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Mini Review

Fecal Calprotectin Test in Clinical Practice

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Abbreviations: RAGE: Receptor for Advanced Glycation End Products; IBD: Inflammatory Bowel Disease; IBS: Irritable Bowel Syndrome; DAMP: Damage-Associated Molecular Pattern

Mini Review

Calprotectin is a protein derived from leukocytes that appears in the intestinal mucosa when there is inflammation. It belongs to the family of low molecular weight proteins S100 and is found in large quantities in the granules of neutrophils where it forms 60% of cytoplasmic proteins. It is a polypeptide formed of one light chain and two heavy chains with a molecular weight of 36.5kDa [1,2]. This protein has antimicrobial and bacteriostatic functions and is attributed an active role in the body's defenses.S100A8 (calgranulin A) and its binding partner S100A9 (calgranulin B) exhibit increased levels in several inflammatory states. Calgranulin A and calgranulin B form the heterocomplex S200A8/9, more commonly known as calprotectin. The effects of calprotectin are mediated by calcium flux after activation of the receptor for advanced glycation end products (RAGE). Calprotectin is released from damaged cells through an atypical pathway that requires protein kinase C and RAGE, thus making calprotectin a damage-associated molecular pattern (DAMP) molecule [3].

When an inflammatory process is carried out in the intestine, neutrophils are attracted to the inflammatory site where they degranulate and secrete calprotectin, which due to its high affinity to calcium, remains stable and resistant to enzymatic degradation for a period of approximately 7 days at room temperature [4]. Being resistant to degradation by enzymes and bacteria, it travels through the intestine along with its contents and is secreted in the stool. This makes fecal calprotectin a simple, non-invasive and easy-to-analyze biomarker that assesses inflammatory bowel activity in patients with Crohn's disease and ulcerative colitis [5].The use of fecal calprotectin has been studied for more than a decade, and its use to differentiate between Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS) has been proven. In Crohn's disease and ulcerative colitis, it has been shown to predict the rate of relapse [5].

The nonspecific clinical manifestations of gastrointestinal inflammatory diseases make it necessary to use tools such as colonoscopy and histology to reach the diagnosis, however, these methods are expensive and invasive. Studies have shown high levels of fecal calprotectin in patients with IBD, compared to healthy controls and patients with IBS. In this way, fecal calprotectin also becomes useful to differentiate between IBD and IBS [6]. Intestinal inflammatory diseases are of unknown etiology, in which mucosal healing is the therapeutic objective [7]. The most appropriate biomarker to assess the activity or remission of the disease is fecal calprotectin. Low levels of fecal calprotectin have been observed after pharmacological treatment, which correlates with the healing of the intestinal mucosa [8].

The maximum limit of fecal calprotectin in healthy individuals is 50μg/g with a sensitivity of 95% and specificity of 91%. There are other studies in which values of 24-150μg/g proves to be normal in patients with inflammatory bowel disease with a sensitivity of 93% and specificity of 96%. For colon cancer, fecal calprotectin turns out to be an unreliable biomarker with 31% sensitivity and 71% specificity [8]. It is well known that chronic inflammation is a risk factor for gastrointestinal malignancy. Patients suffering from IBD have a higher risk of developing colorectal cancer. Fecal calprotectin seems to be a marker with more sensitivity for gastrointestinal cancer than the fecal occult blood test, however, it does not have the specificity necessary to be part of routine laboratory tests in populations with risk factors. Of all the fecal inflammatory markers, calprotectin appears to be the most promising, due to the fact that this protein is elevated in subjects with inflammatory bowel disease and correlates with histological findings of inflammation [9].

Meta-analyzes have been carried out to evaluate the use of fecal calprotectin in colorectal cancer comparing histological findings with fecal calprotectin levels in which a relationship between

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elevated calprotectin levels and histological malignancy has not yet been confirmed [10]. Other studieshave evaluated the role of calprotectin in colorectal cancer resulting in diverse conclusions [3] (Table 1).The British Journal of General Practice suggests there are enough inflammatory components in patients with colorectal cancer to provide high levels of fecal calprotectin [11], which is supported by other studies that indicate fecal calprotectin decreases significantly after colorectal cancer operation [12]. Tibble et al. [12] studied fecal calprotectin concentrations in healthy controls, IBS, adenomatous polyps and cancer, resulting in elevated levels of this biomarker in all three diagnostic groups, cancer being the most significant ($p<0.0001$) [13] (Figure 1). Most colorectal cancer patients have elevated levels of fecal calprotectin and research shows its value depends exclusively on the T-stage. Patients with T3 and T4 tumors tend to have significantly higher fecal calprotectin levels than those with T1 and T2 stages [12].

Table 1

Authors	Year	Study Design	Conclusions	Statistical Analysis
Tibble et al. [4]	2001	Case-control study	Fecal calprotectin is a sensitive non-invasive marker of CRC. It is more sensitive than FOBT at the cost of a some- what lower specificity	Calprotectin: sensitivity=0.79, specificity=0.72. FOBT: sensitivity=0.43, specificity=0.92 for CRC
Meucci et al. [17]	2010	Prospective study	Fecal calprotectin cannot identify those with significant colorectal disease. Normal results can rule out organic disease among patients with bowel symptoms	Organic disease: sensitivity=1 NPV=1 Functional disease: sensitivity=1 NPV=1. $p<0.05$
Parente et al. [18]	2012	Prospective study	For CRC detection: The best combination to predict the risk of CRC was i-FOBT+M2-PK Calprotectin presented a low specificity for the disease	i-FOBT: specificity=0.89, PPV=0.53. M2-PK: sensitivity=0.87, NPV=0.96. Calprotectin: sensitivity=0.93, NPV=0.93, specificity=0.39
Luley et al. [19]	2011	Case–control study	Calprotectin points out a possible biological link between inflammation and neoplastic transformation in CRC	$p<0.04$

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Kim et al. [20]	2014	Case-control study	A combination of FOBT and CALB may have greater sensitivity and specificity for predicting CRC than using a single marker	CALB: specificity=0.90, sensitivity=0.89
Lehmann et al. [21]	2014	Prospective study	Fecal calprotectin decreases significantly after CRC operation. Its value depends exclusively on the individual T-stage	Calprotectin before and after operation: p<0.001. Correlation of calprotectin and tumor parameters: p=0.132
Kristinsson et al. [22]	2001	Cross sectional study	In a high-risk group like first degree relatives of patients with CRC, fecal calprotectin could be considered as first test in selecting patients for endoscopy	Calprotectin levels<20 mg/l: specificity= 0.71, sensitivity=0.31
Hoff et al. [24]	2005	Randomized control trial (RCT)	Fecal calprotectin cannot be recommended for population screening purposes	Calprotectin: PPV=0.25, sensitivity=0.27, specificity=0.76. FOBT: PPV=0.12, sensitivity= 0.35, speci city=0.90
Karl et al. [25]	2008	Case-control study	Depending on the specificity selected, calprotectin was not evaluated as a reliable marker	S100A12 AUC=0.95, TIMP-1 AUC=0.92, hemoglobin-haptoglobin AUC=0.92, hemoglobin AUC=0.91, calprotectin AUC=0.90, carcinoembryogenic antigen AUC=0.66
Khoshbaten et al. [26]	2014	Case-control study	Fecal calprotectin is a useful marker for distinguishing CRC from non-malignant GI conditions. That is not the case for gastric cancer	Calprotectin: sensitivity=0.8 and specificity=0.84

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Kronborg et al. [27]	2000	RCT	Fecal calprotectin is a useful marker for CRC diagnosis in high risk groups, but specificity is too low for screening of average risk persons	Calprotectin: sensitivity=0.74, specificity=0.64
Limburg et al. [28]	2003	Prospective study	In above average risk CRC patients, fecal calprotectin was a poor screening biomarker for colorectal neoplasia	Calprotectin: sensitivity=0.37, specificity=0.63, PPV=0.23, NPV=0.76
Johne et al. [29]	2001	Case-control study	Calprotectin could be used as a screening marker in high risk groups for CRC	Calprotectin: sensitivity=0.89, specificity=0.68, NPV=0.99
Damms et al. [30]	2008	Case-control study	Fecal calprotectin is effective in identifying active IBD and CRC but lacks analytical sensitivity in separating CRC from adenoma as well as adenoma from the control group	Calprotectin: sensitivity=1, specificity=0.79, AUC=0.922

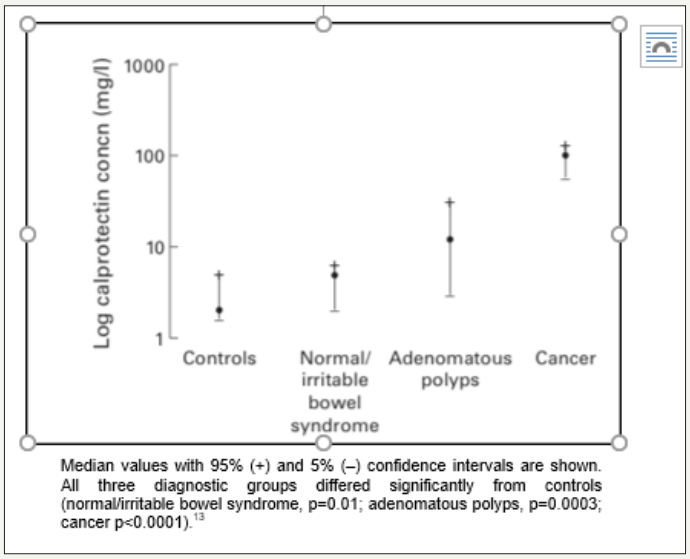

Figure 1: Log fecal calprotectin concentration (mg/l) in the different diagnostic groups [13].

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Even though additional studies are needed to determine the specific cutoff levels of calprotectin associated with colonic pathology, it is proven that the combination of fecal occult blood tests and fecal calprotectin tests together improve the sensitivity and specificity for detection of colorectal cancer and adenoma, compared to each of the tests individually. The measurement of both markers could be effective in excluding causes of gastrointestinal bleeding unrelated to an inflammatory process [10,14]. Fecal calprotectin is a new biomarker that has not been thoroughly studied but seems to be a sensitive, reliable tool in the diagnosis and follow-up of patients with colorectal cancer [15], at the expense of having very little specificity and no proven correlation to the stage of the disease.

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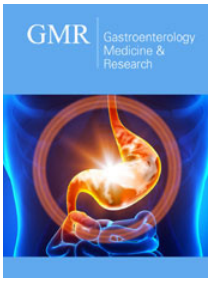

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