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Original Article

Does sericin pleurodesis increase the basic fibroblastic growth factor and high-sensitive C-reactive protein levels in rat plasma?

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ABSTRACT

Background: This study investigates whether or not sericin pleurodesis increases basic fibroblastic growth factor (bFGF) and high-sensitive C-reactive protein (hs-CRP) levels in rat plasma.

Materials and Methods: A total of 42 adults, male, 12-week-old Wistar albino rats were obtained for the study. The rats were divided randomly into three groups, as sericin, talcum powder, and control group. After the administration of an anesthetic, the agents were administrated through a left thoracotomy. The rats were sacrificed 12 days later through cardiac puncture. The bFGF and hs-CRP levels were examined in plasma.

Results: The mean rat plasma bFGF levels were 251.7 pg/mL in the sericin group (range: 101 to 821 pg/mL), 72.3 pg/mL in the talcum powder group (range: 24 to 131 pg/mL), and 133.1 pg/mL in the control group (range: 32 to 320 pg/mL). A significant difference was noted in the results of a Scheffe test between the sericin and talcum powder groups ($p < 0.05$, $p = 0.046$). Mean rat plasma hs-CRP levels were 1.038 ng/mL in the sericin group (range: 0.677 to 2.815 ng/mL), 1.343 ng/mL in the talcum powder group (range: 0.606 to 5.662 ng/mL), and 0.945 ng/mL in the control group (range: 0.586 to 1.261 ng/mL), indicating no significant difference among the groups.

Conclusions: It was found that bFGF levels were significantly higher in the sericin pleurodesis group than in the talcum powder group, indicating the biochemical success of intrapleural sericin administration in inducing pleurodesis. On the other hand, hs-CRP, a marker of inflammation, was not found to be significant, indicating that hs-CRP returns to normal levels due to its short half-life.

Key Words: sericin, fibroblast, fibrosis, growth factor, C-reactive protein, pleurodesis

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Introduction

The cocoon shell of silkworms, Bombyx mori, is composed of two natural proteins, called fibroin and sericin [1,2]. Sericin is a natural, macromolecular, gum-like protein that holds fibroin polymers together, and is a by-product of the textile sector [1]. Previous studies have shown the pleurodesis success of sericin powder [3,4]. Yazicioglu et al. in an experimental study involving rats, concluded that the intrapleural administration of sericin increased fibroblastic activity and fibrosis in the visceral pleura, with no significant adverse effects on lung parenchyma [3]. Besides, no foreign body reactions were noted and there was no evidence of biological glue on the specimens in the sericin pleurodesis group. Furthermore, the rats in the sericin pleurodesis group had lower inflammatory reactions, than the control group [3]. In another study involving rats, Yazicioglu et al. compared sericin pleurodesis with talcum powder, doxycycline, and silver nitrate pleurodesis, and found that sericin pleurodesis was found to be better tolerated, the success of sericin pleurodesis was demonstrated, and the highest level of dense collagen fibers was noted in the sericin group [4]. Compared to the other agents, sericin displayed significantly greater protective characteristics on lung parenchyma and a lower potential for inflammation than the other agents [4]. Additionally, side effects concerning the kidneys and the heart were significantly lower in the sericin group than in the other groups, which led the authors to conclude that the sericin powder is a better-tolerated, more cost-effective agent, associated with fewer side effects and offering superior protection of the lung parenchyma, offering more effective pleurodesis [4].

These histopathological studies demonstrate a sericin-induced increase in the fibroblastic activity that leads to fibrosis, although the levels of basic fibroblastic growth factor (b-FGF), a serum marker of fibroblastic activity, are unknown. Similarly, the effect of the intrapleural administration of sericin on the high-sensitive C-reactive protein (hs-CRP) level is also unknown. If sericin is effective in inducing pleurodesis, b-FGF and hs-CRP levels can be expected to increase in rat serum, although there is only limited data in the literature related to this subject [5-7].

Although many agents have been used to achieve pleurodesis, talcum powder appears to be the most commonly used agent around the world [8]. In the present study, we investigated whether or not sericin pleurodesis increased the basic fibroblastic growth factor (bFGF) and high-sensitive C-reactive protein (hs-CRP) levels in rat plasma.

Materials and Methods

The rat model was selected due to the presence of a valid laboratory license, technical feasibility, and similar physiological characteristics when compared with humans. The sericin powder is commercially available and was purchased from Xi'an Lyphar Biotech Co, LTD, Xi'an, China; the talcum powder was purchase from Novatech SA (Steritalc®), Marseille, France.

It was critically important to determine the appropriate dose of administration of the agents used in this study. The studies previously conducted by Yazicioglu et al. used 30 mg sericin in rats and obtained successful results, and so we used the same dose of sericin in the present study [3,4]. The administrated dose of talcum powder in adults varied between 4 and 5 grams in previous studies, and so a dose of 17 mg was estimated to be appropriate for rats with a mean weight of 250 ± 30 g [9-11]. The study previously conducted by Yazicioglu et al. did the sacrification of rats 12 days later, and so we sacrificed them on the same day [4].

Animals

This experimental study received approval from the Ethics Committee of Kobay AS (Protocol Number-2018/291). A total of 42 adult male 12-week-old Wistar albino rats weighing between 234 and 310 g were used in the study. The rats were divided randomly and equally into three groups: the sericin group, the talcum powder group, and the control group. Each group comprised of fourteen animals. All the animals received humane care in accordance with the Turkish Government Animal Protection and Management Law.

Technique

The sericin powder was divided into 30-mg packs, while the talcum powder was divided into 17-mg packs and added to Eppendorf tubes. The rats were anesthetized using intramuscular injections of 5-mg/kg xylasine hydrochloride (Alfasan International B.V., Woerden, Holland) and 45-mg/kg ketamine hydrochloride (Richter Pharma A.G., Wels, Austria). Subsequently, the left hemithorax was shaved, skin preparation was performed with povidone-iodine solution, and the rats

were placed in the lateral decubitus position. A left thoracotomy incision (2-cm skin incision) was performed at the midsection between the spine and sternum. The muscles were bluntly dissected to allow exposure of the parietal pleura. Under direct inspection, the parietal pleura was opened, and 30-mg sericin powder was administrated into the pleural space of each rat in the sericin group (n = 14). In the talcum powder group, 17-mg talcum powder was administrated into the pleural space of each rat (n = 14). The remaining rats were allocated to the sham thoracotomy group. Subsequently, the muscle layers were sutured using the running suture technique with 3-0 coated and braided polyglycolic acid (Vicryl 3-0; Dogsan, Trabzon, Turkey). The skin incision was closed with 4-0 coated and braided polyglycolic acid (Vicryl 4-0; Dogsan, Trabzon, Turkey) using interrupted suturing technique. The pneumothorax was drained using a 20-gauge plastic catheter connected to a syringe applying negative pressure. The catheter was removed immediately after the closure of the thoracotomy. Subsequently, terramycin wound spray (oxytetracycline HCl with a blue marker dye) was applied to the skin incision. All the rats were weighed before surgery and before scarification, and the respective body weights were recorded.

After the operation, the rats were housed in individual stainless steel cages and closely monitored for any clinical evidence of pain or other abnormalities, such as vocalization, tachypnea, or restlessness. No analgesic drugs were added to food and water. The room temperature was kept at 21^0C (± 2^0C), the relative humidity was approximately 60% (± 10%), and the rats remained under simulated daylight conditions. The rats were given ad-libitum access to food and water. The rats were sacrificed on postoperative day 12, through a cardiac puncture. Blood samples of approximately 8-10 mL were taken slowly from the ventricle of the heart of each rat to avoid cardiac collapse.

Biochemical evaluation

The blood samples were placed in tubes containing ethylenediaminetetraacetic acid (EDTA), and plasma samples were separated from the cells through centrifugation at 1800 g for 10 min (Hettich Universal, 320 R, and Zentrifugen). The plasma samples were subsequently separated from the cells and added to the Eppendorf tubes. The tubes were stored at -80°C until the time of analysis. The biochemistry specialists (investigators AS, CK, and OE) were kept blind to the study groups.

Rat b-FGF/FGF2 enzyme-linked immunosorbent assay (ELISA) and rat hs-CRP ELISA kits were supplied by Elabscience®-USA. The methodology used in the study was based on the manufacturer's instructions.

Statistical Analysis

The statistical analysis was carried out using SPSS version 17.0 statistical software (SPSS Inc., Chicago, IL, USA). The one-way ANOVA test was used to analyze the potential differences between study groups. In cases where a difference was detected between the groups, the Levene test was used to check the differences between the variances and to identify which group was the source of difference. The variances were not equal when p values were < 0.05 based on the Levene tests, and the Tamhane's and Dunnett's t-test were used in such cases. Variances were considered equal when p values were > 0.05 based on the Levene test, and Scheffe test was used in such circumstances. Based on Scheffe, Tamhane's and Dunnett's t-tests, p values of < 0.05 were considered statistically significant [12]. In this study, a power analysis can be the most suitable measurement for deciding how large a sample size we need for performing the planned experiment? An experiment that is too small may fail to observe biologically important aspects; however, an experiment that is too large may lead to wasting the animals. In order to balance those two sensitive concepts, scientists often asked to justify the number of animals they plan to use. According to power analyses calculation, fourteen rats were decided to be appropriate for each group.

Results

All rats were returned to normal feeding and other activities immediately after the operation, and all rats completed the study and were sacrificed on postoperative Day 12. The mean weight of the rats was 270 (range: 247 to 303) g in the sericin group, 263 (range: 237 to 310) g in the talcum powder group, and 244 (range: 234 to 265) g in the control group meaning no statistically significant difference among the groups.

Results of basic Fibroblastic Growth Factor

The biochemical analysis showed that the mean rat plasma b-FGF levels were 251.7 pg/mL in the sericin group (range: 101 to 821 pg/mL), 72.3 pg/mL in the talcum powder group (range: 24 to 131 pg/mL), and 133.1

pg/mL in the control group (range: 25 to 1320 pg/mL). A significant difference was noted in the Scheffe test results of sericin and talcum powder groups ($p < 0.05$, $p = 0.046$). However, no statistically significant difference between pleurodesis groups and the control group was calculated.

Results of high sensitive C-reactive protein

The biochemical analysis revealed mean rat plasma hs-CRP levels of 1.038 ng/mL in the sericin group (range: 0.677 to 2.815 ng/mL), 1.343 ng/mL in the talcum powder group (range: 0.606 to 5.662 ng/mL), and 0.945 ng/mL in the control group (range: 0.586 to 1.261 ng/mL). A Scheffe test revealed no significant differences among the study groups. The b-FGF and hs-CRP results in the rat plasma are presented in Table 1.

Table 1. Mean values, lower-upper limits and statistical results of rat plasma b-FGF and hs-CRP levels in the sericin, talcum powder and control groups.

Parameters	Sericin (n=14)	Talcum powder (n=14)	Control (n=14)	Statistics (A vs B; p value)
bFGF (pg/mL)	251.7 (range: 101-821)	72.3 (range: 24-131)	133.1 (range: 25-320)	Sericin vs talcum powder ($p < 0.05$, $p = 0.046$)
hs-CRP (ng/mL)	1.038 (range: 0.677-2.815)	1,343 (range: 0.606-5.662)	0.945 (range: 0.586-1.261)	No significant difference between groups

Discussion

Sericin is a natural, macromolecular, and a kind of glue protein that holds fibroin polymers together [3,8]. The predominant amino acid in the structure of the sericin protein is serine amino acid and as such, sericin contains strongly polar side groups, such as hydroxyl, carboxyl, amino groups that enable easy cross-linking, and copolymerization that improves both biocompatibility and biodegradation [13,14]. Sericin has many applications, including as an anti-wrinkle, anti-aging, antioxidant and as an additive to cell culture media, and has a healing effect on wounds [1,2,8,13-16]. Sericin has good hydrophilic properties that are widely used in the pharmaceuticals and cosmetic sectors. Furthermore, it is useful in the wound healing process and can be used as a wound dressing and healing agent [16-18]. Ersel et al. evaluated the in vivo wound healing effects of a gel formulation containing sericin in rats [16]. The epidermal thickness and vascularization of the skin increased, whereas hair root degeneration, edema, cellular infiltration, collagen discoloration, and necrosis decreased more in the sericin group than in the control group [16]. They also noted that levels of antioxidative activity increased in the sericin-treated animals [16]. Based on the findings, the authors concluded that sericin had significant positive effects on wound healing and antioxidant activity [16]. Similar antioxidant activity of sericin has also been described by Yazicioglu et al. [19]. In their study, the authors showed that an intrapleural application of sericin increased plasma native thiol and total thiol levels, which promote antioxidant activity and prevent free radical-induced damage [19].

Pleurodesis refers to the obliteration of the pleural space and the symphysis of pleural layers, preventing the collection of either fluid or air in the pleural space. It is an appropriate approach to use a protein that is already a natural adhesive to glue the pleural surfaces together. The efficacy of pleurodesis and the usefulness of sericin powder was first described by Yazicioglu et al. in a study involving rats [3]. A comparison of the results of sericin pleurodesis with talcum powder, doxycycline, and silver nitrate pleurodesis was described by Yazicioglu et al., in another rat study [4]. Aforementioned these studies demonstrated increased fibroblastic activity and fibrosis induced by sericin pleurodesis [3,4]. These studies also demonstrated the lung parenchyma-preserving activity of sericin powder and reported fewer side effects in the sericin pleurodesis group [3,4]. However, it remains unclear, whether an increase occurred in the levels of several hormones, cytokine and chemokines, as plasma markers of fibroblastic activity. If an increase was noted in fibroblastic activity, these parameters would also be expected to increase.

Talcum powder is the most commonly used agent worldwide in inducing pleurodesis, and is considered to have the highest efficiency [20,21]. In a study by Yazicioglu et al. comparing sericin with other pleurodesis agents, sericin pleurodesis was found to be superior in certain aspects when compared to talcum powder [4]. In

an evaluation of visceral and parietal pleurae based on Masson's trichrome staining, Yazicioglu et al. demonstrated that the collagen fibers in the sericin group were more intense than in the talcum powder group ($p < 0.05$) [4]. Additionally, foreign body reaction and emphysema in the parenchyma were less frequent in the sericin group than in the talcum powder group ($p < 0.05$) [4]. The presence of biological tissue in the parenchyma was less prominent in the sericin group than in the talcum powder group ($p < 0.05$) [4]. Similar to parenchyma, foreign body reaction on the thoracic wall was also less common in the sericin group when compared to the talcum powder group ($p < 0.05$) [4]. Finally, the presence of biological tissue glue on the thoracic wall was less prominent in the sericin group than in the talcum powder group ($p < 0.05$) [4]. In summary, sericin pleurodesis was found to be a superior pleurodesis agent compared to talcum powder. Although pathological outcomes and the success of intrapleural sericin administrations have been demonstrated, there is no data in the literature regarding on its biochemical consequences. Under these circumstances, the effects of intrapleural sericin and talcum powder administration on b-FGF and hs-CRP levels and their comparative efficiencies should be known.

The basic fibroblast growth factor, known also as fibroblast growth factor 2 (FGF2) and FGF-β, is a growth factor and signaling protein encoded by the FGF2 gene [22]. The FGF protein was first purified in 1975, and b-FGF is synthesized primarily as a 155 amino acid polypeptide, resulting in an 18 kDa protein [22,23]. The b-FGF has broad mitogenic and cell survival activities, and is involved in a variety of biological processes, such as embryonic development, cell growth, morphogenesis, and tissue repair [24-26]. The primary source of b-FGF is endothelial cells, its primary target is fibroblasts, and its primary effect is the proliferation of fibroblasts with an extracellular matrix formation [27]. It also stimulates mesothelial cell proliferation both in vivo and in vitro [28]. This factor is mitogenic for fibroblasts, smooth muscle cells, and endothelial cells; and is present in the pleural effusions of tumors [29-31]. Antony et al. reported that the intrapleural instillation of talcum powder induces the pleural mesothelial production of b-FGF, which is responsible for pleural symphysis [31]. Antony et al. identified significantly higher levels of b-FGF in the pleural fluids of patients who underwent successful pleurodesis with talcum powder [31]. Therefore, talcum powder pleurodesis activates pleural mesothelial cells to produce significantly higher amounts of b-FGF when compared to the control group, in malignant pleural effusion patients [31].

It is known that the plasma levels of various growth factors increase after thoracic surgery operations. Dikmen et al. reported that plasma hepatocyte growth factor levels increased significantly at postoperative Days 1 and 3 in patients undergoing lung resection [32]. In the present study, no significant increase was noted in the b-FGF levels of the talcum- and sericin-induced pleurodesis groups when compared to the control group. However, when the sericin and talcum powder groups were compared, the increase noted in the sericin group was statistically significant ($p < 0.05$; $p = 0.046$) (Table 1). The lack of a significant difference between the sericin group and the control group is consistent with the findings of previous studies. In a study by Yazicioglu et al. no significant difference was noted in the b-FGF, TGF- β, and IL-2 levels between the rats undergoing intrapleural sericin administration and the control group [33]. The higher b-FGF levels in the sericin group than in the control group and lower b-FGF levels in the talcum powder group than in the control group suggest that the administration of intrapleural sericin has a stimulatory effect on endothelial cells, mesothelial cells, and fibroblasts. On the other hand, according to Hojski et al., the serum level of b-FGF was higher after mechanical pleurodesis compared to those after chemical pleurodesis [5]. The increased plasma b-FGF levels noted in the rats suggest that sericin can induce an increase in b-FGF levels through its stimulatory effect. Sericin administration increases fibroblastic activity by increasing b-FGF levels, accelerating fibrosis and producing successful pleurodesis. In this study b-FGF level is not significantly high in the talcum powder group compared to the control group. However, Antony et al. demonstrated significantly higher levels of b-FGF in the pleural fluid after talcum powder pleurodesis [31]. This difference may be related to analyzing material was pleural fluid in the study of Antony and colleagues, but the plasma sample in our study.

The C-reactive protein was the first acute-phase protein to be described and is a sensitive systemic marker of inflammation and tissue damage [34]. The acute-phase response comprises most forms of tissue damage, infection, inflammation, and malignancies [34,35]. According to Fang et al., the elevated serum CRP levels

in patients with nasopharyngeal carcinoma are associated with a poor prognosis [36]. Elevated CRP levels are not poor prognostic markers only for malignancies, but plasma CRP levels are also found to increase during infections, and under conditions in which tissue damage has become more extensive and inflammatory response has escalated. In this respect, CRP can be considered an important follow-up parameter.

The CRP gene, located on the short arm of chromosome 1, contains only one intron, and consists of five identical, non-covalently associated protomers that are arranged asymmetrically around a central pole [37]. CRP is produced and synthesized primarily in the liver, in response to inflammatory cytokines, and assists in the phagocytosis of macrophages [35]. It also synthesized in other cell types, such as smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes [38]. CRP is a member of the pentraxin protein group, which is an integral part of the innate immune system [35]. The level of CRP tends to be proportional to the intensity of the inflammatory process, and is sensitive to changes in response to inflammation [35]. Froudarakis et al. examined the systemic inflammatory reaction after thoracoscopic talcum poudrage, and showed that the white blood cell count, percentage of neutrophils, and CRP levels were significantly increased in the group of patients who underwent talcum poudrage [39]. In our study, no significant increase was noted in the CRP levels of the talcum powder group, and this difference in results can be attributed to the fact that Froudarakis et al. studied human subjects, while the present study was conducted on rats. Furthermore, Froudarakis et al. measured CRP levels on day two after surgery, while the rats in the present study were sacrificed on Day 12. Levels of CRP fall quickly due to its short half-life of only 4 - 7 hours [35]. Therefore, hs-CRP levels in the blood are likely to regress and return to normal levels after the alleviation of inflammation.

Although the mean hs-CRP levels in the sericin and talcum powder groups were higher than in the control group, the difference was not statistically significant (Table 1). This finding can be attributed to the short half-life of hs-CRP. In the study by Yazicioglu et al., sericin pleurodesis was compared with pleurodesis induced by talcum powder, doxycycline, and silver nitrate [4]. The authors reported that their study evaluated many parameters, including the inflammatory parameters of the lung parenchyma and chest wall [4]. According to the results of the study conducted by Yazicioglu et al., the evaluation of inflammation in the lung parenchyma indicated that mild, moderate and severe inflammation were noted in three (25%), three (25%) and six rats (50%) in the sericin group, respectively [4]. While there was no inflammation in two rats (18.2%) in the talcum group, moderate and severe inflammation was observed in two (18.2%) and seven rats (63.6%), respectively. The statistical analyses of inflammation in the parenchyma did not reveal any significant difference between the two groups. On the other hand, the evaluation of the inflammation on the thoracic wall indicated that mild, moderate and severe inflammation was noted in two (18.2%), five (45.5%) and four rats (36.3%) in the talcum powder group, respectively. While no inflammatory reaction was detected in three (25%) rats in the sericin group, mild, moderate and severe inflammation was noted in three (25%), three (25%), and three rats (25%) in the sericin group, respectively. Similarly, to the inflammation of the parenchyma, the statistical analyses did not indicate any significant difference between the two groups. As hs-CRP is an inflammation marker, and the lack of any difference in this parameter between the study groups supports the pathological findings of the study by Yazicioglu et al. [4].

There are some limitations to this study. First, we did not evaluate any other fibrosis or inflammation markers, such as transforming growth factor-β1, vascular endothelial growth factor, platelet derived growth factor, interleukin-2,-8,-10 and various other cytokines. Other markers of fibrosis were not evaluated, as it was not clear whether an increased fibroblastic activity would increase the plasma levels of b-FGF. This pilot study identified an increase in b-FGF levels, and investigations of other cytokines and chemokines in subsequent studies would further facilitate our understanding of fibrosis mechanisms.

In conclusion, sericin is a natural intrinsic protein, and sericin pleurodesis is a successful, better-tolerated, more cost-effective, and investigable approach with low potential for side effects. Increased fibroblastic activity in response to sericin pleurodesis has not been demonstrated biochemically, to date. The findings of significantly higher b-FGF levels in the sericin pleurodesis group than in the talcum powder pleurodesis group indicates a higher efficiency of sericin in the induction

of pleurodesis. Based on these results, the success of intrapleural sericin administration in inducing pleurodesis can be biochemically confirmed. On the other hand, hs-CRP, a marker of inflammation, was not found to be significant, and it is considered that hs-CRP returned to normal levels due to its short half-life. The researches of sericin as a pleurodesis agent will add value to the practice of thoracic surgery and pulmonology.

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