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Title: Oral melatonin supplements for patients with non-proliferative diabetic retinopathy – a randomized double-masked placebo-controlled crossover trial.

Background: Melatonin is a key regulator of the circadian rhythm. We have previously shown that melatonin level is significantly reduced in patients with diabetic retinopathy. Currently, there is no treatment available for non-proliferative diabetic retinopathy (NPDR).

Methods: We conducted a phase 3 study involving 32 diabetic patients with NPDR. Four patients withdraw their consents. The patients were randomized either to receive melatonin 4 mg (arm 1) or placebo (arm 2) every evening 2 hours before bedtime for 3 weeks (period 1). After washout period of minimum 1 week, the participants changed the treatment arms (period 2). Primary endpoint was retinal function measured with electroretinography (ERG) including oscillatory potential amplitudes (Op1-Op3) and implicit times (It2-3). Secondary endpoints were circadian rhythm parameters measured as melanopsin-mediated post-illumination pupillary response (PIPIR), salivary melatonin level and Pittsburg sleep quality index (PSQI).

Results: The It1 and 3 were significantly shortened during the first period of melatonin treatment ($p \leq 0.01$), but not in the second period ($p \geq 0.17$). The Op1-3 were not significantly changed after melatonin- or placebo treatments ($p \geq 0.05$). The implicit time of rod-initiated DA0.01 b-wave in the ff-ERG was significantly shortened after melatonin treatment during the second period ($p = 0.01$). The implicit time of cone-dominated a-wave was significantly shortened after melatonin treatment during the first period $p = 0.002$), but not in the second period (0.26).
The pupillometry outcomes including melanopsin-mediated PIPR was not changed by melatonin- or placebo treatments (all $p \geq 0.30$). The PSQI-score was not affected by melatonin- or placebo ($p \geq 0.10$). Salivary melatonin level increased significantly in the melatonin group during both treatment periods ($p \leq 0.04$). The PSQI global scores were not affected by melatonin- or placebo treatments.

Safety: No serious adverse events (SAE) or Serious Adverse (Drug) Reaction (SAR) were observed.