Accepted Manuscript

The American Journal of Surgery®

Diabetes Increases the Risk of an Appendectomy in Patients with Antibiotic Treatment of Non-complicated Appendicitis

Ming-Chieh Tsai, MD, Herng-Ching Lin, PhD, Cha-Ze Lee, MD, PhD

PII: S0002-9610(16)30441-X

DOI: 10.1016/j.amjsurg.2016.07.026

Reference: AJS 12037

To appear in: *The American Journal of Surgery*

Received Date: 2 May 2016

Accepted Date: 23 July 2016

Please cite this article as: Tsai M-C, Lin H-C, Lee C-Z, Diabetes Increases the Risk of an Appendectomy in Patients with Antibiotic Treatment of Non-complicated Appendicitis, *The American Journal of Surgery* (2016), doi: 10.1016/j.amjsurg.2016.07.026.

Diabetes Increases the Risk of an Appendectomy in Patients with Antibiotic Treatment of Non-complicated Appendicitis

Ming-Chieh Tsai, MD[1,2] Herng-Ching Lin, PhD[2,3] Cha-Ze Lee, MD, PhD[4]

[1]Division of Gastroenterology, Department of Internal Medicine, Hsinchu Cathay General Hospital, Taipei, Taiwan

[2] School of Health Care Administration, Taipei Medical University Hospital, Taipei, Taiwan

[3]Sleep Research Center, Taipei Medical University, Taipei, Taiwan

[4] Division of Gastroenterology, Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan

Corresponding author: Cha-Ze Lee, Division of Gastroenterology, Department of Internal Medicine, National Taiwan University Hospital,No.280, Sec. 4, Ren'ai Rd., Da'an Dist., Taipei City, Tel: 27082121, E-mail address: czl@ntu.edu.tw

Ming-Chieh Tsai and Herng-Ching Lin have equal contributions to this study

Running title: Appendicitis and Diabetes

Disclosure: No conflict of financial interest to declare.

No funding source

ABSTRACT

Background: This retrospective cohort study examined whether diabetic patients have a higher risk for recurrent appendicitis during a 1-year follow-up period after successful antibiotic treatment for patients with acute uncomplicated appendicitis than non-diabetic patients using a population-based database.

Methods: We included 541 appendicitis patients who received antibiotic treatment for acute appendicitis. We individually tracked each patient for a 1-year period to identify those who subsequently underwent an appendectomy during the follow-up period.

Results: Cox proportional hazard regressions suggested that the adjusted hazard ratio (HR) of an appendectomy during the 1-year follow-up period was 1.75 for appendicitis patients with diabetes than appendicitis patients without diabetes. We found that among females, the adjusted HR of an appendectomy was 2.18 for acute appendicitis patients with diabetes than their counterparts without diabetes. However, we failed to observe this relationship in males.

Conclusions: We demonstrated a relationship between diabetes and a subsequent appendectomy in females who underwent antibiotic treatment for non-complicated appendicitis.

Key words: appendicitis; appendectomy; diabetes; antibiotic treatment

INTRODUCTION

An appendectomy is considered the gold standard of treatment for acute appendicitis because of the potential risk of disease progression to perforation, gangrene, and peritonitis.[1,2] However, it is associated with postoperative complications in about 2%~23% of patients who undergo this procedure.[3-5] Previous studies also showed that changes in immune function after an appendectomy may be associated with a variety of diseases such as coeliac disease, ulcerative colitis, Crohn's disease, *Clostridium difficile* infection, ischemic heart disease, pulmonary tuberculosis, rheumatoid arthritis, and diabetes.[6-15]

In 1959, Coldrey first reported the successful treatment of 471 patients with an acute appendicitis with antibiotics therapy.[16] Recent studies suggested that antibiotics are both safe and effective as primary treatment for patients with acute uncomplicated appendicitis in order to avoid an unnecessary appendectomy.[5,17-20] On the other hand, some studies reported that antibiotics are not non-inferior to an emergency appendectomy due to there being an increased risk of recurrence.[1,21] In particular, studies reported that antibiotic treatment failure in patients was due to acute complicated appendicitis or acute uncomplicated appendicitis with a fecalith and diabetes.[1,22] A study by Tsai et al. also indicated that diabetic patients had a higher risk of developing complicated acute appendicitis than nondiabetic patients.[22]

Contrary to a mechanical obstruction cause of acute appendicitis, bacteria and dysfunction of the neuromusculature at the appendicocecal juncture are considered other causes of appendiceal inflammation, which are related to host immunity and autonomic neuropathy.[23-29] Patients with diabetes may have altered gastrointestinal neurohumoral function and impaired host immunity.[22,30] Therefore, it is reasonable to consider the relationship between diabetes and recurrent appendicitis in acute uncomplicated appendicitis patients after successful antibiotic treatment. So, this retrospective cohort study examined whether diabetic patients had a higher risk of recurrent appendicitis during a 1-year follow-up period after successful antibiotic treatment of patients with acute uncomplicated appendicitis than non-diabetic patients using a population-based database.

METHODS

Database

We retrieved data for this study from the "Longitudinal Health Insurance Database 2005" (LHID2005). Taiwan began the National Health Insurance (NHI) program in 1995, and the coverage rate has been maintained at about 98.4% since its inception. The LHID2000 covers registration files and original medical claims for 1,000,000 enrollees randomly selected from all enrollees listed in the 2000 Registry of Beneficiaries under the NHI program (*n*=25.68 million) by the Taiwan National Health Research Institutes. Therefore, the LHID2005 enables researchers in Taiwan to longitudinally follow-up utilization of medical services by these selected 1,000,000 enrollees since the beginning of the NHI in 1995.

This study was exempt from full review by the Institutional Review Board (TMU-JIRB 201412035) since the LHID2005 consisted of de-identified secondary data released to the public for research purposes.

Study sample

We first identified 7747 patients who were hospitalized with a principal discharge diagnosis of non-complicated appendicitis (International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code 540 or 540.9) between January 2001 and December 2012. If a patient had ≥ 2 hospitalizations during

the study period, we only selected the first hospitalization for treatment of non-complicated appendicitis as the index hospitalization. We further excluded 7070 acute appendicitis patients who underwent an appendectomy (ICD-9-CM procedure code 470, 470.1, or 470.9) during their index hospitalization. In addition, we excluded 106 appendicitis patients who were aged <18 years in order to limit the study sample to the adult population. As a result, 571 appendicitis patients who received antibiotic treatment for acute appendicitis were included in this study. The antibiotics used to treat acute appendicitis included cephalosporins, penicillins, aminoglycosides, fluoroquinolones, and metronidazole. Of these 541 appendicitis patients, 108 (20.0%) had been diagnosed with diabetes prior to their index hospitalization. Thereafter, we individually tracked each patient for a 1-year period from the discharge date of their index hospitalization to identify those who subsequently underwent an appendectomy during the follow-up period.

Statistical analysis

We used the SAS system (vers. 9.1, SAS Institute, Cary, NC, USA) for statistical analyses. Pearson Chi-squared tests were performed to compare differences between acute appendicitis patients with and those without diabetes in terms of monthly income (NT$0~15,840, NT$15,841~25,000, ≥NT$25,001; the average exchange rate in 2007 was US$1.00≈New Taiwan (NT)$30), geographical location (northern, central,

eastern, and southern Taiwan), urbanization level of the patient's residence (five levels with 1 being the most urbanized and 5 being the least), and the Charlson Comorbidity Index (CCI). We also performed Cox proportional hazard regressions to calculate the hazard ratio (HR) and its corresponding 95% confidence interval (CI) for a subsequent appendectomy during the 1-year follow-up period between appendicitis patients with and those without diabetes. We used a significance level of 0.05.

RESULTS

Table 1 presents the distributions of demographic characteristics and the CCI between acute appendicitis patients with and those without diabetes. It shows that there was a significant difference in the mean age (p<0.001) and CCI (p<0.001) between appendicitis patients with and those without diabetes. Acute appendicitis patients with diabetes were more likely to be older than their counterparts without diabetes (61.5 vs. 46.1 years). However, we observed no significant difference in monthly income, urbanization level, or geographic region between appendicitis patients with and those without diabetes.

Table 2 presents the incidence of a subsequent appendectomy during the 1-year follow-up period stratified by the presence of diabetes. Of the sampled subjects, 113 (20.9%) underwent an appendectomy during the 1-year follow-up period: 30 (27.8%) among appendicitis patients with diabetes and 83 (19.2%) among appendicitis patients without diabetes. The log-rank test suggests that appendicitis patients with diabetes were more likely to undergo an appendectomy than appendicitis patients without diabetes (p=0.003).

Table 2 also shows the crude and adjusted HRs for a subsequent appendectomy. The Cox proportional analysis suggested that the HR for an appendectomy during the 1-year follow-up period was 1.62 (95% CI=1.00~2.63) for non-complicated

appendicitis patients with diabetes compared to non-complicated appendicitis patients without diabetes. Furthermore, after adjusting for age and the CCI, the HR for an appendectomy during the 1-year follow-up period was 1.75 (95% CI=1.01~3.02) for appendicitis patients with diabetes than appendicitis patients without diabetes.

Table 3 analyzed the crude and adjusted HRs of need for a subsequent appendectomy according to sex. We found that among females, the adjusted HR for an appendectomy was as high as 2.18 (95% CI=1.06~4.50) for acute appendicitis patients with diabetes compared to acute appendicitis patients without diabetes. However, we failed to observe an increased hazard for an appendectomy among acute appendicitis males with diabetes compared to acute appendicitis males without diabetes.

DISCUSSION

This retrospective cohort study shows that among acute uncomplicated appendicitis patients who received antibiotic treatment, diabetic patients were more likely to undergo a subsequent appendectomy during the 1-year follow-up period than those without diabetes (27.8% vs. 19.2%, p=0.003). Furthermore, the Cox proportional analysis suggested that diabetes was significantly associated with an increased risk of a subsequent appendectomy with recurrent appendicitis (adjusted HR=1.72, 95% CI=1.01~3.02).

The high risk of a subsequent appendectomy among acute uncomplicated appendicitis patients with diabetes may be explained by bacterial factors and patient immunity. In contrast to an obstruction of the appendix, bacteria are nowadays considered to play the most important role in appendiceal inflammation, particularly *Fusobacterium nucleatum*/*necrophorum* infection.[23-26] A previous study reported that patients with diabetes had an increased risk of acquiring *Fusobacterium* bacteremia.[27] In addition, plenty of studies have indicated that depressed immunity in patients with diabetes can result in more-severe complications in various gastrointestinal diseases.[22,31-32]

Some studies also reported that a certain portion of appendicitis, such as appendiceal lumen obstruction due to spasms or hypertonicity of the

neuromusculature at the appendicocecal juncture, is caused by an autonomic nervous imbalance.[28,29] Patients with diabetes may develop a neuropathy, which may distort control of the gastric and/or intestinal motor as well as the sensory function.[30]

Associations of gender and age with appendicitis recurrence were also reported, but their conclusions are equivocal.[18,33] In the present study, we found that the relationship between diabetes and a subsequent appendectomy was only observed in females but not in males. The mechanism contributing to this relationship is still unknown. However, recent studies reported that females with diabetes have an increased risk of morbidity and mortality compared to males with diabetes. It was explained that more females with diabetes have a late diagnosis and have diagnoses at higher body-mass index (BMI) levels with poor insulin adherence than males, which suggests that females have a more-immunocompromised status than males.[34,35] Further prospective studies are warranted to confirm our findings and clarify the underlying pathomechanism.

This study has several strengths. First, a population-based dataset was used to explore the relationship between diabetic patients with acute appendicitis and recurrent acute appendicitis with a subsequent appendectomy during the study period. The large sample size afforded a considerable statistical advantage in detecting real differences between the two cohorts. Second, the diagnosis of diabetes had very high

validity since it is diagnosed and prescribed only by certified physicians in Taiwan. In addition, physicians performing an appendectomy on patients with appendicitis should be a strong indication and clinical evidence under Taiwan's national insurance and legal limits.

Nevertheless, the results of this study need to be interpreted in the light of several limitations. The first limitation is that the LHID2005 provides no information on the histology or the existence of fecaliths in appendectomy specimens and no record of glucose data or patient’s BMI level. Second, physicians do not routinely identify the bacterial species in uncomplicated appendicitis in Taiwan. All of these may influence the pathogenesis and risk factors for recurrent acute appendicitis.

Conclusions

Despite the aforementioned limitations, this study demonstrated a relationship between diabetes and a subsequent appendectomy in female patients with antibiotic treatment of non-complicated appendicitis. We suggest that clinicians be alert to the possibility of recurrent appendicitis in acute uncomplicated appendicitis patients with diabetes even prior to their successful treatment with antibiotics.

REFERENCES

1. Vons C, Barry C, Maitre S, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. Lancet 2011;377:1573-1579.

2. Fitzmaurice GJ, McWilliams B, Hurreiz H, Epanomeritakis E. Antibiotics versus appendectomy in the management of acute appendicitis: a review of the current evidence. Can J Surg 2011;54:307-314.

3. Konstantinidis KM, Anastasakou KA, Vorias MN, Sambalis GH, Georgiou MK, Xiarchos AG. A decade of laparoscopic appendectomy: presentation of 1,026 patients with suspected appendicitis treated in a single surgical department. J Laparoendosc Adv Surg Tech A 2008;18: 248-258.

4. Ming PC, Yan TY, Tat LH. Risk factors of postoperative infections in adults with complicated appendicitis. Surg Laparosc Endosc Percutan Tech 2009;19:244-248.

5. Styrud J, Eriksson S, Nilsson I, et al. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. World J Surg 2006;30:1033-1103.

6. Kaplan GG, Pedersen BV, Andersson RE, Sands BE, Korzenik J, Frisch M. The risk of developing Crohn's disease after an appendectomy: a population-based cohort study in Sweden and Denmark. Gut 2007;56:1387-1392.

7. Andersson RE, Olaison G, Tysk C, Ekbom A. Appendectomy is followed by increased risk of Crohn's disease. Gastroenterology 2003;124:40-46.

8. Radford-Smith GL, Edwards JE, Purdie DM, et al. Protective role of appendicectomy on onset and severity of ulcerative colitis and Crohn's disease. Gut 2002;51:808- 813.

9. Chen CH, Tsai MC, Lin HC, Lee HC, Lee CZ, Chung SD. Appendectomy increased the risk of ischemic heart disease. J Surg Res 2015;199:435-440.

10. Lai SW, Lin CL, Liao KF, Tsai SM. Increased risk of pulmonary tuberculosis among subjects with appendectomy in Taiwan. Eur J Clin Microbiol Infect Dis 2014;33:1573-1577.

11. Hallas J, Gaist D, Sorensen HT. Does appendectomy reduce the risk of ulcerative colitis? Epidemiology 2004;15:173-178.

12. Cosnes J, Carbonnel F, Beaugerie L, Blain A, Reijasse D, Gendre JP. Effects of appendicectomy on the course of ulcerative colitis. Gut 2002;51:803-807.

13. Ludvigsson JF, Askling J, Ekbom A, Montgomery SM. Diagnosis underlying appendectomy and coeliac disease risk. Dig Liver Dis 2006;38:823-828.

14. Tzeng YM, Kao LT, Kao S, Lin HC, Tsai MC, Lee CZ. An appendectomy increases the risk of rheumatoid arthritis: a five-year follow-up study. PLoS One 2015;10:e0126816.

15. Wei PL, Tsai MC, Hung SH, Lee HC, Lin HC, Lee CZ. Risk of new-onset type II diabetes after appendicectomy. Br J Surg 2015;102:1267-1271.

16. Coldrey E. Five years of conservative treatment of acute appendicitis. J Int Coll Surg 1959;32:255-261.

17. Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. BMJ 2012;344:e2156.

18. McCutcheon BA, Chang DC, Marcus LP, et al. Long-term outcomes of patients with nonsurgically managed uncomplicated appendicitis. J Am Coll Surg 2014;218:905-913.

19. Hansson J, Korner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. Br J Surg 2009;96:473-481.

20. Di Saverio S, Sibilio A, Giorgini E, et al. The NOTA Study (Non Operative Treatment for Acute Appendicitis): prospective study on the efficacy and safety of antibiotics (amoxicillin and clavulanic acid) for treating patients with right lower quadrant abdominal pain and long-term follow-up of conservatively treated suspected appendicitis. Ann Surg 2014;260:109-117.

21. Salminen P, Paajanen H, Rautio T, et al. Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis: The APPAC Randomized Clinical Trial. JAMA 2015;313:2340-2348.

22. Tsai SH, Hsu CW, Chen SC, Lin YY, Chu SJ. Complicated acute appendicitis in diabetic patients. Am J Surg 2008;196:34-39.

23. Arnbjörnsson E, Bengmark S. Role of obstruction in the pathogenesis of acute appendicitis. Am J Surg 1984;147:390-392.

24. Carr NJ. The pathology of acute appendicitis. Ann Diagn Pathol 2000;4:46-58.

25. Swidsinski A, Dörffel Y, Loening-Baucke V, et al. Acute appendicitis is characterised by local invasion with Fusobacterium nucleatum/necrophorum. Gut 2011;60:34-40.

26. Bennett KW, Eley A. Fusobacteria: new taxonomy and related diseases. J Med Microbiol 1993;39:246-254.

27. Afra K, Laupland K, Leal J, Lloyd T, Gregson D. Incidence, risk factors, and outcomes of Fusobacterium species bacteremia. BMC Infect Dis 2013;13:264.

28. Connell FG. Etiology of appendicitis. Am J Surg 1937;37:232-238.

29. Zalecki M. The Influence of Antral Ulcers on Intramural Gastric Nerve Projections Supplying the Pyloric Sphincter in the Pig (Sus scrofa domestica)-Neuronal Tracing Studies. PLoS One 2015;10:e0126958.

30. Azpiroz F, Malagelada C. Diabetic neuropathy in the gut: pathogenesis and diagnosis. Diabetologia 2015 (in press).

31. Chapman J, Davies M, Wolff B, Dozois E, Tessier D, Harrington J et al. Complicated diverticulitis: is it time to rethink the rules? Ann Surg 2005;242:576-581.

32. Aydin C, Altaca G, Berber I, Tekin K, Kara M, Titiz I. Prognostic parameters for the prediction of acute gangrenous cholecystitis. J Hepatobiliary Pancreat Surg 2006;13:155159.

33. Kaminski A, A, Liu IL, Applebaum H, Lee SL, Haigh PI. Routine interval appendectomy is not justified after initial nonoperative treatment of acute appendicitis. Arch Surg 2005;140:897-901.

34. Roche MM, Wang PP. Sex differences in all-cause and cardiovascular mortality, hospitalization for individuals with and without diabetes, and patients with diabetes diagnosed early and late. Diabetes Care 2013;36:2582-1590.

35. Preis SR, Hwang SJ, Coady S, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. Circulation 2009;119:1728-1735.

*Table 1 Demographic characteristics of the sampled subjects (*N*=541)*

Variable	Patients who received non-operative treatment for acute appendicitis				*p* value
	Patients with diabetes *N*=108		Patients without diabetes *N*=433		
	Total no.	Column %	Total no.	Column %	
Male	47	43.5	207	47.8	0.424
Age (years), mean (SD)	61.5 (15.7)		46.1 (18.4)		<0.001
Urbanization level					0.482
1 (most)	33	30.6	130	30.0	
2	28	25.9	126	29.1	
3	16	14.8	70	16.2	
4	12	11.1	58	13.4	
5 (least)	19	15.6	49	11.3	
Monthly income					0.250
NT$0~15,840	46	42.6	186	43.0	
NT$15,841~25,000	44	40.7	147	33.9	
≥NT$25,001	18	16.7	100	23.1	
Geographic region					0.872
Northern	54	50.0	200	46.2	
Central	20	18.5	92	21.2	
Southern	31	28.7	126	29.1	
Eastern	3	2.8	15	3.5	
Charlson Comorbidity Index score					<0.001
0	62	57.4	392	90.5	
1	35	32.4	38	6.5	
≥ 2	11	10.2	13	3.0	

Note: The average exchange rate in 2007 was US$1.00≈New Taiwan (NT)$30.

Table 2 Crude and covariate-adjusted hazard ratios (HRs) for receiving a subsequent appendectomy among patients who received non-operative treatment for acute appendicitis during the 1-year follow-up period

Received a subsequent appendectomy	Patients who received non-operative treatment for acute appendicitis			
	Patients with diabetes *N*=108		Patients without diabetes *N*=433	
	No.	%	No.	%
One-year follow-up period				
Yes	30	27.8	83	19.2
Crude HR (95% CI)	1.62* (1.00~2.63)		1.00	
Adjusted [a] HR (95% CI)	1.75* (1.01~3.02)		1.00	

*Notes: CI, confidence interval. The HR was calculated by a stratified Cox proportional hazard regression; [a] Adjustments were made for subjects' age and Charlson Comorbidity Index score; ** p*<0.05.*

Table 3 Crude and covariate-adjusted hazard ratios (HRs) for receiving a subsequent appendectomy among patients who received non-operative treatment for acute appendicitis during the 1-year follow-up period by gender

Development of rheumatoid arthritis	Patients who received non-operative treatment for acute appendicitis			
	Males		Females	
	Patients with diabetes (*N*=47) *n*, %	Patients without diabetes (*N*=207) *n*, %	Patients with diabetes (*N*=61) *n*, %	Patients without diabetes (*N*=226) *n*, %
Five-year follow-up period				
Yes	12 25.5	50 24.2	18 29.5	33 14.6
Crude HR (95% CI)	1.08 (0.52~2.23)	1.00	2.45** (1.26~4.75)	1.00
Adjusted [a] HR (95% CI)	1.45 (0.65~3.24)	1.00	2.18* (1.06~4.50)	1.00

*Notes: CI, confidence interval. The HR was calculated by a stratified Cox proportional hazard regression; [a] Adjustments were made for subjects' age and Charlson Comorbidity Index score; * p<0.05; ** p<0.01.*