Does the circadian clock have a role in the pathogenesis of inflammatory bowel disease (IBD)?

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Background: Sleep dysfunction modifies the immune system and has been implicated as a potential trigger of IBD flares. Sleep dysfunction also alters the synchrony among clock genes leading to disruption of overall circadian regulation. Specifically, in the intestine, it is manifested by increased gut cellular permeability. We hypothesized that changes in mucosal immune balance may be reflected by alterations in the circadian clock and constitute an unattended pathogenic mechanism of IBD. Our aim was to investigate intestinal and systemic clock gene expression among healthy and newly diagnosed IBD patients.

Methods: Patients and controls were recruited upon diagnostic endoscopic evaluation. Demographics, familial medical history, sleep questionnaires, disease activity indices and endoscopic scores were recorded. Anthropometric parameters, C-reactive protein (CRP), albumin, haemoglobin (Hb) and fecal calprotectin (Fcal) were measured as well. Peripheral blood and tissue samples were analyzed for clock gene (*Clock*, *Bmal1*, *Cry1*, *Cry2*, *Per1* and *Per2*) expression.

Results: Of the 32 participants recruited (ages 8-25, median: 16.1), 14 were newly diagnosed with IBD and 18 were healthy controls. Age, gender, sleep questionnaire scores and time of endoscopy were not statistically different between the groups. CRP and Fcal levels were significantly higher in the IBD compared to the healthy controls ($p<0.05$), while Hb and albumin were significantly lower ($p<0.05$). Clock gene expression (*Clock*, *Cry1*, *Cry2*, *Per1* and *Per2*) in WBC was decreased in newly diagnosed IBD patients compared with healthy controls ($p<0.05$). Similarly, the expression level of the aforementioned clock genes was lower in inflamed intestinal tissues ($p<0.05$). Interestingly, similar reduction in clock gene expression was seen even in healthy (non-inflamed) intestinal tissue of IBD patients ($p<0.05$).

Conclusions: Clock gene expression is reduced in both inflamed and non-inflamed intestinal tissue in newly diagnosed IBD patients. Moreover, IBD patients show a systemic reduction in clock gene expression.