BY DR. SEAN GOLDEN

PART 6

THE BIG "FOUR":

MELATONIN

A Sleep Hormone for Crohn's and U.C???

Most of us know about melatonin as a "sleep supplement" used to help you fall or stay asleep.

How can a sleep supplement improve the lives of those with Crohn's and U.C.?

Actually, through many different ways!

What is Melatonin?

Melatonin is technically a hormone (like vitamin D) that is produced in multiple places in the body.

Melatonin is most known as "neurohormone" that is produced in the pineal gland in response to darkness and is one of the main regulators of the "circadian rhythm" (i.e. our biological clock).[1]

However, the brain isn't the only organ that produces melatonin.

Melatonin concentrations are actually at least 400 times higher in the gut than in the pineal gland![2]

Melatonin plays many roles in the gut and the body in general, including (but not limited to) detoxification of free radicals and antioxidant actions, bone formation and protection, reproduction, and cardiovascular and immune regulation, as well as protective and therapeutic effects, especially with regard to brain or gastrointestinal protection, psychiatric disorders, cardiovascular diseases and oncostatic (halting the spread of cancer) effects.[3]

It is the effect that melatonin has in the gut that is most important for our discussion here.

Melatonin is a Powerful Antioxidant and Anti-Inflammatory Molecule

Melatonin is one of the most powerful antioxidants that our body creates, and is much more potent than traditional antioxidants such as vitamins E and C and food antioxidants such as garlic oil.[4]

It also has profound anti-inflammatory properties that helps tame down inflammation throughout the body as is able to reduce tissue destruction and molecular damage.[5]

Lower Levels of Melatonin Linked to Crohn's and U.C.

The first clue that melatonin may be linked to conditions such as Crohn's and U.C. came from research showing that shift workers were at an increased risk for these conditions. Circadian rhythm disruptions and poor sleep are repeatedly linked to disease flairs in irritable bowel diseases.[6]

When checking the levels of melatonin, IBD patients only had about 50% as much of a urinary melatonin marker compared to healthy controls, and some IBD patients only had around 18% as much![7]

Melatonin Has Dramatic Effects in Rodents Models

After recognizing the potential for melatonin to be involved in Crohn's and U.C., researchers started testing it on rodents with experimental Cronhn's- and U.C.-type conditions.

...and boy did it work.

One study after another was showing fantastic results no matter *how* they gave the mice colitis or intestinal inflammation/damage.[8,9,10,11,12,13,14,15,16,17,18,19]

Melatonin reduced inflammation and damage through many different mechanisms including lowering TNFa, NF-kB, iNOS, HMGb1, TLR4, IL-17, IL-6, MPO, MMP-9, and MDA (all potent markers of chronic inflammation and tissue damage).

Here is a picture of the colon of one rat who had experimentally-induced colitis vs the colon of a rat with colitis plus melatonin treatment:

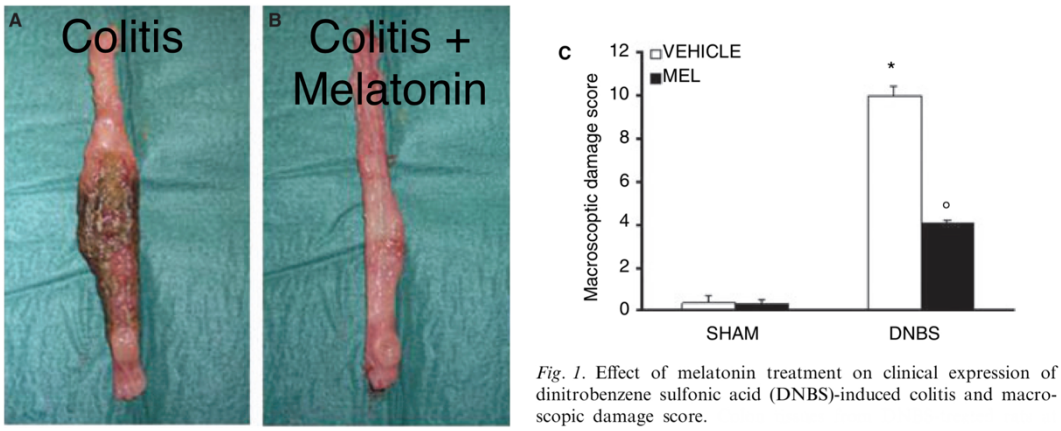

Fig. 1. Effect of melatonin treatment on clinical expression of dinitrobenzene sulfonic acid (DNBS)-induced colitis and macroscopic damage score.

Image from Mazzon et. al. 2006[11]

Furthermore, melatonin treatment didn't just help the gut tissue, it actually helped to reduce gut permeability and reduce systemic inflammation:
"...ulcerative colitis increased gut permeability [AKA "leaky gut"], plasma lipopolysaccharide level [LPS - endotoxin from bacteria that crossed into the bloodstream], systemic inflammation, and genotoxicity [damage to DNA that can promote cancer]. Melatonin treatment led to mucosal healing and reduced ulcerative colitis-induced elevated gut permeability and reduced the plasma LPS level, systemic inflammation, and genotoxicity" [notes are mine].[9]

This means that melatonin helped to seal up the gut, prevented bacteria from getting into the bloodstream, lowered inflammation throughout the body, and prevented overall DNA damage!

Melatonin Works as Well as Standard Crohn's and U.C. Medication in Rodents

In two studies, researchers compared melatonin treatment to a type of standard medication for Crohn's / U.C., 5-aminosalicylic acid (5-ASA: brand names include Lialda, Apriso, Delzicol, Asacol, Pentasa, Dipentum, etc.), and **melatonin was just as effective as the standard drug** at reducing the damage to the colon itself and the microscopic cells![15] (Picture below)

Group	Doses ($mg.kg^{-1}$)	Macroscopic index	Histological index
Normal	—	0.75 ± 0.71^a	1.1 ± 0.83^a
Model	—	6.25 ± 1.39	6.24 ± 1.04
5-ASA	100	1.60 ± 0.53^a	1.35 ± 0.47^a
Melatonin	2.5	5.70 ± 1.21	5.85 ± 0.76
Melatonin	5.0	3.00 ± 0.76^a	3.88 ± 0.99^a
Melatonin	10.0	1.63 ± 0.74^a	1.38 ± 0.52^a

High Dose Melatonin Works WAY Better

Just like with Vitamin D, the dose for melatonin makes a big difference in the rodent studies.

As you can see from the table above, while all melatonin dosages helped, the low dose only helped a little (large scale damage went from 6.25 to 5.70) **whereas the high dose helped a ton (6.25 to 1.63, about the same as the standard drug)**.

This finding that higher dose melatonin has a much larger impact on the course of the condition was found in every single rodent study that tested different dosages.

Does it Also Work in Humans?

While multiple consistent rodent studies is encouraging, what matters most is how well it works in humans.

Sometimes drugs and supplements work very well in rodents but not at all in humans.

Other times, the human studies use dosages that are very different from what was used in rodent studies that got good results.

Luckily, we do have some clinical trials with melatonin that have been done. Let's take a look at the results!

- ✔ In 2005, researchers gave 20 IBS patients either 3 mg of melatonin at bed time or placebo for two weeks. "Compared with placebo, melatonin taken for two weeks significantly decreased mean abdominal pain score (decrease of 2.35 v 0.70; $p<0.001$) and increased mean rectal pain threshold (21.2 v 8.9 mm Hg; $p<0.01$)."[22]

- ✔ In 2007, researchers gave 18 IBS patients either 3 mg of melatonin at bed time or placebo for 2 months. After 2 months, melatonin "significantly improved overall IBS score (45% vs. 16.66%)" and the overall increase in quality of life "was 43.63% in melatonin group and 14.64% in placebo group that is statistically significant. ($P<0.05$)".[23]

- ✔ In 2010, researchers found that adding melatonin to standard therapy for Crohn's and U.C. for 30 days "signs of inflammatory infiltration were absent in 77.8% of the patients with Crohn's Disease" and "the ultrastructure of the colonic mucosa was normal in the patients with UC". The researchers concluded that "The use of melatonin in combined therapy for IBD considerably improves the results of treatment and promotes a more complete ultrastructural recovery of the colonic mucosa."[20]

- ✔ In 2005, 17 IBS patients were given either 3 mg of melatonin or placebo each night for 2 months, then stopped treatment for a month, and then swapped treatments (placebo now given melatonin and vice-versa). Each group never knew which they were being given. Improvements in mean IBS scores were significantly greater after treatment with melatonin (3.9) than with placebo (1.3, $p<0.037$). "Percent response rate, defined as percentage of subjects achieving mild-to-excellent improvement in IBS symptoms, was also greater in the melatonin-treated arm (88% vs. 47%, $p<0.04$)."[24]

- Being encouraged by the great results from rodent studies, in 2011 researchers found 60 patients who had U.C. and achieved remission during the last year. For the next year, they gave half of the patients a standard U.C. drug, mesalazine, along with a placebo and the other half they gave mesalazine plus 5 mg of melatonin at bedtime. **During that next year, patients on melatonin remained in remission with low disease scores** whereas the mesalazine-only group had a significant rise in disease activity. The CRP levels (a standard marker for inflammation) stayed fairly low in the melatonin group but rose quite a bit in the mesalazine-only group [*image below]*. Also, only the mesalazine-only group had a drop in hemoglobin levels (due to bleeding) while the melatonin group did not.[21]

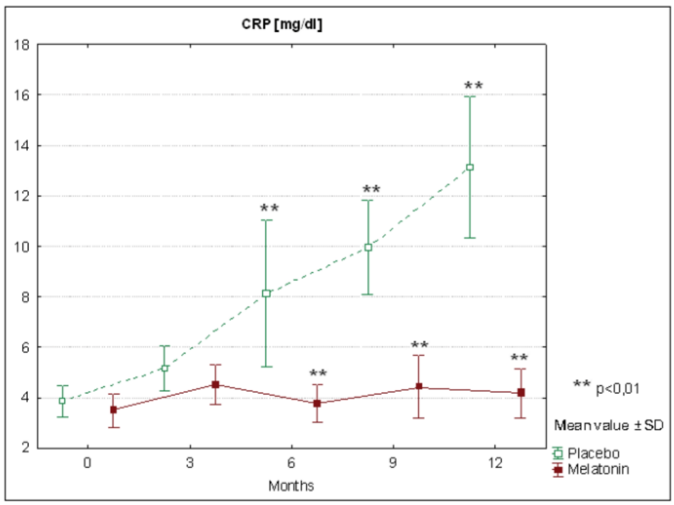

Fig. 2. CRP concentration in patients on adiuvant melatonin (Group I) and placebo (Group II).

Great Results, but What About the Dose?!

As you can see, melatonin is proving to be a fantastic addition to those with IBS, Crohn's, and U.C.!

The most encouraging thing about these human studies is that melatonin was able to achieve good effects even though the dose the researchers used was always very low (3-5 mg) compared to the dosages used in the rodent studies.

The "high doses" used in the rodent studies would translated to a human dose of about 45 mg - 140 mg depending on the particular rodent study and how much the person weighs (the heavier the person, the higher the equivalent dose).

So, those doses are a lot more than what was used in the human studies, yet the studies would suggest that experimenting with higher dosages could bring drastically more beneficial results.

There were virtually no side effects in the human melatonin studies at 3-5 mg except every so often some daytime sleepiness that typically goes away after you get used to it.

So the question is, is "high dose" melatonin safe?

Safety of "High Dose" Melatonin

Melatonin is extremely non-toxic.

One review states: "The acute toxicity of melatonin as seen in both animal and human studies is extremely low. Melatonin may cause minor adverse effects, such as headache, insomnia, rash, upset stomach, and nightmares. In animals, an LD50 (lethal dose for 50% of the subjects) could not be established. Even 800 mg/kg bodyweight (high dose) was not lethal".[25] The equivalent human dose of this would be about 8,000 mg at once.

Furthermore: "Studies of human subjects given varying doses of melatonin (1–6.6 g/day) [**1,000 - 6,600 mg per day**] for 30–45 days, and followed with an elaborate battery of biochemical tests to detect potential toxicity, have concluded that, aside from drowsiness, **all findings were normal** at the end of the test period."25

"Melatonin has also been suggested for use as a contraceptive for women, which might raise the question of whether melatonin damages the female reproductive system. Notably, no side effects were reported in a report of a phase 2 clinical trial in which 1400 women were treated with 75 mg of melatonin nightly for 4 years."[25]

Thus, even high dose melatonin is extremely safe. However, there are some potential side effects to high dose melatonin.

(*Low dose melatonin, as was used in all the human clinical trials, had essentially zero side effects besides some initial drowsiness for some people.*)[28]

When patients were given **1,000 mg of melatonin per day for 1 month, there were no adverse effects at all** except "all of [the] patients complained of persistent sleepiness most marked during the first week of receiving melatonin".[26]

Some are concerned about melatonin lowering testosterone, as this happens with certain types of rodents (but not all). Yet, when 12 adult men were given 100 mg of melatonin nightly for 8 days, while there was a slight decrease in luteinizing hormone, there was no change at all in testosterone levels.[27]

In another study, 80 mg and 240 mg of melatonin increased plasma prolactin, but did not change luteinizing hormone, testosterone, or thyroid stimulating hormone.[29]

Moreover, Voordouw et al. treated 12 women with 300 mg melatonin/daily for 4 months and no significant side effects were reported.[30] Weishaupt et al. gave to severely ill ALS patients 300 mg melatonin daily for 2 years, without any adverse effects.[31]

So, high dose melatonin is unlikely to adversely affect steroid hormone concentrations like testosterone nor have any sort of real adverse effect. However the rise in prolactin is the cause for the most common side effect reported by those taking high dose melatonin: decreased libido.

Besides needing to adjust to it and being a little more tired than usual for a week or so, decreased sex drive is a common side effect on high dose (but not regular dose) melatonin.

The sex drive returns to normal after melatonin is stopped or the dose is reduced.

One last thing to mention is that melatonin may worsen rheumatoid arthritis. The evidence is currently mixed on this, but caution would be needed for now if you also happen to suffer from rheumatoid arthritis.

How to Take Melatonin

Legal Disclaimer: Make sure you discuss supplement, medication, or diet changes with your treating physician before implementing them.

If you want side-effect-free, you would choose the regular dose of 3-5 mg to mimic what they used in the clinical trials.

Even if you want to experiment with high dosages of melatonin, I would start with these regular dosages for a few weeks at least to get used to it. Hopping on high dose melatonin from the beginning can make some people feel quite drowsy.

If you are still feeling groggy in the mornings at these dosages, then you can reduce them further to 1 mg a couple hours before bed time. Once you adjust to this dose, then you can test the 3-5 mg again to see if they still make you groggy in the morning. Some people can take longer to adjust than others.

Melatonin can give people more vivid dreams sometimes as well. This effect can also fade with time. Higher doses may be more prone to do this. If your dreams are too vivid for your liking, reduce your dose for a period of time while you adjust.

After staying on 3-5 mg for a month or two, if everything has been going fine with your Crohn's or U.C. symptoms, then it is up to you if you want to experiment with higher dosages or not.

If you want to experiment with higher dosages, most people do well by increasing the dose my 5 mg or so every few days or every week.

One final caution: There is one report online of melatonin initially worsening a patient's Crohn's symptoms, but then when the patient stopped the melatonin, they went straight into remission. This never happened in the clinical trials, but if you seem to be experiencing a flair up when you start melatonin or increase the dose, I would drop the dose or stop taking it for a few weeks and see how you respond. After you stop, it may make your symptoms even better than before. I've personally never seen this happen, but just putting it in here for extra caution and completeness.

Sincerely,

Dr. Sean Golden

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