ETHIOPATHOGENESIS OF CASEOUS LYMPHADENITIS IN GOATS

By

ZAID KHUDHUR MAHMOOD

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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DEDICATION

TO MY FAMILY WHO MADE MY PROFESSIONAL PROGRESS POSSIBLE; TO MY INSTRUCTORS, TEACHERS, MENTORS WHO MADE IT A REALITY; AND TO THE FELLOW RESEARCHERS WHO MAY BE ABLE TO USE THE RESULTS OF THIS RESEARCH, I DEDICATE MY WORK TO ALL WITH LOVE AND GRATITUDE.

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Chairman: Professor Abd Wahid Haron, Ph.D.
Faculty: Veterinary Medicine

Caseous lymphadenitis (CLA) is an economically important disease of sheep and goats worldwide. However, paucity of literature on CLA research in goats in Malaysia led to this study to investigate the mechanism by which *Corynebacterium pseudotuberculosis* and its exotoxin, phospholipase D (PLD) adversely affects reproduction in mice and goats. This study was also designed to test the hypothesis that acute phase proteins, specifically, haptoglobin and serum amyloid A can be used as diagnostic biomarkers for CLA.

One hundred and five clinically healthy mice of both sexes aged between 10 to 12 weeks, weighing 25-35 g and twenty six clinically healthy crossbred Boer goats (13 bucks and 13 does) aged between 12 to 14 months, weighing 30-35 kg were used in this study. The does were non-pregnant, non-lactating and have been housed separately from the bucks. At the beginning of the experiments, two types of inoculum were used that involved live *C. pseudotuberculosis* and its exotoxin, PLD. The mice were divided into three equal groups of 35 mice each. The crossbred Boer goats were also divided into three groups, the first group consisted of 6 goats, the second group consisted of 10 goats and the third group consisted of 10 goats. The control groups 1 (mice and goats) were inoculated with sterile phosphate buffered saline (PBS 1 ml/mouse intra-peritoneal and 1 ml/goat subcutaneous) whereas group 2 were inoculated with live *C. pseudotuberculosis* (1x109 cfu intra-peritoneal in mice and subcutaneous in goats) and group 3 were inoculated with PLD (1 ml/mouse intra-peritoneal and 1 ml/20 kg B.W. in goats). Mice were observed during the entire experiment, blood was collected into heparinized tubes for sex hormones analyses. Post mortem examination of gross lesions was conducted on ovaries, uterus, testes and epididymis and tissue samples were fixed for

histopathological examination. Goats were also observed during the entire experiment for clinical signs and serial blood collections were conducted. Blood was placed into heparinized, plain, EDTA and sodium citrate tubes for acute phase proteins (APPs), haematology and sex hormones analyses. Post mortem examination of gross lesions was conducted on lungs, heart, liver, spleen, kidneys and lymph nodes and tissue samples were fixed for histopathology and cellular changes were scored.

Mice inoculated with *C. pseudotuberculosis* showed significant decrease ($p<0.05$) in testosterone concentration. Both inoculated groups showed no gross changes in the reproductive organs. However, microscopic examination revealed that *C. pseudotuberculosis* inoculation caused congestion, oedema, infiltration of inflammatory cells, degeneration and necrosis in the ovaries, uterus, testes and epididymis. In addition, mice in PLD inoculated group showed congestion, degeneration and necrosis in the ovaries, uterus, testes and epididymis as well as thrombosis in the ovaries and uterus only.

Goats inoculated with both *C. pseudotuberculosis* and PLD showed significant increase ($p<0.05$) in haptoglobin concentration with significant decrease ($p<0.05$) in albumin concentration. Goats also showed significant increase ($p<0.05$) in body temperature, heart rate, respiratory rate during different times of the experiment post inoculation with both *C. pseudotuberculosis* and PLD. Moreover, body score showed significant decrease ($p<0.05$) in both treated groups toward the end of the experiment. Additionally, the site of inoculation and the superficial lymph nodes showed abscess formation in *C. pseudotuberculosis* inoculated group only.

Corynebacterium pseudotuberculosis inoculated goats showed significant decrease ($p<0.05$) in red blood cell count, haemoglobin, creatine phosphokinase concentrations and significant increase ($p<0.05$) in neutrophils count. Both *C. pseudotuberculosis* and PLD inoculated goats showed significant increase ($p<0.05$) in packed cell volume, mean corpuscular volume, white blood cells, lymphocytes, monocytes, eosinophils and basophils counts and aspartate transaminase, total bilirubin, calcium, creatinine, gamma glutamyltransferase, urea, total protein, globulin, lactate dehydrogenase concentrations, prothrombin time and activated partial thromboplastin time whilst both inoculated groups showed significant decrease ($p<0.05$) in mean corpuscular haemoglobin concentration, neutrophils count, alanine transaminase and alkaline phosphatase concentrations. Inoculation with PLD showed significant decrease ($p<0.05$) in creatine phosphokinase concentration.

Testosterone, progesterone, estrogen hormones, scrotal circumference and semen volume, pH, wave pattern, motility and concentration showed significant decrease ($p<0.05$) post inoculation with *C. pseudotuberculosis* and PLD. In

addition, dead sperm and abnormal sperm percentage showed significant increased ($p<0.05$) in both treated groups. Microscopic examination of the ovaries showed fibrous tissue formation post inoculation with *C. pseudotuberculosis*, whilst in PLD inoculated group the ovaries showed severe congestion, degeneration and necrosis of the stromal cells. In addition, the uterine tissues showed congestion, degeneration and necrosis post inoculation with both *C. pseudotuberculosis* and PLD. The testes showed irregular and shrinkage of seminiferous tubules with oedema, degeneration and necrosis of spermatogonia cells and Leydig cells post inoculation with both *C. pseudotuberculosis* and PLD. Similarly, the epididymis showed oedema, degeneration and necrosis of the lining epithelium of the epididymal tubules post inoculation with both *C. pseudotuberculosis* and PLD.

Corynebacterium pseudotuberculosis inoculated group showed gross changes in lungs represented by grey and red hepatization, deeper inside, spots of congestion and abscess formation. The heart appeared oedematous and the pericardium showed some degree of opacity. The liver showed multiple abscess formation on its surface. The kidneys appeared friable with opaque capsule whilst the spleen showed mosaic appearance. The lymph nodes appeared enlarged, fluctuating and filled with purulent pus. The PLD inoculated group also showed gross changes in the lung represented by some spots of grey hepatization with no abscess formation in its parenchyma. The heart showed no obvious gross changes. The liver appeared congested with white line along the edges of almost all the liver lobes. The kidneys appeared congested with opaque spots on its capsule. The spleen appeared friable with mosaic appearance. The lymph nodes showed no abscess formation; however, when cut, it revealed a rusty yellow discoloration. Microscopic examination of *C. pseudotuberculosis* inoculated group showed significant congestion, oedema, and infiltration of inflammatory cells, degeneration and necrosis in the lungs, heart, liver, kidneys and spleen. The lymph nodes also showed significant granuloma formation with micro-foci of abscess formation. The PLD inoculated group showed significant congestion, oedema, degeneration and necrosis. In addition, hepatic tissue showed significant increase ($p<0.05$) in Kupffer cells number. The lymph nodes showed no abscess formation with some haemosiderin deposits.

Therefore, from this study, it can be concluded that *C. pseudotuberculosis* had detrimental effects on testosterone concentration and reproductive organs in mice. However, in goats, *C. pseudotuberculosis* and PLD had negative effects on testosterone, estrogen and progesterone hormone concentrations as well as semen quality and reproductive organs in both genders. Acute phase reactant, mainly, haptoglobin, showed significant sensitivity in both treated groups; this sensitivity may have potential as diagnostic biomarker for CLA in goats. Similarly, *C. pseudotuberculosis* resulted in classical clinical manifestation of CLA specifically abscess formation in superficial lymph nodes, yet, PLD, showed different clinical manifestation with no abscessation. In addition, *C. pseudotuberculosis* and PLD showed significant changes in all haematological

parameters, yet, PLD showed different response pattern which may indicate a different mechanism of action. The gross and cellular changes were of typical CLA lesions in *C. pseudotuberculosis* inoculated group whilst PLD inoculated group showed less gross changes; however, the cellular changes were severe, this may indicate or reflect the toxic effects of PLD on tissues.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

ETIOPATOGENSIS PENYAKIT BISUL NODUS LIMFA PADA KAMBING

Oleh

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Caseous limfadenitis (CLA) adalah penyakit biri-biri dan kambing di seluruh dunia yang penting secara ekonomi. Walau bagaimanapun, kekurangan bahan penerbitan mengenai CLA padap kambing di Malaysia membawa kepada kajian ini untuk menyiasat mekanisme *Corynebacterium pseudotuberculosis* dan eksotoksinnya, fosfolipase D (PLD) menjejaskan pembiakan dalam mencit dan kambing. Kajian ini juga bertujuan untuk menguji hipotesis bahawa protein fasa akut, khususnya, haptoglobin dan serum amiloid A boleh digunakan sebagai penanda biologi diagnostik untuk CLA.

Kedua-dua jantina untuk satu ratus lima ekor mencit klinikal yang sihat, berusia antara 10 hingga 12 minggu, berat 25-35 g serta dua puluh enam ekor kacukan kambing Boer klinikal yang sihat (13 jantan dan 13 batina) berusia antara 12 hingga 14 bulan, berat 30-35 kg digunakan dalam kajian ini. Batina tidak hamil, tidak menyusu dan ditempatkan berasingan daripada pejantan. Di awal eksperimen, dua jenis inokulum terlibat yang digunakan adalah *C. pseudotuberculosis* hidup dan eksotoksinnya, PLD. Mencit telah dibahagikan kepada tiga kumpulan yang berjumlah 35 ekor setiap kumpulan. Kacukan kambing Boer juga dibahagikan kepada tiga kumpulan. Kumpulan pertama terdiri daripada 6 ekor kambing, kumpulan kedua terdiri daripada 10 ekor kambing dan kumpulan ketiga terdiri daripada 10 ekor kambing. Kumpulan kawalan 1 (mencit dan kambing) telah disuntik dengan fosfat steril masin penimbal (PBS 1 ml / mencit antara peritoneal dan 1 ml / subkutaneus kambing), kumpulan 2 telah disuntik dengan *C. pseudotuberculosis* hidup (1x109 cfu antara peritoneal dalam mencit dan subkutaneus di kambing) manakala kumpulan 3 telah disuntik dengan PLD (1 ml / mouse antara

peritoneal dan 1 ml / 20 kg berat badan di kambing). Mencit telah diperhatikan sepanjang eksperimen, darah dikumpulkan ke dalam tiub heparinized untuk analisis hormon seks. Bedah siasat luka kasar telah dijalankan ke atas ovari, rahim, testis dan epididymis, dan sampel tisu telah ditetapkan untuk pemeriksaan histopatologi. Kambing juga diperhatikan semasa keseluruhan eksperimen untuk tanda-tanda klinikal dan koleksi siri darah telah dijalankan. Darah telah diletakkan ke dalam heparinized, polos, EDTA dan tiub natrium sitrat untuk protein fasa akut (aplikasi), hematologi dan analisis hormone seks. Bedah siasat luka kasar telah dijalankan ke atas paru-paru, jantung, hati, limpa, buah pinggang dan kelenjar limfa, dan sampel tisu telah ditetapkan untuk histopatologi serta perubahan sel dijaringkan.

Mencit yang disuntik dengan *C. pseudotuberculosis* menunjukkan penurunan yang signifikan ($p<0.05$) dalam kepekatan testosteron. Kedua-dua kumpulan suntikan tidak menunjukkan sebarang perubahan kasar dalam organ-organ pembiakan. Walau bagaimanapun, pemeriksaan mikroskopik menunjukkan bahawa penginokulasian *C. pseudotuberculosis* menyebabkan kesesakan, edema, kemasukan keradangan sel, degenerasi dan nekrosis dalam ovari, rahim, testis dan epididimis. Manakala,kumpulan suntikan PLD menunjukkan kesesakan, degenerasi dan nekrosis dalam ovari, rahim, testis dan epididimis dan trombosis dalam ovari dan rahim sahaja.

Kambing yang disuntik dengan kedua-dua *C. pseudotuberculosis* dan PLD menunjukkan peningkatan yang signifikan ($p<0.05$) dalam kepekatan haptoglobin dan penurunan yang signifikan ($p<0.05$) dalam kepekatan albumin. Kambing juga menunjukkan peningkatan yang signifikan ($p<0.05$) dalam suhu badan, kadar denyutan jantung, kadar pernafasan dalam waktu yang berbeza selepas penginokulasian dengan kedua-dua *C. pseudotuberculosis* dan PLD. Selain itu, skor badan menunjukkan penurunan yang signifikan ($p <0.05$) dalam kedua-dua kumpulan yang dirawat pada akhir eksperimen. Selain itu, tapak inokulasi dan nodus limfa dangkal menunjukkan pembentukan nanah di kumpulan suntikan *C. pseudotuberculosis* sahaja.

Kambing yang disuntik dengan *C. pseudotuberculosis* menunjukkan penurunan yang signifikan ($p<0.05$) dalam kiraan sel darah merah, hemoglobin, kepekatan creatine phosphokinase serta peningkatan yang signifikan ($p<0.05$) dalam pengiraan neutrofil. Kambing yang disuntik kedua-dua *C. pseudotuberculosis* dan PLD menunjukkan peningkatan yang signifikan ($p<0.05$) dalam jumlah sel yang padat, bermakna jumlah korpuskel, kiraan sel-sel darah putih, limfosit, monosit, eosinofil dan basophil dan aspartate transaminase, jumlah bilirubin, kalsium, kreatinin, gamma glutamyltransferase , urea, jumlah protein, globulin, kepekatan dehidrogenase laktat, masa prothrombin dan diaktifkan separa masa tromboplastin manakala kedua-dua kumpulan menunjukkan penurunan disuntik signifikan ($p<0.05$) dalam kepekatan hemoglobin korpuskel min, kiraan neutrofil, transaminase alanina dan kepekatan phosphatase alkali.

PengInokulasian dengan PLD menunjukkan penurunan yang signifikan ($p<0.05$) dalam kepekatan creatine phosphokinase.

Hormon testosteron, progesteron, estrogen, lilitan besar buah zakar dan isipadu, pH, corak gelombang, motilitis dan kepekatan air mani menunjukkan penurunan yang signifikan ($p<0.05$) selepas penginokulasian dengan *C. pseudotuberculosis* dan PLD. Di samping itu, sperma mati dan peratusan sperma tidak normal menunjukkan peningkatan yang signifikan ($p<0.05$) dalam kedua-dua kumpulan dirawat. Pemeriksaan mikroskopik ovari menunjukkan pembentukan tisu pecah selepas diinokulasi dengan *C. pseudotuberculosis*, manakala untuk kumpulan suntikan PLD, ovari menunjukkan kesesakan teruk, degenerasi dan nekrosis sel stromal. Di samping itu, tisu rahim menunjukkan kesesakan, degenerasi dan nekrosis selepas diinokulasi dengan kedua-dua C. pseudotuberculosis dan PLD. Testis menunjukkan ketidakaturan struktur dan pengecutan tubul seminiferous dengan edema, degenerasi dan nekrosis sel spermatogonia, dan sel-sel Leydig selepas diinokulasi dengan kedua-dua *C. pseudotuberculosis* dan PLD. Begitu juga epididimis yang menunjukkan edema, degenerasi dan nekrosis lapisan epitelium daripada bedah siasat tubul epididymal yang diinokulasi dengan kedua-dua *C. pseudotuberculosis* dan PLD.

Kumpulan yang disuntik *C. pseudotuberculosis* menunjukkan perubahan kasar dalam paru-paru diwakili oleh hepatization kelabu dan merah, yang lebih mendalam di tempat kesesakan dan pembentukan nanah. Jantung menjadi oedematous dan perikardium menunjukkan beberapa tahap kelegapan. Hati menunjukkan pelbagai pembentukan nanah di permukaannya. Buah pinggang menjadi rapuh dengan kapsul legap manakala limpa menunjukkan penampilan mozek. Nodus limfa menjadi besar, turun naik dan dipenuhi dengan nanah. Kumpulan suntikan PLD juga menunjukkan perubahan kasar dalam paru-paru yang diwakili oleh beberapa tempat di hepatization kelabu tanpa pembentukan nanah di parenchyma itu. Jantung tidak menunjukkan sebarang perubahan kasar yang jelas. Hati kelihatan sesak dengan garis putih hampir di sepanjang semua cuping hati. Buah pinggang kelihatan sesak dengan tempat legap pada kapsul itu. Limpa menjadi rapuh dengan penampilan mozek. Nodus limfa tidak menunjukkan sebarang pembentukan nanah; Walau bagaimanapun, apabila dipotong, ia memperlihatkan perubahan warna kuning berkarat. Pemeriksaan mikroskopik ke atas kumpulan yang disuntik oleh *C. pseudotuberculosis* menunjukkan kesesakan yang ketara, edema, dan penyusupan keradangan sel, degenerasi dan nekrosis dalam paru-paru, jantung, hati, buah pinggang dan limpa. Nodus limfa juga menunjukkan pembentukan granuloma signifikan dengan tumpuan mikro-pembentukan nanah. Kumpulan suntikan PLD menunjukkan kesesakan yang ketara, edema, degenerasi dan nekrosis. Di samping itu, tisu hepatik menunjukkan peningkatan yang signifikan ($p<0.05$) dalam bilangan sel Kupffer. Nodus limfa juga menunjukkan pembentukan abses dengan beberapa deposit haemosiderin.

Daripada kajian ini, dapat disimpulkan bahawa *C. pseudotuberculosis* mempunyai kesan ke atas kepekatan testosteron dan organ-organ pembiakan pada mencit. Walau bagaimanapun, dalam kambing, *C. pseudotuberculosis* dan PLD mempunyai kesan negatif ke atas kepekatan hormone testosteron, estrogen progesteron dan kualiti air mani serta organ-organ pembiakan kedua-dua jantina. Bahan tindak balas fasa akut, terutamanya, haptoglobin, menunjukkan sensitiviti yang ketara dalam kedua-dua kumpulan yang dirawat; kepekaan ini mungkin mempunyai potensi sebagai penanda bio diagnostik untuk CLA dalam kambing. Begitu juga *C. pseudotuberculosis* yang menyebabkan manifestasi klinikal klasik CLA khusus untuk pembentukan nanah di nod limfa cetek, namun, PLD, menunjukkan manifestasi klinikal yang berbeza tanpa pembentukan nanah. Di samping itu, *C. pseudotuberculosis* dan PLD menunjukkan perubahan ketara dalam semua parameter hematologi, namun, PLD menunjukkan corak tindak balas yang berbeza yang mungkin menunjukkan mekanisme yang berbeza tindakan. Perubahan kasar dan selular adalah biasa bagi luka CLA dalam kumpulan suntikan *C. pseudotuberculosis* manakala kumpulan suntikan PLD menunjukkan kurang perubahan kasar; Walau bagaimanapun, perubahan sel adalah teruk dan ini mungkin mencerminkan kesan toksik PLD pada tisu.

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LIST OF ABBREVIATIONS

°C	Degree celsius
cfu	Colony forming unit
CLA	Caseous lymphadenitis
RIA	Radioimmunoassay
PLD	Phospholipase D
APP	Acute phase proteins
AGID	Agar gel immunodiffusion
ELISA	Enzyme Linked Immunosorbent Assay
S.C	Subcutaneous
I.V	Intravenous
IP	Intraperitoneal
DVS	Department of Veterinary Services
Hp	Haptoglobin
OIE	Office of International Epizootic
PBS	Phosphate Buffered Saline
SAA	Serum amyloid A
UPM	Universiti Putra Malaysia
VLSU	Veterinary Laboratories Service Unit

CHAPTER 1

INTRODUCTION

Small ruminant industry, especially goats, in Malaysia is the agricultural sector by the government to increase the goat population and subsequently production of meat. In 2012, the population of sheep and goats were estimated at 129,850 and 482,280 heads respectively (http://www.dvs.gov.my). Caseous lymphadenitis is a chronic disease caused by *Corynebacterium pseudotuberculosis*, a pathogen that infects small ruminant and characterized by abscess formation affecting one or more lymph nodes. However, *C. pseudotuberculosis* can also infect other animals such as cattle, horses, mules, camels, dear, alpacas, but rarely man with a wide range of diseases specific to each species (Yeruham et al., 1997; Connor et al., 2000; Williamson, 2001; Abou-Zaid, 2001; Dorella et al., 2006; Paton, 2010; Guimarães et al., 2011a). *Corynebacterium pseudotuberculosis*, less frequently can also cause orchitis, mastitis, stillbirth, abortion, arthritis, hepatitis, subcutaneous abscesses and pneumonia in small ruminants (Junior et al., 2006; Radostits et al., 2007; Fontaine and Baird, 2008; Paton, 2010).

Caseous lymphadenitis occurs in all major sheep and goat rearing areas across the globe especially in countries with a large sheep population such as Australia and New Zealand. Farmers suffer from heavy economic losses after affected carcasses were degraded and condemned at slaughter and during meat inspection in abattoirs as well as death among affected animals in the farms (Paton, 1990; Williamson, 2001). Despite the significant economic losses and potential zoonoses, the scientific world has yet to come up with an effective vaccine.

The goat's industry in Malaysia partially depends on smallholders contributing to increase the goat population and meat production. These farms are plagued by CLA, the main cause of financial losses to the farmers. However, a survey conducted in East Coast Economic Region (ECER) in Peninsular Malaysia showed that the prevalence of CLA among small ruminant populations in ECER was 11.12% (Abdinasir et al., 2012). The pathogen, *C. pseudotuberculosis* can be identified based on two virulence factors, phospholipase D (PLD) and mycloic acids. Phospholipase D is a potent exotoxin of *C. pseudotuberculosis* and it plays a key role in the development and pathogenesis of CLA (Baird and Fontaine, 2007).

Phospholiase D hydrolyses the sphingomyelin in mammalian cell membrane increasing the vascular permeability especially the endothelial layer, leading to plasma protein leakage from the blood into the surrounding tissue space and from there into the lymphatic system. This helps the dissemination of *C. pseudotuberculosis* from the primary infection location to other parts of the

animal's body (Guimarães et al., 2011a). The notion that PLD is a significant virulence factor has been tested when some isolates of *C. pseudotuberculosis* that had their *pld* genes encoding PLD removed were not capable of causing abscess formation in the lymph nodes of CLA infected sheep (McNamara et al., 1994).

Acute phase proteins (APPs), mainly haptoglobin (Hp) and serum amyloid A (SAA) are appropriate indispensable parameters that can be used objectively and rapidly to evaluate animal health and well-being at any time which make it valuable tools for screening the animal's health status (Murata et al., 2004; Lakota et al., 2011; Piñeiro et al., 2013). They are frequently measured for diagnostic and predictive purposes (Vreugdenhil et al., 1999; Lakota et al., 2011). Hence, quantification of APPs has been established for clinical and research purposes to provide information on APPs behavior and their response mechanisms (Eckersall et al., 1999).

Caseous lymphadenitis has an insidious effect on an animal's fertility with eventual reduction in the reproductive efficiency as well as meat and milk production. Goldberger et al (1981) have isolated *C. pseudotuberculosis* in raw milk of sheep infected with CLA. Some lambs have infected by CLA through suckling their infected dams (Baird et al., 2004).

Little is known about the effects of CLA on reproduction performance in goats (Williamson, 2001; Conner et al., 2000). The reproductive organs that are mainly affected are the epididymis and the mammary gland in sheep and goats (Unanian et al., 1985). Valli and Parry (1993) claimed that the testes and uterus in sheep can also be affected by CLA. Caseous lymphadenitis abscesses have been found in the inguinal and scrotal lymph nodes of rams, but not in the epididymis neither in the testes nor semen (Williamson and Nairn, 1980). The lack of the knowledge and the inconsistent reports in regard to CLA and its impact on reproduction of sheep and goats has led to the current study focusing on the reproductive characteristic of the goats during the course of CLA.

Generally, there is scanty information of the haemogram and APPs response during the course of CLA in goats. There is also no specific report on the hormonal profile (testosterone, progesterone, estrogen) and histopathological changes of reproductive and visceral organs in the goats challenged with *C. pseudotuberculosis* and its exotoxin, PLD. Up-to-date, there is no documentation, report or any citation on pathophysiological changes of the reproductive system in both male and female goats challenged with *C. pseudotuberculosis* and PLD. Thus, this study was designed with the intention for better understanding of the haematological, biochemical, histopathological and hormonal changes that may revolve in the challenged host (mice and goat). Consequently, this will assist to improve our knowledge regarding ethiopathogenesis of CLA in goats.

Problem statement:

1. Caseous lymphadenitis is a chronic disease and difficult to diagnose at an early stage. Acute phase proteins have a significant, sensitive and valid role as diagnostic biomarkers for subclinical, acute and chronic conditions. Therefore, it may be useful to incorporate in the CLA diagnosis in goats.
2. Caseous lymphadenitis also has an insidious effect on reproduction which eventually affects the productivity of the goat. Studies have been reporting CLA lesions in the reproductive organs which influenced the reproductive efficiency in both males and females.

Hypothesis:

Acute phase proteins are more useful for monitoring health than cytokines because the latter have short half-life (few hours) compare to acute phase reactants. Acute phase proteins may have role as biomarkers for chronic conditions because of their presence in circulation can persist beyond the immediate infection time and as the lesion become chronic.
Thus, the objectives of the current study were:

1. To estimate the sex hormones (testosterone, progesterone, estrogen) responses between the infection by *C.pseudotuberculosis* and PLD inoculation in mouse model.
2. To observe the clinical signs between infection by *C. pseudotuberculosis* and PLD inoculated goats.
3. To measure the changes in the haemogram between the infection by *C.pseudotuberculosis* and PLD inoculated goats.
4. To estimate the acute phase proteins responses between infection by *C. pseudotuberculosis* and PLD inoculated goats.
5. To estimate the sex hormones (testosterone, progesterone, estrogen) responses between the infection by *C.pseudotuberculosis* and PLD inoculated goats.
6. To evaluate the histopathological changes of visceral organs, reproductive organs (testes, epididymus, ovary, uterus) and lymph nodes between the infection by *C.pseudotuberculosis* and PLD inoculated goats.

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