

REVIEW

Lactoferrin in Chronic Pancreatitis

Chun Xiang Jin¹, Tetsuo Hayakawa², Motoji Kitagawa³, Hiroshi Ishiguro⁴

¹Second Clinical College of Norman Bethune Medical Division, Jilin University. Changchun, China. ²Meijo Hospital, Nagoya, Japan. ³Department of Nutritional Science, Nagoya University of Arts and Science. Nisshin, Japan. ⁴Department of Human Nutrition, Nagoya University Graduate School of Medicine. Nagoya Japan

Summary

The present review is focused on the clinical significance of lactoferrin in pancreatic secretions and stone formation in chronic pancreatitis, and of serum anti-lactoferrin antibody in autoimmune pancreatitis. Lactoferrin secretion is increased in pancreatic secretions in calcified and non-calcified chronic pancreatitis. Lactoferrin, pancreatic stone protein and trypsin are present in pancreatic stones. We cannot conclude which protein is more important for the precipitate and stone formation. The presence of anti-lactoferrin antibody has been reported in serum in autoimmune diseases, such as autoimmune pancreatitis. The coincidental appearance of autoimmune pancreatitis with extrapancreatic autoimmune diseases strongly suggests a common autoimmune mechanism and lactoferrin is a candidate antigen. Lactoferrin may play an important role as a precipitate protein in pancreatic stone formation in chronic pancreatitis and as an autoantigen in autoimmune pancreatitis. Further studies are required to better understand the role of lactoferrin.

Introduction

Lactoferrin is an iron-binding protein present mainly in external secretions such as breast milk and polymorphonuclear white cells [1, 2, 3, 4]. The protein is synthesized during the transition of neutrophils from promyelocytes to myelocytes and is stored in the secondary granules [5]. Lactoferrin is released from polymorphonuclear leucocytes on activation of these cells, and its presence in body fluids is proportional to the flux of neutrophils [4, 5, 6, 7]. Determination of the lactoferrin content in various body fluids can be a marker inflammation.

Lactoferrin is normally present in low concentration in pancreatic secretions and the concentration tends to increase in chronic pancreatitis [8]. Therefore, lactoferrin was also incriminated in the past in formation of protein plugs in the pancreatic duct by aggregating with acid macromolecules under decreased secretion of bicarbonate in the pancreatic juice [9, 10]. Chronic pancreatitis is characterized by progressive and irreversible pancreatic damage, parenchymal loss

and interstitial fibrosis which eventually result in significant impairment of the exocrine and endocrine pancreatic functions. Additional histopathological features have been described as pancreatic calcification in advanced forms of chronic pancreatitis (regardless of etiology) and a prominent lymphoplasmacytic infiltrate in autoimmune pancreatitis. Additional details of its pathogenesis and mechanism are required regarding its formation in the pancreatic ducts and prominent lymphoplasmacytic infiltrate.

The etiology and prevalence of chronic pancreatitis have been widely reported in India and Asian-Pacific areas as well as in Western countries in the last ten years [11, 12, 13]. The present review will focus on the clinical significance of lactoferrin in pancreatic secretions and stone formation in chronic pancreatitis, and of serum anti-lactoferrin antibody in autoimmune pancreatitis.

Lactoferrin in Pancreatic Juice

An analysis of the protein components of the pancreatic juice is important for clarifying the mechanism of stone formation in the pancreatic duct. Plugs formed by the precipitation of the protein within the interlobular and intralobular ducts are one of the earliest findings in chronic pancreatitis and the protein plugs subsequently perpetuate inflammation of the gland through recurrent obstruction of the pancreatic duct system.

If concentration-dependent precipitation is a cause of protein plug formation, some proteins must be

Received December 21st, 2008 - Accepted February, 20th, 2009

Key words Antibodies; Autoimmune Diseases; Calculi; Lactoferrin; Pancreas; Pancreatitis; Pancreatitis, Chronic

Correspondence Tetsuo Hayakawa
Meijo Hospital, Sannomaru 1-3-1, Naka-ku, Nagoya, Japan 460-0001
Phone: +81-52.201.5311; Fax: +81-52.201.5318
E-mail: t_hayakawa@meijohosp.com

Document URL <http://www.joplink.net/prev/200905/04.html>

increased, at least, in their concentration. Through analysis of the pancreatic juice, the iron-binding protein, lactoferrin, has been found to be secreted in greater amounts in patients with chronic pancreatitis [8, 14, 15, 16, 17, 18]. Lactoferrin may play a role in the formation of the protein plugs frequently seen in chronic pancreatitis because of their ability to produce the aggregation of a large acidophilic protein, such as albumin [19].

Lactoferrin hypersecretion by the pancreas was initially postulated by Figarella and Sarles to be a congenital secretory defect, possibly worsening the damaging effects of alcohol and malnutrition in the pancreas [10]. Subsequent studies failed to reveal a significant correlation between chronic alcohol consumption and lactoferrin concentration in pancreatic secretion, although they confirmed a hyperconcentration of lactoferrin in both non-calcified and calcified chronic pancreatitis [15]. Lactoferrin hyperconcentration has also been reported in pancreatic juice by Fedail *et al.* and by Tympner *et al.* and in duodenal juice by Brugge and Burke [14, 16, 20]. In our previous reports, we demonstrated the increased secretion of lactoferrin in non-calcified and calcified chronic pancreatitis in both pancreatic and duodenal juice [17, 18, 21]. However, the simultaneous elevation of the protein and lactoferrin in pancreatic secretions occurred in European patients with chronic pancreatitis, but not in Japanese patients [14, 16, 17, 18]. The reasons for the discrepancy are not clear. Brugge and Burke revealed that lactoferrin concentration and its output in duodenal juice, not pure pancreatic juice, were both increased in asymptomatic alcoholics, alcoholics recovered from acute pancreatitis and alcoholics with chronic pancreatitis when compared with those in nonalcoholic healthy subjects [20]. Polymorphonuclear leucocytes were commonly encountered in the pancreatic juice of alcoholics even in those without clinical pancreatitis [19]. Therefore, the presence of leucocytes could account for a part of the increased lactoferrin seen in alcoholics and patients with pancreatic disease since one million polymorphonuclear leucocytes contain 3 µg of lactoferrin.

No increase could be found in lactoferrin concentration in either the plasma or parotid saliva of the controls and patients with chronic pancreatitis [10, 22]. However, increased levels were observed in the parotid saliva of patients with parotid gland disease. Benini *et al.* have speculated that increased lactoferrin levels in saliva are secondary to the inflammation [22], and it seems probable that the same is also true of the pancreas.

Lactoferrin in Pancreatic Stones

Protein analysis of the intraductal precipitates and calculi is important in order to elucidate the mechanism of stone formation in the pancreatic duct. Mariani *et al.* compared calcified stones obtained from 20 alcoholic patients with radiolucent stones obtained from five non-alcoholic patients [23]. They speculated that the

formation of these two types of pancreatic stones was mediated by two different mechanisms. The formation of the calcified radiopaque stones was attributed to the precipitation of calcium carbonate occurring as a consequence of the reduced secretion of pancreatic stone protein which normally functions as an inhibitor of calcium carbonate precipitation. Therefore, pancreatic stone protein reduction could be expected to result in the precipitation of calcium carbonate, leading to stone formation in the pancreatic duct. However, reduction of pancreatic stone protein secretion or an inhibitory effect of calcium precipitation specific to pancreatic stone protein has not yet been confirmed in cases of chronic pancreatitis. Mariani *et al.* postulated that the formation of radiolucent stones, on the other hand, could be attributed to precipitation of degraded forms of pancreatic stone protein [23]. Thus, stone formation in chronic pancreatitis could be due to the precipitation of either calcium or proteinaceous materials.

Lactoferrin and pancreatic stone protein are thought to be closely related to pancreatic stone formation in chronic pancreatitis. No significant reduction of pancreatic stone protein was observed in either calcified or non-calcified chronic pancreatitis patients [18].

Allan and White proposed a mechanism of protein plug formation, involving the partial activation of pancreatic secretion resulting in precipitation formation in the ductules as an initial step, followed by the development of protein plugs from these precipitations through the slow adsorption of salts and protein from newly-secreted pancreatic juice [9]. Intraductal activation by pancreatic zymogens with the occasional appearance of precipitates in the ductules has been noted in some patients with pancreatitis [9, 24, 25]. Hayakawa *et al.* observed human cationic trypsin immunoreactivity in protein extracts of pancreatic stones in 11 of 13 patients with chronic calcified pancreatitis, ranging from 0 to 42.3 ng/µg protein [26]. On immunostaining of pancreatic stones, immunoreactivity was observed to be more intense in the amorphous portion of the center of the stones than in the concentric laminar layer of the periphery. Only negligible activity was detected for elastase 1 or amylase in the stone extracts [26]. These results suggest that the presence of trypsinogen in pancreatic stones is not due to coprecipitation or adsorption of pancreatic enzymes but that trypsinogen is more likely involved in an initial step of intraductal precipitate formation than in a subsequent step of stone formation. Jin *et al.* [27] determined pancreatic stone protein and lactoferrin in pancreatic stones obtained from the 13 patients with chronic calcified pancreatitis same as in the previous study [26]. Pancreatic stone protein was measured in pancreatic stones in all 13 patients, but did not differ significantly between alcoholic (n=6) and non-alcoholic (n=7) pancreatitis. Lactoferrin was detectable in 5 of the 13 patients. There was neither a definite common etiology nor clinical features to explain the high lactoferrin contents

[27]. The stone in one patient was predominantly composed of fatty acid calcium [28]. The stones in another two patients were large and were obtained from the markedly dilated main pancreatic duct. Recurrent inflammation in a cystic lesion or dilated ducts in the three patients could be a common factor attributable to high contents of lactoferrin.

Nagai and Ohtsubo reported calcified stones in the pancreata of elderly people autopsied at a geriatric hospital [29]. The incidence of pancreatic calculi increased after 70 years of age: 0% under 69 years of age, 4.2% between 70 and 79 years of age, 7.7% between 80 and 89 years of age and 16.7% over 90 years of age. The small calculi found in the 22 patients were 1-3 mm in diameter and 2-100 in number and were distributed throughout the pancreas. All of the small calculi were composed of calcium carbonate and located in the peripheral branch of the pancreatic duct. No patients had a history of pancreatitis or abdominal pain suggestive of pancreatic abnormality. Lactoferrin was observed in acinar cells to some extent, but it was present in much greater concentrations in the protein plugs and in the cytoplasm of squamous cells of the dilated ducts encasing the plugs. This suggested that lactoferrin may play a role in an initial stage of protein plug formation in the pancreatic duct [29]. On immunogold staining and scanning electron microscopy of pancreatic stones, trypsin immunoreactivity was observed more densely in the amorphous portion of the center of the stones than in the concentric laminar layer of the periphery. Trypsin is more likely involved in an initial step of intraductal precipitate formation than in a subsequent step of stone formation [26]. Distribution of pancreatic stone protein-gold particles differs from the center to the periphery of the stone [27]. The exact distribution of lactoferrin-gold particle is not clear in spite of our expectation of a more intense distribution in the amorphous portion of the center of the stones.

It is still inconclusive whether lactoferrin comes from polymorphonuclear leucocytes or is produced in the pancreatic tissues, such as acinar cells, ductal cells, etc..

We can not conclude which protein is more important for precipitate and stone formation. We found a pancreatic stone containing lactoferrin but only trace amounts of trypsin and pancreatic stone protein in a patient with chronic pancreatitis [26, 27]. In a canine experimental model of pancreatolithiasis, persistent stasis of protein-rich pancreatic juice secondary to partial obstruction in the pancreatic duct leads to calculus formation [30], although dogs lack lactoferrin. These results suggest that additional candidate proteins and mechanisms will be required in stone formation.

Anti-Lactoferrin Autoantibody in Serum

Autoimmune pancreatitis is a relatively uncommon, non-alcoholic-related form of chronic pancreatitis

which has received increasing attention in recent years. Autoimmune pancreatitis is characterized by: i) the presence of increased serum gammaglobulin levels (particularly IgG4); ii) the presence of autoantibodies (anti-lactoferrin autoantibody, anticarbonic anhydrase antibodies, rheumatoid factor, and antinuclear antibodies); iii) pancreatic fibrosis with lymphocytic infiltration and absence of pancreatic calcification; iv) association with other autoimmune diseases and v) response to steroid therapy [31]. Chari recently gave the following definition: "autoimmune pancreatitis is a systemic fibroinflammatory disease which affects not only the pancreas but also a variety of other organs including the bile duct, salivary glands, retroperitoneum and lymph nodes. Organs affected by autoimmune pancreatitis have a lymphoplasmacytic infiltrate rich in IgG4 positive cells and the inflammatory process responds to steroid therapy" [32]. The pathogenesis of this disease remains largely unknown but, from clinical and experimental studies, it has been postulated that aberrant HLA-DR expression (in autoimmune pancreatitis HLA-DR expression has been found in pancreatic ductal and acinar cells) leads to the presentation of autoantigens to lymphocytes, resulting in autoimmune response [31]. The presence of serum anti-lactoferrin autoantibody has been reported in patients with autoimmune-related disease, such as autoimmune pancreatitis [33, 34, 35, 36, 37, 38, 39, 40, 41], autoimmune hepatitis [42, 43, 44], systemic lupus erythematosus [45, 46], ulcerative colitis [44], Crohn's disease [34], primary sclerosing cholangitis [42, 43, 44] and type I diabetes mellitus [39, 41]. The coincidental appearance of autoimmune pancreatitis with extrapancreatic autoimmune diseases strongly suggests a common pathogenesis. Various autoantibodies have been screened in patients with autoimmune pancreatitis and/or other autoimmune diseases. Among these are antinuclear antibodies, antibodies against lactoferrin carbonic anhydrase type II and pancreatic secretory trypsin inhibitor, etc. Okazaki *et al.* have reported detection rates of autoantibodies in 54 patients with autoimmune pancreatitis: anti-lactoferrin autoantibody: 75%, antinuclear: 65%, anticarbonic anhydrase: 55%, anti-pancreatic secretory trypsin inhibitor: 33%, and rheumatoid factor: 25% [40]. Uchida *et al.* have demonstrated that mice developed pancreatitis as well as sialadenitis and cholangitis after subcutaneous injection with lactoferrin or carbonic anhydrase [47]. These findings described above suggest that an autoimmune mechanism may be involved in the pathogenesis of autoimmune pancreatitis, and lactoferrin is a candidate antigen as well as the other above-mentioned antigens. However, positivity for anti-lactoferrin autoantibody is not associated with a particular clinical or biochemical profile of the underlying disease and seems to reflect an immune reaction state. Overinterpretation is the major pitfall in the clinical application of the serological results.

Conclusion

In conclusion, lactoferrin may play various roles as a precipitate protein in pancreatic stone formation in chronic calcified pancreatitis and as an autoantigen in autoimmune pancreatitis. Further studies are required to better understand the role of lactoferrin.

Conflict of interest The authors have no potential conflicts of interest

References

1. Johansson B. Isolation of an iron containing red protein from human milk. *Acta Chem Scand* 1960; 14:510-2.
2. Iyer S, Lönnerdal B. Lactoferrin, lactoferrin receptors and iron metabolism. *Eur J Clin Nutr* 1993; 47:232-41. [PMID 8491159]
3. Broch J. Lactoferrin: a multifunctional immunoregulatory protein? *Immunology Today* 1995; 16:417-9. [PMID 7546203]
4. Martins CA, Fonteles MG, Barrett LJ, Guerrant RL. Correlation of lactoferrin with neutrophilic inflammation in body fluids. *Clin Diagn Lab Immunol* 1995; 2:763-5. [PMID 8574844]
5. Rado T A, Bollekens J, St Laurent G, Parker L, Benz E J Jr. Lactoferrin biosynthesis during granulocytopenia. *Blood* 1984; 64:1103-9. [PMID 6593100]
6. Guerrant RL, Araujo V, Soares E, Kotloff K, Lima AA, Cooper WH, Lee AG. Measurement of fecal lactoferrin as a marker of fecal leukocytes. *J Clin Microbiol* 1992; 30:1238-42. [PMID 1583125]
7. Parsi MA, Saadeh SN, Zein NN, Davis GL, Lopez R, Boone J, et al. Ascitic fluid lactoferrin for diagnosis of spontaneous bacterial peritonitis. *Gastroenterology* 2008; 135:803-7. [PMID 18590731]
8. Hayakawa T, Harada H, Noda A, Kondo T. Lactoferrin in pure pancreatic juice in chronic pancreatitis. *Am J Gastroenterol* 1983; 78:222-4. [PMID 6837546]
9. Allan J, White TT. An alternate mechanism for the formation of protein plugs in chronic calcifying pancreatitis. *Digestion* 1974; 11:428-31. [PMID 4618542]
10. Figarella C, Sarles H. Lactoferrin, a protein of human pancreatic external secretion. *Scand J Gastroenterol* 1975; 10:449-51. [PMID 1098131]
11. Garg PK, Tandon RK. Survey on chronic pancreatitis in the Asia-Pacific region. *J Gastroenterol Hepatol* 2004; 19:998-1004. [PMID 15304116]
12. Pezzilli R, Lioce A, Frulloni L. Chronic pancreatitis: a changing etiology? *JOP. J Pancreas (Online)* 2008; 9(5):588-92. [PMID 18762689]
13. Balakrishnan V, Unnikrishnan AG, Thomas V, Choudhuri G, Veeraraju P, Singh SP, et al. Chronic pancreatitis. A prospective nationwide study of 1,086 subjects from India. *JOP. J Pancreas (Online)* 2008; 9(5):593-600. [PMID 18762690]
14. Fedail SS, Harvey RF, Salmon PR, Brown P, Read AE. Trypsin and lactoferrin levels in pure pancreatic juice in patients with pancreatic disease. *Gut* 1979; 20:983-6. [PMID 527874]
15. Multigner L, Figarella C, Sahel J, Sarles H. Lactoferrin and albumin in human pancreatic juice: a valuable test for diagnosis of pancreatic diseases. *Dig Dis Sci* 1980; 25:173-8. [PMID 6768533]
16. Tymptner F. Selectively aspirated pure pancreatic secretion. Viscosity, trypsin activity, protein concentration and lactoferrin content of pancreatic juice in chronic pancreatitis. *Hepatogastroenterology* 1981; 28:169-72. [PMID 7250899]
17. Hayakawa T, Kondo T, Shibata T, Murase T, Harada H, Ochi K, Tanaka J. Secretory component and lactoferrin in pure pancreatic juice in chronic pancreatitis. *Dig Dis Sci* 1993; 38:7-11. [PMID 7678385]

18. Hayakawa T, Naruse S, Kitagawa M, Nakae Y, Harada H, Ochi K, et al. Pancreatic stone protein and lactoferrin in human pancreatic juice in chronic pancreatitis. *Pancreas* 1995; 10:137-42. [PMID 7716137]
19. Hekman A. Association of lactoferrin with other proteins, as demonstrated by changes in electrophoretic mobility. *Biochim Biophys Acta* 1971; 251:380-7. [PMID 11452880]
20. Brugge WR, Burke CA. Lactoferrin secretion in alcoholic pancreatic disease. *Dig Dis Sci* 1988; 33:178-84. [PMID 3338366]
21. Ito K, Hayakawa T. Lactoferrin of duodenal juice in pancreatitis. *Jpn J Gastroenterol (Nippon Shokakibyō Gakkai Zasshi)* 1981; 78:914-22. [PMID 7277799]
22. Benini L, Harvey RF, Vantini I, Piubello W, Lucchin L, Brocco G, et al. Lactoferrin concentration in the parotid saliva of patients with chronic pancreatitis. *Digestion* 1983; 28:77-81. [PMID 6653928]
23. Mariani A, Bernard JP, Provansal-Cheylan M, Nitsche S, Sarles H. Differences of pancreatic stone morphology and content in patients with pancreatic lithiasis. *Dig Dis Sci* 1991; 36:1509-16. [PMID 19160597]
24. Renner IG, Rinderknecht H, Douglas AP. Profiles of pure pancreatic secretions in patients with acute pancreatitis: the possible role of proteolytic enzymes in pathogenesis. *Gastroenterology* 1978; 75:1090-8. [PMID 710862]
25. Geokas MC, Rinderknecht H. Free proteolytic enzymes in pancreatic juice of patients with acute pancreatitis. *Am J Dig Dis* 1974; 19:591-8. [PMID 4835329]
26. Hayakawa T, Kondo T, Shibata T, Kitagawa M, Nakae Y, Hayakawa S. Trypsin(ogen) content of pancreatic calculi in chronic calcified pancreatitis in man. *Dig Dis Sci* 1994; 39:1345-50. [PMID 8200269]
27. Jin CX, Naruse S, Kitagawa M, Ishiguro H, Kondo T, Hayakawa S, Hayakawa T. Pancreatic stone protein of pancreatic calculi in chronic calcified pancreatitis in man. *JOP. J Pancreas (Online)* 2002; 3(2):54-61. [PMID 11884767]
28. Kitagawa M, Hayakawa T, Kondo T, Shibata T, Sakai Y, Sobajima H, et al. Pancreatic stone predominantly composed of fatty acid calcium. *Gastroenterology* 1992; 102:2151-4. [PMID 1587438]
29. Nagai H, Ohtsubo K. Pancreatic lithiasis in the aged. Its clinicopathology and pathogenesis. *Gastroenterology* 1984; 86:331-8. [PMID 6690361]
30. Okumura N, Sakakibara A, Hayakawa T, Noda A. Pancreatic endocrine function in experimental pancreatolithiasis in dogs. *Am J Gastroenterol* 1982; 77:392-6. [PMID 7046428]
31. Witt H, Apte MV, Keim V, Wilson JS. Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis, and therapy. *Gastroenterology* 2007; 132:1157-73. [PMID 17466744]
32. Chari ST. Current concepts in the treatment of autoimmune pancreatitis. *JOP. J Pancreas (Online)* 2007; 8(1):1-3. [PMID 17228127]
33. Okazaki K, Uchida K, Ohana M, Nakase H, Uose S, Inai M, et al. Autoimmune-related pancreatitis is associated with autoantibodies and a Th1/Th2-type cellular immune response. *Gastroenterology* 2000; 118:573-81. [PMID 10702209]
34. Klöppel G, Lüttges J, Löhr M, Zamboni G, Longnecker D. Autoimmune pancreatitis: pathological, clinical, and immunological features. *Pancreas* 2003; 27:14-9. [PMID 12826900]
35. Okazaki K. Autoimmune pancreatitis: etiology, pathogenesis, clinical findings and treatment. The Japanese experience. *JOP. J Pancreas (Online)* 2005; 6(1 Suppl):89-96. [PMID 15650291]
36. Klöppel G, Lüttges J, Sipos B, Capelli P, Zamboni G. Autoimmune pancreatitis: pathological findings. *JOP. J Pancreas (Online)* 2005; 6(1 Suppl):97-101. [PMID 15650292]
37. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol* 2006; 41:613-25. [PMID 16932997]

38. Löhner JM. What are the useful biological and functional markers of early-stage chronic pancreatitis? *J Gastroenterol* 2007; 42:66-71. [PMID 17238031]
 39. Hardt PD, Ewald N, Bröckling K, Tanaka S, Endo T, Kloer HU, et al. Distinct autoantibodies against exocrine pancreatic antigens in European patients with type 1 diabetes mellitus and non-alcoholic chronic pancreatitis. *JOP. J Pancreas (Online)* 2008; 9(6):683-9. [PMID 18981548]
 40. Okazaki K, Uchida K, Fukui T. Recent advances in autoimmune pancreatitis: concept, diagnosis, and pathogenesis. *J Gastroenterol* 2008; 43:409-18. [PMID 18600384]
 41. Taniguchi T, Okazaki K, Okamoto M, Seko S, Tanaka J, Uchida K, et al. High prevalence of autoantibodies against carbonic anhydrase II and lactoferrin in type 1 diabetes: concept of autoimmune exocrinopathy and endocrinopathy of the pancreas. *Pancreas* 2003; 27:26-30. [PMID 12826902]
 42. Ohana M, Okazaki K, Hajiro K, Uchida K. Antilactoferrin antibodies in autoimmune liver diseases. *Am J Gastroenterol* 1998; 93:1334-9. [PMID 9707061]
 43. Muratori L, Muratori P, Zauli D, Grassi A, Pappas G, Rodrigo L, et al. Antilactoferrin antibodies in autoimmune liver disease. *Clin Exp Immunol* 2001; 124:470-3. [PMID 11472410]
 44. Peen E, Eneström S, Skogh T. Distribution of lactoferrin and 60/65 kDa heat shock protein in normal and inflamed human intestine and liver. *Gut* 1996; 38:135-40. [PMID 8566841]
 45. Sinico RA, Pozzi C, Radice A, Tincani A, Li Vecchi M, Rota S, et al. Clinical significance of antineutrophil cytoplasmic autoantibodies with specificity for lactoferrin in renal diseases. *Am J Kidney* 1993; 22:253-60. [PMID 8352249]
 46. Chikazawa H, Nishiya K, Matsumori A, Hashimoto K. Immunoglobulin isotypes of anti-myeloperoxidase and anti-lactoferrin antibodies in patients with collagen diseases. *J Clin Immunol* 2000; 20:279-86. [PMID 10939715]
 47. Uchida K, Okazaki K, Nishi T, Uose S, Nakase H, Ohana M, et al. Experimental immune-mediated pancreatitis in neonatally thymectomized mice immunized with carbonic anhydrase II and lactoferrin. *Lab Invest* 2002; 82:411-24. [PMID 11950899]
-