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Smoking is associated with extra-intestinal manifestations in inflammatory bowel disease

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Background: Smoking influences the disease activity in inflammatory bowel disease (IBD). We aimed to study the association between smoking and extra- intestinal manifestations (EIMs) in IBD.

Methods: The association between smoking and EIMs such as joint complaints, chronic skin disorders and eye complaints was investigated in three cohorts. The COIN- study is a large prospective cohort study with data collected by questionnaires about demographics, disease course and associated cost items. In the Groningen cohort, questionnaires on cigarette smoke exposure and disease behaviour in IBD patients were collected. The JOINT- study is a prospective longitudinal study focused on IBD patients with and without back pain and peripheral joint complaints. A putative dose-response relationship between smoking and EIMs, and the association between smoking and specific phenotypes of arthropathies was explored.

Results: In the COIN study, 3,030 patients (1,558 Crohn's disease (CD), 1,054 ulcerative colitis (UC) and 418 IBD-unspecified) were enrolled; 16.0% were current smokers. In the Groningen cohort, 780 IBD patients (420 CD, 298 UC, 62 IBD-unspecified) were included; 23.6% were current smokers. In the JOINT study, 255 patients (186 CD, 69 UC) were enrolled; 23.5% were current smokers. EIMs were significantly more prevalent in the smoking IBD population (COIN: 39.1% vs. 29.8%, p <0.001 and Groningen: 42.8% vs. 31.2%, p <0.001). This association was more pronounced in CD than in UC. Joint complaints were the most prevalent EIM in both CD and UC. Of all EIMs, smoking appeared to have the most significant association with joint complaints (COIN: CD 30.7% vs. 22.1%, p <0.001, UC 25.3% vs. 18.5%, p =0.11 and Groningen: CD 46.4% vs. 40.4%, p =0.26, UC 31.0% vs. 23.0%, p =0.34). Likewise, in the JOINT study, smoking was more prevalent in IBD patients with artropathies (30.3% s. 13%, p =0.001). A dose-response relationship is suggested by the fact that EIMs were more prevalent in heavy smoking patients compared to low exposure smokers (56.0% vs. 37.1%, p =0.10). Smoking was not associated with a specific phenotype of spondylarthropathy.

Conclusions: The results of three cohort studies confirm a positive association between smoking and extra-intestinal manifestations in IBD. This association appears to be subject to a dose-response effect.

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Anti-TNF improves iron availability in Inflammatory Bowel Diseases, modulating Pro-hepcidin in an Erythroferrone-independent fashion

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Background: Anaemia is a common feature of Inflammatory Bowel Disease (IBD), resulting from a combination of iron deficiency and of anaemia of chronic disease (ACD). ACD is characterized by macrophage iron retention induced by inflammatory conditions. Hepcidin, an acute phase protein, is the master inducer of iron accumulation during ACD. Hepcidin is potently induced by pro-inflammatory cytokines, such as IL-6 and inhibited by Erythroferrone, a newly discovered hormone, which is produced by erythroblasts in response to erythropoietin (EPO) stimulation (Kautz L, Nat Genet 2014; Kautz L, Blood 2014). Remarkably, TNF downregulates EPO, thus it reduces Erythroferrone production. Aim of the study was to evaluate whether anti-TNF therapy, while downregulating several pro-inflammatory mediators, modulates hepcidin and Erythroferrone production, leading to a restoration of normal iron homeostasis in IBD.

Methods: Sera were collected from 21 IBD patients undergoing Infliximab or Adalimumab therapy, before each anti-TNF administration, for the first 6 weeks of therapy. Pro-hepcidin, a dosable hepcidin precursor, EPO, Erythroferrone, C reactive protein (CRP), iron markers and haemoglobin levels were measured by means of immunoassays and clinical activity indexes evaluated.

Results: Serum pro-hepcidin was significantly decreased between baseline and week 6 (139.42 ± 18.96 vs. 94.14 ± 9.19 ng/ml, p=0.0048); consistently, circulating levels of other acute phase proteins, such as ferritin and CRP were reduced (68.19 ± 18.23 vs. 37.48 ± 13.22 ng/ml, p=0.0223 and 1.80 ± 0.42 vs. 0.53 ± 0.11 mg/dl, p=0.0036, respectively); we also detected an increase in serum iron (37.71 ± 2.77 vs.