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RESEARCH ARTICLE

Matrix gla protein, a potential marker of tissue remodelling and physiological ageing of the gut in crohn's disease

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ABSTRACT

Background: The inactive dephosphorylated and uncarboxylated form of the matrix Gla protein (dp-ucMGP) has been shown to be increased in plasma of inflammatory bowel disease (IBD) patients. Our aim was to assess if the plasmatic level of dp-ucMGP could reflect disease endoscopic activity, presence of strictures and cumulative structural bowel damage in Crohn's disease (CD) patients.

Methods: The plasmatic level of dp-ucMGP was measured in a monocentric cohort of prospectively recruited patients. The analysis was done by chemiluminescent immunoassay on blood samples collected the day of a planned ileocolonoscopy. In addition to classical clinical data (gender, age, body mass index (BMI), disease duration, current treatment), endoscopic data (disease location, Crohn's Disease Endoscopic Index of Severity (CDEIS), mucosal healing (MH), presence of 9 CD lesion types) and biological markers (faecal calprotectin and C-reactive protein (CRP)) were collected. The association between dp-ucMGP level and Lémann index was also investigated. Univariate linear regression was used to investigate the relationship between dp-ucMGP level and different parameters collected.

Results: A total of 82 ileocolonoscopies and dp-ucMGP assays were performed in 75 CD patients (45 females; 37 ileocolonic, 19 ileal and 19 colonic diseases) between October 2012 and November 2019. A total of 24 patients (29.3%) showed MH. The dp-ucMGP levels were not associated with MH, CDEIS, faecal calprotectin or CRP levels. Plasmatic dp-ucMGP levels increased significantly with age ($p=0.0032$), disease duration ($p=0.0033$), corticosteroids use ($p=0.019$) and tended to increase in patients with intestinal strictures ($p=0.086$) but not with the Lémann index.

Conclusion: The significant increase of plasmatic dp-ucMGP levels with age, disease duration and the trend observed in patients with non-ulcerated strictures may suggest that this extracellular matrix protein could be a marker of tissue remodelling and physiological ageing of the gut.

Abbreviations: BMI: body mass index; CD: Crohn's disease; CDEIS: Crohn's Disease Endoscopic Index of Severity; CRP: C-reactive protein; dp-ucMGP: dephosphorylated and uncarboxylated form of the matrix Gla protein; eGFR: estimated glomerular filtration rate; FC: faecal calprotectin; IBD: inflammatory bowel disease; MGP: matrix Gla protein; MH: mucosal healing; MRI: magnetic resonance imaging

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dp-ucMGP; crohn's disease; tissue remodelling; physiological ageing; intestinal fibrosis

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD), characterized by a relapsing-remitting course, affecting any part of the gastrointestinal tract, from the mouth to the anus. This inflammation (often subclinical) leads to complications including development of strictures, fistulae, or abscesses which can require bowel resections [1, 2]. These events contribute to structural bowel damage, which accumulates over time in CD and may be assessed by the Lémann index [3]. In order to prevent this damage, treatments, that were once aimed at improving clinical symptoms, have now more ambitious goals aiming to induce mucosal healing (MH) [4]. MH has been associated with a lower risk of relapse, a greater proportion of corticosteroids-free remission and of CD-related surgery-free period [5–8].

While endoscopy remains the gold standard to evaluate MH, this technique is invasive, associated with a risk of complications and is poorly accepted by patients [9,10]. Finding a surrogate marker allowing an equally accurate but non-invasive and inexpensive evaluation of the mucosa is an unmet medical need [11]. Although faecal calprotectin (FC) is

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the best validated marker to date for assessing MH, it cannot replace endoscopy [12]. Its application being limited by the lack of specificity [13], the variability between measurement assays [14], the lack of consensus for the optimal cut-off value [15], and a lack of sensitivity, in particular in ileal diseases, reported in few studies [16–18]. Since blood tests are more acceptable for patients than stool tests, it would be ideal to find a blood marker reflecting mucosal healing [9].

While most teams searching for these markers focus on cellular processes involved in inflammation and signalling molecules, others consider that studying proteins from the tissue environment in which this process occurs, in particular the extracellular matrix (ECM) which is continuously remodelled, could be more sensitive if detectable in blood [19–22]. There is indeed a growing body of evidence showing that ECM morphological and structural changes could be observed before any histological evidence of inflammation [19]. Among these ECM proteins, the matrix Gla protein (MGP), has already been reported to be over-expressed in the inflammatory mucosa of IBD patients and its expression has been demonstrated as significantly correlated with inflammatory biomarkers [23]. Dp-ucMGP, the inactive dephosphorylated and uncarboxylated form of MGP, has recently been found significantly higher in the plasma of IBD patients compared to healthy controls [24]. In this context, the aim of this study was to assess whether the plasmatic level of dp-ucMGP could be correlated to CD endoscopic activity, could be a marker of mucosal healing, or a marker of cumulative structural bowel damage.

Materials and methods

Study design and patient selection

The plasmatic level of dp-ucMGP was measured in a prospectively recruited monocentric cohort of CD patients. All adult CD patients, for whom diagnosis was made according to classical diagnostic criteria [25], undergoing endoscopy at Liège University Hospital between 2012 and 2019, were considered eligible. Endoscopic disease activity was evaluated using the Crohn's Disease Endoscopic Index of Severity (CDEIS) [26] and the presence or absence of mucosal healing, defined by a CDEIS < 3 and by the absence of ulceration was also established [27]. In addition to the location of the disease (past or present), the presence or absence of 9 CD lesion types (frank erythema, frankly swollen mucosa, aphtoid ulceration, superficial or shallow ulceration, deep ulceration, ulcerated stricture, non-ulcerated stricture, healed ulceration and pseudopolyp) was recorded [28]. All patients provided blood samples (plasma EDTA) the day of endoscopy before sedation (stored at −80 °C, after centrifugation) for further analysis. Patients were also asked to collect stool sample, within a 3-month time window (before or after the ileocolonoscopy), to measure FC. We retrospectively verified that the patient's clinical status and IBD treatment at the time of FC measurement were the same as at the time of ileocolonoscopy and dp-ucMGP dosage.

Patients for whom the FC measurement or CDEIS was not available or could not be assessed (whatever the reason including insufficient preparation, the presence of a non-passable stricture or an incomplete endoscopy), with stoma or no plasma sample available were excluded. Furthermore, as one of our aims was to assess whether the level of dp-ucMGP could be a marker of mucosal healing, patients with upper disease L4 according Montreal classification, who have not had the necessary investigations (gastroscopy, magnetic resonance enterography) at the same time as the colonoscopy to re-evaluate the activity of the upper disease, were excluded. Finally, we also excluded patients with condition that could influence the plasmatic level of dp-ucMGP including chronic renal failure, patients treated with vitamin K antagonist or vascular calcifications of the carotids, aorta or coronary [29–36].

Data collection

Classic clinical data, including gender, age, body mass index (BMI), smoking habits, family history of IBD, disease duration, Montreal classification (age at diagnosis, disease location, disease behaviour and perianal disease) [37], previous IBD surgery and current IBD treatments were collected. C-reactive protein (CRP) levels measured within 4 weeks' time window from endoscopy, were also recorded.

dp-ucMGP measurement

Plasma dp-ucMGP levels were analysed by chemiluminescent immunoassay using IDS-iSYS InaKtif MGP (Immunodiagnostic Systems, Frankfurt, Germany) according to the manufacturer's instructions (single measurement). Minimum limit of detection was 200 pmol/L.

Lémann index evaluation

Associations between dp-ucMGP levels and structural bowel damage were also investigated using the Lémann index, calculated by the same experienced radiologist (R.G.) [38]. Index at the time of the sampling was measured when the patient had undergone, over a 3-months window from ileocolonoscopy, the necessary examinations to calculate the index (small-bowel imaging, upper gastro-intestinal endoscopy, pelvic magnetic resonance imaging (MRI) for patients with perineal involvement) and had not undergone any therapeutic change between. To investigate the association between the dp-ucMGP level and the Lémann index, this latter was expressed in different ways: (1) the Lémann index at the time of the sampling; (2) the ratio of the Lémann index/disease duration at the time of sampling; and (3) the Lémann index progression between the time of sampling and the last follow-up visit (whatever therapeutic changes have been made), assessed by the ratio between the delta of the Lémann index at both times [time of sampling - last follow-up] and the elapsed time, to see if the dosage of dp-ucMGP could be associated to structural bowel damage in the future.

Statistical analysis

The results are presented as mean and standard deviation (SD) or as median and interquartile range (IQR) for quantitative variables and as frequency tables for qualitative variables.

Some of the parameters were log or square root transformed to normalise their distribution. To investigate the relationship between dp-ucMGP protein and endoscopy outcomes, univariate linear regression was used. Results are reported as estimates (β) and standard error (SE) of the regression model. The results are considered significant at the 5% uncertainty level ($p < 0.05$). The calculations were performed using SAS version 9.4 and figures were realized in R version 4.2.2.

Ethical considerations

The study protocol was approved by the Ethic Committee of the University Hospital of Liège, Belgium [Belgian reference: 707201317029]. All patients agreed to participate in the study and signed written informed consent forms.

Results

Patients' characteristics

The patient inclusion-exclusion flow chart is shown on Figure 1. Of the 252 ileocolonoscopies performed on the 147 eligible CD patients, between October 2012 and November 2019, data (FC or CDEIS) were missing for 145 ileocolonoscopies (performed in 47 patients), the plasma sample was not available for 11 patients, 3 had an upper disease L4 according the Montreal classification, 2 had a stoma and 9 had a chronic renal failure. A total of 82 ileocolonoscopies and blood samples from 75 patients were therefore selected and the characteristics of those are listed in Table 1. The total study population included 45 females (60.0%) and 30 males (40.0%), with a mean age of 42.9 ± 14.3 years. Half of the patients had ileocolic disease and the other 2 quarters had colonic and ileal disease, respectively, at the time of colonoscopy. Of these patients, 21 (28.0%) were active smokers and 35 (46.7%) had undergone previous IBD surgery. A total of 24 (29.3%) patients were in mucosal healing at the time of endoscopic evaluation.

Absence of association between dp-ucMGP, disease activity and endoscopic assessments

Table 2 shows the results of the statistical analyses carried out to study associations between dp-ucMGP levels and the different parameters studied. No significant difference was found between the mean concentration of dp-ucMGP in the MH patients' group and in the non-MH group ($p = 0.53$). Similarly, no association was found between dp-ucMGP levels and different measures of disease activity (whether for the CDEIS, the FC level and the CRP level) (Figure 2).

Regarding association between dp-ucMGP and disease location, dp-ucMGP values tend to be lower in patients with ileal disease compared to other locations, but without reaching significance ($p = 0.067$). Dp-ucMGP values tend also to be higher in patients with non-ulcerated strictures ($p = 0.086$).

Association between dp-ucMGP and demographic and clinical data

Dp-ucMGP increased significantly with age at the time of the endoscopy ($p = 0.0032$) and disease duration ($p = 0.0033$), but not with the BMI ($p = 0.19$) (Figure 3).

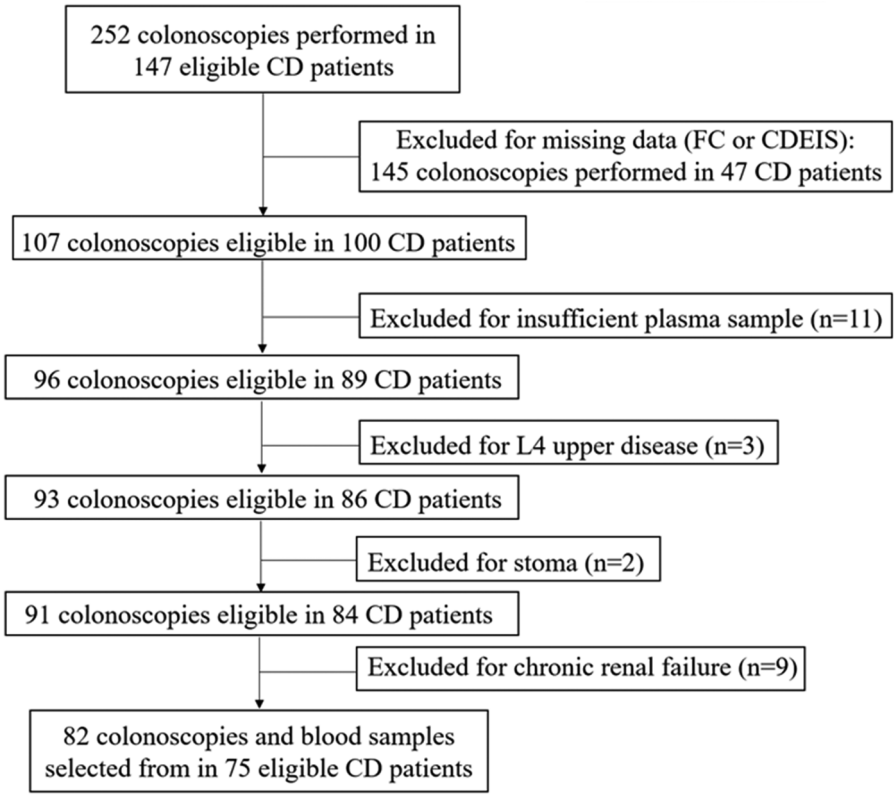

Figure 1. Patients flow chart. CD: Crohn's disease; CDEIS: Crohn's Disease Endoscopic Index of Severity; FC: faecal calprotectin.

Table 1. Patients' characteristics.

Parameters	$n=75$
Female gender, *n* (%)	45 (60.0)
Age at colonoscopy (years, mean ± SD)	42.9 ± 14.3
Disease duration (years, median [IQR])	12.0 [3.5–19.5]
Smoking habits	
Never, *n* (%)	30 (40.0)
Past smoker, *n* (%)	24 (32.0)
Active smoker, *n* (%)	21 (28.0)
BMI (kg/m^2, mean ± SD)	24.9 ± 4.6
Disease location at time of colonoscopy	
Ileal disease, *n* (%)	19 (25.3)
Colonic disease, *n* (%)	19 (25.3)
Ileocolonic disease, *n* (%)	37 (49.3)
Montreal behaviour	
B1, non-stricturing, non-penetrating, *n* (%)	44 (58.7)
B2, stricturing, *n* (%)	20 (26.7)
B3, penetrating, *n* (%)	11 (14.7)
Montreal perianal disease	
No perianal disease, *n* (%)	58 (77.3)
Perianal disease, *n* (%)	17 (22.7)
Previous IBD surgery	
No, *n* (%)	40 (53.3)
Yes, *n* (%)	35 (46.7)
Medication at time of endoscopy	
None, *n* (%)	20 (26.7)
Corticosteroids, *n* (%)	11 (14.7)
5-ASA, *n* (%)	12 (16.0)
Immunomodulators	16 (21.3)
Anti-TNF therapy, *n* (%)	25 (33.3)
Anti-α4β7 integrin, *n* (%)	6 (8.0)
Anti-IL-12/IL-23 p40 monoclonal antibody, *n* (%)	5 (6.7)

5-ASA: 5-amino-salacylic acid; BMI: body mass index; IBD: inflammatory bowel disease; IL: interleukin; IQR: interquartile range; TNF: tumour necrosis factor.

Patients with stricturing or penetrating phenotypes (B2 or B3 according Montreal classification) had a higher dp-ucMGP level compared to those with non-stricturing non-penetrating disease but this was not statistically significant (813 ± 283 pmol/mL vs 719 ± 181 pmol/mL; $p=0.10$). Regarding the associations between dp-ucMGP levels and IBD medications, plasmatic dp-ucMGP levels significantly increased with corticosteroids treatment ($p=0.019$).

Association between dp-ucMGP and Lémann index

There was no significant association between dp-ucMGP and the Lémann index at the time of collection ($p=0.21$) which could be calculated for 13 patients, between the dp-ucMGP level and the ratio of the Lémann index/disease duration at the time of the sampling ($p=0.99$) and between the dp-ucMGP level (at the time of sampling) and the Lémann index progression between the time of the sampling and the last follow-up ($p=0.64$), calculated for 13 patients.

Discussion

The significant increase of plasmatic dp-ucMGP levels with age, disease duration and the trend observed in patients with non-ulcerated strictures may suggest that this extracellular matrix protein could be a marker of tissue remodelling or gut physiological ageing than a marker of CD disease activity.

Several arguments support this hypothesis. First, an increased MGP mRNA and protein expression have been reported in several tissues with a fibrotic component. MGP transcript and protein expression were found to be up-regulated in idiopathic pulmonary fibrosis (up to 19 times than control patients) [39–41]. Similarly, in kidney, MGP expression strongly correlated with interstitial fibrosis as well as tubular atrophy and higher levels of MGP were associated with an increased risk of estimated glomerular filtration rate (eGFR) decline, end-stage renal disease and progression to kidney fibrosis [42]. Tveitarås MK, et al. also reported that in unilateral ureteral obstruction, the obstructed kidney usually developing fibrosis, had an up-regulated expression of the *mgp* gene [43]. More strikingly, in order to identify genes important for fibrosis in IBD, Jerala et al. recently looked at genes expressed significantly differently in fibrotic liver and kidney tissues compared to the corresponding normal ones [44]. The *mgp* gene had significantly up-regulated expression in liver and kidney fibrosis compared with normal ones [44]. They next analysed the same genes expression in CD and UC

Table 2. Results of univariate linear regression performed to study association between plasmatic level of dp-uc matrix gla protein and the different parameters studied.

	β	SE	*p* Value
Mucosal healing	−0.041	0.065	0.53
CDEIS	0.037	0.025	0.14
Faecal calprotectin	0.015	0.022	0.49
CRP	0.016	0.023	0.47
Ileal disease	−0.13	0.069	0.067
Colonic disease	0.077	0.070	0.28
Ileocolonic disease	0.039	0.061	0.53
Frank erythema	0.017	0.063	0.79
Frankly swollen mucosa	0.20	0.13	0.13
Aphtous ulceration	0.016	0.080	0.84
Superficial or shallow ulceration	0.019	0.061	0.76
Deep ulceration	0.0027	0.099	f0.98
Ulcerated stricture	−0.0068	0.11	0.95
Non-ulcerated stricture	0.21	0.12	0.086
Healed ulceration	0.21	0.27	0.42
Pseudopolyps	0.20	0.12	0.093
Age at the time of the endoscopy	0.0062	0.0020	**0.0032**
Disease duration	0.054	0.018	**0.0033**
BMI	0.0087	0.0066	0.19
Disease behaviour			
Stricturing or penetrating disease	0.10	0.063	0.10
IBD treatment at time of endoscopy			
5-ASA	−0.16	0.089	0.086
Corticosteroids	0.21	0.088	**0.019**
Purines	−0.015	0.088	0.87
Methotrexate	−0.058	0.14	0.68
Infliximab	−0.056	0.11	0.61
Adalimumab	0.061	0.081	0.46
Vedolizumab	0.12	0.11	0.30
Ustekinumab	−0.054	0.13	0.67
At the time of the sampling	0.013	0.0094	0.21
Lémann index/disease duration	−0.000	0.041	0.99
Lémann index progression between the time of the sampling and the last-follow-up	0.074	0.12	0.64

5-ASA: 5-amino-salacylic acid; BMI: body mass index; CD: Crohn's disease; CDEIS: Crohn's Disease Endoscopic Index of Severity; CRP: C-reactive protein; IBD: inflammatory bowel disease; β: estimate of the parameter by the regression; SE: Standard error of the estimate.

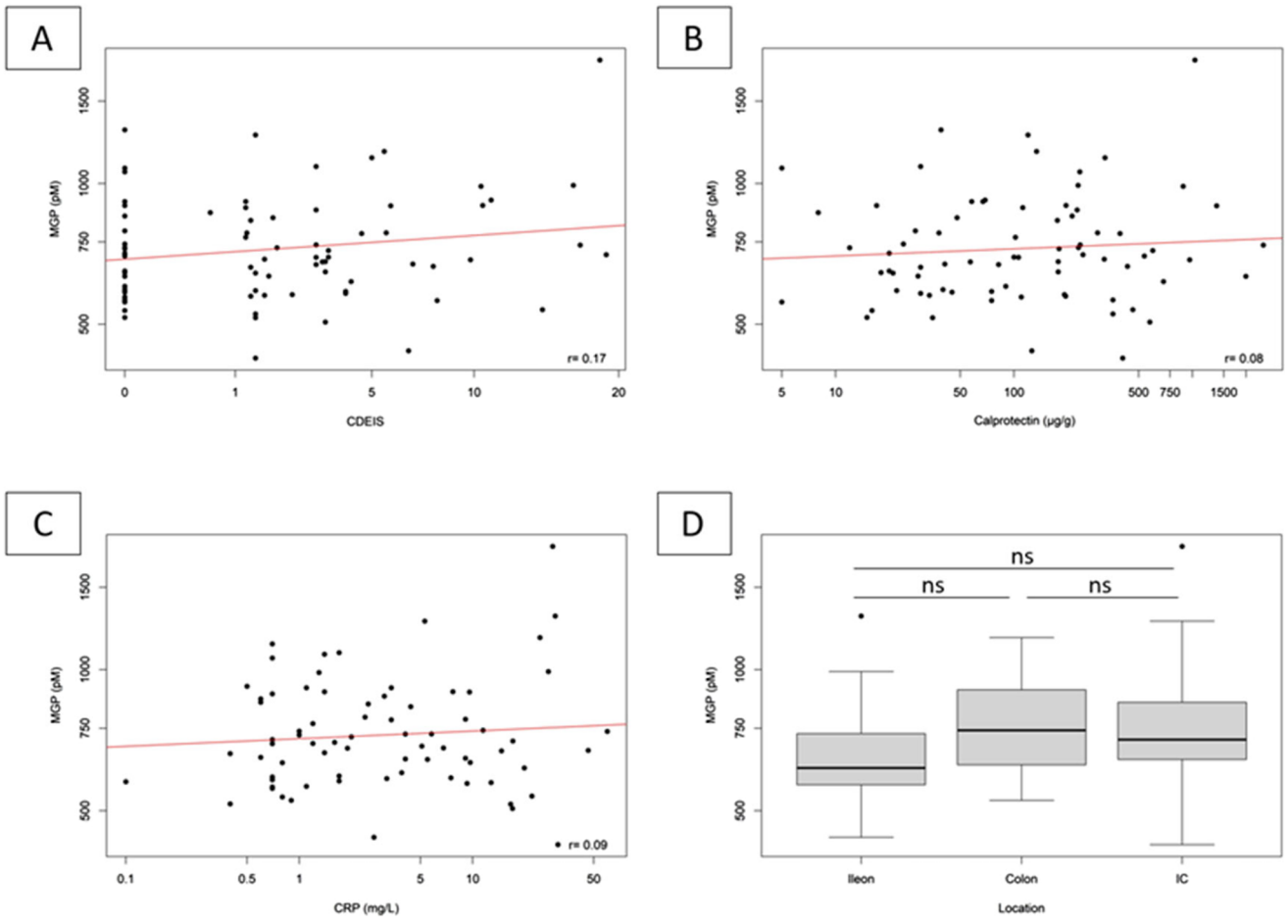

Figure 2. Absence of significant association between dp-uc matrix gla protein and crohn's disease endoscopic index of severity (a), faecal calprotectin (B), C-reactive protein (C) and disease location (D). For the box plots, the bottom edge of the box indicates the 25th percentile, the black line within the box marks the median, and the upper limit of the box indicates the 75th percentile. Points located above the box indicate outliers outside the 90th percentiles. CDEIS: Crohn's Disease Endoscopic Index of Severity; CRP: C-reactive protein; dp-ucMGP: inactive dephosphorylated-uncarboxylated Matrix Gla-Protein; IC: ileocaecal; ns, not significant.

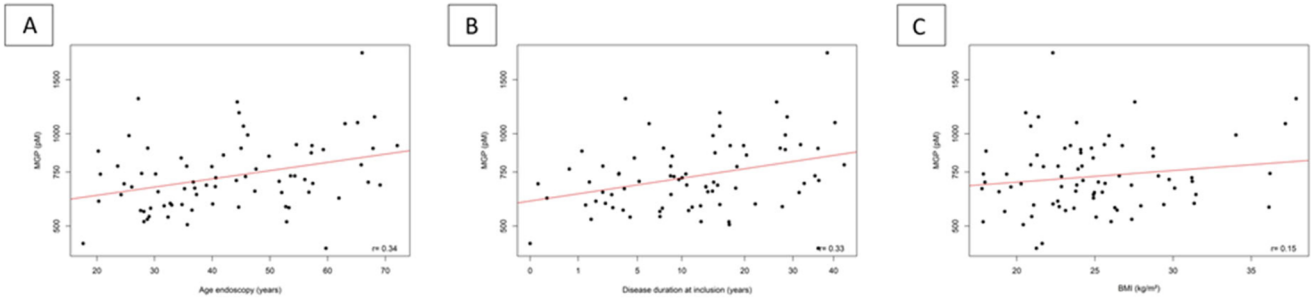

Figure 3. Association between dp-uc matrix gla protein and age at the time of the ileocolonoscopy (a), disease duration (B) and body mass index (C). BMI: body mass index

and found that the *mgp* gene expression was significantly up-regulated in colon of CD patients with fibrosis compared to colon of CD patients without fibrosis and to normal colon [44]. In addition to these associations between tissue MGP levels and fibrosis, associations between blood dp-ucMGP levels and tissue remodelling have also been reported. In chronic obstructive pulmonary disease patients, a strong positive correlation was found between dp-ucMGP dosage and the plasmatic levels of desmosine and isodesmosine, two amino acids resulting from the elastin degradation (indicating ECM degradation as well) [41,45].

Interestingly, some authors have pointed out a pathophysiological rationale for the association between this high level of dp-ucMGP and elastin degradation [46]. In particular, elastin-derived peptides lead to: (1) an up-regulation of matrix metalloproteinases (contributing to the degradation of the ECM, preventing its accumulation), which further stimulate elastin degradation, therefore contributing to a vicious circle [46,47]; and (2) the differentiation of several cells into osteoblast-like cells, stimulating elastin calcification, which promote its degradation [46]. When elastin calcium content rises (especially during the ageing process), the synthesis of MGP,

which is a strong calcium and calcification inhibitor, increases [46,48]. To be active and carry out its role, the uncarboxylated form of MGP (ucMGP) must be converted in the active carboxylated one (cMGP), a reaction catalysed by γ-glutamyl carboxylase, of which vitamin K2 is the cofactor [49]. In the presence of a vitamin K2 deficiency, MGP is not sufficiently activated (resulting in an accumulation of the dp-ucMGP form), the protein cannot exert its anti-calcifying activity and thus results in an even more accelerated elastin degradation [46,50–52]. The increase in dp-ucMGP could therefore reflect a tissue remodelling in patients with vitamin K2 deficiency, a common situation in IBD, as a result of malnutrition and malabsorption due to inflammatory damages or due to surgical resections reducing the intestinal absorptive surface [53–57].

In view of the association with matrix metalloproteinases and elastin degradation described in the literature, tissue remodelling associated with the increase in dp-ucMGP could be counterbalancing an ongoing fibrogenesis. This might explain why we did not find any association with the Lémann index (influenced by surgeries, while the resected parts of the intestine can no longer influence the dp-ucMGP level), but we found a trend towards increased dp-ucMGP levels in patients with stricture (for whom the ongoing anti-fibrotic process was probably active at the time of sampling). The increase of MGP protein in response to the use of corticosteroids has already been reported in the lung and the authors suggested that MGP could play a role in the steroid-induced changes in lung growth [58].

As in our study, the study of Brnic et al. reported a positive correlation between the level of dp-ucMGP and the IBD patients' age (this correlation between age and dp-ucMGP levels has also been reported in other cohorts of non-IBD patients [29,33,59–64], but they did not find any association between the dp-ucMGP dosage results and the disease duration [24]. This may be related to the fact that their cohort included both UC and CD patients whereas our cohort, only included CD patients, for whom the involvement may be transmural and therefore could lead to more significant tissue remodelling over time. Finally, compared to Brnic et al. we did not find any association between dp-ucMGP measures and active inflammation (neither with biomarkers nor using endoscopic assessment) [24]. The role of MGP protein in intestinal inflammation remains unclear. Some studies have shown that MGP mRNA and protein expression increased in both dextran sulfate sodium-induced colitis and UC patients compared to the controls (and that expression was positively correlated to inflammatory markers) suggesting that the MGP protein may play a pro-inflammatory role [23]. On the contrary, other studies described an anti-inflammatory role for this protein, which could alleviate intestinal inflammation [65,66]. Likewise, these differences with data presented by Brnic et al. may be explained by the cohort composition including both CD and UC patients whereas it was only CD patients in this study. While we were more accurate in dp-ucMGP sampling as samples were taken the same day as colonoscopy compared to a 2-week window in Brnic et al. to determine any association with endoscopic inflammation, they accepted a shorter delay between FC and dp-ucMGP dosage taken within a 3 days-window versus 3 months in our study. However and interestingly, Jerala et al. have shown that CD patients with colonic inflammation without fibrosis showed no change in expression of the *mgp* gene compared to normal colons, whereas the expression change was significant in CD patients with colonic fibrosis compared to the normal colon [44]. Consistent with this data, our results suggest that this MGP protein may be more related to the fibrotic than to the inflammatory process in CD[44].

Our study has several limitations. First, there is most likely a recruitment bias to assess the association between the dp-ucMGP level and the presence of stricture as patients with an non-passable stricture, that do not allow a complete evaluation of the CDEIS, were excluded. It would be interesting to measure the level of dp-ucMGP in these patients and to compare it to that of patients without stricture lesions to determine if there is an association. The time windows for the collection of biomarkers (CRP and FC) were quite long and the association between dp-ucMGP level and these markers should therefore be interpreted with caution. Similarly, the time window between the dp-ucMGP measurement and tests used to calculate the Lémann index was fairly long and was assessed in a small number of patients, and therefore require a study in better conditions to be able to draw conclusions. The associations between dp-ucMGP levels and vascular health in IBD patients have not been evaluated in our cohort and would benefit from investigation in a dedicated study. Another limitation is that we did not investigate vitamin K2 levels in our patients but this fluctuates from day to day depending on the diet [67]. Finally, it cannot be excluded that the dp-ucMGP level is influenced by other unmeasured confounding factors such as bone fragility. However, the association between dp-ucMGP and disease duration (and the trend to increase in patients with stricture) suggests that the level of this protein could also be influenced by the intestinal pathological process.

In conclusion, at a time when no marker exists to assess tissue remodelling or gut physiological ageing in CD, the plasma measurement of dp-ucMGP, increasing with age, disease duration, and maybe in patients with strictures, could be particularly interesting and requires further investigations.

Author contributions

PD, EC, and EL conceive the study. SV collected clinical data and wrote the article. RG protocolled MRIs. LS performed statistical analyses. RG, PD, LS, EB, CS, MAM, CM, NP, PM, EC and EL critically reviewed the content of the paper. The manuscript was approved by all authors.

Disclosure statement

S Vieujean: speaker fees from Ferring, Janssen, Abbvie and Takeda. P Delanaye has served as consultant for iDS. E Cavalier has served as consultant for iDS. Edouard Louis: Research grant: Janssen, Pfizer, Ferring, Falk, Abbvie and Takeda; educational grant: AbbVie, Janssen, Fresenius-Kabi and Takeda; speaker fees: Abbvie, Falk, Ferring, Janssen, Pfizer, Galapagos and Takeda; advisory board: Abbvie, Celgene, Ferring, Janssen, BMS, Pfizer, and Takeda, Galapagos, Gilead, Arena, Elli Lilly; consultant: Abbvie. R Gillard, L Seidel, E Bequet, C Salée, MA Meuwis, C Massot, N Pierre, P Meunier declares no conflict of interest.

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Data availability statement

The data underlying this article are available in the article.

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