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Review Article

Re-evaluating the Human Appendix: Vestigial or Immunological Guardian

Nidhi Sharma[1*], Baljeet Kaur[2], Anamika Saxena[3]

[1]*Department of Quality Assurance, College of Pharmacy, COER University, Roorkee, Uttarakhand, India.*

[2]*Department of Pharmaceutics, College of Pharmacy, COER University, Roorkee, Uttarakhand, India.*

[3]*Department of Pharmaceutics, Dev Bhoomi Institute of Pharmacy and Research, Dev Bhoomi University, Dehradun, Uttarakhand, India.*

**Corresponding author: ranakotinids@gmail.com*

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ABSTRACT

The vermiform appendix, once deemed vestigial and largely overlooked in medical circles, has recently captured renewed attention for its potential immunological functions. This review comprehensively explores various aspects related to the appendix, including its historical marginalization, anatomical characteristics, and emerging insights into its role in immunity. Discussion extends to the clinical relevance of the appendix in human health and disease. Additionally, evolutionary perspectives shed light on its persistence across species and potential adaptive significance. As researchers explore further into its immunological roles, new avenues for investigation emerge, promising to uncover further complexities in human physiology. This review aims to present a nuanced understanding of the appendix, encouraging ongoing exploration and recognition of its importance within the human body.

Keywords: Appendix, Vestigial organ, Immunological functions, Microbiome, Infection, Appendicitis.

INTRODUCTION

The vermiform appendix, once deemed functionally obsolete, is now recognized as a site of potential immunological significance. This review aims to re-examine its purpose in the setting of human physiology, addressing historical perceptions, anatomical features, immunological functions, clinical implications, evolutionary origins, and prospects for future research.[1] To gain insight into the impact of the intestinal immune system, it is imperative to examine its typical physiology and the significance of its biofilm. Additionally, evaluating its evolution can help identify which characteristics have remained unchanged over time. This approach intends to furnish a deeper understanding of how the intestinal immune system influences overall health.[2]

The human appendix has long been considered a vestigial organ, a remnant from our evolutionary ancestors with little to no function. However, current research suggests that this small, tube-shaped organ attached to the cecum may play a more momentous role, particularly in the immune system. The review process involved a comprehensive exploration of various research articles sourced from diverse online journals, including Google Scholar and PubMed, among others. Additionally, we delved into historical perspectives to enhance our understanding and gain clarity of thought regarding the topic of re-evaluating the human appendix: its status as either vestigial or an immunological guardian.[3]

Historical Perspective

Early anatomists classified the appendix as vestigial, attributing its presence to evolutionary remnants. Nevertheless, recent perspectives contest this perspective, prompting a reassessment of its purported redundancy. During the 1500s, anatomists successfully identified its anatomical structure within the body, yet its function remained a matter of speculation. Nonetheless, physicians acknowledged its potential to undergo inflammation, leading to severe illness.[4,5]

In 1735, Dr. Claudius Amyand conducted the world's inaugural successful appendectomy at St. George's Hospital in London. The patient, an 11-year-old boy, had ingested a pin, leading to perforation of the appendix. Shortly after, in 1759, the initial successful operation to manage acute appendicitis occurred in Bordeaux.[6] Given the absence of general anesthesia until 1846, these procedures necessitated numerous assistants to control patients amid what were assuredly excruciating experiences.[5,7]

Surgical intervention for appendicitis gained momentum during the 1880s. While medical professionals grappled with determining which patients warranted surgery – as some could recover spontaneously – advancements in surgical technique and anesthesia markedly improved outcomes, establishing surgery as the prevailing approach. By the late 20th century, laparoscopic surgery supplanted open surgery in most instances, with laparoscopic appendectomy now recognized as a key & the safest and least complicated surgical procedure available.[8]

Despite its impressive historical success, numerous enigmas regarding the appendix persist. The precise causes of acute appendicitis remain elusive, and the factors determining whether the appendix ruptures or resolves spontaneously remain unclear.[9] It was only in 2007 that researchers presented a compelling argument

for the appendix's function: the small organ appears to contribute to both the digestive and immune systems by serving as a reservoir for beneficial bacteria, which are deployed when the gastrointestinal tract loses its healthy microbiota.[10]

Recently, researchers have revisited the question of whether antibiotics could be as effective as surgery in treating acute appendicitis. In the 1940s and 1950s, physicians in England began administering antibiotics to patients with remarkable success. During the Cold War, submariners received antibiotics instead of undergoing appendectomy, as submarines could stay underwater for prolonged durations, and patients reportedly fared well with this approach. Five recent European research produced findings in line with these anecdotes: 70% of patients healed solely with antibiotics, without requiring surgery. Considering this evidence, a new study in California aims to ascertain whether antibiotics could offer a comparable alternative to surgery and provide a less intrusive therapy choice for appendicitis.[11,12]

Anatomical Features

Anatomically, the human appendix is a tubular structure attached to the cecum, enriched with lymphoid tissue resembling other immune organs. Its strategic positioning hints at potential interactions with gut microbiota and immunological processes. Furthermore, a study conducted at the National Library of Medicine (NIH) involved the examination of 200 cadavers, comprising 153 males (76.5%) and 47 females (23.5%). The average age of the cohort was 39.3 years. Analysis of the data revealed a predominant anatomical localization of the appendix within the pelvic region in 111 individuals (55.8%), with observed appendix lengths ranging from a minimum of 15 mm to a maximum of 175 mm.[13,14]

Immunological Functions

Emerging evidence suggests the appendix contributes to immune surveillance and response, harboring lymphoid follicles pivotal in antibody production and pathogen defense. In humans, the appendix is a remarkably conserved structure, with malformations being exceedingly rare, indicating its likely importance. Research suggests that the appendix may serve a dual purpose. Firstly, it acts as a concentrated hub of lymphoid tissue akin to Peyer's patches, playing a critical role in the production of immunoglobulin A. This antibody is essential for regulating the density and the standard of the intestinal flora, which is crucial for gut health. Secondly, due to its unique shape and position, the appendix may serve as a specialized niche for commensal bacteria within the body. Rich in biofilms that continuously shed bacteria into the intestinal lumen, the appendix harbors a microbiota as diverse as that identified in the colon. This diversity could facilitate the replenishment of healthy flora in the large intestine, particularly following episodes of diarrhea.[15]

While modern hygiene and healthcare practices have rendered the appendix seemingly non-essential for many, there is evidence points to its removal could have subtler effects on health. Reports suggest associations between appendectomy and including inflammatory bowel disease (IBD) and similar inflammatory conditions and cardiovascular disease. Surprisingly, research also links the deficiency of an appendix to an increased risk of conditions such as Parkinson's disease. Moreover, individuals without an Appendix may face worse outcomes in cases of recurrent *Clostridium difficile* infection, a common hospital-acquired infection.[16,17]

Overall, while not vital for survival in contemporary settings, the appendix may play nuanced roles in maintaining overall health and preventing certain diseases. The rich concentration of lymphoid tissue within the vermiform appendix has spurred speculation since as early as 1900 regarding its potential involvement in immune responses. Additionally, its distinctive shape and location indicate that the appendix might serve as a sanctuary for symbiotic gut microbes, shielding them from damage during gastrointestinal infections. These dual functions likely underwent selection pressures, contributing to the evolutionary persistence of the appendix over time. As such, it's plausible that the appendix fulfills a distinct purpose rather than being an organ without significance.[5,18,19]

Protective Role Against Infection

The appendix's proposed function as a sanctuary for beneficial gut flora has implications for post-infection recovery and immune homeostasis, potentially mitigating harmful immune reactions. Recent investigations have revealed that the appendix of the human body contains lymphoid cells, indicating its involvement in the body's defense against infections. This highlights a clear function for the appendix within the immune system.[20]

Studies in recent years have elucidated the involvement of the appendix in mammalian mucosal immune function. It is believed to contribute to extrathymically derived T-lymphocytes and B-lymphocyte-mediated immune responses. Additionally, the appendix is considered to generate initial defenses that aid in the prevention of serious infections in humans.[21]

Evolutionary Implications

Debates persist regarding the appendix's evolutionary purpose, necessitating comparative studies across species and populations to elucidate its adaptive significance.[22]

Efforts to uncover a potential function for the appendix in the human body have led to investigations into its homology with the appendices of other mammals. Historically, the comparatively larger size of the appendix in certain "lower" mammals, like rabbits, has led to the perception of the appendix in the human body as a vestigial organ. Yet, the lack of a distinct morphological caecal appendage in some evolutionarily closer primate species challenges this hypothesis.[23]

In evolutionary assessments, the appendix in the human body is often regarded as a vestige of the mammalian caecum. Originally, this intestinal segment served a digestive function, particularly aiding in the breakdown of cellulose with the assistance of resident microorganisms. While humans have lost this cellulose-digesting ability in the caecum, the appendix in the human body retains a significant presence of microorganisms within biofilms alongside lymphoid tissue.[24]

In rabbits, the vermiform appendix is crucial for the formation of lymphoid tissue associated with the intestine (GALT). Following the independent formation of follicle centers, the existence of symbiotic bacteria in the intestines is essential for expanding the range of primary antibodies and advancing the formation of T and B cell regions within the lymphoid tissue.[25,26]

Certain non-human primates like white-eyelid mangabeys and tamarins, along with other mammals like mice and rats lacking a caecal diverticulum, exhibit a dense concentration of lymphoid tissue in the caecal apex, known as the "caecal patch." Moreover, in amphibians and reptiles that do not possess a caecum or appendix, the first part of the large intestine serves as the main area for communication between the host and symbiotic bacteria.[27]

These observations suggest that the appendix, with its favorable conditions for harboring commensal gut flora, may have evolved independently of the caecum, possibly predating it. Hence, it is suggested that the digestive characteristic could have evolved concurrently with the enlargement of the nearby part of the large intestine, which eventually formed the caecum. This implies that the immunological function preceded the digestive function.[28]

The appendix's worm-like morphology and its location within the gut hint at its enduring immunological role, providing a sanctuary for commensal intestinal flora. This interpretation suggests that the appendix's structure and position may signify its ongoing significance in immune function rather than serving as evidence of its vestigial nature.[29]

Further investigations are warranted to unravel the intricacies of the appendix's immunological contributions and implications for human health, which may include longitudinal studies assessing post-appendectomy outcomes.

To enhance clarity, we curated data from the official website of the World Health Organization (WHO), comprising a graphical chart depicting the statistics of appendicitis-related deaths in the United States of America for the year 2021. The data is segmented by gender (male, female) and age groups (0, 1-4, 5-14, 15-24, 25-34, 35-54, 55-74, 75+).[12,30]

The provided data presents a breakdown of appendix-related deaths by gender and age group (Fig. 1). Overall, it's evident that males tend to have a higher incidence of appendix-related fatalities compared to females across most age groups. Notably, males aged 50 and above demonstrate significantly higher mortality rates, with a sharp increase observed in the 50 to 54 age bracket and continuing to rise steadily with age, peaking among males aged 85 and above. In contrast, females generally exhibit lower mortality rates across all age groups, with a notable increase in deaths among females aged 60 to 64 and a subsequent gradual rise with advancing age. This gender discrepancy in appendix-related mortality rates could be attributed to various factors such as differences in anatomy, hormonal influences, and possibly variances in healthcare-seeking behavior. Further analysis may delve into the specific risk factors contributing to these disparities and explore potential interventions aimed at reducing appendix-related fatalities, particularly among high-risk demographic groups.

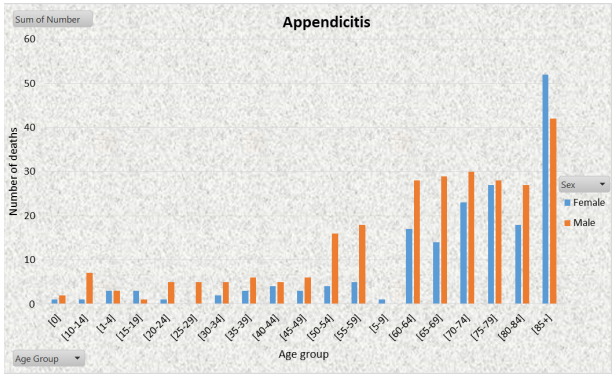

Fig. 1: Statistics of appendicitis-related deaths

CONCLUSION

In summary, while historically deemed vestigial, the appendix's potential immunological functions underscore its significance within human physiology. Continued research endeavours are essential to unravel its complexities and shed light on its evolutionary origins and clinical implications.

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