In the name of GOD

THE 14th INTERNATIONAL CONGRESS OF
ENDOCRINE DISORDERS
22nd - 24th November 2023

The effect of melatonin supplementation on serum levels of leptin and adiponectin: A systematic review and meta-analysis of randomized clinical trials

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Content:

- Obesity
  - Comorbidities
  - Prevalence
  - Causes
- Melatonin
- Leptin
- Adiponectin
- Methods
- Results
- Discussion

Obesity-associated co-morbidities

Global overweight and obesity prevalence

- worldobesity.org atlas:
  2035: over 4 billion people may be affected
- 2020: over 2.6 billion
- 38% of the world's population in 2020 → over 50% by 2035

- expected to be steepest among children and adolescents,
- Low income countries
- No country has reported a decline in obesity prevalence across their entire population, and none are on track to meet the World Health Organization's (WHO) target of 'no increase on 2010 levels by 2025'.

Global overweight and obesity prevalence

Table 1.1: Global overweight and obesity 2020–2035

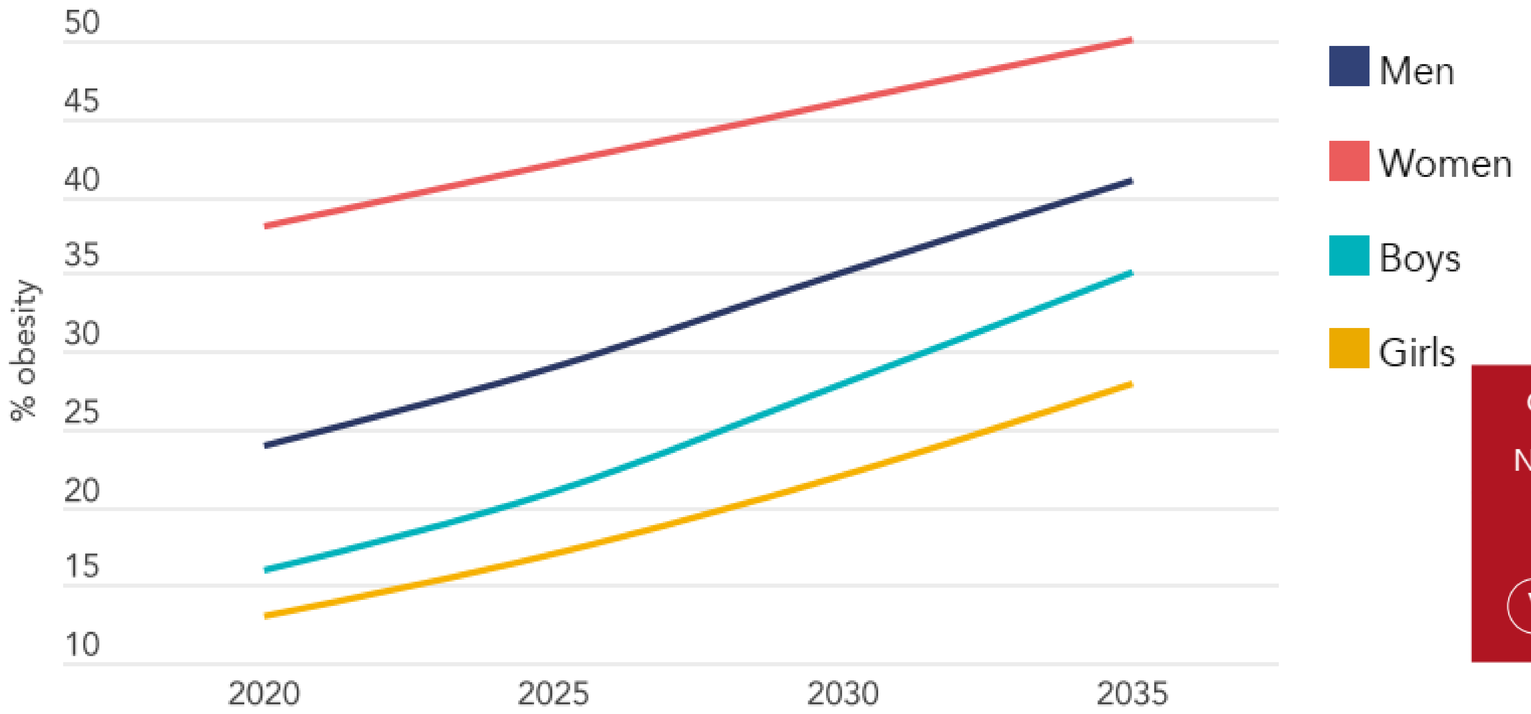
Numbers of people (aged over 5 years) and percentage of the population with overweight or obesity*

	2020	2025	2030	2035
Number with overweight or obesity (BMI≥25kg/m²) (millions)	2,603	3,041	3,507	4,005
Number with obesity (BMI ≥30kg/m²) (millions)	988	1,249	1,556	1,914
Proportion of the population with overweight or obesity (BMI ≥25kg/m²)	38%	42%	46%	51%
Proportion of the population with obesity (BMI ≥30kg/m²)	14%	17%	20%	24%

** For children and adolescents, overweight and obesity are defined using the WHO classification of +1SD and +2SD above median growth reference.*

Iran

PROJECTED TRENDS IN THE PREVALENCE OF OBESITY (BMI ≥30kg/m²)



ADULTS WITH OBESITY 2035
46%
VERY HIGH

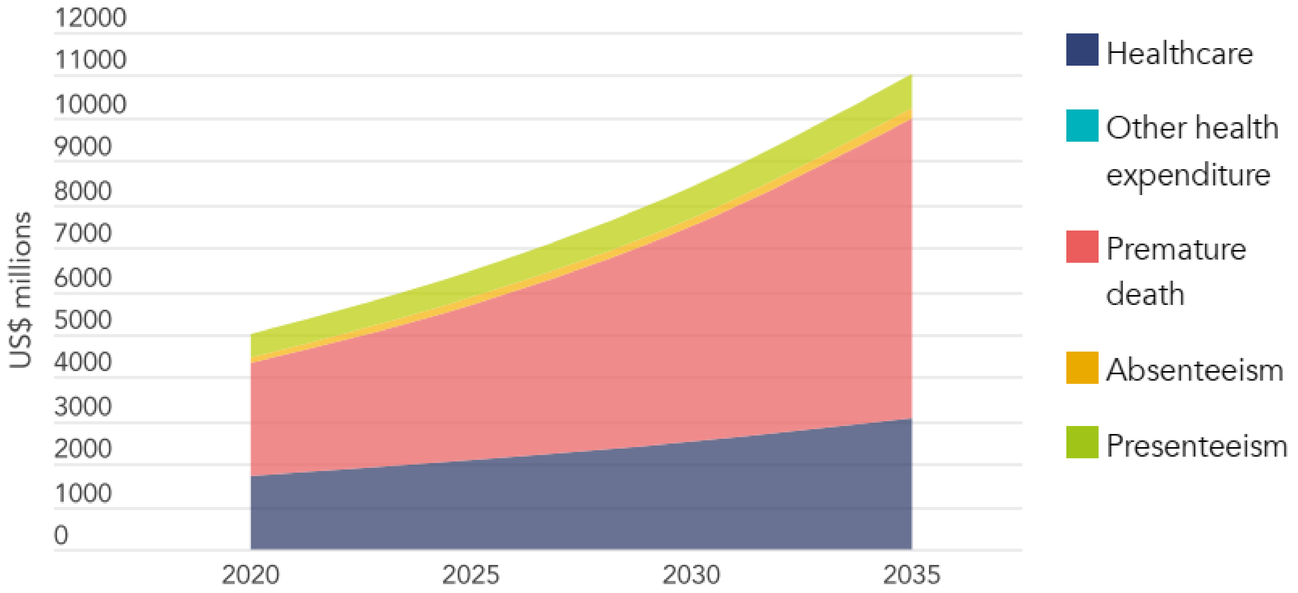
ANNUAL INCREASE IN ADULT OBESITY 2020–2035
2.6%
HIGH

OVERWEIGHT IMPACT ON NATIONAL GDP 2035
2.6%
VERY HIGH

ANNUAL INCREASE IN CHILD OBESITY 2020–2035
5.3%
VERY HIGH

GLOBAL PREPAREDNESS RANKING
45/183
FAIRLY GOOD

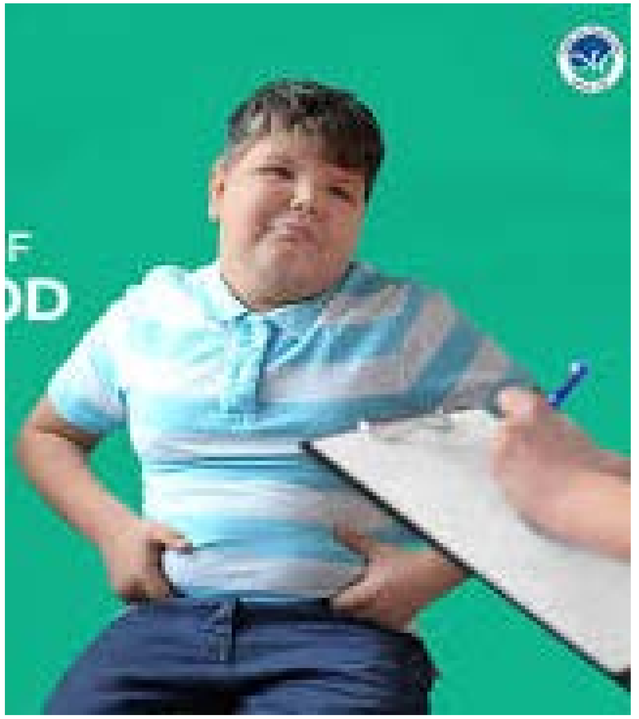
PROJECTED ECONOMIC IMPACT OF OVERWEIGHT (BMI ≥25kg/m²)



IMPACT OF OVERWEIGHT (BMI ≥25kg/m²) 2020–2035

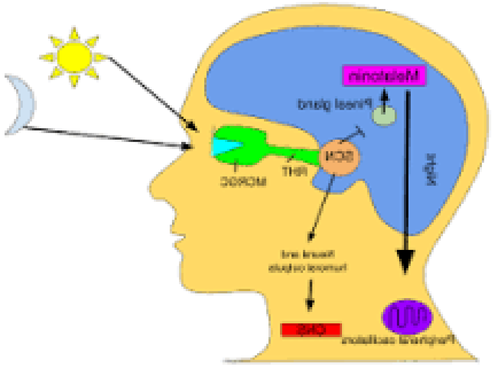
	Healthcare impact of BMI ≥25kg/m², US$ million	Total economic impact of BMI ≥25kg/m², US$ million	Estimated GDP US$ billion	Impact of BMI ≥25kg/m² on GDP
2020	1,692	4,992	296	1.7%
2025	2,071	6,458	337	1.9%
2030	2,503	8,382	377	2.2%
2035	3,019	11,015	425	2.6%

- Hyperleptinemia
- Resistance to a reduction of body mass



Melatonin

- an indoleamine, is secreted by the pineal gland from tryptophan amino acid.
- is released into the circulation ↑ in darkness ↓ in light,
- widely distributed melatonin receptors.
  - ✓ vascular function
  - ✓ antioxidant
  - ✓ anti-inflammatory
  - ✓ immunomodulatory
  - ✓ vasomotor effects
  - ✓ may improve metabolic syndrome components



✓ positive effect of melatonin on energy and lipid metabolism,

✓ alleviate the body weight gain in mice, appetite, and behaviors.

Add to this, the diversity of melatonin binding sites in gastrointestinal tracts suggest various possible function of melatonin in appetite regulation.

Leptin

Production sites:

- **white adipose tissue.**
- brown adipose tissue (BAT),
- placenta,
- fetal tissue,
- stomach,
- muscles,
- bone marrow,
- teeth,
- brain

A complex array of endocrine, neuroendocrine, and paracrine signals governs **leptin synthesis and secretion**

Food intake,
Total body fat,
Several hormones (**Insulin** and, to a lesser extent, other pancreatic peptide hormones, including amylin, glucagon, and pancreatic polypeptides)

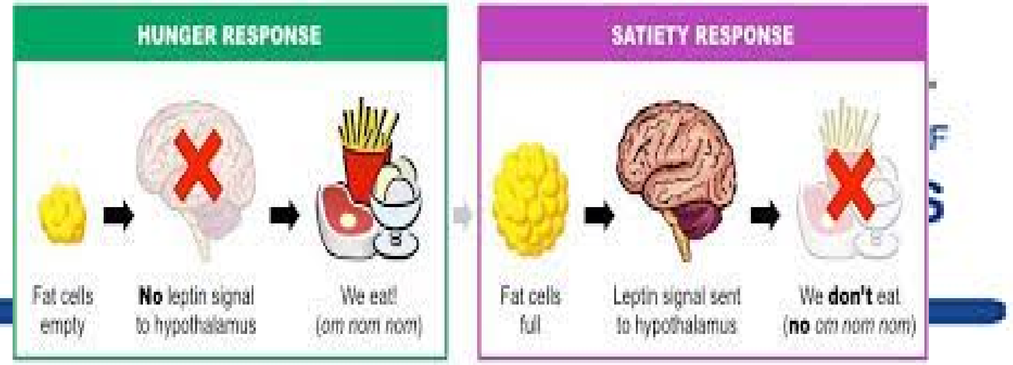
Hyperinsulinemia

✓Prolonged (increase in leptin's plasma concentration)
✓ Short-term hyperinsulinemia (does not cause such a change).

Leptin regulates:

✓food intake,
✓body mass,
✓reproductive functioning
✓ plays a vital role in fetal growth,
✓proinflammatory immune responses,
✓angiogenesis, lipolysis

Leptin and obesity



- ↓ fasting or energy restriction
- ↑ during refeeding, overfeeding, as well as during surgical stress

fat cells increase

leptin levels increase proportionally

bind to leptin receptors (LEP-R) in the brain

send signals to inhibit food intake and increase energy expenditure

- Sustained positive energy balance ➡ weight is gained

Leptin and obesity

- Hyperleptinemia and resistance to reducing body mass are two characteristics of typical obesity
- *Although* Leptin is overexpressed at the gene level in the adipose tissue of individuals with obesity
- *some other* studies point towards leptin resistance.

- Several studies have shown that leptin serum concentration is correlated with fat mass, and by decreasing the fat mass, leptin concentration will be decreased

Adiponectin

- derived from adipose tissue
- in the main tissue cells of the liver, osteoblasts, monocytes, epithelial cells and placenta
- improves insulin sensitivity:
  - ↑ in glucose uptake into the muscle, inhibition of glucose production in the liver, and enhancement of fatty acid oxidation
- acts directly in the CNS, regulating appetite and energy expenditure
- <u>has antiinflammatory and insulin-resistant properties</u>

Adiponectin

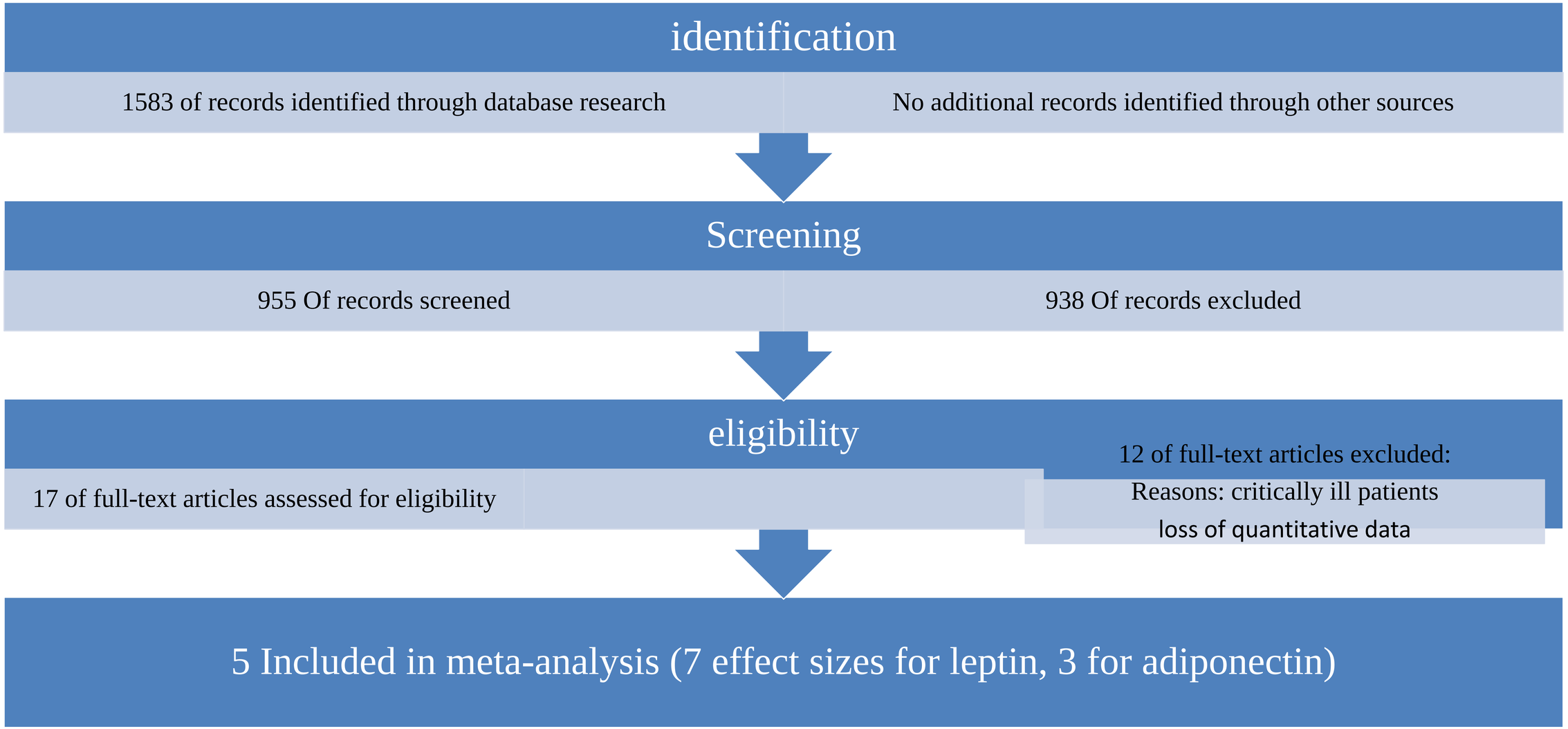
- **Dysregulation:**
  - wide variety of metabolic disorders such as insulin resistance, abdominal obesity, glucose intolerance, dyslipidemia, high blood pressure and nonalcoholic fatty liver disease
  - pathogenesis of metabolic syndrome

- **Secretion of adiponectin** is influenced by hormones, including prolactin, testosterone, growth hormone, and osteocalcin, as well as by b-adrenergic agonists
- **Pro inflammatory** cytokines (such as in obesity and related diseases) belong to the factors that reduce adiponectin gene expression
- Hypo-adiponectinemia has been found to be a strong indicator of metabolic and vascular disorders.

Methods:

- Electronic databases, including PubMed, SCOPUS, and Web of science were searched
- from inception to 2023
- Original clinical trials published in English language that investigated the effect of melatonin on leptin and adipokines
- The random-effect model

Methods:


identification
1583 of records identified through database research
No additional records identified through other sources
Screening
955 Of records screened
938 Of records excluded
eligibility
17 of full-text articles assessed for eligibility
12 of full-text articles excluded:
Reasons: critically ill patients
loss of quantitative data
5 Included in meta-analysis (7 effect sizes for leptin, 3 for adiponectin)

Methods:

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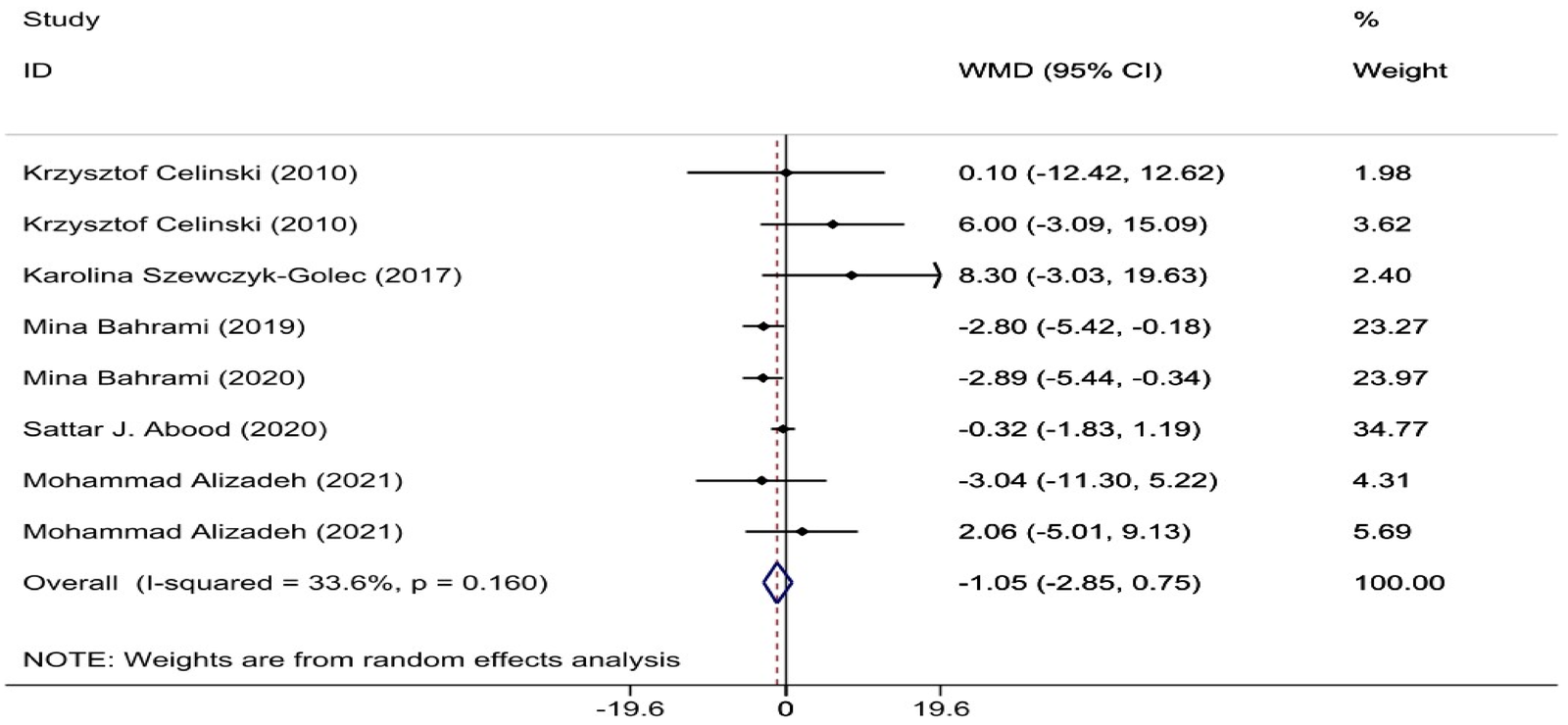
First author	Year	Country	RCT type	health status	Mean Age	gender	sample size_ treatment group	sample size_ control group	control group	duration (week)	Dose	type of supplement
Mina Bahrami	2020	Iran	RCT	patients with NAFLD	44 ± 9.62(Melatonin Group); 37.71± 11.31 (Placebo group)	m/f	24	21	placebo	12 weeks	6 mg/d	Melatonin tablet
Mina Bahrami	2019	Iran	RCT	patients with Metabolic Syndrome	42.5 ± 9.8(Melatonin Group); 42.6 ± 10.2 (Placebo group)	m/f	36	34	placebo	12 weeks	6 mg/d	Melatonin tablet
Karolina Szewczyk-Golec	2017	Poland	RCT	obese (class 1 or 2) patients on a calorie-restricted diet	37.7 ± 3.40(Melatonin Group); 36.3 ± 4.18 (Placebo group)	m/f	15	15	placebo	30 days	10 mg/d	Melatonin Supplementation (cachets) with a calorie-restricted
Krzysztof Celinski	2010	Poland	RCT	patients with duodenal ulcers	28-50 years	m/f	14	14	placebo + omeprazole	21 days	5 mg twice a day (10 mg/day)	Melatonin Supplementation (tablet) + omeprazole
Krzysztof Celinski	2010	Poland	RCT	patients with gastric ulcers	28-50 years	m/f	14	14	placebo + omeprazole	21 days	5 mg twice a day (10 mg/day)	Melatonin Supplementation (tablet) + omeprazole
Sattar J. Abood	2020	Iraq	RCT	Women with Metabolic Syndrome	45.80 6.53 48.07 ± 7.43 (metformin) 45.80 ± 6.53 (met+mel)	f	19	13	placebo	3 months	10 mg/d	capsule dosage form
Mohammad Alizadeh	2021	Iran	RCT	women with PCOS	25.57 ± 4.99(Melatonin Group); 26.200 ± 5.72 (Placebo group)	f	21	20	placebo	8 weeks	6 mg/d	Melatonin Supplementation
Mohammad Alizadeh	2021	Iran	RCT	women with PCOS	28.22 ± 6.38(Melatonin + Mg); 25.57 ± 4.88 (Mg)	f	22	21	placebo (Mg)	8 weeks	6 mg/d	Mel+ Mg

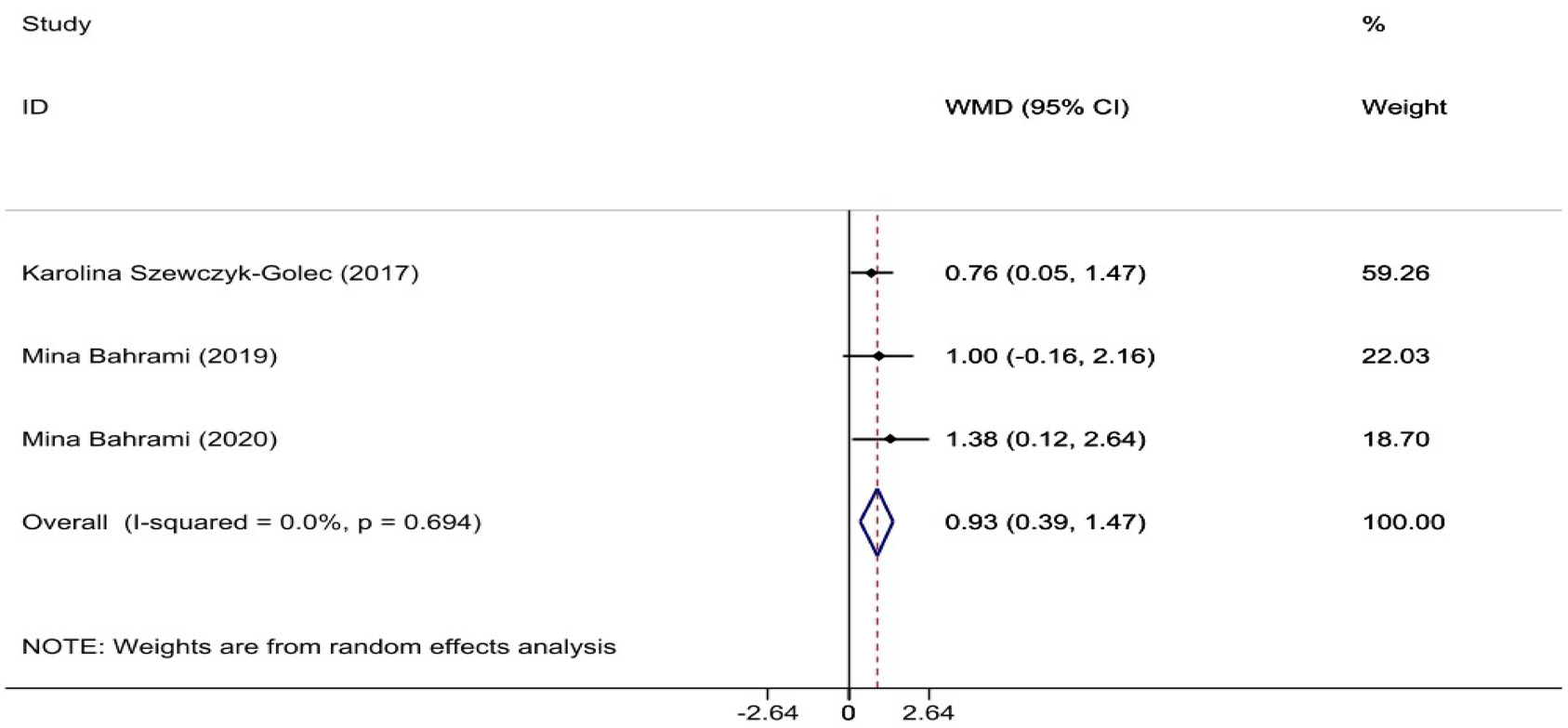
Results:

Forest plot displaying weighted mean differences and 95% confidence intervals for the impact of melatonin supplementation on leptin concentrations.



Results:

Forest plot displaying weighted mean differences and 95% confidence intervals for the impact of melatonin supplementation on adiponectin concentrations.



Results:

Subgroup analyses for the effects of melatonin on serum levels of leptin in the participants of included studies						
	Effect sizes, n	WMD (95% CI)	P-within	P-between	I^2	P-heterogeneity
Overall	8	−1.05 (−2.85, 0.75)	0.253		33.6	0.160
Intervention duration						
≤8 weeks	5	2.23 (−1.84, 6.29)		0.08	0.0	0.49
>8 weeks	3	−1.08 (−2.73, 0.16)			28.8	0.09
Dosage						
≤6 mg/d	4	−2.56 (−4.30, −0.83)		0.07	0.0	0.63
>6 mg/d	4	1.83 (−2.53, 6.19)			33.3	0.15
Gender						
Both	5	−0.66 (−4.30, 2.98)		0.86	58.20	0.13
Female	3	−0.31 (−1.59, 0.98)			0.0	0.15
Baseline level of leptin						
≤5 ng/mL	2	1.18 (−4.09, 6.44)		0.22	45.04	0.18
>5 ng/mL	6	−1.08 (−2.73, 0.58)			28.87	0.15
Data are pooled weighted mean differences (95% CIs) by a random-effects model.						

Discussion

- The beneficial effects of melatonin on serum levels of adiponectin and leptin

1.Gender ….

2.Study population

- ❑ Age
- ❑ Baseline levels of melatonin
- ❑ disease

Discussion

Effect of melatonin on leptin and adiponectin (animal studies)

Study	Animal model	Route of melatonin administration	Dose of melatonin	Diet type	Circulating leptin	Circulating adiponectin	Circulating insulin	Body weight
Ríos-Lugo et al. [131]	Adult male Wistar rats	Continuous in drinking water	25 μg/mL for 9 wk	Normal	24-hr rhythm disrupted	24-hr rhythm disrupted	↓	↓
			25 μg/mL for 11 wk	High-fat	↓	↓	↓	↓
Agil et al. [118]	Male Zucker diabetic fatty rats (fa/fa)	Continuous in drinking water	10 mg/kg/daily for 6 wk	Normal	↓	↑	↓	–
	Male Zucker lean rats (fa/–)				No effect	No effect	No effect	–
de Oliveira et al. [120]	Neonatally STZ-induced diabetic male Wistar rats	Nocturnal in drinking water	1 mg/kg/day for 8 wk	Normal	↓ non significant	↑	↓	No effect
Kitagawa et al. [121]	Adult male Wistar rats	Intraperitoneal injection once a day between 06:00 and 07:00 hr	1 mg/kg/day for 2 wk	Normal	No effect	No effect	No effect	No effect
				High-fructose	↓	↑	↓	No effect
			10 mg/kg/day for 2 wk	Normal	No effect	No effect	No effect	No effect
				High-fructose	↓	↑	↓	No effect
Ríos-Lugo et al. [133]	Adult male Wistar rats	Continuous in drinking water	25 μg/mL for 10 wk	Normal	↑	↑	–	No effect
				High-fat	↓	↓	–	↓

Discussion

Effect of melatonin on leptin and adiponectin (Human studies)

Study	Study group	Dose of melatonin	Time of melatonin administration	Circulating leptin	Circulating adiponectin
Cagnacci et al. [138]	Postmenopausal women estradiol or placebo treated	Single dose 1 mg	At 8:30 hr	No effect	–
			At 15:30 hr	No effect	–
		Single dose 2 mg	1 mg at 8:30 hr and 1 mg at 15:30 hr	No effect	–
Celinski et al. [137]	Male patients with liver cirrhosis	Single dose 10 mg	Morning after overnight fasting	↓	–
	Male healthy volunteers		before a test meal	↑	–
Gonciarz et al. [136]	Overweight patients with nonalcoholic steatohepatitis	10 mg/day for 28 days	Twice a day: 5 mg at 09:00 hr and 5 mg at 21:00 hr	↑	↑

Gender differences:

- The beneficial effects of melatonin on serum levels of adiponectin and leptin

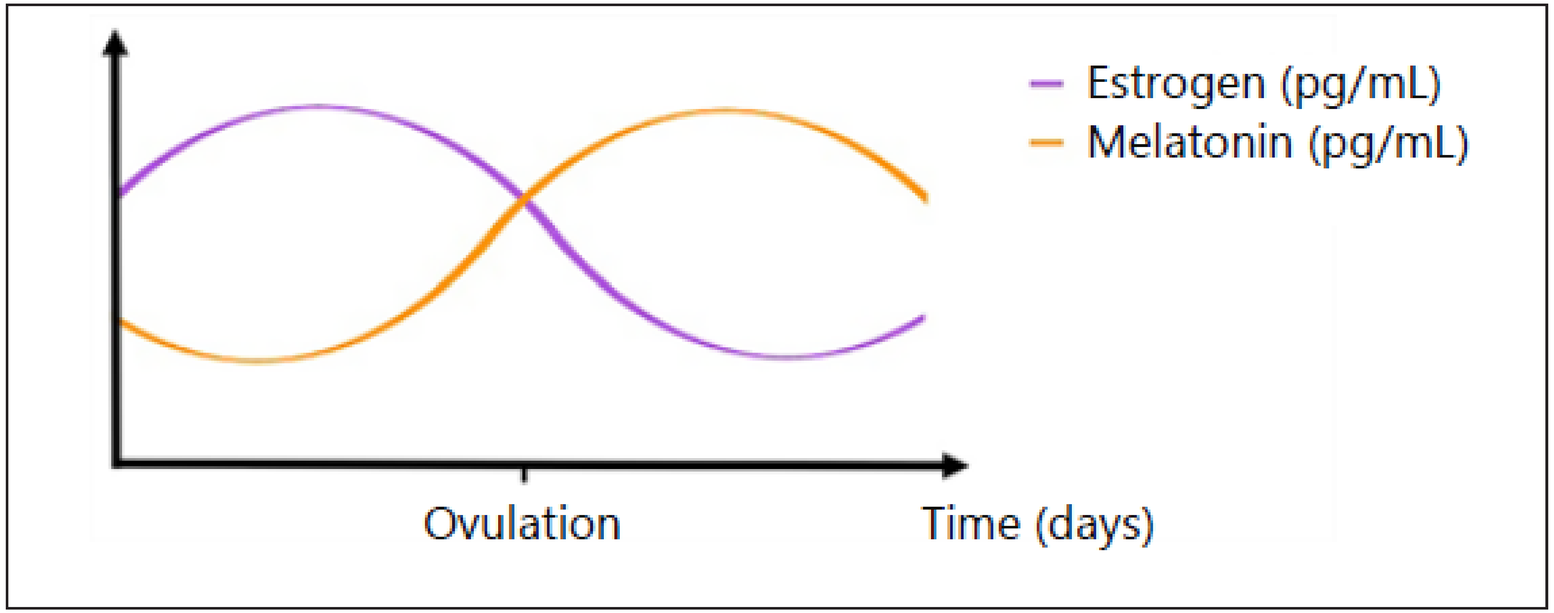
1.Gender ….

2.Study population

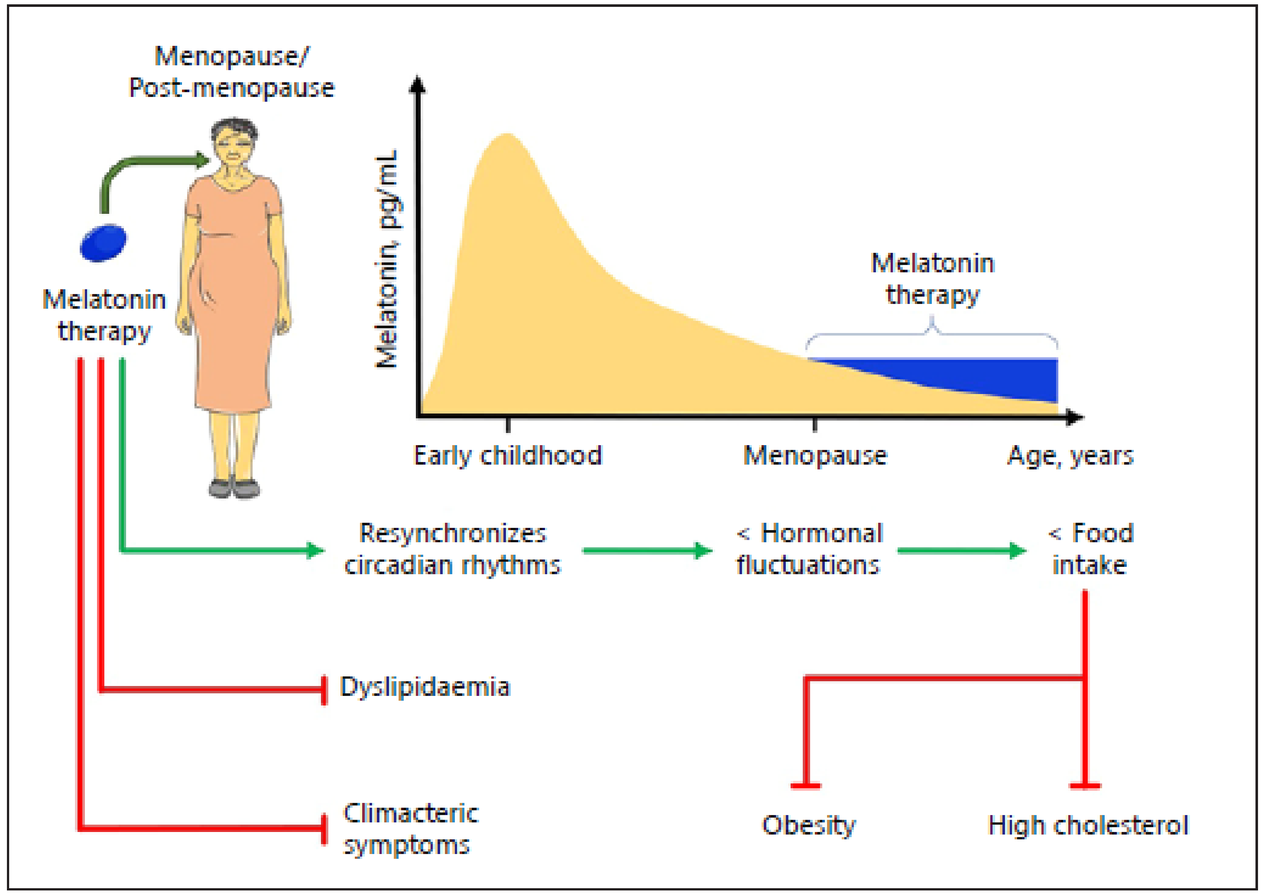
- ❑ Age
- ❑ Baseline levels of melatonin
- ❑ disease

Gender differences:

- hormonal birth control pills
- bidirectional communication



Age and Gender differences:



Discussion

10 weeks of daily melatonin administration:

- ✓ middleaged (10-month-old) male rats ⊣ intraabdominal fat, plasma leptin, and plasma insulin,

- ✓ Young adult (3-month-old) rats ⟷ same factors

<u>aging-associated decrease</u> in endogenous melatonin secretion.

Adiponectin

- high-fat diet and fasting resulted in disruptions of the circadian expression of adiponectin signaling components

- The rhythmicity is attenuated in obese subjects

- Whereas weight loss:
  - associated with the recovery of homeostatic control of adiponectin secretion
  - and with a rise in plasma adiponectin.

Concluaion

- To sum up, we can say that melatonin should be considered as a supplementary approach to alleviate obesity and related disease.
- It is recommended to consider the cost and limited evidence of habituation and tolerance.
- Further research is needed to examine the long-term benefits of melatonin on amelioration of obesity and related conditions.


Thank You
For Your
Attention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