Microbiota, Inflammation, and Circadian Rhythms: Role of Circadian Disruption in Inflammatory Bowel Disease
Inflammatory Bowel Disease

Ulcerative colitis

Crohn’s disease
Treatment Goal

- Optimize Quality of Life
- Induce remission [treat flare up]
- Maintain remission [avoid flare up]
- Prevent & treat complications
Efficacy of AZA as Maintenance Therapy in Patients with Active CD*

* Remission induced by prednisolone tapered over 12 wk


% Patients Not Failing Trial

Duration of Trial (months)

AZA 2.5 mg/kg/d (n=33)
Placebo (n=30)

$P=0.001$
Impact of environmental factors on IBD pathogenesis.

Inflammatory bowel disease: the role of environmental factors
Autoimmunity Reviews, Volume 3, Issue 5, 2004, 394 - 400
Sleep Deprived
subjective sleep quality assessed by PSQI in patients with inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS)
Correlation between sleep quality and disease-specific quality of life in patients with inflammatory bowel disease.

Impact of Sleep Disturbance in Inflammatory Bowel Disease.
*Journal of Gastroenterology and Hepatology, Volume 22, Issue 11, 2006*
Effect of sleep deprivation on severity of 2% DSS-induced colitis

Sleep deprivation worsens inflammation and delays recovery in a mouse model of colitis
Sleep Medicine, Volume 10, Issue 6, 2009
Possible Factors Causing Sleep Disruption in IBD

Sleep disturbances and inflammatory bowel disease: a potential trigger for disease flare?
Acknowledgements

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National Institute on Alcohol Abuse and Alcoholism
AA020216: Brain-Gut Interactions in Alcohol-Induced Gut Leakiness
AA023417: Role of Alcohol and Circadian Disruption in Inflammation and Colon Cancer
AA019966: Circadian Desynchrony in Alcohol Induced Gut Leakiness
Monitoring Circadian Rhythms: Behavior
Circadian disruption augments vulnerability to chemically induced intestinal injury (DSS)
Salivary melatonin profiles of 4 patients with asymptomatic IBD.

Endogenous melatonin profiles in asymptomatic inflammatory bowel disease
The sleep parameters of the four IBD patients and eight matched control subjects during 7 days of baseline sleep.

<table>
<thead>
<tr>
<th></th>
<th>Sleep onset</th>
<th>Wake time</th>
<th>Sleep onset latency (min)</th>
<th>Sleep efficiency</th>
<th>Wake after sleep onset (min)</th>
<th>Total sleep time (min)</th>
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<tbody>
<tr>
<td>IBD1</td>
<td>23:38</td>
<td>7:12</td>
<td>34.9</td>
<td>74.1</td>
<td>78.6</td>
<td>375.4</td>
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<tr>
<td>IBD2</td>
<td>22:46</td>
<td>5:20</td>
<td>38.2</td>
<td>77.5</td>
<td>37.4</td>
<td>356.1</td>
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<tr>
<td>IBD3</td>
<td>22:40</td>
<td>7:09</td>
<td>15.2</td>
<td>73.9</td>
<td>106.3</td>
<td>403</td>
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<tr>
<td>IBD4</td>
<td>00:35</td>
<td>10:22</td>
<td>5.4</td>
<td>86.6</td>
<td>68.4</td>
<td>518.1</td>
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<tr>
<td>IBD mean</td>
<td>23:25</td>
<td>7:30</td>
<td>23.4*</td>
<td>78*</td>
<td>72.7</td>
<td>413.2</td>
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<tr>
<td>Control mean</td>
<td>00:18</td>
<td>8:29</td>
<td>6.32</td>
<td>87</td>
<td>54.9</td>
<td>436.7</td>
</tr>
</tbody>
</table>

Abbreviation: IBD = inflammatory bowel disease.

*p < 0.05, Mann-Whitney U test between patients and controls.
Corrected Munich Midpoint of Sleep in IBD subjects

**Watson Williams F test P < 0.05**

Keshavarzian et al. DDW, 2016
Dinner Timing in IBD subjects

**Watson Williams F test P < 0.01**

Keshavarzian et al. DDW, 2016
How does disrupted circadian rhythms worsen IBD?
Host Immune Response

1. Altered genetics making it ready for an immune system
2. Overactive T cells
3. Altered cytokine balance towards inflammation
4. Lack of simple defense such as innate immune system

Intestinal Milieu

1. Altered bacterial contents
2. Altered diet contents

Intestinal Barrier

- Primary defects of mucous?
- Defects in tissue repair
View of the Microbial Composition across Different IBD Cohorts
How does disrupted circadian rhythms worsen IBD?

- Changes in Microbiota Composition
- Increased intestinal permeability
- Promote pro-inflammatory immune response
- Promotes mucosal and systemic inflammation
CAN DISRUPTED CIRCADIAN HOMEOSTASIS PROMOTE GUT LEAKINESS?
**Impaired Intestinal Barrier Integrity Can Trigger Systemic Inflammation**

**Intestinal Barrier Function:**
- **Intestinal Permeability**

**Administer:** Sucralose, Sucrose, Lactulose, Mannitol

**Measure:** Urinary sugar content

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[Graph showing comparison of sucrose excretion between NS (n=34) and S (n=39) groups with statistical significance indicated by ***.]
CAN DISRUPTED CIRCADIAN HOMEOSTASIS PROMOTE GUT LEAKINESS IN MAN?
Serum LBP in day shift and night shift workers (n=11). (A) Subjects with evidence of circadian rhythm disruption (i.e., night shift workers) have higher plasma LBP. (B) Cosinor analysis reveals significantly altered pattern of plasma LBP in night shift workers over a 24h period compared to day shift workers; day versus night shift workers mesor: 11109 v 13136, respectively (p=0.04). These results are indicative of increased endotoxemia and intestinal barrier dysfunction in subjects with circadian rhythm disruption.
Microbiota and Bioinformatics Collaboration Team

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Environmental CRD Alters the Intestinal Microbiota Under “Challenging” Conditions

- Family level
- Genus level

Fecal microbiota analysis in day shift and night shift workers (n=3). Genomic DNA was extracted from feces, and profiling was performed using 16S rRNA gene amplicon sequencing. Analysis reveals that bacteria from the families Peptostreptococcaceae, Turicibacteraceae, and Clostridiaceae are more abundant in night shift workers compared to day shift workers. These data suggest that circadian rhythm disruption is associated with intestinal dysbiosis, particularly an increase in pro-inflammatory bacteria.
**Butyrate production as a ratio of total SCFA production (n=4).** (A) Night shift workers with evidence of circadian rhythm disruption have significantly less plasma butyrate as a ratio compared to total SCFA production. (B) Cosinor analysis reveals significantly altered levels of butyrate to total SCFA production over a 24 h period; day versus night shift workers amplitude (p<0.05). These data suggest that the amount of butyrate produced as a proportion of total SCFA production is altered in subjects with circadian rhythm disruption which may contribute to altered intestinal barrier integrity and immune function.
Plasma IL-6 in day shift and night shift workers (n=11). (A) Night shift workers have elevated levels of IL-6. (B) Cosine analysis demonstrates that night shift workers have significantly altered circadian pattern of IL-6; day versus night shift workers mesor: 1.73 v 2.20, respectively (p<0.02). These data suggest that circadian rhythm disruption promotes systemic inflammation.
What Factors Disrupt the Circadian Clock?

Consequences of Circadian Disruption

- We propose that circadian rhythm disruption promotes inflammation via effects on the intestine:
  - Disrupted intestinal barrier integrity
  - Intestinal microbiota dysbiosis
  - Immune consequences

- Circadian misalignment could promote inflammation in patients with IBD and trigger IBD flare up.
- Circadian misalignment [disrupted sleep/wake cycle; abnormal eating pattern] could worsen IBD course.