Faecal calprotectin levels differentiate intestinal from pulmonary tuberculosis: An observational study from Southern India

Geir Larsson^{1,2}, Koticherry Thrivikrama Shenoy³,
Ramalingom Ramasubramanian⁴, Lakshmikanthan Thayumanavan⁵,
Leena Kondarappassery Balakumaran³, Gunnar A Bjune⁶ and Bjørn A Moum⁷

Abstract

Background: Current methods to establish the diagnosis of intestinal tuberculosis are inadequate.

Objectives: We aimed to determine the clinical features of intestinal tuberculosis and evaluate inflammatory biomarkers in intestinal as well as pulmonary tuberculosis.

Methods: We recruited 38 intestinal tuberculosis patients, 119 pulmonary tuberculosis patients and 91 controls with functional gastrointestinal disorders between October 2009 and July 2012 for the investigation of clinical features, C-reactive protein (CRP), faecal and serum calprotectin. Faecal calprotectin $\geq 200 \mu\text{g/g}$ was used as a cut-off to determine intestinal inflammation of clinical significance. Three patient categories were established: (a) pulmonary tuberculosis and faecal calprotectin $< 200 \mu\text{g/g}$ (isolated pulmonary tuberculosis); (b) pulmonary tuberculosis and faecal calprotectin $\geq 200 \mu\text{g/g}$ (combined pulmonary and intestinal tuberculosis); (c) isolated intestinal tuberculosis.

Results: Common clinical features of intestinal tuberculosis were abdominal pain, fatigue, weight loss and watery diarrhoea. Intestinal tuberculosis patients had elevated median CRP (10.7 mg/l), faecal calprotectin (320 $\mu\text{g/g}$) and serum calprotectin (5.7 $\mu\text{g/ml}$). Complete normalisation of CRP (1.0 mg/L), faecal calprotectin (16 $\mu\text{g/g}$) and serum calprotectin (1.4 $\mu\text{g/ml}$) was seen upon clinical remission. Patients with combined pulmonary and intestinal tuberculosis had the highest levels of CRP (53.8 mg/l) and serum calprotectin (6.5 $\mu\text{g/ml}$) and presented with signs of more severe disease.

Conclusion: Calprotectin analysis reveals intestinal tuberculosis in patients with pulmonary tuberculosis and pinpoints those in need of rigorous follow-up.

Keywords

Intestinal tuberculosis, calprotectin, biomarker, diagnosis, pulmonary tuberculosis, CRP, follow-up, treatment response, clinical features

Received: 1 April 2014; revised: 20 May 2014; accepted: 29 June 2014

Background

Tuberculosis (TB) is an old disease which still harms mankind more than any other infectious disease.¹ Intestinal TB (ITB) is a common form of extra-pulmonary TB in India, the aetiologic agent being *Mycobacterium tuberculosis* (*M.tb*). Disease manifestation depends on the site of lesion in the gastrointestinal tract, although general signs such as fever, weight loss, cachexia and diarrhoea and symptoms of abdominal pain and malaise are usually present.^{2–8} However, the presentation and pathological findings of ITB may

¹Unger-Vetlesen Institute, Department of Medicine, Lovisenberg Diaconal Hospital, Oslo, Norway

²Faculty of Medicine, University of Oslo, Norway

³Population Health and Research Institute, Medical College, Trivandrum, Kerala, India

⁴Thoothukudi Government Medical College, Tuticorin, Tamil Nadu, India

⁵Government Rajaji Hospital, Madurai, Tamil Nadu, India

⁶Institute of Health and Society, Faculty of Medicine, University of Oslo, Norway

⁷Department of Gastroenterology and Hepatology, Institute of Clinical Medicine, Oslo University Hospital Ullevål, Oslo, Norway

Corresponding author:

Geir Larsson, Unger-Vetlesen Institute, Department of Medicine, Lovisenberg Diaconal Hospital, NO-0440 Oslo, Norway.

Email: larsson.geir@gmail.com

vary and be non-specific, and the disease may easily be confounded with other gastrointestinal diseases.⁹

Gastrointestinal endoscopic examination plays a key role in the diagnosis of ITB. However, endoscopy with biopsies, histopathological investigation and advanced molecular laboratory work-up are costly and require highly qualified staff. This also applies to complementary diagnostic modalities such as computer tomography, magnetic resonance imaging and explorative laparotomy. Expensive interferon- γ release assays can be used to screen for TB in non-endemic settings, but have proved rather unspecific for detection of active TB in endemic areas. Co-existing malnutrition and helminth infections may further decrease the sensitivity of these assays.¹⁰ All of the above require resources which are not easily available in economically deprived TB-endemic areas. Unfortunately, inexpensive diagnostic modalities such as acid-fast staining of biopsies or sputum, Mantoux tuberculin skin tests, *M.tb* cultures and chest X-rays have shown poor diagnostic performance in ITB.^{2,4-6} Consequently, prescribing a course of empiric anti-tuberculous chemotherapeutic drug treatment (ATT), with clinical re-evaluation of the diagnosis after 2 months, still seems to be the diagnostic method of choice in many TB-endemic regions.^{3,4,8}

Calprotectin is a complex of myeloid-related proteins (MRP 8/14) released from neutrophilic granulocytes and monocytes/macrophages during activation or cell death.¹¹ Faecal calprotectin (FC) is routinely measured in patients with inflammatory bowel disease to monitor relapse of disease and/or effect of treatment.¹² Serum calprotectin (SC) has been found elevated in various inflammatory diseases such as rheumatoid

arthritis, systemic lupus erythematosus, bacterial infections including sepsis and active pulmonary TB (PTB).^{13,14}

The aim of this study was to describe the initial disease characteristics of ITB in Southern India and to evaluate calprotectin in ITB and PTB.

Materials and methods

In this observational study, 38 ITB patients, 22 men and 16 women, were consecutively enrolled from one secondary and three tertiary care centres in South India between October 2009 and July 2012 (see Appendix 1). Only patients with clinical, endoscopic and histological hallmarks of ITB were included in the study. The median age was 34 years (range 21–68) (Table 1), irrespective of sex (data not displayed).

Exclusion criteria were age below 18 years, co-existing malignancy or Human Immunodeficiency Virus infection. Demographic information and disease-associated signs and symptoms were recorded in electronic case record forms prior to physical examination and further investigations. Abdominal pain and/or diarrhoea were classified as the 'first appearance of disease' in the patient history.

Blood samples were drawn for serum C-reactive protein (CRP) and SC analyses in parallel with the collection of faeces spot samples for FC analysis at baseline and on follow-up. Faecal aliquots and separated blood serum vials were stored at -20°C until analysis. As recommended by the local laboratory, CRP $<6.0\text{ mg/l}$ was regarded as normal. FC and SC were analysed with ELISA technology using EK-CAL and MRP 8/14 kits

Table 1. Demographic and biometric variables of controls, pulmonary TB patients (PTB), intestinal TB (ITB) patients and patients with combined PTB and ITB (PITB)

Demographic data	Controls (<i>n</i> = 91)	<i>p</i> -value	PTB (<i>n</i> = 103)	<i>p</i> -value	PITB (<i>n</i> = 16)	ITB (<i>n</i> = 38)
Age, median	34	NS ^a	50	$<0.01^a$	44	34
<i>min-max</i>	19–61		19–78		19–70	21–68
Male gender, <i>n</i> (%)	63 (69)	NS ^b	88 (86)	$<0.01^b$	10 (63)	22 (58)
Body Mass Index, median	22.8	$<0.01^a$	17.9	0.02 ^a	18.7	19.7
<i>min-max</i>	13.7–32.5		12.2–29.9		11.7–22.1	11.2–26.0
Household monthly income (€), median	46	NS ^a	6	$<0.01^a$	4	59
<i>min-max</i>	5–352		1–763		4–23	4–469
Running water in dwelling, <i>n</i> (%)	84 (92)	$<0.01^b$	84 (82)	NS ^b	14 (88)	26 (68)
High school degree, <i>n</i> (%)	85 (93)	$<0.01^b$	33 (32)	NS ^b	6 (38)	20 (53)
Years of schooling, Median	12	$<0.01^a$	7	$<0.01^a$	8	10
<i>min-max</i>	2–22		0–17		0–15	0–20

Statistical differences between groups calculated against ITB, NS = non-significant.

^aMann-Whitney Wilcoxon Test.

^bPearson Chi Square Test.

respectively, according to the manufacturer's recommendations (Bühlmann Laboratories AG, Basel, Switzerland). For SC, cut-off levels are yet to be established and levels depend on the underlying condition.¹³ For FC, a threshold of 200 µg/g was used as a cut-off to predict intestinal inflammation of clinical importance.^{15,16}

In addition, 91 subjects with functional gastrointestinal disorders such as irritable bowel syndrome or functional dyspepsia were consecutively recruited as controls during the same period of time. Similarly, 119 patients with smear-positive PTB were recruited as TB controls, and these were further divided into two sub-groups based on their FC levels. Thus, three separate categories of TB patients were established: (a) patients with smear-positive pulmonary disease and FC <200 µg/g, hereafter designated 'PTB'; (b) patients with smear-positive pulmonary disease and FC ≥200 µg/g, hereafter defined as combined pulmonary and intestinal TB, designated 'PITB'; and (c) patients with primarily intestinal disease as per modified Paustian's criteria,¹⁷ hereafter designated 'ITB'.

Statistics

As data were skewed, the continuous variables were described with median and inter-quartile range (IQR), while categorical variables were listed as counts and percentages. Crude differences between the groups were assessed with χ^2 or Fischer's exact tests for the categorical variables and Mann-Whitney Wilcoxon tests for the continuous variables. $P < 0.05$ was considered statistically significant to differentiate between

the groups. Statistical Package for the Social Sciences software Version 18.1 was used to perform all analyses. The choice of statistical methods and interpretation of results were assisted by a biomedical statistician.

Ethics

The study was approved with respect to the Helsinki declaration by the The Ethical Committee of Sree Gokulam Medical College and Research Foundation, Trivandrum, India. Written informed consent was obtained from every participant.

Results

The ITB group had significantly elevated FC, SC and CRP levels compared with the controls (Table 2). The differences were highly significant with regards to FC and CRP. Follow-up data after a 2-month course of ATT were available in nine patients, all of whom were in clinical remission and showed normalisation in laboratory variables (median FC 16 µg/g, IQR 75; and median SC 1.4 µg/ml, IQR 13.3; median CRP 1.0 mg/l, IQR 1.25). Six patients agreed to undergo follow-up endoscopic investigation and all showed complete endoscopic normalisation. The remaining three patients refused follow-up colonoscopy.

Both the ITB and the PITB groups showed significantly elevated median FC levels when compared with the PTB group and the controls, respectively (Table 2, Figure 1(a)). Although median SC levels were higher in all TB groups compared with the controls, only the ITB group showed significantly elevated median SC

Table 2. Laboratory variables of controls, pulmonary TB patients (PTB), intestinal TB (ITB) patients and patients with combined PTB and ITB (PITB)

Laboratory variables	Controls (n = 83)	PTB (n = 95)	PITB (n = 16)	ITB (n = 36)
F-calprotectin (µg/g), median	12	21	345 ^a	320 ^b
<i>max</i>	450	185	1000	1800
(Inter-quartile range)	(23)	(41)	(510)	(942)
S-calprotectin (µg/ml), median	3.2	4.9	6.5	5.7 ^c
<i>max</i>	27	30	15.5	18
(Inter-quartile range)	(8.2)	(8.7)	(12.6)	(7.0)
CRP (mg/l), median	1.0	9.4 ^d	53.8	10.7 ^e
<i>max</i>	40.6	67.9	106.0	70.5
(Inter-quartile range)	(1.4)	(35.7)	(43.9)	(37.6)

^a $p < 0.001$: PITB vs. PTB.

^b $p < 0.001$: ITB vs. PTB.

^c $p = 0.024$: ITB vs. controls.

^d $p = 0.002$: PTB vs. PITB.

^e $p = 0.002$: ITB vs. PITB.

Figure 1. (a) Faecal calprotectin and (b) CRP levels in tuberculosis.

PTB = pulmonary tuberculosis, ITB = intestinal tuberculosis, PITB = combined PTB and ITB. CI = Confidence Interval. Thresholds for raised CRP- and FC-levels marked by dotted horizontal lines.

(Table 2). The highest median SC was recorded in the PITB group. Median CRP was significantly elevated in all TB groups compared with the controls. Furthermore, median CRP was significantly higher in the PITB group compared with the PTB and the ITB groups, respectively (Table 2, Figure 1(b)).

The majority of ITB patients reported of abdominal pain and fatigue as their leading symptoms (Figure 2).

With regards to signs of disease, weight loss, watery diarrhoea and cachexia were most commonly observed (Figure 2). Low-grade fever was found in half of the patients. One-third presented with abdominal mass on physical examination. The median duration of symptoms prior to diagnosis was 6 months, but a considerably longer disease course was observed in some of the patients. The distribution of symptoms and signs was

Figure 2. Intestinal tuberculosis: disease-associated features in 38 patients. PTB = pulmonary tuberculosis.

equal between patients with short and long courses of disease, respectively. Yet, more patients with long-standing disease reported fatigue and presented with abdominal mass on physical examination (data not shown).

Of our patients, 59% reported that their symptoms were constant. However, disease manifestation did not differ significantly from those with a more fluctuating course of symptoms.

Five ITB patients had PTB and one-quarter of the ITB patients reported previous exposure to PTB either in their own or in their family history. Typically, ITB patients with PTB also reported coughing and daily tobacco smoking.

There was no statistical significant difference between men and women with regards to the distribution of signs and symptoms (data not shown). Of socioeconomic variables, the average monthly household income was 59€. Two-thirds of the patients lived in households with running water. The average educational level was 10 school years and half of the patients had completed a high school degree or higher (Table 1).

The distribution of signs and symptoms commonly seen in TB is described in Figure 3. Weight loss and fatigue were significantly more frequent in the ITB group when compared with the PTB group ($p=0.002$ and $p=0.037$, respectively). Fever and coughing were most common in the PITB group (Figure 3). Body mass index was significantly lower in all TB groups compared with the controls (Table 1). Signs of cachexia were significantly more frequent in the ITB group compared with the PTB group (61 vs. 10%, $p < 0.001$).

Discussion

Recently, a correlation was found between calprotectin levels, the number of neutrophils, the levels of

neutrophil-attracting chemokines and the extent of lung inflammation in patients with active PTB.¹⁴ Also, the pro-inflammatory cytokine interleukin-17, which mediates calprotectin release and neutrophil accumulation, has been found upregulated in peripheral blood mononuclear cells of ITB patients.¹⁸ In this study, we demonstrated high calprotectin levels in patients with ITB. Clinical remission and a consistent decrease in CRP, SC and FC levels were observed on follow-up after ATT, suggestive of a positive treatment response. Endoscopic normalisation was observed in the six patients who agreed to undergo follow-up endoscopic investigations. The remaining patients, although in clinical and biochemical remission, refused follow-up endoscopy. Calprotectin could become a surrogate marker for remission in this patient category, similar to its application in inflammatory bowel disease.¹⁹ Adherence to follow-up is crucial to assure an adequate treatment outcome and to decrease the risk of *M.tb* dissemination. This could be achieved by offering simple, non-invasive and affordable screening tools.

Median FC was significantly elevated in the PITB group as well as in the ITB group, suggestive of comparable pathology. Conversely, FC was normal in the PTB patients and not differing from the median FC in the controls. Median SC was moderately elevated in the PITB group, suggestive of systemic inflammation. Although the highest SC levels were detected in the PITB group, SC did not allow for discrimination between the patient categories. Larger study populations are needed to investigate the role of SC in TB.

By being a chronic granulomatous disease of the gut, Crohn's disease (CD) resembles ITB in pathophysiological, histological and even immunological ways.⁹ Therefore, considering the lack of previous studies on FC in ITB, we anticipated similar results in ITB as those reported in studies on FC in CD. There is an

Figure 3. Distribution of disease characteristics in tuberculosis.

PTB = pulmonary tuberculosis, ITB = intestinal tuberculosis, PITB = combined PTB and ITB.

ongoing debate with regards to which FC threshold levels should be used as a cut-off to determine intestinal inflammation of clinical significance in CD. Previously, a cut-off level of 200 µg/g was suggested to predict endoscopically active disease,²⁰ whereas lately a cut-off level of 250 µg/g has been suggested.^{16,21,22} Just recently, an even higher cut-off level of 274 µg/g was suggested to determine endoscopic remission.¹⁵ Also of interest, a cut-off of 150 µg/g has been suggested to determine organic intestinal disease in a primary health care setting.²³ Different FC kit manufacturers operate with different calprotectin antigens, thereby causing considerable inter-assay variability. The latter studies established FC with kits from the same manufacturer as in our study.^{15,23} Based on the aforementioned studies we chose an FC cut-off level of 200 µg/g to rule out intestinal inflammation of clinical significance in PTB.

Interestingly, some studies have shown a higher increase in the incidence of extra-pulmonary TB than of pulmonary TB.^{3,24} Whether the rise is a result of increased awareness or because of specific virulence factors in certain *M.tb* strains is unknown. Regardless, PTB patients with co-existing gastrointestinal TB lesions have been described as more seriously ill than patients with isolated PTB.²⁵ However, according to the case

definitions of TB established by the World Health Organisation, these patients are classified as PTB. We question whether PTB cases with concomitant TB infestation in other organs should be described as such, in order to receive appropriate follow-up investigations. Furthermore, the evaluation of transmission mechanisms, treatment outcomes and mortality rates of the various types of TB may be facilitated if patients with combined TB infections are reported as such to the central TB registries.

The importance of distinguishing PITB as a more severe form of TB is supported by several findings. First, when asked about their levels of energy, three-quarters of the ITB patients confirmed that they felt deprived of energy since the onset of disease. Previous reports on TB patients' perception of disease are scarce, but the few ones published have shown that during the course of disease and treatment half of all PTB patients feel deprived of energy.^{26,27} Fatigue could be related to the release of systemic inflammatory mediators in response to TB itself, but also due to ITB-associated anaemia and/or diarrhoea with malabsorption. We found that the proportion reporting of fatigue increased in the following order: PTB–PITB–ITB, and a significant difference was seen between the PTB and the ITB groups.

Second, we recorded lower body weight and body mass index in the ITB patients compared with the controls with functional gastrointestinal disorders. Leptin, an appetite-stimulating hormone produced in adipocytes, has been shown to decline in cachectic TB patients.²⁸ Compared with the PTB patients, a substantial number of the ITB patients were cachectic. This could reflect reduced energy uptake and additional mechanisms of weight loss, i.e. malabsorption of nutrients and/or decreased intestinal transit time.²⁹

Third, CRP levels may be elevated in both pulmonary and extra-pulmonary active TB.^{30,31} A small study on TB-diseased children found an inverse relationship between CRP and body mass index and between leptin levels and CRP, with poorer prognosis in patients with the highest CRP levels.³² We recorded a five-fold increase in CRP and lower body weight in the PITB group compared with the other groups, suggestive of a more severe disease.

Finally, fever was reported in two-thirds of the PITB patients. In contrast, less than half of the patients in the two other TB groups had fever. Previously, low-grade fever has been described as frequent in ITB,^{7,33,34} while others have described it as less frequent.^{2,4,35} Coughing was mostly observed in the PITB patients, indicating a more active pulmonary disease.

Therefore, a more severe form of TB should generally be suspected in patients with PITB, although the severity of disease may vary between patients. As a 'proof of concept' of the association between PTB, high FC and suspected intestinal pathology, one of our high FC PTB patients showed ulcerohypertrophic lesions in the ascending colon upon endoscopy. Unfortunately, the remainder of the PITB patients refused lower gastrointestinal endoscopy. We believe that distinguishing patients with severe TB is important because they require more rigorous follow-up. The combination of CRP and FC analysis could be useful supplements in the initial investigation and follow-up of this patient category. International guidelines on case registration of PTB are perhaps not uniform, and may need refinement according to the population and setting in question. This especially counts for smear-negative TB patients where the diagnosis is the crux and tools for detecting active TB are missing. Calprotectin could prove as a useful adjunct in this regard as raised levels indicate active infection.

A median symptom duration of 6 months prior to diagnosis was found in another recent prospective study on ITB from India.³³ However, most studies from South and East Asia describe a symptom history of 1–2 years prior to diagnosis.^{2,4} However, these were retrospective and exclusively conducted in tertiary care centres. Nevertheless, the most common features detected were consistent with the literature: abdominal pain, weight loss, cachexia and diarrhoea.^{2,4,5,33}

Only the minority of the ITB patients had concurrent PTB, similar to other studies.^{2,4,6} Rather than indirect infestation of bacilli first harboured in the lungs, we therefore suggest that the intestines are primarily infested by mycobacteria directly acquired from oral ingestion. The challenge of curbing the TB epidemic could partly be due to the relatively long-lasting and rather silent hideaway of *M.tb* in the intestinal lymphatics.

Our study has some limitations. First, the small number of 38 ITB patients only allows for crude statistical analyses, and the comparison of our results with previous studies may be difficult. Second, the study has some missing data as a complete record of all study variables was difficult to achieve, thus limiting statistical analyses. Third, because sampling and preservation of blood serum for SC analysis was performed at four different centres, variations in sample handling may have occurred. Even so, all technicians followed pre-defined standard operating procedures and only minimal alterations in SC concentrations were expected. We believe that our study is of clinical relevance because the data were population based and collected from routine clinical practice in secondary and tertiary care centres. To our knowledge, this is the first study which describes calprotectin in ITB. To further assess calprotectin in patients in clinical remission, future studies should aim at strict adherence to follow-up investigations.

In summary, FC may be used as a biomarker in the diagnostic work-up of ITB. FC analysis in PTB patients with abdominal symptoms is a simple and non-invasive tool to reveal ITB co-infection and pinpoints patients in need of a more rigorous follow-up. Also, calprotectin may be used in the evaluation of treatment response after ATT.

Funding

This work was supported by The South-Eastern Norwegian Regional Health Authority [grant number 2011132].

Acknowledgements

G Larsson would like to thank the staff at the Population Health and Research Institute in Trivandrum, India, with special regards to Mrs. Suja, for handling and preparing patient samples and filing the data. Special thanks also to investigator Dr. VG Mohan Prasad at Coimbatore centre for recruiting patients, and to Dr. B Holm and Mrs. AM Tangen at Lovisenberg Diaconal Hospital for allowing the initiation and financial support of this study. Thanks to Ms. MC Småstuen for assisting on the choice of statistical methods. Dr. PC Klepp is acknowledged for proofreading and thorough support during the study. Calprotectin analyses were performed with kits provided without cost by Bühlmann Laboratories AG, Basel, Switzerland. Dr. A Røseth kindly advised on the analysis of calprotectin.

References

- Muruganathan A, Thomas A, Muniyandi M, et al. Revised National Tuberculosis Control Programme (RNTCP). *J Indian Med Assoc* 2010; 108: 868–870.
- Li X, Liu X, Zou Y, et al. Predictors of clinical and endoscopic findings in differentiating Crohn's disease from intestinal tuberculosis. *Dig Dis Sci* 2011; 56: 188–196.
- Epstein D, Watermeyer G and Kirsch R. Review article: The diagnosis and management of Crohn's disease in populations with high-risk rates for tuberculosis. *Aliment Pharmacol Ther* 2007; 25: 1373–1388.
- Makharia GK, Srivastava S, Das P, et al. Clinical, endoscopic, and histological differentiations between Crohn's disease and intestinal tuberculosis. *Am J Gastroenterol* 2010; 105: 642–651.
- Alvares JF, Devarbhavi H, Makhija P, et al. Clinical, colonoscopic, and histological profile of colonic tuberculosis in a tertiary hospital. *Endoscopy* 2005; 37: 351–356.
- Patel N, Amarapurkar D, Agal S, et al. Gastrointestinal luminal tuberculosis: establishing the diagnosis. *J Gastroenterol Hepatol* 2004; 19: 1240–1246.
- Li Y, Zhang LF, Liu XQ, et al. The role of in vitro interferon-gamma-release assay in differentiating intestinal tuberculosis from Crohn's disease in China. *J Crohns Colitis* 2012; 6: 317–323.
- Tai WP, Hu PJ, Zhai HZ, et al. The clinical analysis of 34 cases of intestinal tuberculosis in China's big city hospitals. *Int J Colorectal Dis* 2011; 26: 1339–1343.
- Larsson G, Shenoy K, Ramasubramanian R, et al. Routine diagnosis of intestinal tuberculosis and Crohn's Disease in Southern India. *World J Gastroenterol* 2014; 20: 5017–5024.
- Thomas TA, Mondal D, Noor Z, et al. Malnutrition and helminth infection affect performance of an interferon gamma-release assay. *Pediatrics* 2010; 126: e1522–e1529.
- Johne B, Fagerhol MK, Lyberg T, et al. Functional and clinical aspects of the myelomonocyte protein calprotectin. *Mol Pathol* 1997; 50: 113–123.
- Tibble J, Teahon K, Thjodleifsson B, et al. A simple method for assessing intestinal inflammation in Crohn's disease. *Gut* 2000; 47: 506–513.
- Striz I and Trebichavsky I. Calprotectin – a pleiotropic molecule in acute and chronic inflammation. *Physiol Res* 2004; 53: 245–253.
- Gopal R, Monin L, Torres D, et al. S100A8/A9 proteins mediate neutrophilic inflammation and lung pathology during tuberculosis. *Am J Respir Crit Care Med* 2013; 188: 1137–1146.
- Lobaton T, Lopez-Garcia A, Rodriguez-Moranta F, et al. A new rapid test for fecal calprotectin predicts endoscopic remission and postoperative recurrence in Crohn's disease. *J Crohns Colitis* 2013; 7: e641–e651.
- D'Haens G, Ferrante M, Vermeire S, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis* 2012; 18: 2218–2224.
- Logan VS. Anorectal tuberculosis. *Proc R Soc Med* 1969; 62: 1227–1230.
- Pugazhendhi S, Jayakanthan K, Pulimood AB, et al. Cytokine gene expression in intestinal tuberculosis and Crohn's disease. *Int J Tuberc Lung Dis* 2013; 17: 662–668.
- Gisbert JP, Bermejo F, Perez-Calle JL, et al. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. *Inflamm Bowel Dis* 2009; 15: 1190–1198.
- Sipponen T, Savilahti E, Kolho KL, et al. Crohn's disease activity assessed by fecal calprotectin and lactoferrin: Correlation with Crohn's disease activity index and endoscopic findings. *Inflamm Bowel Dis* 2008; 14: 40–46.
- Schoepfer AM, Beglinger C, Straumann A, et al. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *Am J Gastroenterol* 2010; 105: 162–169.
- Louis E, Mary JY, Vernier-Massouille G, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology* 2012; 142: 63–70.
- Pavlidis P, Chedgy FJ and Tibble JA. Diagnostic accuracy and clinical application of faecal calprotectin in adult patients presenting with gastrointestinal symptoms in primary care. *Scand J Gastroenterol* 2013; 48: 1048–1054.
- Rasheed S, Zinicola R, Watson D, et al. Intra-abdominal and gastrointestinal tuberculosis. *Colorectal Dis* 2007; 9: 773–783.
- Pettengell KE, Larsen C, Garb M, et al. Gastrointestinal tuberculosis in patients with pulmonary tuberculosis. *Q J Med* 1990; 74: 303–308.
- Chang B, Wu AW, Hansel NN, et al. Quality of life in tuberculosis: A review of the English language literature. *Qual Life Res* 2004; 13: 1633–1642.
- Rajeswari R, Muniyandi M, Balasubramanian R, et al. Perceptions of tuberculosis patients about their physical, mental and social well-being: A field report from south India. *Soc Sci Med* 2005; 60: 1845–1853.
- Van CR, Karyadi E, Netea MG, et al. Decreased plasma leptin concentrations in tuberculosis patients are associated with wasting and inflammation. *J Clin Endocrinol Metab* 2002; 87: 758–763.
- Tandon RK, Bansal R, Kapur BM, et al. A study of malabsorption in intestinal tuberculosis: Stagnant loop syndrome. *Am J Clin Nutr* 1980; 33: 244–250.
- Sahin F and Yildiz P. Distinctive biochemical changes in pulmonary tuberculosis and pneumonia. *Arch Med Sci* 2013; 9: 656–661.
- Sevgi DY, Derin O, Alpaz AS, et al. Extrapulmonary tuberculosis: 7 year-experience of a tertiary center in Istanbul. *Eur J Intern Med* 2013; 24: 864–867.
- Herlina M, Nataprawira HM and Garna H. Association of serum C-reactive protein and leptin levels with wasting in childhood tuberculosis. *Singapore Med J* 2011; 52: 446–450.

33. Amarpurkar DN, Patel ND and Rane PS. Diagnosis of Crohn's disease in India where tuberculosis is widely prevalent. *World J Gastroenterol* 2008; 14: 741–746.
34. Yu H, Liu Y, Wang Y, et al. Clinical, endoscopic and histological differentiations between Crohn's disease and intestinal tuberculosis. *Digestion* 2012; 85: 202–209.
35. Mukewar S, Mukewar S, Ravi R, et al. Colon tuberculosis: Endoscopic features and prospective endoscopic follow-up after anti-tuberculosis treatment. *Clin Transl Gastroenterol* 2012; 3: e24.