Melatonin and Insulin Resistance

Connecting melatonin, insulin resistance, leaky gut, and T cell polarization.

Cogence Clinical Pearl

What the research says…

Melatonin is well known to be involved in healthy sleep functions, particularly related to the initiation of sleep. Melatonin is also a useful Th1 promoter. **Melatonin and insulin are connected in ways that can be clinically important.** The consensus in the research is that the relationship is inverse, and includes the presence of melatonin receptors on the pancreas and insulin receptors on the pineal. There are nuances to appreciate that may be important in specific cases. Sun, et al. (Melatonin Treatment Improves Insulin Resistance and Pigmentation in Obese Patients with Acanthosis Nigricans) showed that **melatonin administration improved insulin resistance in human subjects.** Peschke, et al. (Diabetic Goto Kakizaki rats as well as type 2 diabetic patients show a decreased diurnal serum melatonin level and an increased pancreatic melatonin-receptor status) showed that melatonin levels are lower in fasting patients, suggesting a role for glucose in melatonin production.

Mayo, et al. (Melatonin Uptake by Cells: An Answer to Its Relationship with Glucose?) have shown that adequate glucose is required for melatonin production. Mulder (Melatonin signalling and type 2 diabetes risk: too little, too much or just right?) has proposed a model by which differences in types of melatonin receptor polymorphisms might suggest that there is **a "sweet spot" level of melatonin that promotes optimally low risk for type 2 diabetes.**

Lastly, recalling the work of Thaiss, et al. (Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection) from a previous clinical pearl, it's useful to remember that hyperglycemia drives leaky gut.

Applications…

These papers, as a group, suggest some clinical takeaways:

1. Melatonin may be a valuable adjunct in the care of patients with insulin resistance.

2. Patients with insulin resistance and insomnia related to poor sleep initiation may have low melatonin levels.

3. Assessment of the melatonin system may require both measurement of melatonin levels (expensive but possible) as well as appreciation that there may be downregulation of melatonin receptor biology or poor melatonin production related to low serum glucose. The association of low glucose to low melatonin production may also contribute to the understanding of nighttime eating, since raising blood sugar appears to contribute to adequacy of melatonin production. Patients who are using intermittent fasting or a fasting mimicking diet, but are having trouble initiating sleep while

using this approach, might especially benefit from melatonin supplementation.
This point combines usefully with the realization that M1 macrophages, the type of macrophage that does much of the anti-microbial work for the innate immune system, gets its energy from glycolysis. We've all seen thin, hypoglycemic patients who have trouble fighting infections. We can now understand that there are likely two reasons they have impaired anti-pathogenic immunity. First, their M1 macs are under-fueled when glucose levels are low. Second, persistence of low serum glucose may be associated with diminished melatonin. Since melatonin is a known Th1 cell promoter, low melatonin may yield inadequate Th1 response, yielding diminished NK cell activity and macrophage phagocytosis, via inadequate activation of the IL-12 and interferon gamma mediated activation of macs and NK cells.

4. Mulder's paper suggests the need for discernment about melatonin dose, rather than a more-is-better approach. If that is correct, it suggests that melatonin supplementation should be targeted to the amount that restores functional optimization of sleep initiation, rather than levels higher than that.

5. The work of Thaiss on hyperglycemia and leaky gut tells us that, when you have a patient with increased gut permeability, it's useful to focus on glycemic control and reducing insulin resistance. Melatonin may have a useful role there. Because insulin inhibits vagus nerve function, hyperglycemia that drives insulin resistance will create additional GI dysfunction via the vagus inhibition, yielding poor motility and increased GI inflammation. Overall, the connections between these factors suggest that melatonin support, glycemic control, leaky gut, and the need for vagal motor outflow are interconnected. In cases of insulin resistance, the addition of melatonin to lower insulin may help to remove the insulin "brakes" from vagal motor outflow, with the result of helping to reduce inflammation and improve GI motility.

6. Because vagal motor outflow inhibits Kupfer cell IL-6 production, melatonin inhibition of insulin may also participate in quieting Th17 dominance by allowing vagal inhibition of IL-6, in addition to the more direct activation of Th1 that inhibits Th17.

The Research…

Melatonin Treatment Improves Insulin Resistance and Pigmentation in Obese Patients with Acanthosis Nigricans
Sun H, Wang X, Chen J, Gusdon AM, Song K, Li L, Qu S. Int J Endocrinol. 2018 Mar 12;2018:2304746.
(Color and bold added.)
Abstract

OBJECTIVE: This study aimed to determine the effects of melatonin on insulin resistance in obese patients with acanthosis nigricans (AN).
METHODS: A total of 17 obese patients with acanthosis nigricans were recruited in a 12-week pilot open trial. Insulin sensitivity, glucose metabolism, inflammatory factors, and other biochemical parameters before and after the administration of melatonin were measured.
RESULTS: After 12 weeks of treatment with melatonin (3 mg/day), homeostasis model assessment **insulin resistance index** (HOMA-IR) (8.99 ± 5.10 versus 7.77 ± 5.21, $p < 0.05$) **and fasting insulin** (37.09 5 ± 20.26 μU/ml versus 32.10 ± 20.29 μU/ml, $p < 0.05$) **were significantly decreased.** Matsuda index (2.82 ± 1.54 versus 3.74 ± 2.02, $p < 0.05$) was significantly increased. There were also statistically significant declines in the AN scores of the neck and axilla, body weight, body mass index, body fat, visceral index, neck circumference, waist circumference, and inflammatory markers.
CONCLUSIONS: **It was concluded that melatonin could improve cutaneous symptoms in obese patients with acanthosis nigricans by improving insulin sensitivity and inflammatory status.**

Diabetic Goto Kakizaki rats as well as type 2 diabetic patients show a decreased diurnal serum melatonin level and an increased pancreatic melatonin-receptor status.
Peschke E, et al. J Pineal Res. 2006 Mar;40(2):135-43.
(Color and bold added.)
Abstract
There are functional inter-relationships between the beta cells of the endocrine pancreas and the pineal gland, where the synchronizing circadian molecule melatonin originates. The aim of this study was to elucidate a putative interaction between insulin and melatonin in diabetic patients and a diabetic rat model. We analyzed **glucose, insulin, and melatonin levels of type 2 patients, as well as type 2 diabetic Goto Kakizaki (GK) rats** by radioimmunoassay. Expression of pancreatic melatonin and pineal insulin receptors, as well as arylalkylamine-N-acetyltransferase (AANAT), was determined by real-time reverse transcriptase polymerase chain reaction (RT-PCR). The AANAT enzyme activity was measured in pineal homogenates. **Diabetic patients showed a decrease in melatonin levels,** while in the pancreas of GK rats an upregulation of the melatonin-receptor mRNA was determined. The pancreatic islets of GK rats showed expression of the mRNA for the pancreatic melatonin (MT1) receptor, which had previously been identified in rats and insulinoma (INS1) cells. Besides their presence in animal cells, the MT1-receptor transcript was also detected in human pancreas by RT-PCR. Whereas the rat pancreatic mRNA expression of the MT1-receptor was significantly increased, the activity of the pineal AANAT enzyme was reduced. The latter observation was in accordance with plasma melatonin levels. The insulin-receptor mRNA of the pineal gland was found to be reduced in GK rats. **Our observations suggest a functional inter-relationship between melatonin and insulin, and may indicate a reduction of melatonin in the genesis of diabetes.**

Melatonin Uptake by Cells: An Answer to Its Relationship with Glucose?
Mayo JC, et al. Molecules. 2018 Aug 10;23(8). pii: E1999.
Abstract *(partial)*
Numerous reports have provided the molecular components underlying the regulatory actions of melatonin on insulin secretion in pancreatic beta-cells, mainly involving membrane receptors MTNR1A/B, which would be partially responsible for the circadian rhythmicity of insulin in the organism. More recently, a new line of evidence has shown that glucose transporters GLUT/SLC2A are linked to melatonin uptake and its cellular internalization. Beside its binding to membrane receptors, melatonin transportation into the cytoplasm, required for its free radical scavenging abilities, still generates a great deal of debate. Thus, GLUT transporters might constitute at least one of the keys to explain the relationship between glucose and melatonin. These and other potential mechanisms responsible for such interaction are also discussed here.

Melatonin signalling and type 2 diabetes risk: too little, too much or just right?
Mulder H, et al. Diabetologia. 2017 May;60(5):826-829.
(Color and bold added.)
Abstract
Of the associations of genetic variants with type 2 diabetes, the one of an SNP in an intron of the gene encoding the melatonin receptor 1B (MTNR1B) has been remarkably robust. Work from our group and others has provided support for a model where carriers of this risk G allele exhibit increased MTNR1B expression in islets of Langerhans. **Most published studies to date favour that melatonin's action on the beta cell is inhibition of insulin secretion.** Hence, our model proposes that this inhibitory effect of melatonin is exaggerated in carriers of the MTNR1B risk G allele. This would explain why this genetic association causes reduced insulin secretion and greater risk of future type 2 diabetes, as has been observed in numerous studies. Concurrently, another body of work has shown that rare MTNR1B alleles, which could perturb receptor function, also associate with type 2 diabetes. In this commentary, it is suggested that such apparently conflicting observations can be reconciled by the fact that non-coding (intronic; frequent) and coding (exonic; rare) alleles of MTNR1B give rise to different phenotypes. Thus, altered gene transcription may

explain why SNPs, which do not alter coding sequences, exhibit cell-specific effects. In contrast, SNPs that change protein sequences are more likely to exert generalised effects since an altered protein will appear in all cells expressing the gene.

Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection.
Thaiss CA1, Levy M1, Elinav E, et al. Science. 2018 Mar 23;359(6382):1376-1383.
(SY: Color and bold added.)

Abstract
Obesity, diabetes, and related manifestations are associated with an enhanced, but poorly understood, risk for mucosal infection and systemic inflammation. Here, we show in mouse models of obesity and diabetes that **hyperglycemia drives intestinal barrier permeability,** through GLUT2-dependent transcriptional reprogramming of intestinal epithelial cells and alteration of tight and adherence junction integrity. Consequently, **hyperglycemia-mediated barrier disruption leads to systemic influx of microbial products and enhanced dissemination of enteric infection.** Treatment of hyperglycemia, intestinal epithelial-specific GLUT2 deletion, or inhibition of glucose metabolism restores barrier function and bacterial containment. **In humans, systemic influx of intestinal microbiome products correlates with individualized glycemic control, indicated by glycated hemoglobin levels.** Together, our results mechanistically link hyperglycemia and intestinal barrier function with systemic infectious and inflammatory consequences of obesity and diabetes.