



## DOES HIGH ALTITUDE MEDDLE WITH THE APPENDIX TOO- THROMBOSIS OF APPENDICULAR ARTERY IN PATHOGENESIS OF ACUTE APPENDICITIS IN HIGH ALTITUDE

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**ABSTRACT** **BACKGROUND:** High altitude induced prothrombotic state in the human body predisposes to many disease process. Acute appendicitis in the setting of high altitude is also attributed partly to thrombosis of the appendicular artery and its branches and maybe an independent factor contributing to the development of acute appendicitis. Studies on this aspect are non-existent and requires more research.

**AIM:** To study the role of high altitude induced prothrombotic state in the pathogenesis of acute appendicitis in high altitude.

**MATERIALS AND METHODS:** This was a retrospective observational study on 172 cases of acute appendicitis who presented to our peripheral hospital in the setting of the high altitude terrain of Laddakh between June 2019 to August 2021. Data collection was ostensibly done using the operative findings as endorsed in the case sheets looking specifically for presence of thrombosis of the appendicular artery and its branches on gross examination.

**RESULTS:** 247 cases of acute appendicitis who underwent emergency open appendectomy were examined of which 172 underwent open appendectomy and 75 underwent laparoscopic appendectomy. Only the 172 cases undergoing open appendectomy were considered for the study. The age group under study was 20 to 60 years with a median of 28 years. A significant 43 cases (25%) were found to have a thrombotic pathology with visible thrombosis of appendicular artery or its branches.

**CONCLUSIONS:** Exposure of high altitude to the individuals living there-in incites a prothrombotic state in them leading to development of acute appendicitis and the thrombosis of the appendicular artery and/or its branches, has a major contributory independent factor in the etio-pathogenesis of acute appendicitis considering the low flow end arterial nature of the same.

**KEYWORDS :** Appendicitis, Appendicular artery, Thrombosis, Appendectomy, high altitude

### INTRODUCTION

High altitude presents a unique scenario altering the physiology of the human body and inciting a myriad of changes in metabolism, physiology and pathology in the human body. It induces a hypoxia and hypo-barc environment induced pro-thrombotic state in the body resulting in a transient and a sustained hypercoagulable state by multiple mechanisms. [1,2,3] A study by Anand et al describes a 30 times higher risk of spontaneous vascular thrombosis in both arterial and venous systems, owing to elongated high altitude stay at 3000 to 6500 metres altitude, presenting as deep vein thrombosis, pulmonary thromboembolism, mesenteric, portal and splenic vein thrombosis, stroke and peripheral arterial thrombosis. [4] Multiple studies have indicated without doubt the role of hypercoagulable state in the pathogenesis of these diseases. [5]

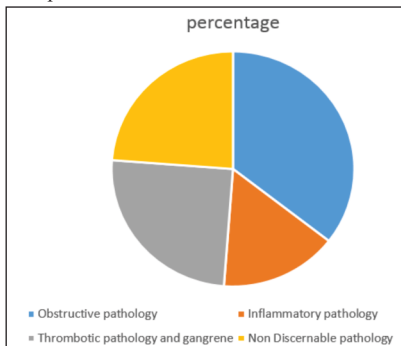
Acute appendicitis is a frequently encountered surgical emergency in clinical practice. Multiple data and studies regarding its pathogenesis exist in medical literature and have been documented in standard textbooks. However acute appendicitis in high altitude is a seldom studied scenario and very few studies exist describing its pathology and presentation. Though most of the pathogenesis still remain to be decrypted, standard teachings and textbooks describe the two common and accepted mechanisms to be obstructive and inflammatory. [11] In our studies, we encountered a third discernable and distinct entity in the etio-pathogenesis of acute appendicitis in high altitude, namely end arterial thrombosis of appendicular artery. This study aims to highlight this particular pathology based on our intra-operative findings of patients operated for acute appendicitis in the setting of high altitude and is a novel and unique report to the best of our knowledge.

### MATERIALS AND METHODS

This was a retrospective observational study of patients of acute appendicitis who underwent emergency open appendectomy at a peripheral hospital in the high altitude terrain of Leh, Laddakh (Altitude 11,800 feet above Mean sea level). During the time frame period of June 2019 to August 2021 (27 months), a total of 247 cases underwent emergency Appendectomy for acute appendicitis at our centre of which 172 were open and 75 underwent laparoscopic appendectomy. There was no selection bias in deciding the method of surgery. It was simply governed by the availability of laparoscopy in our institute after February 2020, where-in after overcoming the learning curve we had gradually shifted to laparoscopy. However only the 172 cases undergoing open appendectomy were considered in the study to clearly highlight naked eye observation and palpation of the thrombosed appendicular artery and simultaneously negate the confounding factor of laparoscopic vision of an extremely thin vessel not appreciable and palpable otherwise. The age group under study was 20 to 60 years with a median of 28 years. All patients were males. As per the documents and case sheets, requisite consent had been taken from all patients, prior to administering anaesthesia and conducting the surgical procedure. Pre-operative hematological, biochemical, serological viral marker workup was done in all cases along with blood grouping and cross matching in high risk cases. A pre-operative ultrasonography scan was done in most cases to rule out any concomitant pathology and aid in the diagnosis and approach. All cases after June 2020 underwent COVID testing by Rapid antigen kits for emergency cases. All participating Surgeons, anesthesiologists and operating room assistants had taken adequate precautions and Personal protective equipment in all cases after COVID-19 emergence. Surgical safety checklist and procedures had been meticulously followed.

All open cases had been administered spinal anaesthesia. 13 cases (7.5%) had required conversion to general anaesthesia due to a patchy spinal effect or prolonged duration of surgery especially in difficult cases. Standard operating procedures had been followed as described in text books. All retrieved appendix specimen had been subsequently sent for histo-pathological examination (HPE) and corroborated.

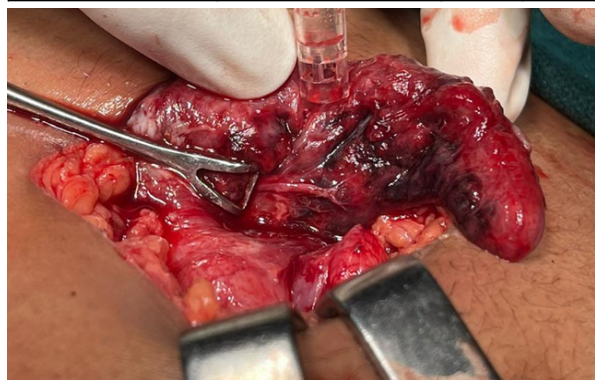
All cases had been meticulously documented from pre-operative work-up, operative procedures and findings, anaesthesia notes, post-operative course, histo-pathological reporting and documentation and regular follow-up.



**Chart 1: Depicting Percentage Of Intra-operative Pathological Findings Of Appendix**

**Table 1: Depicting Distribution Of Gangrenous Appendix Due To Thrombotic Vs Non-thrombotic Pathology**

	GANGRENOUS APPENDIX (COMPLETE/PATCHY)	NON GANGRENOUS	TOTAL
Thrombotic pathological findings in Appendicular vessels	39	04	43
Non thrombotic pathology (obstructive/inflammatory/ non-discernable)	24	105	129
<b>TOTAL</b>	<b>63</b>	<b>109</b>	<b>172</b>



**Figure 1: Showing Thrombosed Branches Of Appendicular Artery**



**Figure 2: Showing Thrombosis Of The Stump Of Appendicular Artery At The Base**

**RESULTS**

All the 172 cases undergoing emergency open appendectomy for acute appendicitis were considered in the study for intra-operative findings documented in the case sheets for the pathology of the appendix. Intra-operative findings were as follows. [CHART 1]

1. Obstructive pathology was found in 61 cases (35.5%) with a palpable fecolith or evidence of a passed fecolith before or during surgical handling.
2. A total of 27 cases (15.7%) were inflammatory or catarrhal type where there had been evidence of past episodes of clinical or subclinical appendicitis – both reported and unreported.
3. Thirdly, a significant 43 cases (25%) were found to have a thrombotic pathology with visible thrombosis of appendicular artery or its branches. The condition of appendix in these cases grossly, was either gangrenous in case of thrombosis of appendicular artery and with patchy islets of interspersed gangrene or pale patches when the branches of appendicular artery were thrombosed instead. [FIGURE 1,2] These cases also had documented operative evidence of early onset gangrene of the appendix (both complete and patchy) and evidence of early onset lump formation in early stages. [TABLE 1] Corroboratively these cases also had an early onset pain localized in right iliac fossa in the pre-operative notes. The early onset localized pain and features of early lump formation ( within 24 hours of onset of pain) with gangrenous changes in appendix was found in 39 out of the 43 cases (91%) which is grossly different from the standard traditional teaching of lump formation in 72-96 hours available in literature and standard textbooks. [6,7]
4. In the balance, 41 cases (23.8%) no discernable pathology could be found on gross intra-operative examination.

All cases were subjected to histo-pathological examination, post appendectomy, which confirmed presence of acute appendicitis. However, the exact pathology could not be defined in the HPE report since post-operatively, surgical handling of the tissues and pre-operative pathology often tend to intermix, leading to a confounding of factors causing the primary pathology per say.

**DISCUSSION**

There have been two postulated etiological pathologies described in standard literature in the development of acute appendicitis namely the obstructive pathology leading to the acute form and the inflammatory or the catarrhal pathology leading to a more acute on chronic presentation. [6]

The role of obstruction in appendicitis has been extensively studied in the past. According to Wangenstein's postulates, the mucosal folds and sphincter-like orientation of muscle fibres of the appendix at orifice, makes the appendix susceptible to obstruction. Based on his studies, he proposed a temporal sequence of pathogenesis of appendicitis. (1) Closed loop obstruction caused by a fecolith and edema of mucosal and sub-mucosal lymphoid tissue at appendicular base. (2) Rise in intraluminal pressure due to fluid secretion by mucosa inside the closed loop obstruction (3) rise of pressure in appendix wall more than the capillary pressure causing mucosal ischaemia (4) bacterial transmigration from lumen across the wall of appendix causing inflammation, edema and finally necrosis and perforation. [7,8] However this is just one of the postulated etiological possibility. Most patients with appendicitis show no evidence of fecolith and also conversely many patients with appendiceal fecoliths with no evidence of appendicitis. [9,10,11]

The second inflammatory or catarrhal presentation of appendicitis is more of an acute on chronic presentation where-in an inflammatory or infective focus in the appendix leads to periods of remission and exacerbation before leading to an acute event where-in the symptoms forces the patient to seek medical attention.

High altitude is known to cause a myriad of physiological changes in the body for adaptation. It induces a hypoxia and hypo-baric environment induced pro-thrombotic state in the body resulting in a transient and a sustained hypercoagulable state by multiple mechanisms. [1,2,3] A study by Anand et al describes a 30 times higher risk of spontaneous vascular thrombosis in both arterial and venous systems, owing to elongated high altitude stay at 3000 to 6500 metres altitude, presenting as deep vein thrombosis, pulmonary thromboembolism, mesenteric, portal and splenic vein thrombosis, stroke and peripheral arterial thrombosis. [4] Multiple studies have indicated without doubt the role of hypercoagulable state in the pathogenesis of these diseases. [5]

In our studies on appendicitis in high altitude, we examined the various causes and possibilities of pathogenesis of acute appendicitis. We found a significant fraction of patients undergoing emergency appendectomy for the same to have thrombosed vessels ie thrombosis of the appendicular artery or its terminal branches per-operatively. This finding was present in the cases even before the serial ligation of the meso-appendix indicating that surgical handling was not contributory to the same. These cases also had documented operative evidence of early onset gangrene of the appendix (both complete and patchy) and evidence of early onset lump formation. [TABLE 1] The condition of appendix in these cases grossly, was either gangrenous in case of thrombosis of appendicular artery and with patchy islets of interspersed gangrene or pale patches when the branches of appendicular artery were thrombosed instead. Corroboratively these cases also had an early onset pain localized in right iliac fossa in the pre-operative notes meaning thereby that it was the thrombosis which happened earlier leading to higher incidence of gangrene in high altitude areas. We therefore deduced that probably primary thrombosis of the appendicular artery and its branches may in-fact be one major contributory factor in the development of acute appendicitis in high altitude.

The exact cause for this finding is mostly unknown. However the low flow velocities in appendicular artery owing to it being a terminal end artery, in the pro-thrombotic milieu of high altitude may be contributory and causative.

There are three theoretical modalities to confirm the same however each one as impractical as the other. The first is a pre-operative CT angiography to specifically look at the appendicular artery if thrombosed. This modality is probably the most plausible one however restricted by the availability of CT scan in a peripherally situated high altitude centre as ours and also since the majority of CT scan consoles being 16 slice scanners makes the diagnosis really difficult to observe in the scans taken for the same. The second possibility is to look for thrombosed vessel changes in the post-operative Histo-pathological examination (HPE) of the appendix specimen. However post-operative thrombosis is quite a common finding due to the handling of appendix during the surgery and cannot be used to specifically implicate the cause of acute appendicitis to a primary thrombosis of the vessels. The third theoretical modality we postulated was an intra-operative frozen section of the appendix specimen with a quick transit time to the lab after a targeted gentle handling of the appendix during surgery. This modality may be explored in a higher centre with facilities for frozen section for quick processing of specimen and where such a research study can be carried out with a very targeted and truncated approach with a gentle tissue handling, micro-ligation of the branches of appendicular artery and a rapid transit time to the pathology lab.

Our study was limited by hospital bias, which is unfortunately intrinsic to the nature of the study since we could only observe and study the patients who reported directly to our centre. Also being a peripheral set-up we lacked a thrombotic profile work-up for our patients to study any pro-thrombotic pre-disposition to spontaneous micro-vascular thrombosis on exposure to high altitude. Needless to remark hereby that acute appendicitis being an extremely common surgical emergency such a work-up in every patient may neither be practical nor cost effective. There have been no previous publications to the best of our knowledge and searches highlighting this phenomenon in such a significant fraction of patients undergoing emergency appendectomy.

## CONCLUSION

High altitude presents a myriad of symptoms in individuals exposed to the same due to multiple physiological and biochemical changes in the body, some of which like stroke, deep vein thrombosis, peripheral arterial disease, pulmonary thromboembolism etc have been extensively studied. Acute appendicitis is a surgical emergency which may present anywhere. Traditional teachings and textbooks describe obstructive and an inflammatory pathology in the development of acute appendicitis, however most of them remain cryptogenic and no discernable pathology is determined in them. Exposure of high altitude to the individuals living there-in incites a pro-thrombogenic state in them leading to development of acute appendicitis and the thrombosis of the appendicular artery and/or its branches, has a major contributory independent factor in the etio-pathogenesis of acute appendicitis. With improvement in logistics and infrastructure it is possible to study this further and carry out multi-centric studies to establish the same.

## Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures, intervention and experiments of

this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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## Conflicts of Interest:

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

## Authors' contributions:

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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