Clinical: Diagnosis and Outcome

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Distinct Hepcidin Dynamics in Crohn's Disease and Ulcerative Colitis: Links to Iron Homeostasis and Inflammatory Activity

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Background: Hepcidin, the master regulator of systemic iron metabolism, is influenced by iron availability and inflammation.[1] In inflammatory bowel disease (IBD), iron deficiency and anaemia are common, yet how hepcidin is regulated in relation to disease phenotype, iron status and inflammatory burden remains incompletely understood.[2] We aimed to characterise hepcidin regulation in ulcerative colitis (UC) and Crohn's disease (CD) according to iron status and inflammatory markers.

Methods: In this cross-sectional multicentre study, 589 individuals were enrolled (178 healthy controls, 130 UC, 281 CD). Patients were stratified by iron status and activity. Serum hepcidin, iron parameters, and inflammatory and clinical data were collected. Iron deficiency was defined using the ECCO criteria[2], which focuses on ferritin, and a combined ferritin and transferrin saturation definition. Group comparisons, correlations, and multivariable linear regressions were performed.

Results: Hepcidin correlated positively with C-reactive protein (CRP) in CD ($r = 0.125$; $p = 0.038$) and negatively with faecal calprotectin (FCAL) in UC ($r = -0.311$; $p < 0.001$) (Figure 1).

Using the ECCO definition, median hepcidin levels in CD were higher than in controls within comparable iron-status categories (iron deficiency: 4.359 ng/mL [2.094-8.906] vs 2.300 [1.375-4.950], $p = 0.019$; normal iron stores: 10.402 [6.398-17.683] vs 8.500 [5.30012.150], $p = 0.023$). In UC, no significant differences from controls were observed, under the same criteria (Figure 2).

In multivariable regression, ferritin was the strongest independent determinant of hepcidin in all groups (UC $\beta = 0.569$; CD $\beta = 0.526$; $p < 0.001$). Additional predictors included FCAL in UC ($\beta = -0.153$; $p = 0.052$), and in CD, CRP ($\beta = 0.197$; $p < 0.001$), age at diagnosis ($\beta = 0.155$; $p = 0.002$), and transferrin saturation ($\beta = 0.140$; $p = 0.007$).

Conclusion: Ferritin was the main driver of hepcidin in IBD, but regulation differed by phenotype. In UC, hepcidin suppression associated with active disease measured by FCAL, whereas in CD, systemic inflammation may have sustained hepcidin expression despite iron deficiency. These findings highlight hepcidin's potential as a biomarker linking iron status and inflammatory phenotype in IBD.

References:

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Conflict of interest:

Prof. Dr. Magro, Fernando: Fernando Magro served as speaker and received honoraria from Abbvie, Arena, Biogen, Bristol-Myers Squibb, Falk, Ferring, Hospira, Janssen, Laboratórios Vitoria, Pfizer, Lilly, Merck Sharp & Dohme, Sandoz, Takeda, UCB, Vifor.

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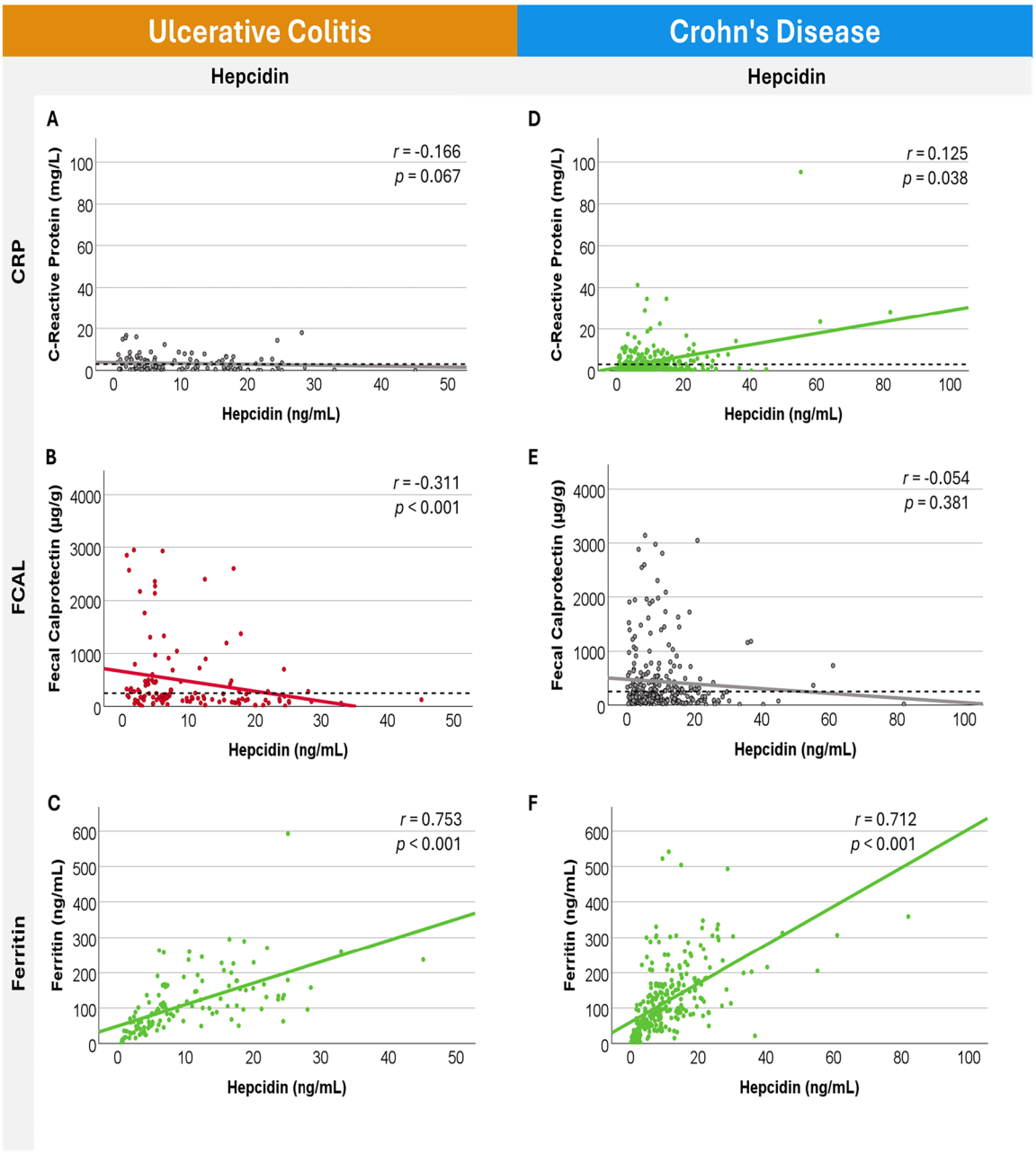

Figure 1. Association between hepcidin levels and biomarkers (CRP, FCAL and ferritin) in UC and CD. Scatter plots illustrate the relationship between serum hepcidin (ng/mL) and biomarkers in patients with UC (A, B, C) and CD (D, E, F). Panels A and D display hepcidin versus CRP (mg/L), panels B and E show hepcidin versus FCAL (µg/g), and panels C and F present hepcidin versus ferritin (ng/mL). Dot colours reflect the direction and statistical significance of the Spearman correlation: green indicates a significant positive correlation, red indicates a significant negative correlation, and grey indicates a non-significant correlation. Dashed horizontal lines mark commonly used inflammation thresholds: CRP = 3 mg/L and FCAL = 250 µg/g. CRP: C-reactive protein; CD: Crohn's disease; FCAL: Faecal calprotectin; UC: Ulcerative colitis.

Figure(s)/Table(s): see next page

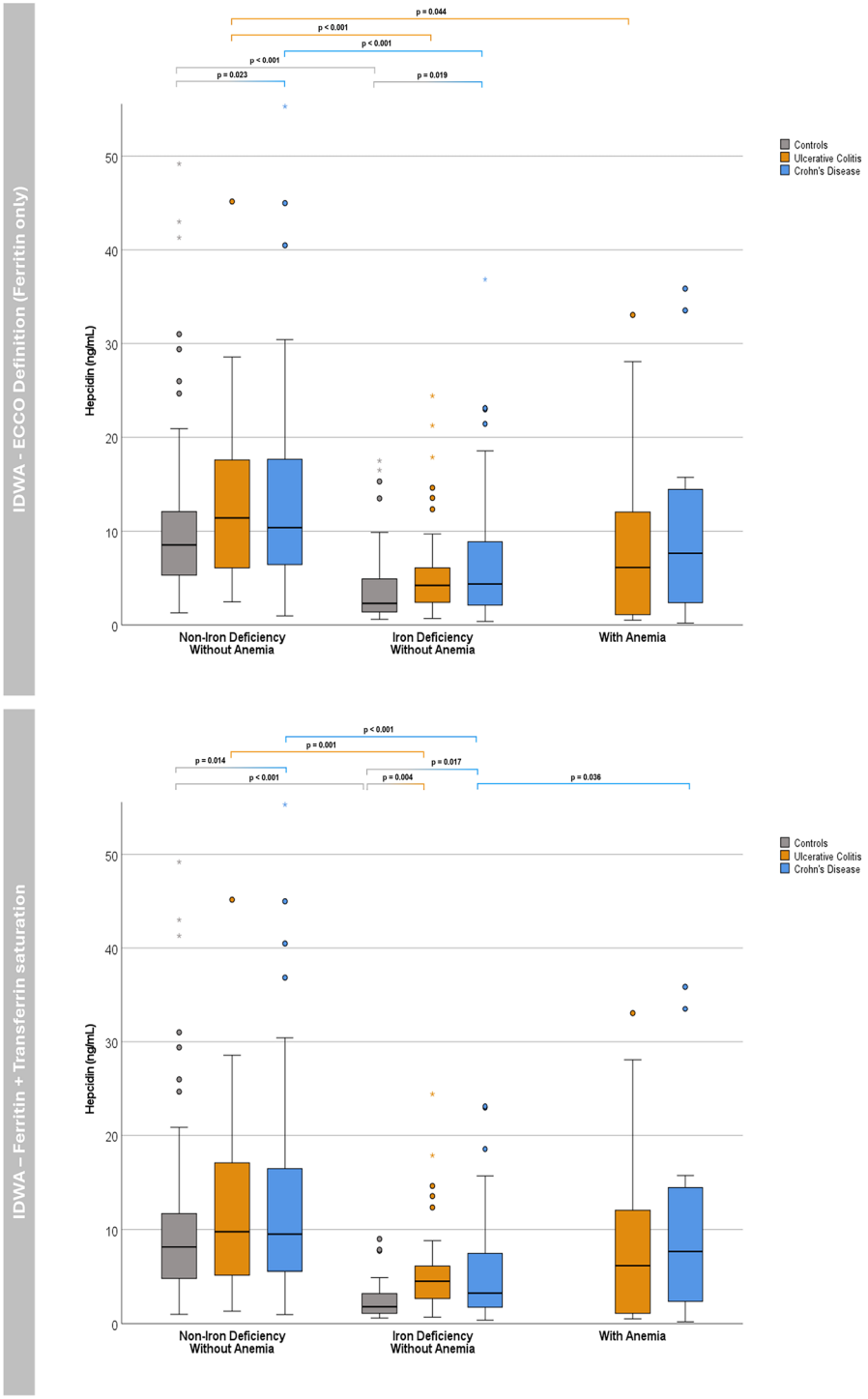

Figure 2. Hepcidin levels (mg/L) across iron status categories, using two definitions of iron deficiency without anaemia: ECCO consensus criteria, based solely on ferritin, and a stricter approach combining ferritin and transferrin saturation. Statistically significant p-values are shown. CD: Crohn's disease; ECCO: European Crohn's and Colitis Organization; IDWA, Iron deficiency without anaemia; UC: Ulcerative colitis.