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The importance of biglycan, decorin and TGF-1 levels in the diagnosis of non-small cell lung cancer

Fatih Karataş[a,*], Murat Acat[b], Hatice Gulsah Karatas[c], Fatih İnci[a] and Özlem Sengören Dikiş[d]
[a]*Department of Medical Oncology, Faculty of Medicine, Karabuk University, Karabuk, Turkey*
[b]*Cagsu Hospital, Department of Pulmonary Disease, Düzce, Turkey*
[c]*Department of Physical Treatment and Rehabilitation, Faculty of Medicine, Karabuk University, Karabuk, Turkey*
[d]*Department of Pulmonary Disease, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey*

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Abstract.
BACKGROUND: Despite Non-small cell lung cancer (NSCLC) ranks among the most deadly cancers worldwide, and currently, apart from a low percentage, targetable molecules have not been identified in its etiopathogenesis. The relationship between the proteoglycans decorin and biglycan, which are present in the extracellular matrix of cells, and transforming growth factor Beta-1 (TGF-B1), has been shown in many cancers. We investigated the significance of these molecules in NSCLC.
METHODS: Fasting serum levels of decorin, biglycan, and TGF-B1 were obtained from 48 newly diagnosed NSCLC patients and compared with those of 48 adult control subjects matched for age and demographics. Demographic data, baseline laboratory values, and ELISA results were compared between the groups.
RESULTS: The median age was 65(39–83) similar in both groups. There was no relation between demographic and clinical parameters and the levels of decorin, biglycan, and TGF-B1 in the NSCLC group. However, in comparison to the control group, NSCLC patients had significantly higher levels of biglycan (42.55 $\pm$ 27.40 vs. 24.38 $\pm$ 12.05 ng/mL, $p = 0.026$) and TGF-B1 (15.55 $\pm$ 9.16 vs. 10.07 $\pm$ 7.8 pg/mL, $p = 0.001$), while decorin levels were significantly lower (6.64 $\pm$ 1.92 vs. 10.28 $\pm$ 3.13 ng/mL, $p = 0.002$). In the multivariate regression analysis; Decorin $<$ 8.13 ng/mL (OR, 10.96; 95% CI: 3.440–34.958), current smoking (OR, 3.81; 95% CI: 1.320–10.998), COPD (OR, 43.6; 95% CI: 2.082–913.081), and lower BMI (OR, 1.22; 95% CI: 1.070–1.405, $p = 0.003$) were identified as independent predictive markers for NSCLC diagnosis.
CONCLUSION: The decreased serum decorin level is an independent marker for NSCLC. Further studies are needed to investigate the prognostic significance of decorin on survival and its potential as a target in treatment.

Keywords: Non small cell, lung cancer, decorin, biglycan, TGF-B1

1. Introduction

In the normal cellular physiology, it is well-known that transforming growth factor beta-1 (TGF-B1), one of the key molecules involved in the inflammatory pathway, plays a role in the development or clinical progression of inflammation and is overexpressed in serum and genetically in cancer. During the proliferative process, receptor tyrosine kinases in the receptors that initiate cell proliferation promote signal transduction to the nucleus, and these signals, in turn, induce proliferation in the cell nucleus by triggering other downstream signaling pathways. TGF-B1 is a molecule that stimulates the expression of proto-oncogenes and is secreted in excessive amounts in cancer patients. Increased expression

*Corresponding author: Fatih Karataş, Department of Medical Oncology, Faculty of Medicine, Karabuk University, Alparslan Street, No.1, Karabuk 78100, Turkey. Tel.: +90 370 415 17 18; Mobile: +90 5057505270; E-mail: drfatihkaratas@gmail.com.

and levels of biglycan are one of the stimulatory factors involved in the excessive activation and secretion of TGF-B1. Elevated levels of biglycan serve as receptors for tyrosine kinases within the cell, which transmit signals promoting cell proliferation. Decorin is one of the molecules that functions as a suppressor, helping to regulate these receptor tyrosine kinases, and low levels or expression of decorin may lead to reduced tumor suppression activity. The receptor tyrosine kinases to which decorin binds cannot transmit oncogenic signals to the cell nucleus. Thus decorin is known as a potent tumor suppressor molecule [1,2]. Proteoglycans are among the most important molecules in the formation and maintenance of cell integrity. Both decorin and biglycan bind to collagen [3] and TGF-B1 in the cell matrix, with decorin also binding to proto-oncogenic and oncogenic receptor tyrosine kinases [4]. Therefore, absence or deficiency of decorin may reduce the inhibition of oncogenic receptor tyrosine kinases, potentially facilitating development or progression of cancer. Biglycan, on the other hand, is a proteoglycan structurally similar to decorin and is located in the extracellular matrix, binding to receptors that affect cellular inflammation, with pro-inflammatory effects [5,6]. Increased inflammation within tumors and their microenvironments has been associated with elevated serum levels of biglycan or increased expression of the biglycan gene in various cancers including pancreatic, gastric, and breast cancers [7–10]. Although it is known that TGF-B1 is overexpressed in the serum of patients with non-small cell lung cancer (NSCLC) compared to healthy adults, the role of decorin and biglycan that interact with TGF-B1, has only been minimally studied in NSCLC, primarily in cell lines and tumor tissues [11,12]. Therefore, we planned this study with the hypothesis that TGF-B1 and bigylcan may be higher in NSCLC patients than in the control group in serum samples at the time of diagnosis, while decorin may be lower and this may be an independent predictor for the diagnosis of NSCLC.

2. Materials and methods

This study with a prospective case-control design was conducted between February 2018 and December 2020 at our Departments of Chest Diseases and Medical Oncology. The study included 48 newly diagnosed patients with non-small cell lung cancer (NSCLC) at various stages. Additionally, we included an age- and gender-matched control group of 48 healthy adults. The subjects in the control group underwent assessments, which confirmed absence of any clinical, radiological, or physical evidence of cancer. All participants gave informed consent after being provided detailed information about the study. Ethical approval for the research was obtained from the local ethics committee with the decision number 2/20 dated 07.02.2018.

Fasting serum samples were collected from all participants to analyze the levels of decorin, TGF-B1, and biglycan. Demographic data, smoking habits, and comorbidities of both the patients and control group were recorded prior to the study. During follow-up, we obtained and documented the clinical and histopathological characteristics of the patients, including histopathological subtype, grade, stage, lymph node involvement, and metastasis. We also extracted data from the electronic medical records to gather information on complete blood counts, routine biochemical tests, and hormone analyses for all participants. The patients' performance status was assessed and recorded using the Eastern Cooperative Oncology Group (ECOG) criteria.

Serum samples were stored at $-80°C$ until the ELISA test was performed. The levels of decorin, TGF-B1, and biglycan in these serum samples were measured using the sandwich ELISA method with the Human Decorin, biglycan, and TGF-B1 ELISA Kit®.

Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 25.0. The results were presented as frequencies, percentages, means, and standard deviations (SD). The normal distribution of numerical variables was assessed using the Shapiro-Wilk test. To compare means, we used independent samples t-test and one-way ANOVA. The Chi-square test was employed to compare categorical variables. Receiver Operating Characteristic (ROC) analysis was carried out to determine the cutoff values for decorin, TGF-B1, and biglycan in predicting NSCLC. Multivariate logistic regression analysis was conducted to identify independent variables predicting NSCLC. A p-value less than 0.05 was considered statistically significant.

3. Results

The study included a total of 48 patients with non-small cell lung cancer (NSCLC), of whom 32 (66.7%) had adenocarcinoma and 16 (33.3%) had squamous cell carcinoma. Additionally, we included 48 patients without a cancer diagnosis as the control group. The demographic characteristics of all participants are presented in Table 1.

A comparison between the NSCLC patients and the control group showed that the NSCLC group had a

Table 1
Baseline characteristics of NSCLC patients

Variables	NSCLC ($n = 48$)
Age (years), median (range)	65 (39–81)
Gender, n (%)	
Male	40 (83.3)
Female	8 (16.7)
BMI (kg/m^2), mean $\pm$ SD	24.51 $\pm$ 4.92
Diabetes mellitus, n (%)	
Yes	13 (27.1)
Hypertension, n (%)	
Yes	14 (30.4)
Alcohol use, n (%)	
Yes	12 (25)
ECOG PS, n (%)	
0–1	38 (79)
> 1	10 (21)
Current smoker, n (%)	
Yes	33 (68.8)
COPD, n (%)	
Yes	21 (43.8)
Histology, n (%)	
Adenocarcinoma	**32 (66.7)**
Squamous cell	**16 (33.3)**
Histopathological grade, n (%)	
1	**35 (72.9)**
2–3	**13 (27.1)**
Clinical nodal involvement, n (%)	
Yes	**30 (62.5)**
No	**18 (37.5)**
Clinical metastases, n (%)	
Yes	31 (64.6)
No	17 (35.4)
Clinical T stage, n (%)	
T1–2	8 (16.7)
T2–4	40 (83.3)
Serum CEA (ng/mL), median (range)	6 (0 – 953)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CEA, carcinoembryonic antigen; SD, standard deviation.

lower body mass index (BMI) and a higher prevalence of current smoking. However, they were similar in age, alcohol use, hypertension, gender, diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD) (Table 2).

There was no relation between demographic (smoking, obesity . . . etc) and clinical parameters and the levels of decorin, biglycan, and TGF-B1 in the NSCLC group. The NSCLC patients demonstrated significantly higher levels of biglycan (42.55 $\pm$ 27.40 vs. 24.38 $\pm$ 12.05 ng/mL, $p = 0.026$) and TGF-B1 (15.55 $\pm$ 9.16 vs. 10.07 $\pm$ 7.8 pg/mL, $p = 0.001$) compared to the control group, while the levels of decorin were significantly lower (6.64 $\pm$ 1.92 vs. 10.28 $\pm$ 3.13 ng/mL, $p = 0.002$) (Table 3). Within the NSCLC group, there was no significant association between the levels of decorin, biglycan, TGF-B1, and the factors such as metastasis, T stage, nodal involvement, age, BMI, current smoking, and other clinical parameters ($p > 0.05$ for all). While decorin, biglycan and TGF-B1 levels were similar in obese and non-obese individuals, bigycan and TGF-B1 levels were similar in smokers, but decorin level was lower in current smokers (9.8 vs 7.3 ng/mL, $p < 0.001$).

The ROC analysis yielded the following cut-off values: decorin: 8.13 ng/mL (81% sensitivity, 80% specificity, Area: 0.836, SE: 0.042, $p = 0.000$, 95% CI: 0.754–0.919); TGF-B1: 9.4 pg/mL (59% sensitivity, 58% specificity, area: 0.682, SE: 0.55, $p = 0.002$, 95% CI: 0.575–0.789); biglycan: 31.3 ng/mL (64% sensitivity, 63% specificity, area: 0.727, SE: 0.051, $p = 0.000$, 95% CI: 0.619–0.821).

In the multivariate logistic regression analysis, the following factors were identified as independent predictive markers for the diagnosis of NSCLC: Decorin $<$ 8.13 ng/mL (OR: 10.96; 95% CI: 3.440–34.958), current smoker (OR: 3.81; 95% CI: 1.320–10.998), COPD (OR: 43.6, 95% CI: 2.082–913.081), and low BMI (OR: 1.22; 95% CI: 1.070–1405) (Table 4).

4. Discussion

Proteoglycans play a crucial role in regulating the integrity of the extracellular matrix and its interactions with cells, making them one of the most important molecules in this process. Among these proteoglycans, decorin and biglycan are known to have additional effects on cell signaling apart from their established functions [13–16]. Cell signaling pathways are of significant importance in various cancers, and targeting these pathways has proven to be a more rational and effective approach to cancer treatment, and their relation to proteoglycans [17]. Despite their divergent functions, both decorin and biglycan ultimately impact cell proliferation by modulating TGF-B1 levels [14].

In our study, we investigated the levels of decorin, biglycan, and TGF-B1 in NSCLC patients compared to a control group. We observed a significant decrease in decorin levels in NSCLC patients, whereas biglycan and TGF-B1 levels were significantly elevated. Furthermore, through multivariate analysis, we identified low serum decorin levels (< 8.13 ng/mL) as an independent predictive marker for the diagnosis of NSCLC. These findings align with existing literature, which reports elevated levels of biglycan and TGF-B1 in various cancers such as gastric, pancreatic, and NSCLC. This observation regarding the association of biglycan and TGF-B1 with cancer has gained general acceptance within the scientific community. For example, Sandeed Apuni and colleagues reported similar results in patients with

Table 2
Comparison of baseline characteristics between the study and control groups

Variables	NSCLC ($n = 48$)	Control ($n = 48$)	P
Age (years), median (range)	65 (39–81)	65 (43–83)	0.823
Gender, n (%)			
Male	40 (83.3)	40 (83.3)	1
Female	8 (16.7)	8 (16.7)	
BMI (kg/m^2), mean ± SD	24.51 ± 4.92	26.77 ± 4.46	0.020
Diabetes mellitus, n (%)		0.814	
Yes	13 (27.1)	11 (22.9)	
Hypertension, n (%)		0.395	
Yes	14 (30.4)	20 (41.7)	
Alcohol use, n (%)		0.603	
Yes	12 (25)	9 (18.8)	
Current smoker, n (%)		0.002	
Yes	33 (68.8)	17 (35.4)	
COPD		0.085	
Yes	21 (43.8)	12 (25)	
Hemoglobin (g/dL), mean ± SD	13.2 ± 1.3	13.4 ± 1.2	0.867
Lymphocyte count ($\times 10^3$/mm^3), mean ± SD	2.1 ± 0.7	1.8 ± 1.1	0.760
Platelet count ($\times 10^3$/mm^3), mean ± SD	256 ± 43	278 ± 39	0.421
Neutrophil count ($\times 10^3$/mm^3), mean ± SD	4.6 ± 1.2	4.4 ± 1.5	0.820

NSCLC, non-small cell lung cancer; BMI, body mass index; SD, standard deviation; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Table 3
Serum levels of decorin, TGF-B1 and biglycan by groups

Variables	NSCLC	Control	P
Decorin (ng/mL), mean ± SD	6.648 ± 1.9	10.28 ± 3.1	0.002
TGF-B1 (pg/mL), mean ± SD	15.55 ± 9.1	10.07 ± 7.8	0.001
Biglycan (ng/mL),mean ± S	42.55 ± 27.40	24.38 ± 12.05	0.026

NSCLC, non-small cell lung cancer; TGF-B1, transforming growth factor beta-1; SD, standard deviation.

Table 4
Multivariate logistic regression analysis for the diagnosis of NSCLC

Variables	OR	95% confidence interval	P
Age	1.019	0.962–1.078	0.526
Low BMI	1.22	1.070–1.405	0.003
COPD	43.606	2.082–913.081	0.015
Current smoking	3.81	1.320–10.998	0.013
Decorin $<$ 8.1 ng/mL	10.96	3.440–34.958	0.000
TGF-B1 $>$ 9.4 pg/mL	2.36	0.816–6.867	0.113
Biglycan $>$ 31.3 ng/mL	1.90	0.639–5.658	0.248

NSCLC, non-small cell lung cancer; BMI, body mass index; SD, standard deviation; COPD, chronic obstructive pulmonary disease; TGF-B1, transforming growth factor beta-1.

urothelial cancer, where they observed higher serum levels of biglycan and lower levels of decorin compared to a control group [18]. For decorin, previous studies have demonstrated lower levels in several cancer types compared to healthy individuals, while some studies have indicated reduced decorin expression in tumor tissue relative to non-tumor tissue. However, the number of studies investigating serum decorin levels in NSCLC patients remains limited. Xufei Shi and colleagues published an article in 2015, suggesting that decorin may play a significant role in cancer cell proliferation in NSCLC and could serve as an independent marker for this disease [11]. The inhibitory role of decorin in carcinogenesis is well-established, as it has been shown to suppress the activity of the Met receptor in cancer cells and exhibit anti-tumoral effects [19]. Decorin acts as an inhibitor ligand for several receptors, including the epidermal growth factor receptor and growth hormone receptor. It also functions as a "pan-tyrosine kinase inhibitor," inhibiting multiple tyrosine kinases [20,21].

The anti-proliferative activity of decorin is well known, and a study has demonstrated its role in preventing metastasis in breast cancer [22]. Decorin is also an inhibitory factor in tumor formation, and several studies demonstrated lower levels of decorin in the tumor microenvironment [23–26]. In line with the literature, our study also identified other independent predictive markers for NSCLC, including current smoking [27], low body mass index [28], and the presence of chronic obstructive pulmonary disease [29].

Despite the significance of our findings, it is important to acknowledge certain limitations within our

study. Although we had sufficient number of patients, our ability to conduct a more detailed subgroup analysis was limited, which could have provided insights into the impact of concomitant medications on the studied molecules. Additionally, the unknown post-study treatments received by the patients prevented us from assessing the relationship between the treatment and the changes in decorin, biglycan, and TGF-B1 levels.

In conclusion, our study presents novel evidence to the existing body of knowledge by demonstrating that low serum decorin levels can serve as an independent predictor for the diagnosis of non-small cell lung cancer, regardless of the cancer stage. To gain a more comprehensive understanding of decorin's impact on survival and treatment outcomes of NSCLC patients, prospective randomized studies are warranted. Furthermore, our study reinforces the association of other independent predictive markers for NSCLC, including smoking, low body mass index, and the presence of chronic obstructive pulmonary disease, with the development of this disease.

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Conflict of interest

All authors declared that they have no conflict of interest.

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Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Ethical approval for the research was obtained from the local ethics committee with the decision number 2/20 dated 07.02.2018.

Patient consent for publication

All participants gave informed consent after being provided detailed information about the study.

Author contribution

Conception: F.K; M.A.
Interpretation or analysis of data: F.K; H.G.K; F.I; O.S.D.
Preparation of the manuscript: F.K; H.G.K; O.S.D.
Revision for important intellectual content: M.A; F.I; F.K; O.S.D.
Supervision: F.K; H.G.K; M.A.

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