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Point of care testing of fecal calprotectin as a substitute for routine laboratory analysis

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ABSTRACT

Objectives: Fecal calprotectin (FC) is widely used to monitor the activity of inflammatory bowel disease (IBD) and to tailor medical treatment to disease activity. Laboratory testing of fecal samples may have a turnaround time of 1–2 weeks, whereas FC home testing allows results within hours and thus enables a rapid response to clinical deterioration.

Design and methods: Fifty-five stool samples were analyzed by the IB*Doc*® Calprotectin Home Testing kit and the BÜHLMANN fCAL® turbo assay on a Roche Cobas 6000 c501. The correlation between the assays was assessed using Spearman's Rho correlation coefficient and the intermediate imprecision of both assays was calculated.

Results: We found a strong correlation coefficient of 0.887 between FC measured on IB*Doc*® and the laboratory assay BÜHLMANN fCAL® turbo. The coefficients of variation (CVs) at three different FC levels were in the range 2.3–5.5% (BÜHLMANN fCAL® turbo) and in the range of 4.8–26.6% (IB*Doc*®).

Conclusions: This study suggests that IB*Doc*® is a suitable alternative for the assessment of disease activity in IBD patients.

1. Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are the two most prevalent forms of inflammatory bowel disease (IBD), with the highest prevalence and incidence in Europe and North America. UC and CD can in most cases be distinguished by differences in clinical presentation, endoscopic and histological appearance, risk factors and genetic predisposition [1]. Continuous monitoring of IBD is crucial to tailor treatment to active disease, maintain remission and reduce the risk of relapse. Recent research has shown that apart from steroid-free remission and symptom control alone, achieving endoscopic and maybe even histological mucosal healing has a major impact on disease control and progression. Achieving mucosal healing minimizes hospital admissions and surgery, lowers the risk for relapse and intensification of medical therapy and improves quality of life [2]. Endoscopic procedures are unpleasant for the patient, time-consuming and bear the risk of intestinal perforation. Thus noninvasive monitoring of disease activity is preferable, though no ideal biomarker has been identified. FC is more sensitive than serum C-reactive protein (CRP) in reflecting disease activity in IBD [3], and can be used to identify patients at risk of relapse and predict both endoscopic and histological mucosal healing [4].

Abbreviations: FC, Fecal calprotectin; IBD, Inflammatory bowel disease; CRP, C-reactive protein; UC, Ulcerative colitis; CD, Crohn's disease

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Calprotectin is a heterodimer of the two calcium-binding proteins, S100A8 and S100A9, and is elevated in serum in several inflammatory conditions [5]. Calprotectin is primarily released by activated neutrophils at sites of inflammation, and when measured in feces serves as an indirect estimate of the neutrophil infiltrate in the gastrointestinal tract [6]. Laboratory testing of fecal samples may require transportation from outpatients to the laboratory, and may have a turnaround time of 1–2 weeks, which hampers fast medical treatment response to relapses and increase the risk of clinical deterioration before treatment commences. In the capital region of Denmark fecal samples from outpatients are transported by the normal postal service, and at Copenhagen University Hospital Hvidovre 16% of the fecal samples received are either discarded because of prolonged transport (> 5 days) or results are released from the laboratory with caution, which decreases the clinical utility of the lab results and is costly. Home testing of FC achieves a faster turnaround time (hours) and enables patients and clinicians to act on FC results without delay. The aim of this study was to investigate the correlation between FC measured by the BÜHLMANN fCAL® turbo assay on a Roche Cobas 6000 c501, and the BÜHLMANN home test kit, IB*Doc*® using the CalApp® for data transfer.

2. Material and methods

2.1. Sample collection, preparation and storage

All stool samples were collected in plastic tubes by the patients and sent in by ordinary mail. The samples were immediately frozen at −20 °C upon receipt and analyzed within 1–2 days. A total of fifty-five stool samples were analyzed for direct comparison of IB*Doc*® and the BÜHLMANN fCAL® turbo methods. The selection of samples was based on volume (visual evaluation to ensure enough sampling material for testing) and stool consistency (hard lumps were excluded). Stool samples older than 5 days were excluded. Samples with FC concentrations > 1000 μg/g or < 30 μg/g (BÜHLMANN fCAL® turbo) were excluded, as the measuring range on IB*Doc*® is limited to 30–1000 μg/g. Three fecal samples with different FC levels were analyzed 10 times to determine the intermediate imprecision (coefficient of variation [CV], %) of the assays. The levels analyzed were low (FC < 50 μg/g), medium (50 μg/g > FC > 200 μg/g,) and high (FC > 200 μg/g). respectively, as it is well established that the normal range for FC is considered to be < 50 μg/g [7] and clinical studies have proposed that FC concentrations in the range 150–250 μg/g can be used to distinguish between active disease and mucosal healing [7,8]. Clinical data of the patients whose samples were studied were not collected.

2.2. Biochemical measurements

FC was measured using the immunoturbidimetric method BÜHLMANN fCAL® turbo with the CALEX® Cap extraction device from BÜHLMANN Laboratories AG (Schönenbuch, Switzerland) on a Cobas 6000 c501 analyzer (Roche Diagnostics A/S, Mannheim, Germany), according to the instructions of the manufacturer. The assay is standardized against the BÜHLMANN fCAL® ELISA by the manufacturer and the measuring range is 20–8000 μg/g. The intermediate imprecision (CV %) was 7% (at level 74.79 μg/g) and 1.4% (at level 252.14 μg/g). The assay is subject to external quality control through participation in the EQUALIS external quality control scheme (EQUALIS, Uppsala, Sweden), with a deviation from the method mean (own output group) of 5.5% (mean value own group 316 μg/g) and −1.5% (mean value own group 1138 μg/g) respectively in the latest (June 2017) EQA distribution.

FC was measured in parallel using the IB*Doc*® Calprotectin Home Testing kit from BÜHLMANN Laboratories AG according to the instructions of the manufacturer. IB*Doc*® is a lateral flow-based calprotectin test and the kit consists of a stool extraction device, the CALEX® Valve, and a test cassette. An iPhone 5c was used to install the CalApp®, enabling the phone to read the test cassette and calculate a quantitative calprotectin concentration. IB*Doc*® is not subject to external quality control.

2.3. Statistics

The correlation between FC (BÜHLMANN fCAL® turbo) and FC (IB*Doc*®) was assessed by using Spearman's Rho correlation coefficient. The intermediate imprecision of both assays was calculated.

Statistical analyses and graphics were performed using IBM SPSS Statistics version 22 (IBM, Armonk, NY, USA).

3. Results

Fifty-five samples were included in this study, covering clinically relevant concentrations in the range 38 –796 μg/g (BÜHLMANN fCal ® turbo). Fig. 1 shows the correlation between FC (BÜHLMANN fCAL® turbo) and FC (IB*Doc*®), with a Spearman rank correlation coefficient of 0.887. Over FC concentrations close to clinically relevant cut off values (range 30–300 μg/g), the Spearman rank correlation coefficient was 0.689 (n = 36, minimum = 38 μg/g, maximum: 298 μg/g). The Bland-Altman plot (Fig. 2) shows no fixed bias.

Ten extractions of three fecal samples with low (< 50 μg/g), medium (50–200 μg/g) and high (> 200 μg/g) FC concentrations were performed in each assay, showing an intermediate imprecision in the range of 2.3–5.5% (BÜHLMANN fCAL® turbo) and in the range of 4.8–26.6% (IB*Doc*®) as shown in Table 1. As the measuring range on IB*Doc*® is limited to 30–1000 μg/g, the intermediate imprecision of IB*Doc*® (L) is only calculated on four test results, as the other six was < 30 μg/g and thus excluded. The difference in the sample means may suggest bias, but the Bland Altman plot shows no fixed bias. The difference in the sample means probably reflects heterogeneity in the specimens.