Melatonin’s Potential Side Effects: It May Be in Your Genes

To the Editor: According to a recent study using data from the 1999-2010 through 2017-2018 cycles of the National Health and Nutrition Examination Survey (NHANES), the prevalence of melatonin supplement consumption, including self-reported use of more than 5 mg/d of melatonin, significantly increased over time. More specifically, the overall reported prevalence of melatonin use increased from 0.4% in 1999-2000 to 2.1% in 2017-2018. Furthermore, the prevalence of melatonin use of more than 5 mg/d rose from 0.08% in 2005-2006 to 0.28% in 2017-2018. These NHANES findings received a great deal of public attention (Altmetric score on March 31, 2022: 1014), including a discussion of possible safety concerns about melatonin. But what are the potential adverse effects of melatonin? According to a recent meta-analysis including data from 79 studies with 3861 participants, melatonin, even when taken in a higher dose (≥10 mg/d) and for 3 months or longer, was not associated with an increased risk of serious adverse effects events. However, a 40% increase in adverse events was found, but these were primarily limited to headache, dizziness, and drowsiness.

Surprisingly, in the discussion of melatonin’s safety profile, little attention has been paid to the genetic polymorphism rs10830963 in the melatonin receptor 1B (MTNR1B) gene carried by about 30% of the general population. Carriers of the risk G allele of single-nucleotide polymorphism rs10830963 show higher expression of MTNR1B in β cells in pancreatic islets compared with noncarriers. Through binding to MTNR1B, melatonin acutely blocks glucose-induced insulin secretion by β cells. Thus, those carrying copies of the G allele where pancreatic expression of MTNR1B is increased may show impaired postprandial glucose disposal under the impact of melatonin. In line with this assumption, a randomized crossover study of 845 participants found that an oral glucose tolerance test scheduled 1 hour before habitual bedtime (ie, a time of the day when endogenous melatonin rises in the blood) resulted in lower insulin release and higher plasma glucose concentration. Notably, the effect of late eating impairing glucose tolerance was stronger in carriers of the G allele than in noncarriers. These findings could also explain why the G allele of MTNR1B rs10830963 confers an increased risk of type 2 diabetes.

Findings that adverse effects of exogenous melatonin supplements appear to be limited to headache, dizziness, and drowsiness may mislead the patients to believe that melatonin supplements are generally safe. However, as pointed out in this Letter to the Editor, users of melatonin supplements should undergo periodic glycated hemoglobin (HbA1c) monitoring. In this context, physicians and researchers should pay particular attention to those carrying the G allele of MTNR1B rs10830963.

Malignant Histiocytosis With PD-L1 Expression—Dramatic Response to Nivolumab

To the Editor: A woman in her 60s was admitted to the hospital for exploration of erythema nodosum, lower limb edema, and asthenia. Clinical examination revealed no other abnormalities, and autoimmune and