Melatonin treatment of aging women: doses, side effects, how to manage them

4th European Congress in Anti-aging medicine –
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Palais des Congrès de Paris (Porte Maillot)
The amount of melatonin secretion from human pineal gland during various time of day

Long-Day Suppressed Expression of Type 2 Deiodinase Gene in the Mediobasal Hypothalamus of the Saanen Goat, a Short-Day Breeder: Implication for Seasonal Window of Thyroid Hormone Action on Reproductive Neuroendocrine Axis. Shinobu Yasuo, Nobuhiko Nakao, Satoshi Ohkura, and Coll. Endocrinology 2005: Vol. 147, No. 1 432-440
Melatonin treatment: doses
Melatonin deficiency: plasma levels at night

http://www.fit-zone.com/library/M/melatonin/melaton.html
Melatonin Plasma Levels Decline Rapidly with Age

% decrease from the young adult value

40 years: ↓50%
50 years: ↓75%
60 years: ↓91%

People over age 60 may show no increase in melatonin production at night.
Melatonin deficiency: plasma levels at night

- Optimal: 130 pg/ml
- Mild: < 80
- Moderate: < 55
- Severe: < 30
<table>
<thead>
<tr>
<th>Severity</th>
<th>24 h urine 6-sulfatoxy-melatonin</th>
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<tbody>
<tr>
<td>Optimal</td>
<td>50 mcg / 24h</td>
</tr>
<tr>
<td>Mild</td>
<td>&lt; 35 mcg / 24h</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt; 25 mcg / 24h</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 15 mcg / 24h</td>
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# Melatonin treatment: doses & timing

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<table>
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<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>0.1 to 3 mg daily</td>
</tr>
<tr>
<td><strong>Physiological secretion</strong></td>
<td>0.05 to 0.2 mg daily</td>
</tr>
<tr>
<td><strong>Absorption</strong></td>
<td>10 - 50% of melatonin dose, depending on the individual</td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td>Before bedtime</td>
</tr>
<tr>
<td><strong>Sublingual M. supplements</strong></td>
<td>10 - 15 minutes</td>
</tr>
<tr>
<td><strong>Oral M. supplements</strong></td>
<td>30 - 60 minutes</td>
</tr>
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</table>
Average concentrations of melatonin in plasma (black, average N=133), saliva (blue, average N=28) and 6-sulphatoxymelatonin (aMT6s) in urine (red, average N=88), all measurements by radioimmunoassay. Diagrammatic representation of mean normal values (healthy men and women over 18 years old) from the author’s laboratory.
Melatonin Side Effects
How to manage them
Very deep sleep during 3 to 5 hours with precocious waking up.

Tachicardia

« Heavy » head in the morning

Sweating events
Cause

- Melatonin overdosage
- Melatonin stimulates too much and too fast after 3 to 5 hours the conversion of T4 to T3 while normally it takes 6 to 8 hours.
At present we assert that the six-month treatment with 3mg Melatonin daily produced a remarkable and highly significant improvement of thyroid function.
• Oral melatonin administration tended to exert a more marked effect on enzyme activity than s.c. injection of the hormone.

• Changes in 5’-MonoDeiodinase activities were accompanied by an increase in serum iodothyronine (T4, T3, and rT3) concentrations.

• The rise in the serum T4 was probably due to the stimulatory effect of melatonin on the secretory activity of the thyroid gland itself.

• The T3 and rT3 increases may result from the deiodinating processes by the type I 5’-MD and 5-MD, respectively.
Artificial long-day conditions (16 h light, 8 h dark).

- A, Rostral; B, middle; C, caudal parts of the MBH are shown. In each part of the MBH, representative autoradiograms for Dio2 expression under natural photoperiod and artificial long-day conditions, and a schematic drawing are shown. Each graph shows the relative OD of Dio2 mRNA level in the external zone of the ME (ez, large arrowheads), the cell-clear zone overlying the TIS (small arrowheads), the EC (small arrows), and cARC (large arrows), respectively. Solid bars, Natural daylength; open bars, artificial long days. Asterisks shows the significant difference detected by Mann-Whitney U test ($P < 0.05$). Each value is the mean ± SEM (n = 4). Iz, Internal zone of the ME; PT, pars tuberalis; TMv, the ventral tuberomammillary nucleus; Fx, fornix; IIIv, third ventricle.

MBH : Medio Basal Hypothalamus

Long-Day Suppressed Expression of Type 2 Deiodinase Gene in the Mediobasal Hypothalamus of the Saanen Goat, a Short-Day Breeder: Implication for Seasonal Window of Thyroid Hormone Action on Reproductive Neuroendocrine Axis. Shinobu Yasuo1, Nobuhiro Nakao1, Satoshi Ohkura, and Coll. Endocrinology 2005 : Vol. 147, No. 1 432-440
Melatonin overdosage

- Deep prolonged sleep(iness) the whole night through until late in the morning
Treatment

- ↓ dose of melatonin from at least 50 up to 95%!
Too vivid dreams

- Melatonin overdosage ⇒ stimulates too much and too fast after 3 to 5 hours the conversion of T4 to T3 (normally 6 to 8 hours after)
Treatment

• ↓ dose of melatonin from at least 50 up to 95%!
Too dark office room

- ↓ Melatonin production (circadian cycle)
- ↓ Melatonin receptor
Treatment

- Respect the circadian cycle
- Daylight exposure at least > 2.500 Lux
- Add light sources if needed

A 30 kHz bright light therapy lamp (Innosol Rondo) used to treat seasonal affective disorder. Provides 10,000 lux at a distance of 25 cm.
• Before bedtime ↑ melatonin by 50 to 150% of the routine dose.
Melatonin doesn’t work for sleep
Factors that decrease melatonin receptor or endogenous secretion at night

• Excess light in bedroom at night

• Insufficient daylight exposure during the day

Long-Day Suppressed Expression of Type 2 Deiodinase Gene in the Mediobasal Hypothalamus of the Saanen Goat, a Short-Day Breeder: Implication for Seasonal Window of Thyroid Hormone Action on Reproductive Neuroendocrine Axis. Shinobu Yasuo1, Nobuhiro Nakao1, Satoshi Ohkura, and Coll.
Endocrinology 2005: Vol. 147, No. 1 432-440
Synthesis and secretion of melatonin is dramatically affected by light exposure to the eyes.

The duration of melatonin secretion each day is directly proportional to the length of the night.

Examples of the circadian rhythm in melatonin secretion in humans is depicted in the figure to the right (adapted from Vaughn, et al, J Clin Endo Metab 42:752, 1976). The dark gray bars represent night, and serum melatonin levels are shown for two individuals (yellow versus light blue). Note that blood levels of melatonin are essentially undetectable during daytime, but rise sharply during the dark.
Plasma melatonin and temperature were measured repeatedly during a constant routine (hatched bars) and subsequent episodes of sleep (solid bars). The light intensity was less than 0.02 lux during the sleep episodes, 10 to 15 lux during the constant routine, and approximately 10,000 lux during 90 to 100 minutes of exposure to bright light (open columns) 22 to 23 hours after the initial temperature minimum (crosses). In both subjects, plasma melatonin concentrations decreased markedly in response to bright light and then increased after the return to dim light.

Suppression of Melatonin Secretion in Some Blind Patients by Exposure to Bright Light

Charles A. Czeisler, Ph.D., M.D., Theresa L. Shanahan, B.Sc., Elizabeth B. Klerman, M.D., Ph.D., Heinz Martens, M.D., Daniel J. Brötman, A.B., Jonathan S. Emens, B.A., Torsten Klein, M.D., and Joseph F. Rizzo, M.D.

The New England Journal of Medicine Volume 332:6-11 January 5, 1995 Number 1
Results of Melatonin-Suppression Tests with and without a Blindfold

- The plasma melatonin concentrations did not fall during the bright-light exposure when the blindfold was in place (left-hand panel), but they fell abruptly during the exposure when the patient's eyes were not blindfolded (right-hand panel).

Suppression of Melatonin Secretion in Some Blind Patients by Exposure to Bright Light
Charles A. Czeisler, Ph.D., M.D., Theresa L. Shanahan, B.Sc., Elizabeth B. Klerman, M.D., Ph.D., Heinz Martens, M.D., Daniel J. Brötman, A.B., Jonathan S. Emens, B.A., Torsten Klein, M.D., and Joseph F. Rizzo, M.D.
The New England Journal of Medicine Volume 332:6-11 January 5, 1995 Number 1
Melatonin doesn’t work for sleep

Apparent cause

- Excess adrenaline and cortisol decrease melatonin secretion & effects on sleep

Too cold bedroom

Too warm bedroom
Melatonin doesn’t work for sleep

**Treatment**

- ↑ Melatonin at bedtime by 1.5 to 2 times of the routine dosage
Medical treatment that may interfere with melatonin secretion
Influence of beta-blockers on melatonin release.

Melatonin is mainly produced during the night by stimulation of adrenergic beta1- and alpha1-receptors.

αMT6s in urine after intake of the drugs.

The effects of the beta-adrenergic agonist, isoproterenol, on induced increase in melatonin production in the pineal gland of young and old rats, at different circadian stages.

The intensity of the response to $10^{-6}$ M isoproterenol infusion was greater in young than in old rat pineal glands ($P<0.001$).

Isoproterenol-stimulated melatonin production by perifused rat pineal glands: age- and time-related effects.

In vivo, a single acute subcutaneous administration of DZP (3 mg/kg body weight) significantly affected pineal melatonin synthesis and plasma melatonin levels, while administration of the metabolites under the same conditions did not.

Melatonin therapy may reduce or stop benzodiazepine therapy prescribed in case of sleep disorders.

1. 22 subjects (16 females), mean +/- S.D. age 60.1 +/- 9.5 years.
2. All patients received 3 mg of melatonin per os daily for 6 months, 30 min before expected sleep time.
3. Twenty of 22 patients were on benzodiazepine treatment and they continued this treatment for part of or for the entire melatonin administration period.

Urinary 6-sulphatoxymelatonin (aMT6s) excretion was measured.

Increased bioavailability of oral melatonin after fluvoxamine coadministration.


Fluvoxamine, a selective serotonin reuptake inhibitor, is known to elevate melatonin serum concentrations.

Thers is an increase in the bioavailability of oral melatonin by coadministration of fluvoxamine.

Fold increase in serum melatonin concentration compared to fluvoxamine alone.
Melatonin and glucocorticoids

1 mg of dexametasona caused a significant reduction in plasma melatonin levels in 9 of 11 healthy volunteers.

Effect of corticosterone, deoxycorticosterone and dexamethasone on melatonin secretion by the pineal gland at different circadian stages.

High concentrations of corticosterone and dexamethasone resulted in a significant inhibitory effect on melatonin production whatever the circadian stage, whereas lower concentrations of both steroids did not affect melatonin production.

Excess stress

- Excess stress leads to increased cortisol and adrenaline production from the adrenal gland.
- This stimulates the hypothalamus and CRH, which in turn affects the pituitary gland and ultimately the adrenal gland.
- Reduced melatonin production is observed.
- Increased melatonin dosage is recommended as a countermeasure.

Diagram details:
- Hypothalamus
- CRH
- Pituitary
- Adrenal gland
- Adrenaline
- Cortisol

Upward arrows indicate increased levels, while downward arrows indicate decreased levels.
Oral contraceptives alter circadian rhythm parameters of cortisol, melatonin, blood pressure, heart rate, skin blood flow, transepidermal water loss, and skin amino acids of healthy young women. 

Suppression of nocturnal plasma melatonin levels by evening administration of sodium valproate in healthy humans.
Institute of Psychiatry, School of Medicine, Second University of Naples

To investigate the role of gamma-aminobutyric acid (GABA) in the modulation of human melatonin production, we studied the effects of the acute administration of the GABAergic drug, sodium valproate (VAL), on nocturnal blood melatonin levels in healthy subjects. To this purpose, 4 healthy men and 3 healthy women, aged 24-33 years, underwent three experimental sessions in which they received orally 400 mg VAL, 800 mg VAL, or placebo, in random order, according to a double-blind design. The drug administration was done at 19:00 hours; thereafter, blood samples were collected over the night, in dark conditions with the help of a red light. As compared to placebo, VAL, significantly suppressed nocturnal blood melatonin levels, the higher dose being slightly more effective than the lower one. At the dosage of both 400 and 800 mg, the maximum suppression coincided with the highest plasma levels of valproic acid. These findings support the view that endogenous GABA may participate in the modulation of the activity of the human pineal gland.

Sodium Valproate significantly suppressed nocturnal blood melatonin levels.
The maximum suppression coincided with the highest plasma levels of valproic acid.
Effect of fluoxetine on melatonin in patients with seasonal affective disorder and matched controls.


University Department of Psychiatry, Royal South Hants Hospital, Southampton.

• BACKGROUND. The aim was to investigate the secretion profile of melatonin and seasonal affective disorder before and after treatment with fluoxetine. METHOD. A six-week case-controlled study with repeated overnight blood sampling was conducted. Ten patients fulfilling the criteria for major depressive disorder, seasonal type, with a 29-item Hamilton Depression Rating Scale (HDRS) score of at least 20 were compared with ten age- and sex-matched healthy controls in a clinical laboratory. The effects of fluoxetine (20 mg/day) on the HDRS and melatonin concentration were measured. RESULTS. Fluoxetine significantly reduced melatonin levels in both groups. There was no significant difference in melatonin secretion between the groups. CONCLUSIONS. The effect of fluoxetine differs from tricyclics and fluvoxamine, both of which increase melatonin.
Coffee consumption and plasma melatonin levels
Caffeinated coffee caused a decrease in 6-SMT excretion throughout the following night.

- Individuals who suffer from sleep abnormalities should avoid caffeinated coffee during the evening hours.

Drinking regular caffeinated coffee, compared to decaffeinated coffee, caused:

- ↓ in the total amount of sleep
- ↓ in sleep quality
- ↑ in the length of time of sleep induction.

The effects of coffee consumption on sleep and melatonin secretion.

Caffeine was found to increase the oral bioavailability of melatonin probably due to an inhibition of the CYP1A2 catalysed first-pass metabolism of melatonin.

When caffeine was coadministered the Cmax of melatonin were increased on average by 142% ($P = 0.001$).

Melatonin serum concentration after oral administration of melatonin alone (closed circles, dotted line) or together with caffeine (3 × 200 mg) given 1 h before and 1 and 3 h after melatonin intake (open squares, solid line). Melatonin serum concentrations were significantly (*$P < 0.05$; **$P < 0.01$) higher at all time points between 0.5 and 6 h after melatonin intake when caffeine was coadministered.

Effects of caffeine intake on the pharmacokinetics of melatonin, a probe drug for CYP1A2 activity
Sebastian Härtter,1 Anna Nordmark,3 Dirk-Matthias Rose,2 Leif Bertilsson,3 Gunnel Tybring,3 and Kari Laine4.
Smoking habit and melatonin secretion
Higher pack-years of smoking were associated with significantly lower aMT6s levels. 459 healthy, primarily premenopausal (age range 33-50 yr) women from the Nurses' Health Study II (NHS II).

Alcohol consumption and plasma melatonin levels
Evening alcohol suppresses salivary melatonin in young adults.

Rupp TL, Acebo C, Carskadon MA. Chronobiol Int. 2007;24(3):463-70
Alcohol consumption and urinary concentration of 6-sulfatoxymelatonin in healthy women.

A total of 203 randomly selected healthy women between the ages of 20 and 74 years.

6-sulfatoxymelatonin decreases in a dose-dependent manner with increase consumption of alcoholic beverages.

Alcohol consumption and melatonin secretion in healthy women.

Alcohol consumption and melatonin secretion


A moderate dose of alcohol in the evening suppress melatonin in young adults.

29 adults (nine males) ages 21 to 25 (M=22.6, SD=1.2) yrs.

Alcohol (vodka: 0.54 g/kg for men and 0.49 g/kg for women) or placebo beverage was consumed over 30 min, ending 1 h before stabilized bedtime.
Evening alcohol suppresses salivary melatonin in healthy young adults. 

Rupp TL, Acebo C, Carskadon MA. 

Chronobiol Int. 2007;24(3):463-70

Mean and standard error of the mean melatonin values (pg/ml) are displayed for placebo (dashed line) and alcohol (solid line) conditions. The mean and standard error BrAC values on the alcohol night are depicted by the dotted line. Values for melatonin are labeled on the left y-axis and for BrAC on the right y-axis. Time on the x-axis is labeled in minutes relative to the end of beverage administration, which is time 0; the stabilized at home bedtime is +60 minutes. Asterisks indicate significant (p < .05) differences in melatonin levels between conditions. The arrow indicates DLMO phase (Dim light melatonin onset).
Intake of ethanol between 1900-1945 h inhibited the nocturnal melatonin secretion dose-dependently during the first half of the night, with no changes in urinary excretion of melatonin.

Ethanol inhibits melatonin secretion in healthy volunteers in a dose-dependent randomized double-blind cross-over study. 

Magnetic field exposure & Melatonin secretion

Magnetic field exposure & Melatonin secretion
Effect of 60-Hz Magnetic Field Exposure on Nocturnal 6-Sulfatoxymelatonin, Estrogens, Luteinizing Hormone, and Follicle-Stimulating Hormone in healthy Reproductive-Age Women: Results of a Crossover Trial. SCOTT DAVIS, PhD, DANA K. MIRICK, MS, CHU CHEN, PhD, AND FRANK Z. STANCZYK, PhD


This study provides further evidence that exposure to magnetic fields is associated with decreased nocturnal melatonin levels.

n = 132 (20 to 45 years)
Ovulator exposed n = 126
Ovulator not exposed n = 119
This study provides further evidence that exposure to magnetic fields is associated with decreased nocturnal melatonin levels.
The excretion rates of aMT6s (µmol/h) in operators under high-level and low-level radiofrequency EMR exposure and control group during fast-rotating extended shifts.


<table>
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<tr>
<th>Operator</th>
<th>Exposure</th>
<th>Time-weighed average (µW/cm²)</th>
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<tr>
<td></td>
<td>TWAmean</td>
<td>TWAmax</td>
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<tr>
<td>BC station</td>
<td>6-25 MHz</td>
<td>3.10</td>
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<tr>
<td>N = 12</td>
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<tr>
<td>TV station</td>
<td>66.5-900 MHz</td>
<td>1.89</td>
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<tr>
<td>N = 12</td>
<td></td>
<td></td>
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<tr>
<td>SAT station</td>
<td>5.850-6.245 GHz</td>
<td>1.6</td>
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<td>N = 12</td>
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Interaction between melatonin and sexual hormones
The study was performed on 14 women (volunteers), aged from 64 to 80 years (mean age 71+/−4.6 years).

Melatonin (2 mg daily at 19:00 h)

Effect of 6six months melatonin treatment on sleep quality and serum concentrations of estradiol, cortisol, dehydroepiandrosterone sulphate, and somatomedin C in elderly women.

Effect of six months melatonin 2 mg treatment on serum concentrations of estradiol, cortisol, DHEAS and IGF1 in elderly women.

Effect of six months melatonin treatment on sleep quality and serum concentrations of estradiol, cortisol, dehydroepiandrosterone sulphate, and somatomedin C in elderly women.


Fig. 1. Serum concentrations of estradiol (A), IGF-I (B), cortisol (C), and DHEAS (D) in elderly women before and after 6-months melatonin therapy; * p < 0.05, ** p < 0.001.
Interaction between melatonin and non sexual hormones
Melatonin decreases Prolactin secretion by pituitary gland

Effects of melatonin on basal PRL release by cultured pituitary glands and by dissociated pituitary cells. A, Pituitary glands were cultured in the presence of melatonin at the concentrations and durations indicated. Medium was renewed every 3 h. Mean ± SEM (n = 12); *P < 0.05 (ANOVA) for all the four curves. B, Same as in A, with dissociated pituitary cells cultures on polycarbonate membrane inserts; mean ± SEM (n = 12); *P < 0.0001 (ANOVA) for all three curves. C, Cultured pituitary glands were challenged for 3 h, either with melatonin (10^-8 M), or luzindole (10^-7 M), or both. Mean ± SEM (n = 6); *, *P < 0.05 (Student’s t test). Similar results were obtained in two other experiments.

Effects of melatonin on basal GH release by cultured pituitary glands.

A, Glands were cultured in the presence of melatonin, at the indicated concentrations, for 30 min, 3 h and 12 h. This resulted in a dose-dependent increase in GH release. Mean ± SEM (n = 6); P < 0.05 for all three curves (one-way ANOVA). Similar results were obtained in two other experiments. B, Under pharmacological conditions as in A, the stimulatory effect of melatonin (mel), detected at the concentration of 10^-8 M, was antagonized in the presence of 10^-7 M luzindole. Mean ± SEM (n = 6) P < 0.05 (Student’s t test). Similar results were obtained in another experiment.


Lack of changes in serum prolactin, FSH, TSH, and estradiol after melatonin treatment in doses that improve sleep and reduce benzodiazepine consumption in sleep-disturbed, middle-aged, and elderly patients.
Significant negative correlation between the peak serum melatonin concentration and the serum 17 beta-estradiol concentration in premenopausal women aged 40-50 years ($r = -0.661$, $P<0.0005$).

Melatonin & Jet Lag
Jet Lag

Causes:

- Disturbance in circadian hormone rhythm
- Too low melatonin at night
- Too low cortisol rhythm during day
- => Disturbance of other hormone cycle: TH, GH, Sexual hormones, etc

Treatment:

- First 3 days in the new location:
  1. ↑ Melatonin 2-3 X routine dose before bedtime
  2. ↑ Cortisol therapy 2-2.5 X routine dose

- Following 3 days:
  1. ↑ Melatonin 1.5-1.75 X
  2. ↑ Cortisol therapy
     1.5-1.75 X
Melatonin treatment: the good habits
Increase nightly melatonin production by:

- Very dark bedroom (dark curtains, eyemask,…) => ↑ 50 to 200% melatonin secretion
- More outdoor daylight (especially in the morning) > 2000 lux
- Light therapy
Increase nightly melatonin production by:

- More relaxation time (especially in the second half of the day)
- Limit stress & excitement in your life (especially in the late afternoon & evening)
Avoid any situation that decreases melatonin production

1. Coffee, thea, Cola (caffeine)
2. Alcohol
3. B Blockers, high dosade glucocorticoids, benzodiazepin,....
4. Chronic stress
5. Light at night
Melatonin treatment: balance with other hormones
<table>
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<th>MELATONIN supplements can</th>
<th>MECHANISM</th>
<th>SOLUTION</th>
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<tbody>
<tr>
<td>↓ GLUCOCORTICOIDS (fatigue, diziness, sugar craving,...)</td>
<td>↓ Cortisol production</td>
<td>↓ Melatonin in untreated or not sufficiently treated cortisol deficiency patients = Melatonin and correct cortisol deficiency</td>
</tr>
<tr>
<td>↓ OVARIAN ACTIVITY (only in case of excess melatonin)</td>
<td>↓ Oesrtgen production</td>
<td>↓ Melatonin posology (&lt; 10 mg)</td>
</tr>
<tr>
<td>↑ THYROID ACTIVITY (Palpitation, excess sweating, hunger, earlier morning wake up)</td>
<td>↑ T4 → T3 conversion</td>
<td>↓ dosage of thyroid therapy in treated hypothyroid patients</td>
</tr>
<tr>
<td>↑ SOMATOTROPE ACTIVITY</td>
<td>↑ GH production</td>
<td>↓ dosage of GH therapy in treated GH deficient patients</td>
</tr>
</tbody>
</table>
Melatonin contraindications
Women wanted to conceive

- Pregnant women should avoid melatonin, since its teratogenic effect is not known. Melatonin deficiencies in women. Rohr UD, Herold J. Maturitas. 2002 Apr 15;41 Suppl 1:S85-104.

• Melatonin levels are significantly higher in functional hypothalamic amenorrheic patients than in normal controls.

• A dose of 75 mg melatonin was tested as contraception: melatonin inactivated the GnRH pulse generator.

• Nursing: melatonin has not been tested in pregnancy: unknown risks, small amount of melatonin are transmitted through breast milk.
Melatonin & Autoimmune diseases

Erythematous Lupus

Multiple Sclerosis

Rheumatoid Arthritis
Melatonin alters the balance of T helper (Th)-1 and Th-2 cells mainly towards Th-1 responses.

Melatonin has been shown to be involved in the regulation of cellular and humoral immunity.
Melatonin stimulates the production of natural killer cells, monocytes and leukocytes.
Melatonin increases the production of relevant cytokines such as interleukin (IL)-2, IL-6, IL-12 and interferon-gamma.
• MLT serum level reached the peak at least two hours before in RA patients than in controls (p < 0.05).

• Subsequently, in RA patients, MLT concentration showed a plateau level lasting two to three hours, an effect not observed in healthy controls.

• Several clinical symptoms of RA, such as morning gelling, stiffness, and swelling, which are more evident in the early morning, might be related to the neuroimmunomodulatory effects exerted by MLT on synovitis and might be explained by the imbalance between cortisol serum levels (lower in RA patients) and MLT serum levels (higher in RA patients).

Patients were treated with nonsteroidal anti-inflammatory drugs (naproxene or ketoprofene) and antacids. No one had been treated with corticosteroids or disease-modifying antirheumatic drugs during the last two months before entry, and no TNF-α blockers had been administered.
Conclusions

• Several clinical symptoms of RA, such as joint gelling, stiffness, and swelling, which are more evident in the early morning, might be related to the neuroimmunomodulatory effects exerted by MLT on synovitis and might be explained by the imbalance between cortisol serum levels (lower in RA patients) and MLT serum levels (higher in RA patients).