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Commentary: Appendectomy and Increased the Risk of Ischemic Heart Disease

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The appendix is a secondary lymphoid organ and a prominent part of the mucosa-associated lymphoid tissue (MALT) system. In 2011, appendectomy accounted for 2.1% of all operating room procedures in the United States,¹ the vast majority of which are performed in the acute setting for appendicitis. Removal the appendix and other MALT tissue has immune effects such as decreasing immunoglobulin A levels. As such, an understanding of both the role of the appendix as well as the role of its removal in the development of disease, has become increasingly important. Recent studies have evaluated the role of the appendix and appendectomy in inflammatory disorders demonstrating an increased risk of Crohn's disease and decreased risk of ulcerative colitis after appendectomy. Appendectomy has also been shown to be associated with increased risk of Hodgkin lymphoma and autoimmune diseases such as rheumatoid arthritis.

In addition to well-recognized risk factors for coronary artery disease, such as smoking, diabetes, and hypertension, there has been a growing understanding of the role of inflammation in the development and progression of coronary plaques, as well as their unstable progression and eventual disruption.² Given the biological and epidemiological evidence linking inflammation to ischemic heart disease, it is reasonable to hypothesize that appendectomy with removal of MALT tissue may alter atheroprotective immunity. Decreased capability of the immune system to clear pathogens after appendectomy may lead to chronic inflammation and increased risk of ischemic heart disease.³ Considering the scope and impact of ischemic heart disease which compromises 12.7% of total global mortality and is the leading cause of death worldwide,⁴ as well as the frequency of appendectomy, examining the association between appendectomy and ischemic heart disease is intriguing

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The current study by Chen et al.⁵ was prompted by a 2011 study by Janszky et al.,³ which hypothesized that the surgical removal of the MALT tissue in children (appendectomy and tonsillectomy) would increase the risk of developing ischemic heart disease. The Janszky study was a prospective matched cohort study that followed children for an average of 23.5 years and found that children who underwent appendectomy or tonsillectomy prior to the age of 20 did, in fact, have a higher risk for premature acute myocardial infarction.³ Although the study controlled for a family history of acute myocardial infarction and socioeconomic status, the study did not control for other risk factors such as smoking, hypertension, hyperlipidemia, and diabetes. The study intentionally focused on appendectomy in children, based on the fact that MALT tissue becomes less physiologically significant around the age of 20. However, the limited the study because the average age the end of the study period was young and earlier than the expected peak in ischemic heart disease.

Chen et al.⁵ used the Longitudinal Health Insurance Database of Taiwan to perform a longitudinal, prospective cohort study to determine the association between appendectomy and risk of subsequent risk of developing ischemic heart disease. They identified 5413 patients who underwent appendectomy in Taiwan between 2002 and 2009. They matched these patients to a control group of 16,329 patients (3:1) who did not undergo appendectomy; matching was based on age, hypertension, hyperlipidemia, diabetes, and year of diagnosis. Appendectomy was associated 1.54-fold increase in the risk of coronary heart disease in the appendectomy population during the three year follow-up period, which persisted when stratified by age. Their results support the theory that appendiceal tissue may have a role in the development of coronary heart disease, and that further investigation is warranted.

Although the observational data presented by the authors or that of Janszky et al. cannot prove causation between appendectomy and increased risk of developing ischemic heart disease, they raise interesting questions. The potential cardiovascular ramifications of appendectomy have implications on both postoperative management as well as preoperative decision-making. At the very least, these data suggest that appendectomy may be considered a potential cardiac risk factor. Based on these data, should all patients who undergo appendectomy have cardiac surveillance post-operatively irrespective of their other risk factors? Are specific subgroups at higher risk? And if so, how do we develop formal recommendations regarding such surveillance?

With regard to preoperative decision-making, recent studies have questioned the need for appendectomy in acute appendicitis. A 2011 Cochrane review assessed five randomized control trials comparing appendectomy versus antibiotics for treatment of acute appendicitis.⁶ The five studies include 901 patients. 73.4% (95% CI 62.7% to 81.9%) of patients who were treated with antibiotics and 97.4 (95% CI 94.4% to 98.8%) patients treated with an appendectomy were cured within two weeks of the initial episode and did not have major complications (including recurrence) within one year.⁶ While the data favor appendectomy, the small numbers of patients lead to wide confidence intervals. The systematic review concludes that due to the low to moderate quality of the studies included, until more definitive studies are available, appendectomy should remain the standard

treatment for acute appendicitis.⁶ While appendectomy remains the gold standard therapy, the data do suggest that there may be patients who can be managed with antibiotics alone. Given this, with better understanding of risk and risk stratification, the role of appendectomy in future development of cardiovascular disease could potentially be an integral part of the decision when to offer patients conservative management versus operative intervention.

Although the current study does raise several salient points there are several limitations. As with most administrative datasets that are not designed for research purposes, their reliance on the use of ICD-9 codes 410-414 and 492.2 to identify patients with the diagnosis of ischemic heart disease may underestimate the true incidence if accurate coding was not utilized. Moreover, the chosen codes do not account for those patients with a diagnosis of peripheral vascular disease (440.2, a known risk factor for coronary heart disease), congestive heart failure (428), or hypertensive heart disease with heart failure (402). In addition, it is unclear how long the disease processes had been present in both cohorts prior to the index date and also not clear how well controlled they were in either cohort. The presence of poorly controlled diabetes matched with controlled diabetes can lend to bias. Furthermore, it is possible that the initial presentation with acute appendicitis lead to incidental further workup for concurrent but unrelated illnesses (such as diabetes, or hypertension or heart disease) that was present prior to but unrecognized. The authors attempted to address this by excluding patients who had heart disease diagnosed within the 30 days following the index date. Although the use of data from the Longitudinal Health Insurance Database of Taiwan does provide a large dataset, it raises limitations in and of itself, including the generalizability of this data to other populations with differing risk of ischemic heart disease.

In summary, although the exact nature of the relationship between appendectomy and inflammatory processes including coronary heart disease is not known, the study by Chen et al.⁵ supports the need for further investigation both into the role of appendectomy in the development of ischemic heart disease. Additional population-based studies are need to confirm the association and improve generalizability to other populations, were the incidence of ischemic heart disease may differ. Clinical studies assessing the correlation between appendectomy and inflammatory markers such as CRP may provide more mechanistic proof that this association is real. A better understanding of the risk and the ability to stratify patients into risk groups may guide the development of postoperative cardiac surveillance guidelines and may guide decision-making in the subset of patients with high cardiac risk who can potentially be managed non-operatively.

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