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The role of MMP-9 and TIMP-1 in nasal polyp formation

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Summary

Objective: The complex structure of polyp formation is still unknown. Matrix metalloproteinases (MMPs), a family of zinc-dependant endopeptidases with proteolytic activities towards several components of extracellular matrix, play an important role in connective tissue remodeling. Tissue inhibitors of matrix metalloproteinases (TIMPs) are natural inhibitors of MMPs. The balance between MMP/TIMP is very critical in matrix remodeling and various physiological processes. Imbalances between these enzymes and inhibitors may cause pathological processes such as chronic inflammation, degenerative disease and tumour invasion. In our study we aimed at demonstrating MMP/TIMP imbalance in nasal polyposis, similar to other pathological processes.

Study design and setting: Nasal polyp specimens were obtained from twenty patients with nasal polyposis during endoscopic sinus surgery. Bullous middle turbinates with normal appearing mucosa of fifteen non-smoker patients free of any allergic or infectious diseases of nose or sinuses were used as controls. We measured the MMP-9 and TIMP-1 levels in tissue specimens using an ELISA method.

Results: MMP-9 levels were significantly increased and TIMP-1 levels were significantly decreased in polyp tissues in comparison to controls with no correlation observed between MMP-9 levels and inflammatory cell populations.

Conclusion: MMP-9 and TIMP-1 may play an active pathogenic role in nasal polyp formation. MMP-9 levels are regulated independently from inflammatory cell populations.

Key words: Nasal polyp; polyp formation; matrix metalloproteinases; polyp etiopathogenesis; MMP-9; TIMP-1; nasal polyp physiopathogenesis

Introduction

Nasal polyposis is a chronic inflammatory disease of sinonasal mucosa characterised by oedema, fibrous tissue, vascularisation, inflammatory cells and glands. Different kinds of theories have been proposed for nasal polyp physiopathogenesis. However, none of these theories are accepted as being definitive. Proposed mechanisms for polyp formation include chronic diseases, aerodynamic changes, aspirin intolerance, epithelial rupture, epithelial cell defects, gene deletions, inhalant or food allergies, increased sodium absorption [1]. Hereditary factors play an important role in polyp formation, however, mucosal inflammation and local inflammatory mediators are thought as main factors in polyp aetiopathogenesis [1, 2].

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases having proteolytic activities and role in tissue remodeling. It is also known that in nasal polyposis there is injury of sinonasal mucosa and remodeling of this tissue [3]. In the present study we investigated a probable imbalance between MMP and TIMP. Based on the broad literature on MMPs and TIMPs, we considered a possible role of MMP-9 and TIMP-1 in nasal polyp formation. MMP-9 can degrade gelatins, collogens IV, V, XIV, elastin, aggrecan, vitronectin, almost all components of extracellular matrix. Therefore we choose MMP-9 as indicator for MMPs activity and TIMP-1 which is an inhibitor of MMP-9.

The authors have no actual or potential conflict of interest in relation to this paper.

Methods

Tissue samples

Nasal polyps were obtained by endoscopic surgery from twenty patients with nasal polyposis who were referred to Afyon Kocatepe University Otolaryngology Department. The age range was between 17 and 65 (mean 41). There were 7 female and 13 male patients. Five patients had history of asthma and seven patients had allergic rhinitis which was proved by skin prick test. Two of asthmatic patients also had aspirin intolerance. Children, patients with cystic fibrosis, and ciliary dyskinesia were not included in the study. The patients had not received any medications (antihistamines, antibiotics, topical or oral steroids) at least one month before surgery. The diagnosis of nasal polyposis was established based on rhinoscopic examination findings, diagnostic nasal endoscopy, and computed tomography. None of the patienets had had any previous nasal surgery.

Fifteen non-smokers, free of any allergic or infectious disease, with a bullous middle turbinate and normal appearing mucosa were accepted as a control group. The age range was between 22 and 52 (mean 33). There were 6 female and 9 male patients. The control group patients had the compliant of nasal obstruction. To overcome the nasal obstruction patients underwent an endoscopic surgery for opening of the choncha bullosa.

All the patients were informed about the study before operations.

Histomorphological studies

Biopsy specimens were dyed with Haemotoxiline-eosin and examined under the light microscope. Eosinophils, polymorphonuclear (PMN) leucocytes, lymphocytes, plasma cells and mast cells were countered and results were semi-quantitatively evaluated and scored on the basis of the number of cells as follows: 0. no cells, 1. few cells, 2. moderate, 3. plentiful. All the specimens were examined by the same senior pathologist. MMP-9 and TIMP-1 levels were statistically compared with inflammatory cell numbers in nasal polyp patients.

Biochemical studies

The tissues were homogenised in 0.1M phosphate-buffer (pH 7.4) with Ultra Turrax homogeniser (IKA T18 basic, Wilmington NC, USA). After the homogenates were sonicated (LIP 50H, Dr. Hielscher, GmbH, Germany) and centrifuged at 5000 rpm, +4 ^{0}C for 10 min respectively the supernatants were removed and used for TIMP-1 and MMP-9 assays. TIMP-1 ve MMP-9 levels were measured by using commercial ELISA kits supplied from R&D Systems (Minneapolis, MN, USA). High and low controls which were included in ELISA kits were used to prevent false negative and false positive results. Results were recorded as ng/g tissue.

Statistical analysis

Results were given as "mean ± standard deviation". The Kolmogorov-Smirnov test was used to determine the data distribution was normal. We used the "T test" to compare the two groups. Levene's test was used for variance homogeneity. A $p < 0.05$ was considered to be significant.

Results

These histomorphological studies showed us that all polyp tissues contained eosinophils, plasma cells and lymphocytes. Table 1 demonstrates the inflammatory cell scores of the nasal polyp tissues.

MMP-9/TIMP-1 ratios were 1.96 ± 0.98 in nasal polyp patients and 0.18 ± 0.08 in the control group (table 2) with statistical significance ($p < 0.001$).

High rates of MMP-9 levels were found in nasal polyps (5131.2 ± 1294.2 ng/g tissue). In the control group lower rates of MMP-9 levels were found (719.51 ± 143.7 ng/g tissue). MMP-9 levels were significantly higher in nasal polyps than the control group ($p < 0.001$). Tissue TIMP-1 rates were 3121.6 ± 1512.1 ng/g tissues in nasal polyps and 4691.03 ± 2451.6 ng/g tissue in control group. TIMP-1 levels were significantly low in nasal polyp tissues ($p = 0.04$). There was no correlation between MMP-9 levels and inflammatory cell populations ($p = 0.512$).

Discussion

There is only little data about MMP-9 and TIMP-1 levels in nasal polyps. Recently, few studies were conducted for MMP and TIMP levels in nasal polyps with similar nasal polyp sample sizes to our study. Nasal polyps are not rare. So the nasal polyp sample size could be bigger. But it is difficult to find pure concha bullosa patients without any infectious or allergic disease. Therefore this difficulty limited our control sample size and hereby our study. These former studies and our study can be accepted as pilot studies and sample sizes will be bigger in further studies. Among the possible theories of nasal polyp formation, inflammatory theories seem more plausible. Morinaka and Nakamura showed eosinophil, macrophage, plasma cell and lymphocyte counts were increased in nasal polyps [4]. In our study we found that all the polyp tissues contain eosinophils, plasma cells and lymphocytes. As high as 60% of the nasal polyp tissues were observed to contain mast cells.

Along with an increase in the number of in-

Table 1

The inflammatory cell scores of the nasal polyp tissues.

		Scores			
		0 (number of patients)	**1** (number of patients)	**2** (number of patients)	**3** (number of patients)
Inflammatory Cell type	Eosinophils	0	11	5	4
	PMN leucocytes	1	15	3	1
	Mast cells	8	12	0	0
	Lymphocytes	0	12	5	3
	Plasma cells	0	15	3	2

(No cell: 0, few cells: 1, moderate: 2, plentiful: 3)

Table 2

MMP-9/TIMP-1 ratio in polyp tissues and control group.

Patient No. (Nasal polyp)	MMP-9/ TIMP-1	Control No. (Concha bullosa)	MMP-9/ TIMP-1
1	1.2888	1	0.0615
2	3.2514	2	0.1101
3	1.1184	3	0.0743
4	2.7471	4	0.1015
5	1.9849	5	0.1941
6	1.7886	6	0.3204
7	0.8532	7	0.3045
8	2.4681	8	0.2366
9	1.6570	9	0.1154
10	2.4342	10	0.1378
11	4.0448	11	0.1857
12	1.5999	12	0.2261
13	0.8293	13	0.2984
14	1.2863	14	0.2442
15	0.8568	15	0.1570
16	3.6363		
17	1.1409		
18	1.3665		
19	1.5965		
20	3.2230		

P <0.001

flammatory cells, quantity of pro-inflammatory cytokines and chemokines are also increased in nasal polyps. These cytokines and chemokines support the eosinophilic inflammation by the migration and the activation of eosinophils [1]. It was shown that quantity of histamine, Interleukin (IL)-1β, IL-4, IL-5, IL-6, IL-8, IL-13, interferon gamma, matrix metalloproteinase 1 (MMP-1), matrix metalloproteinase 9 (MMP-9) were increased in nasal polyp tissues [1, 5, 6].

Extracellular matrix is composed of glycosaminoglycans (such as hyaluronic acid), fibrous proteins (collagen, elastin), and adhesive proteins (fibronectin and laminin). MMP-9 can degrade almost all components of the extracellular matrix. Extracellular matrix comprises basal membrane and interstitial matrix and is a complex structure that surrounds and supports the mucosal cells, and plays an important role in physiological changes of these cells. Balance between synthesis and destruction of the extracellular matrix is important for homeostasis. Turnover and remodeling of extracellular matrix have to be controlled firmly. An uncontrolled proteolysis and extensive destruction of these components form part of the pathological process. MMPs are the main enzyme group regulating matrix integrity [7, 8].

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases with proteolytic activity and a role in tissue remodeling [7, 8]. They play active roles in pathological as well as physiological tissue remodeling, examples of which include embryonic maturation, implantation of blastocytes, organ morphogenesis, nervous system development, ovulation, cervical dilatation, postpartum uterus involution, endometrial cycles, hair follicle cycles, bone remodeling, wound repair, angiogenesis, and apoptosis. Pathological examples can be listed as arthritis, cancer, cardiovascular disease, nephritis, neurological disease, periodontal disease, skin ulcer, gastric ulcer, corneal ulcer, hepatic fibrosis, emphysema and fibrotic lung disease [7]. High levels of MMP-9 were found in epithelial lining fluid of patients with Status asthmaticus. The authors thought this increase of MMP-9 may contribute to the oedema, excessive bronchial permeability and destruction of airways [9]. There is clear evidence that smoke exposure produces increased levels of lung MMP-9 and MMP-12. These increases have a role in smoke-induced emphysema development and specific inhibitor of MMP-9/MMP-12 (AZ11557272) can ameliorate this emphysema formation [10]. Pawankar et al. found high levels of MMP-9 but low levels of MMP-2 and MMP-13, and suggested that MMP-9 has a probable role in structural changes in nasal polyps [11]. Other studies also showed elevated levels of MMP-9 in nasal polyps [12–15]. Active form of MMP-9 was also studied in nasal polyps and found higher than control groups [12].

Against excessive tissue destruction, MMPs' proteolytic activity must be limited by inhibitory factors. Growth factors, expression of oncogens, tissue inhibitors of matrix metalloproteinases, cell to extracellular matrix or cell to cell interactions regulate MMP activities [8].

Tissue inhibitors of metalloproteinases (TIMPs) are natural inhibitors of matrix metalloproteinases (MMPs) found in most tissues and body fluids. By inhibiting MMPs activities, they participate in tissue remodeling of the extracellular matrix [16]. TIMPs also exhibit cellular activi-

ties such as cell growth promotion, gonadal steroidogenesis, anti-apoptotic activity, survival of some cells and inhibition of angiogenesis. In the way of binding pro-MMP-9, TIMP-1 limits MMP-9 activity [16]. Different studies have showed different results of TIMP-1 levels in nasal polyps. Watelet et al found high levels, Chen et al found no difference and Can et al found low levels of TIMP-1 compared to control groups [13–15]. We found low levels of TIMP-1. In the study which TIMP-1 was found in high levels, there were 3 allergic patients in the control group. The information about TIMP-1 levels in allergic patients was limited. In our opinion the control group should be healthy and free of any allergic or infectious disease. In the study in which TIMP-1 was found in low levels as well as in our study concha bullosa specimens were used for the control group. Concha bullosa is a variation of normal anatomy. With a deviation of nasal septum, it can cause narrowing in internal nasal valve area. However we do not expect any alteration of inflammatory cascade in Concha bullosa. Two other studies used the inferior turbinate in the control group. The control group patients underwent inferior turbinectomy because of allergic or vasomotor rhinitis in these studies [13, 14]. Dissimilarity in control groups may be the cause of different results for TIMP-1 levels.

In normal wound repair both MMP-9 and TIMP-1 levels were found high in animal studies [17]. MMP-9 and TIMP-1 transcripts peaked 1 to 3 days after wounding and had a definite return to baseline after 3 days and 14 days respectively. Soo et al suggested that loss of orderly MMP and TIMP expression may lead to abnormal extracellular matrix degradation followed by abnormal remodeling with consequent failure to heal through the different stages of repair [17]. Armstrong and Jude pointed out the high MMP levels and low TIMP levels in chronic wounds [8]. High levels of MMP-9 were found in abdominal aortic aneurysms [18]. Expression of MMP-9 is upregulated and TIMP-1 downregulated in human monocyte-derived macrophages by oxidised low-density lipoprotein, suggesting that these may contribute to matrix degradation in atherosclerotic plaque, predisposing to plaque rupture and/or vascular remodeling [18]. Lee et al. also pointed MMP-9/TIMP-1 imbalance in nasal polyps and suggested that this imbalance may play a role in regulating inflammatory response in nasal polyps [19].

Beside the fact that the nasal polyp formation mechanism is still unknown, we know that remodeling of the Lamina propria is necessary for polyp formation [3]. Tos proposed epithelial rupture theory. According to this theory, the main stages of polyp formation are epithelial rupture, prolapse of the Lamina propria, gland formation and elongation due to gravity and changes of the epithelium and stroma such as cell infiltration, oedema and vascularity of stroma. Tos thought the epithelial rupture due to tissue pressure by inflammatory oedema and infiltration of cells [20]. In our opinion a MMP/TIMP imbalance may cause epithelial rupture. The degradation of extracellular matrix proteins may be the key point for epithelial rupture. The degradation of type XVII collogen by MMP-9 was thought as a posible mechanism for destruction of airways and excessive bronchial permeability [9]. Type XVII collogen is a large extracellular and collagenous portion of transmambrane protein located in the hemidesmosomes of basal bronchial epithelial cells. Excessive secretion of MMP-9 which is not balanced with TIMP-1 secretion may cause excessive extracellular matrix degradation and epithelial rupture which are specific for polyp formation. Lechapt-Zalcman et al. showed that MMP-9 immunolabelling was more intense in epithelial area with morphological changes such as secretory and basal hyperplasia [12]. They also detected MMP-9 labelling in typical cystically dilated nasal polyp glands. On the other hand we should also mention that elevated MMP-9 levels could also be secondary to the epithelial rupture. However experimental studies showed us that specific inhibition of MMPs prevents animals or cells from pathological processes such as abdominal aortic aneurysms, smoke-induced emphysema and arsenic caused derogation of wound repair [10, 21, 22]. These findings make us think MMPs are not secreted secondary to the pathological processes but it is very likely that MMPs play primary roles in pathogenesis.

Additionally, the MMP/TIMP imbalance can play a role in vascularisation of polyp tissue. The importance of MMP and TIMP levels for tumour invasion, extravasation and angiogenesis are well known [23]. Toi et al. showed MMP-9 and TIMP-1 play role in angiogenesis. They suggested aleration of the balance between MMPs and TIMPs might play a role as a switch to initiate neovascularisation [24]. MMPs have an inducing effect on angiogenesis; however the effect of TIMPs is inhibiting [13]. In our study we found MMP-9 levels high, and the TIMP-1 levels low. These results seem compatible with presence of angiogenesis in polyp tissues. High levels of MMP-9 induce endothelial activating factors; low levels of TIMP-1 reduce the inhibition of angiogenesis. These factors facilitate the vascularisation of nasal polyps.

MMP-9 is produced predominantly by leukocytes [8]. It is probable in nasal polyposis that most of inflammatory cells secrete MMPs. Different kind of mechanisms affects MMP secretion. Cytokines, growth factors, hormones, oncogenes, contacting with extracellular matrix or other cells can regulate MMP secretion [25]. Pawankar noticed that fibronectin, chymase and tryptase were able to upregulate the production of MMP-9 [5]. In our study we didn't find any correlation between the number of cell populations and levels of MMPs ($p = 0.512$). This showed us that MMP-9 secretion can be regulated by different mecha-

nisms independent from number of inflammatory cell population.

Conclusion

We demonstrated high levels of MMP-9 and low levels of TIMP-1 in nasal polyposis. We believe that the MMP-9/TIMP-1 imbalance has a vital role in nasal polyp formation mechanism and that discovering drugs (systemic or topic) to reduce MMP-9/TIMP-1 levels can help to develop new means of therapy.

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