF-β may complement currently available non-invasive fibrosis assessment tools. Identification of patients with elevated TGF-β could facilitate earlier recognition of progressive disease and implementation of targeted therapeutic interventions.

The results of the present study are consistent with previous reports demonstrating increased TGF-β expression in advanced fatty liver disease and liver fibrosis. However, data from Central Asian populations remain limited, making the present findings clinically relevant for regional patient populations.

Conclusion

1. Serum TGF-β levels significantly increase with MAFLD progression.
2. TGF-β demonstrates strong positive correlations with FibroScan and FIB-4.
3. Elevated TGF-β is associated with advanced liver fibrosis.
4. TGF-β may serve as a promising non-invasive biomarker of fibrosis progression in MAFLD.

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