

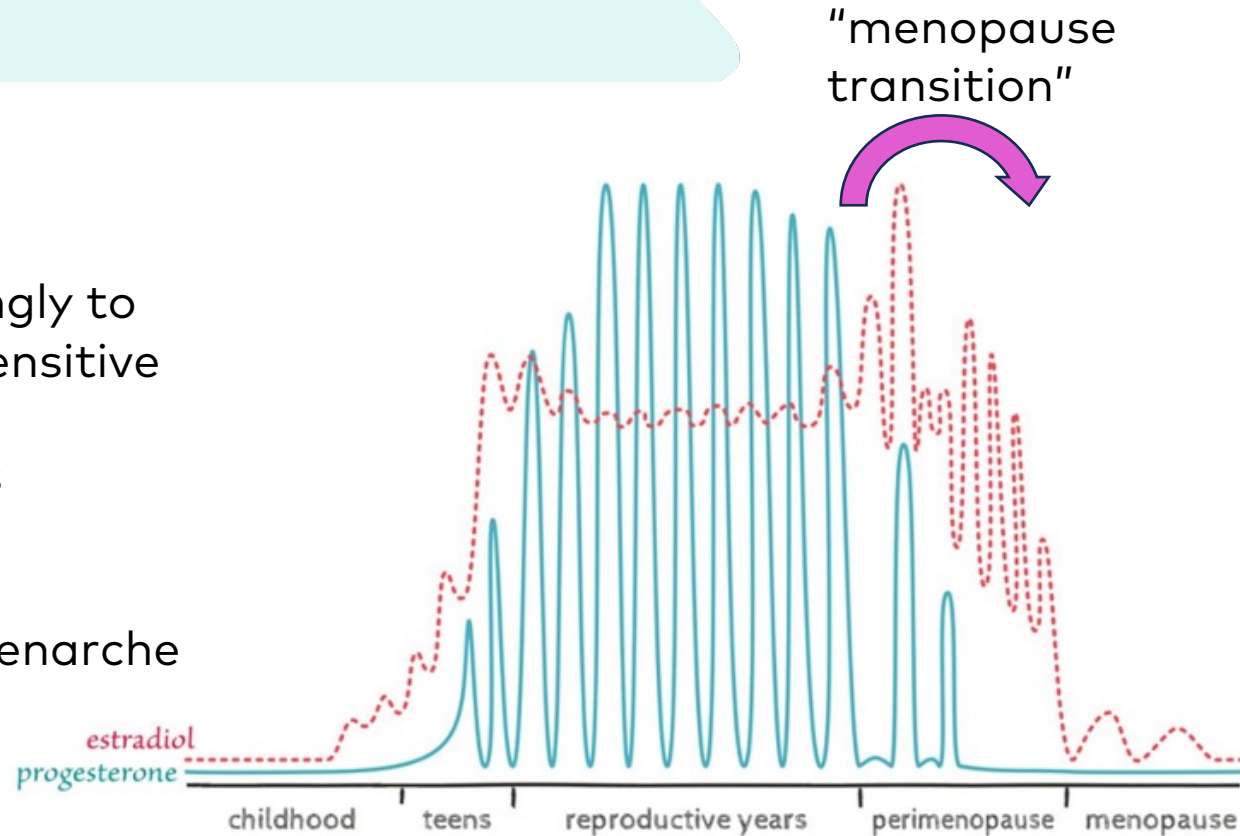
# The Roadmap Series

Mapping The Perimenopausal Metabolic Switch

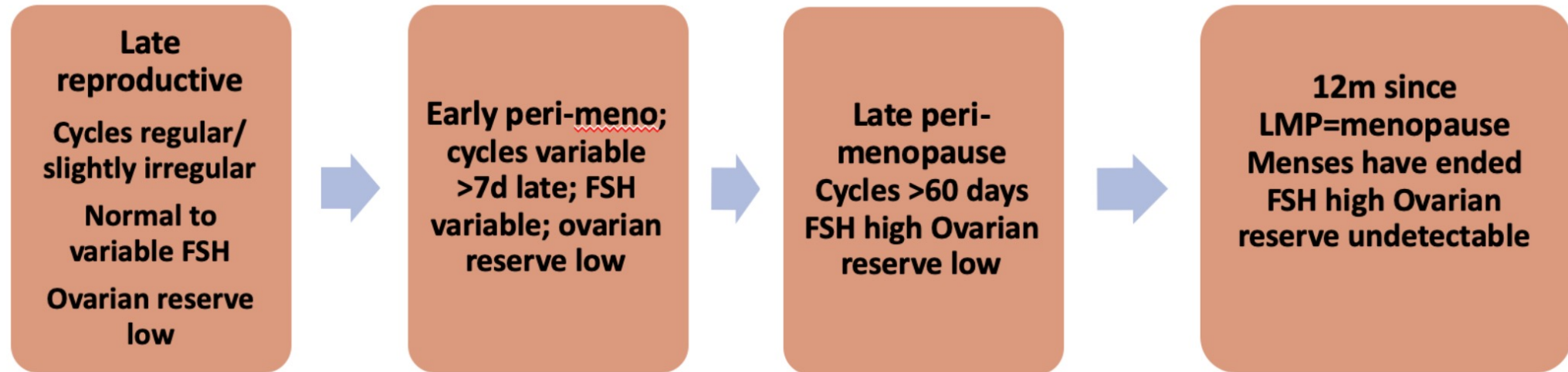
Tanya Borowski  
Head of Education

# The hormonal journey

- At a young age women react strongly to oestrogen - receptors are super sensitive
- Not ovulating to counterbalance oestrogen = heavy periods in teens
- Can take up to 12 years to mature menstrual cycle
- **Perimenopause** – the isomer of menarche



# menopause transition

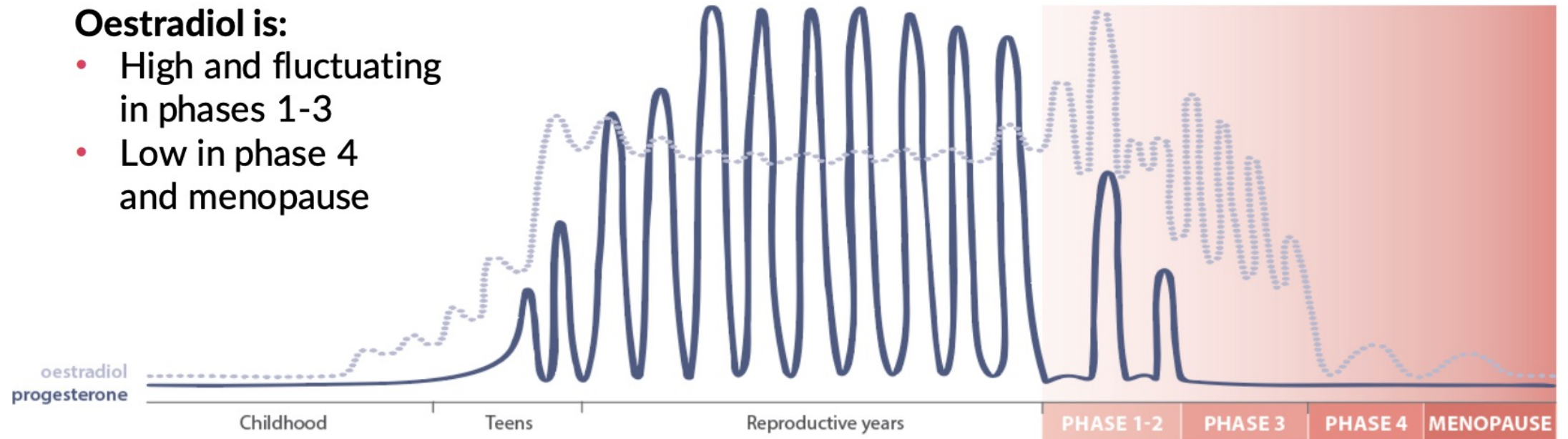


simplified timeline of the transition into menopause adapted from the *summary data of the Staging of Reproductive Aging Workshop* (<https://www.ncbi.nlm.nih.gov/pmc/art-cles/PMC3580996/>)

# menopause transition

## Oestradiol is:

- High and fluctuating in phases 1-3
- Low in phase 4 and menopause

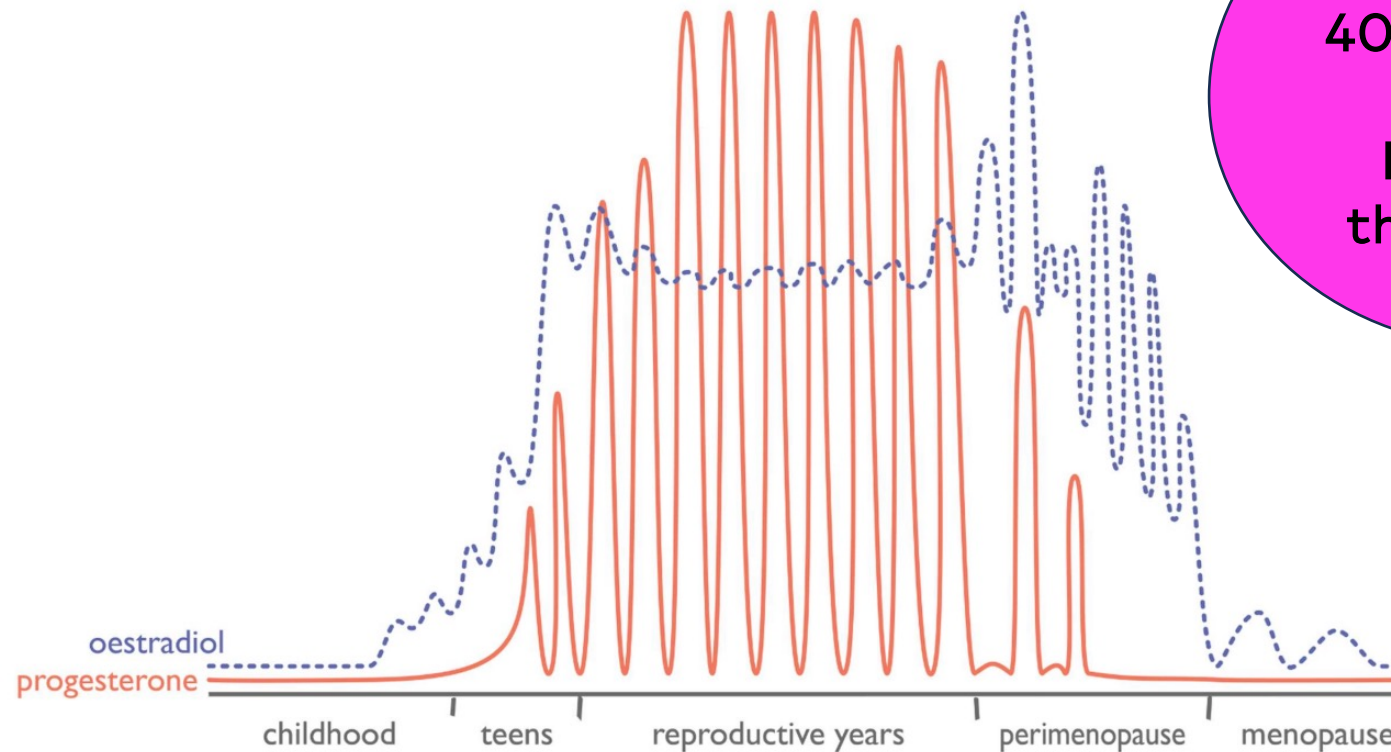


Ovarian hormones through the lifespan

(Lara Briden, 2021)

# menopause transition

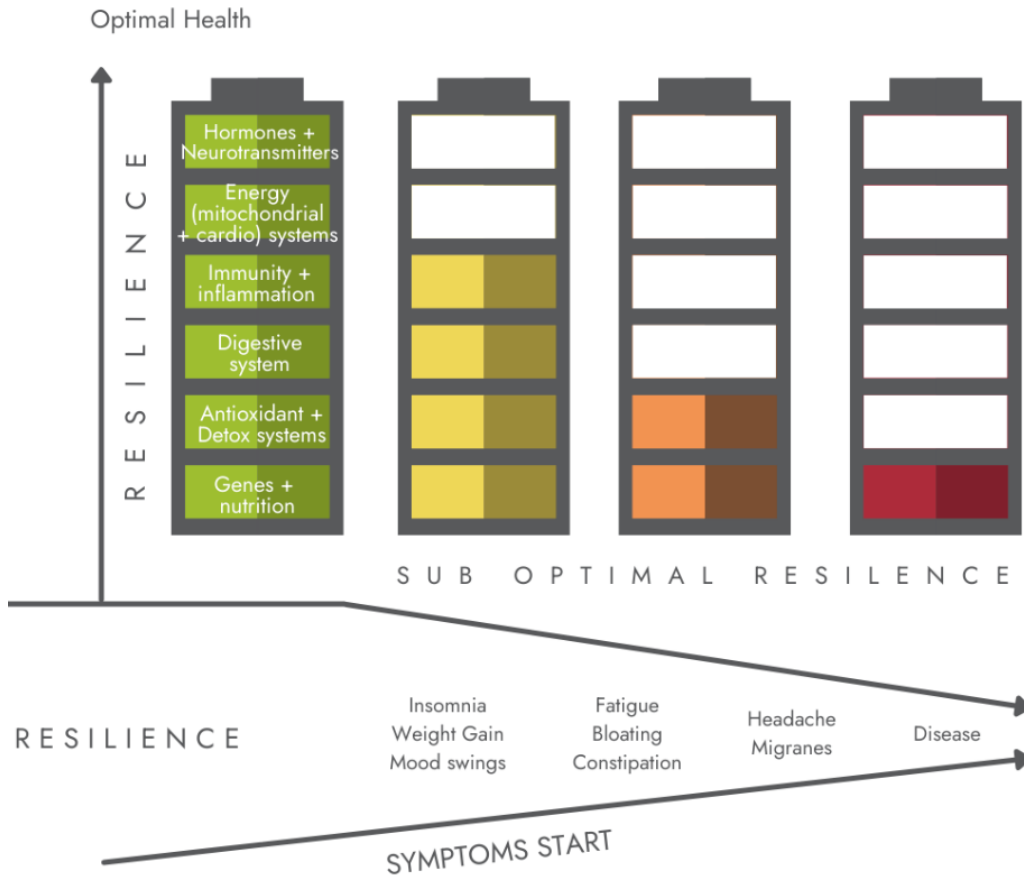
## -Perimenopause-



Women in 40's can have up to 3 x MORE E2 than in 30's

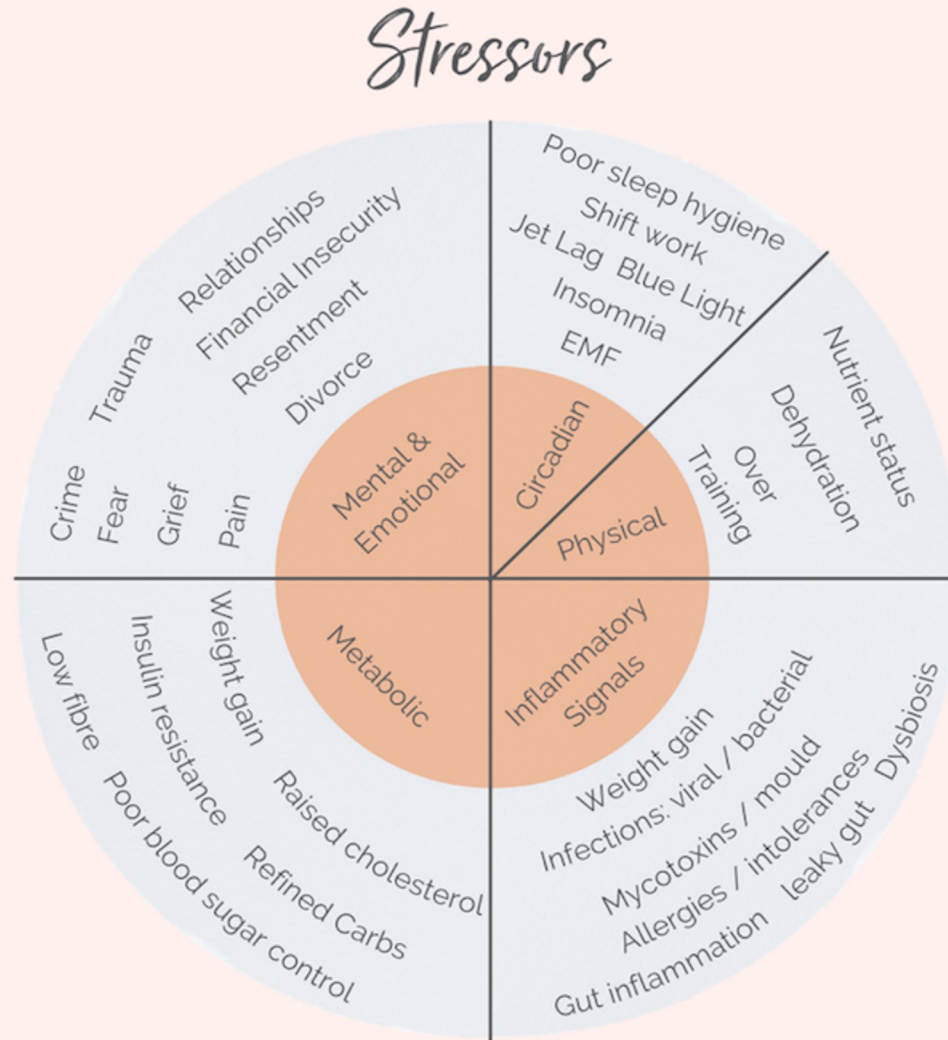
Building of metabolic reserve

# Metabolic Reserve



- Cell membrane integrity & receptor sensitivity
- Antioxidant Capacity
- Micronutrient reserves
- Mitochondrial capacity & health
- Digestive system and barriers
- Immune system
- Neuro-Endocrine systems
- Liver Detoxification
- Nutrigenomics

# Stressors & Metabolic Reserve



# menopause transition -Perimenopause-



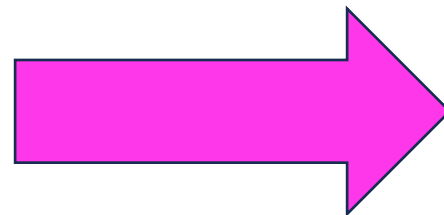
## Autoimmune Disease in Women: Endocrine Transition and Risk Across the Lifespan

Maunil K. Desai<sup>1</sup> and Roberta Diaz Brinton<sup>2</sup>

<sup>1</sup> School of Pharmacy, University of Southern California, Los Angeles, CA, United States, <sup>2</sup> School of Life Sciences, University of Arizona, Tucson, AZ, United States, <sup>3</sup> School of Medicine, University of Arizona, Tucson, AZ, United States

Women have a higher incidence and prevalence of autoimmune disease compared to men, and 85% or more patients of multiple autoimmune diseases. Autoimmune disease is associated with sweeping endocrinological changes at the time of menopause, with many women undergoing an additional transition: pregnancy, which may or may not be accompanied by breastfeeding. These endocrinological transitions

“...hormonal flux in susceptible women may trigger downstream changes that disturb the fragile balance between inflammation and immune regulation.”



### Midlife Aging

40 - 65 Years Old

#### The Menopause Transition

- Heterogeneous patterns of E2 decline and FSH rise
- Menstrual cycle irregularity
- Between-woman heterogeneity is related to factors such as race/ethnicity

Changes in Symptoms and Mental Health

- ↑ Depression and Anxiety *Transient*
- ↑ Urinary Incontinence
- ↓ Cognitive Performance (After Menopause)
- ↑ Vasomotor Symptoms (Hot Flashes and Night Sweats) *Transient*
- ↑ Sleep Complaints
- ↑ Cognitive Difficulties *Transient*
- ↑ Vaginal Dryness
- ↑ Sexual Pain ↓ Sexual Desire

Changes in Physiological Systems and Functions

- ↓ Physical Function Performance *Transient*
- ↑ Lipids ↑ Vascular Remodeling ↑ Metabolic Syndrome
- ↑ Body Mass Index ↑ Blood Pressure
- ↓ Bone Mineral Density
- ↓ Lean Mass ↑ Fat Mass

Window of Opportunity

+ Awareness  
Adopt health behaviors  
Design early preventive practices



# Menopause, high-risk stage



Metabolic dysfunction  
& Insulin Resistance



Sarcopenic  
Obesity



Chronic Inflammation

So whats going on ..... Why do these occur

# Divya Oestrogen – except when unopposed

## Oestrogen is our beauty & vitality hormone:

- Creates an hourglass shape
- Promotes insulin sensitivity
- Supports healthy muscle mass- essential for metabolism
- Maintains metabolic rate
- Acts as a natural appetite suppressant

## But, when high and fluctuating:

- Climacteric symptoms
- Sleep disturbances and migraines
- Heavier periods and pain
- Weight gain
- Mood disturbances

# Main factors contributing menopausal body composition changes

## Genetic Factors

- Genetic predisposition
- Ethnicity
- Epigenetic changes  
(Lifecode Metabolics Panel)

## Hormonal Factors

- Rapid hypoestrogenaemia
- Relative hyperandrogenemia
- Low SHBG levels

## Stressors

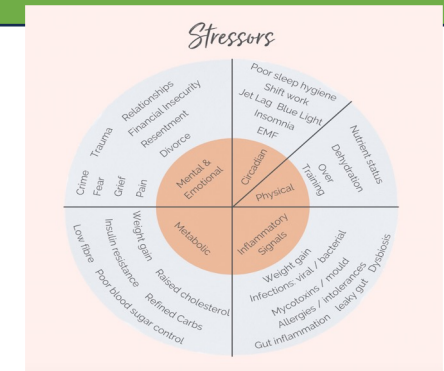
- Poor nutrition/alcohol
- Low physical activity
- Medications
- Diseases
- And on.....



Increase in body weight

Increase and redistribution of fat mass (from gynoid to abdominal obesity)

Decrease in fat-free mass



# Common challenges- Solutions

1

Sarcopenia

2

Insulin Resistance  
&  
Metabolic dysfunction

3

Chronic Inflammation  
&  
Weight gain

# Sarcopenia

"It is known that the decline of oestrogen levels and receptors contributes to the loss of muscle function and the development of sarcopenia in postmenopausal women".

Buckinx and Aubertin-Leheudre, 2022

# Sarcopenia



International Journal of Women's Health

Dovepress

open access to scientific and medical research

 Open Access Full Text Article

REVIEW

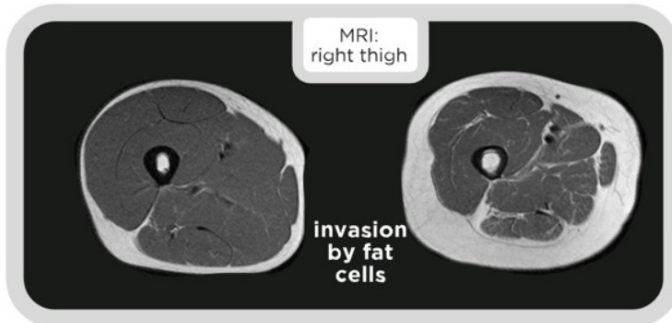
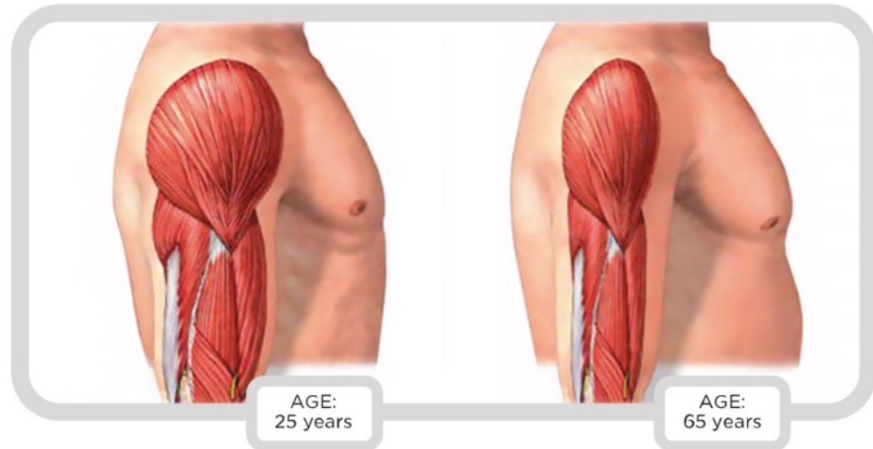
## Sarcopenia in Menopausal Women: Current Perspectives

Fanny Buckinx<sup>1,2</sup>, Mylène Aubertin-Leheudre<sup>1,2</sup>

'During the menopausal transition, lean body mass decreased by 0.5% (annually) while fat mass increased by 1.7% per year... being postmenopausal is associated with a **higher risk of presenting with sarcopenia.**'

# Sarcopenia = Osteoporosis of muscle

Physically inactive women can lose as much as 5% of their muscle mass each decade after age 30.



- ↓ Muscle fibre number and size
- ↓ Muscle strength, power, anaerobic capacity
- ↓ Anabolic hormones
- ↓ Physical activity

↓ Muscle mass

- ↓ Physical activity
- ↑ Risk for fall and fractures

- ↑ Pro-inflammatory milieu
- ↑ Oxidative stress
- ↑ Insulin resistance
- ↓ Resting energy expenditure

↑ Adipose tissue

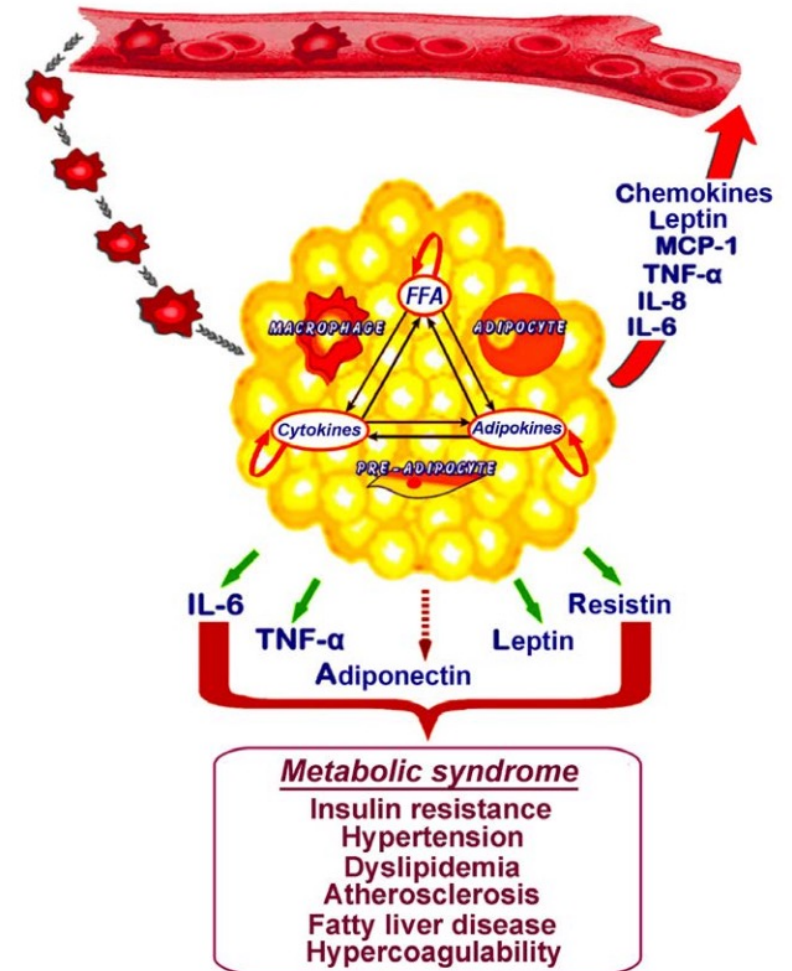
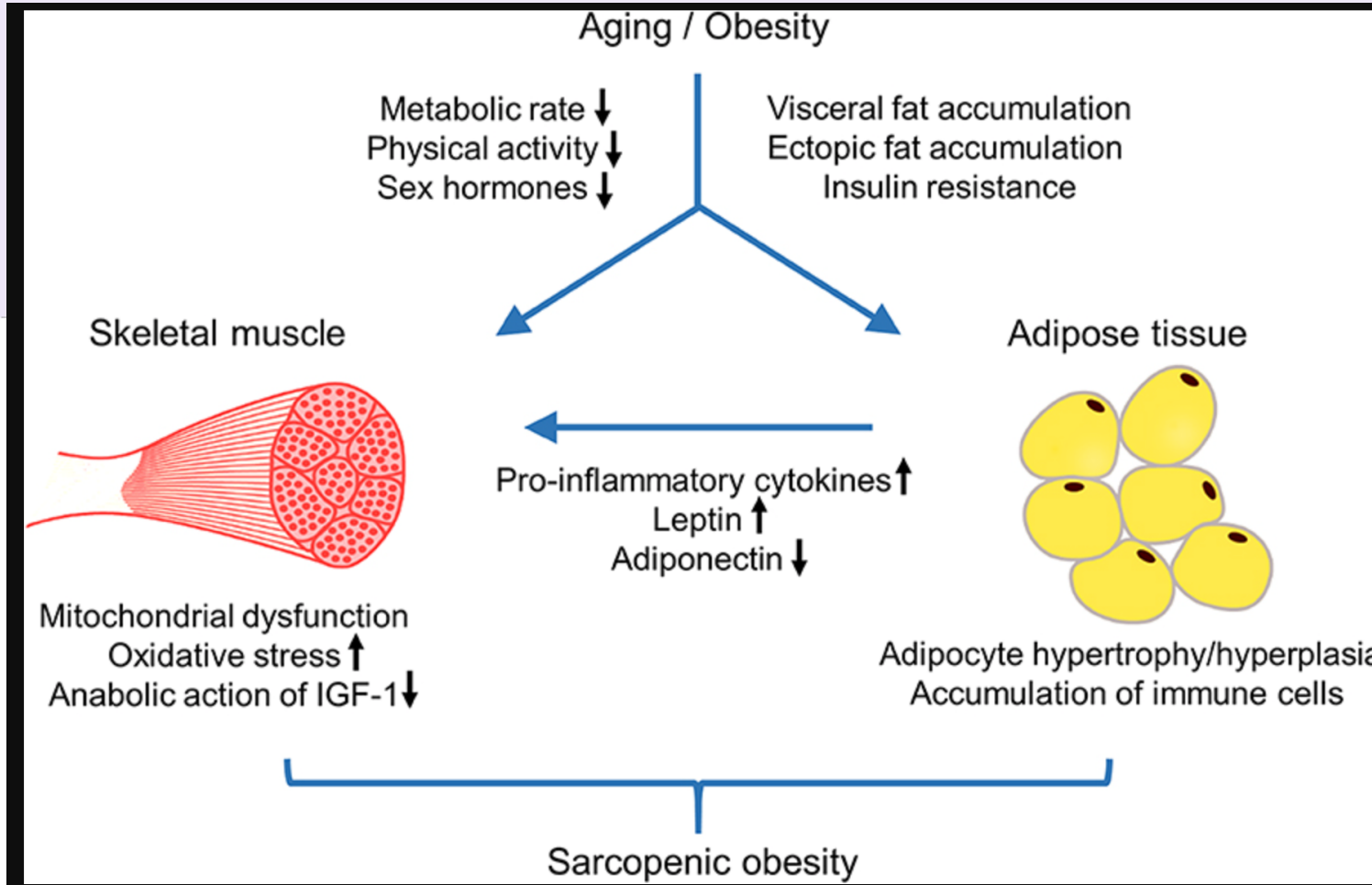
- ↓ GH, ↓ IGF
- Inflammation

- Fat infiltration → ↑ IMAT
- ↓ Lipid oxidation

- ↑ ROS production
- ↓ Osteoblast activity
- ↑ Osteoclast activity

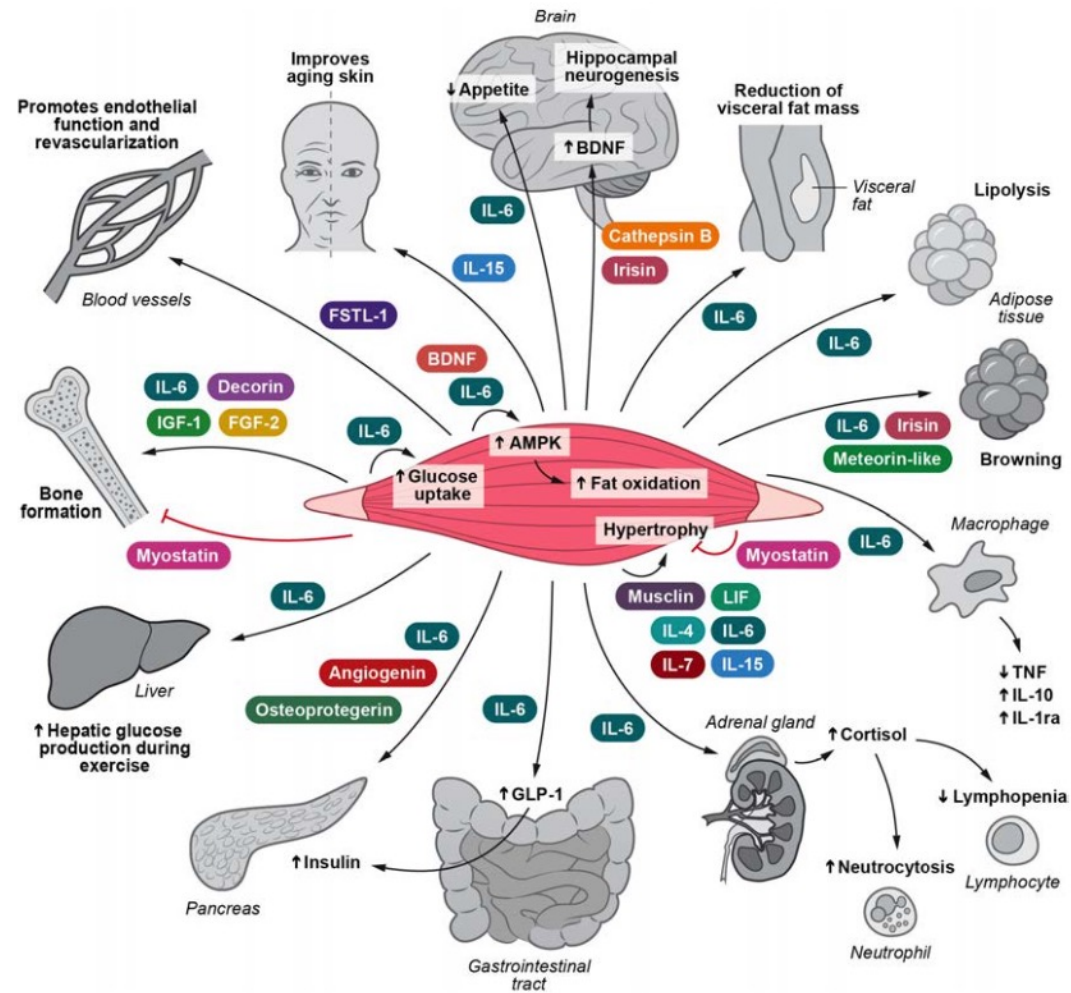
↓ Bone mineral density

# Sarcopenia obesity





# Muscle Activation & Immuno-metabolic Modulation

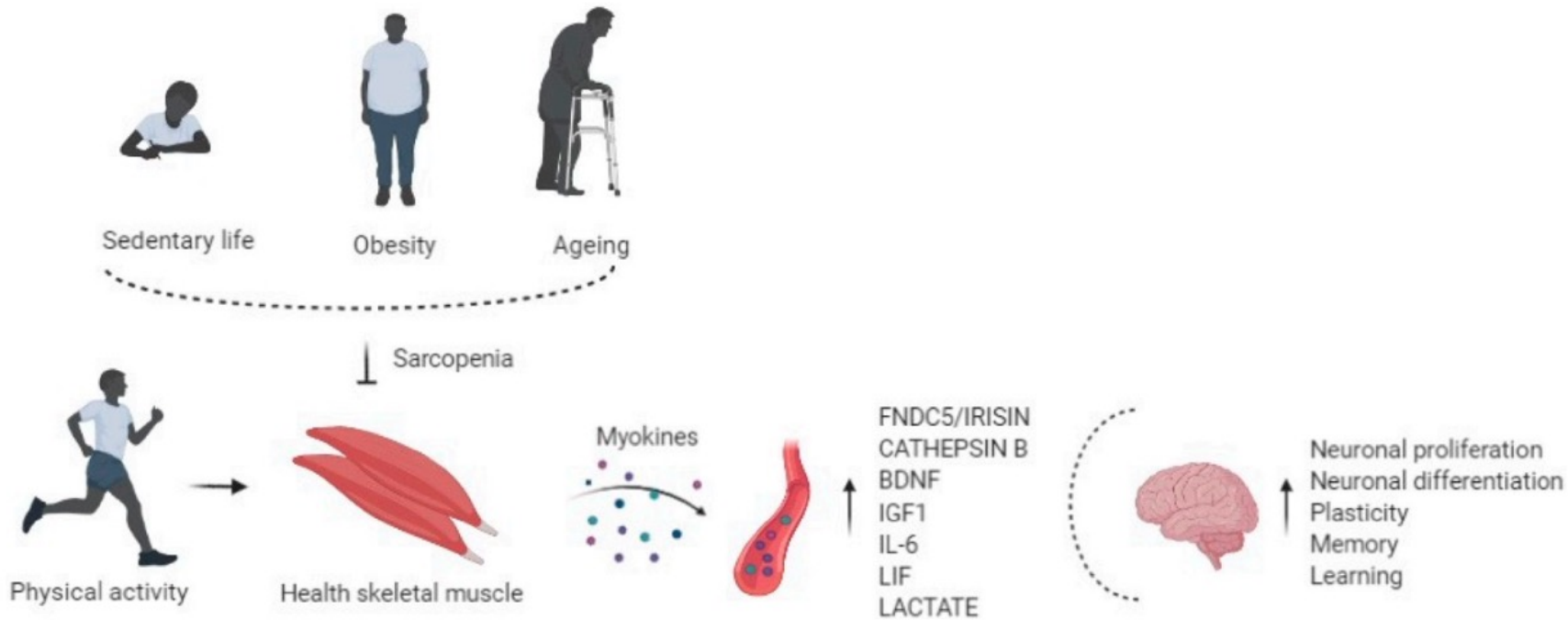


Muscle-Organ Crosstalk: Focus on Immunometabolism

Immunometabolism.  
Front. Physiol. 11:567881.



# Muscle – Myokines – Brain Functionality

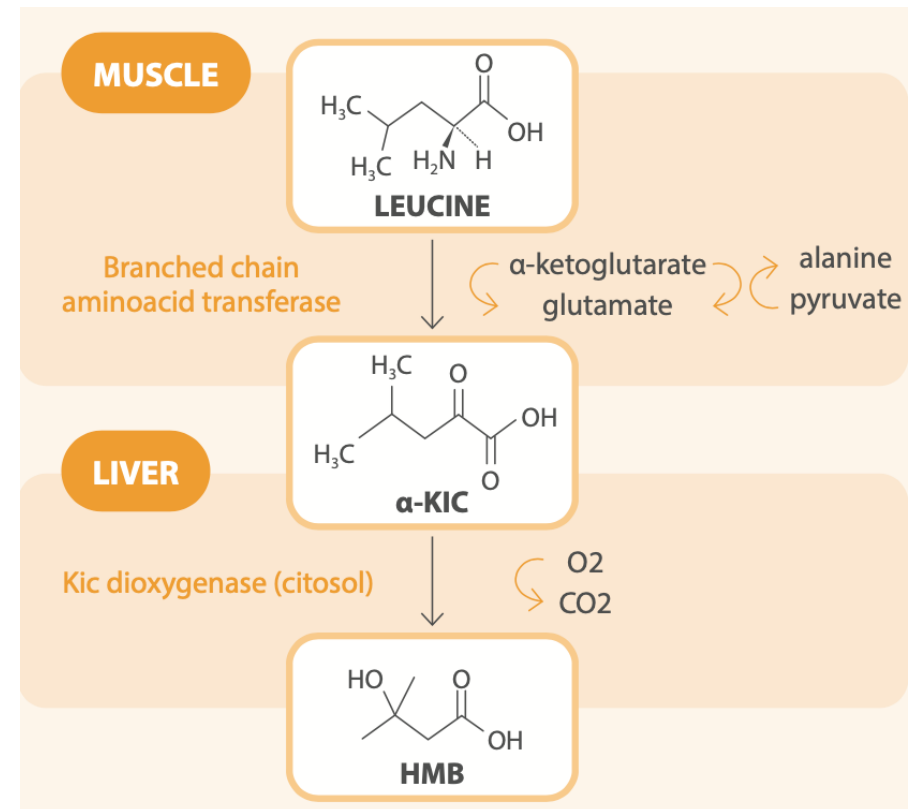


“Physical activity enhances circulating levels of myokines in the bloodstream, affects the brain regulating neuronal proliferation and differentiation, plasticity, memory, and learning.”

# HMB

beta-hydroxy beta-methylbutyrate

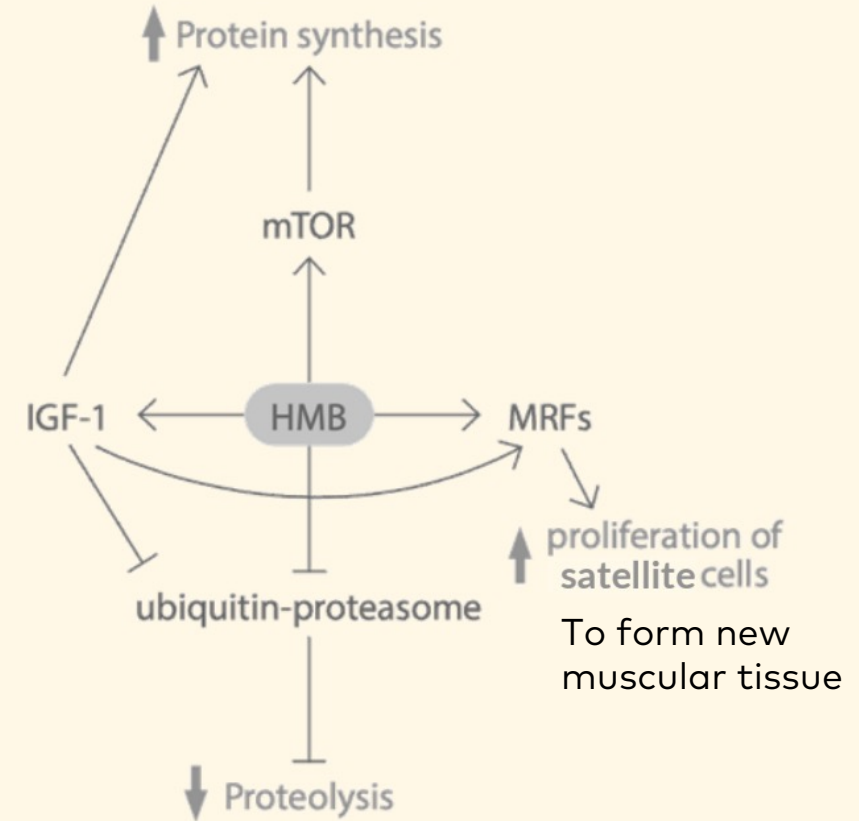
It has been estimated that approximately 2–10% of leucine is oxidised into HMB.



# HMB

beta-hydroxy beta-methylbutyrate

- Supercharges muscle gains, with or without exercise
- Improves lean body mass
- Mitigates the attack on muscle, even as we sleep



bioconcepts

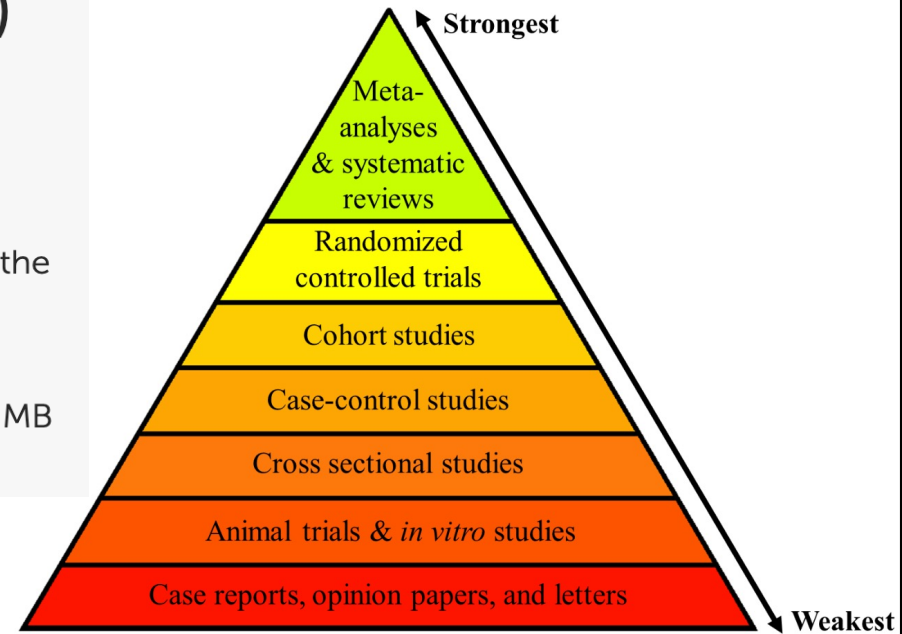
# Potential in sarcopenia



## Effect of $\beta$ -hydroxy- $\beta$ -methylbutyrate (HMB) on the Muscle Strength in the Elderly Population: A Meta-Analysis

**Results:** A total of 9 randomized controlled trials (RCT) studies were included in the study, which comprised 896 subjects. The overall impact on muscle strength-related indicators (SMD = 0.41; 95% CI: 0.28, 0.54);  $p < 0.00001$ ) was statistically significant. Conclusion: Supplementation of HMB and preparations containing HMB ingredients aid in increasing muscle strength in the elderly population.

Hierarchy of Scientific Evidence



# HMB combined with exercise

The purpose of this study was to determine whether HMB would similarly benefit 70-y-old adults undergoing a 5 d/wk exercise program. Thirty-one men ( $n = 15$ ) and women ( $n = 16$ ) ( $70 \pm 1$  y) were randomly assigned in a double-blind study to receive either capsules containing a [placebo](#) or Ca-HMB (3 g/d) for the 8-wk study



The Journal of Nutrition  
Volume 131, Issue 7, July 2001, Pages 2049-2052



## Body Composition in 70-Year-Old Adults Responds to Dietary $\beta$ -Hydroxy- $\beta$ -Methylbutyrate Similarly to That of Young Adults 1

[Yukovich Matthew D.](#)  , [Stubbs Nancy B.](#)\*, [Bohlken Ruth M.](#)\*

### Results

Fat-free mass gain ( $P=0.08$ ) and percentage of body fat loss ( $P = 0.05$ )

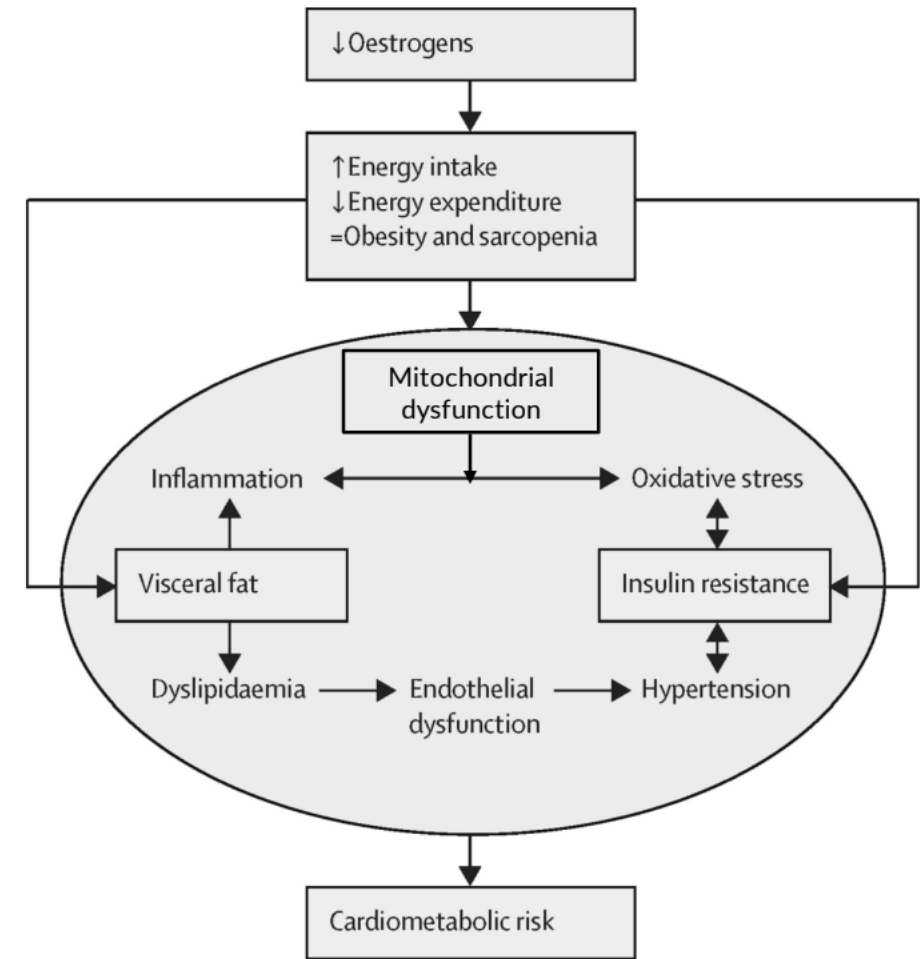
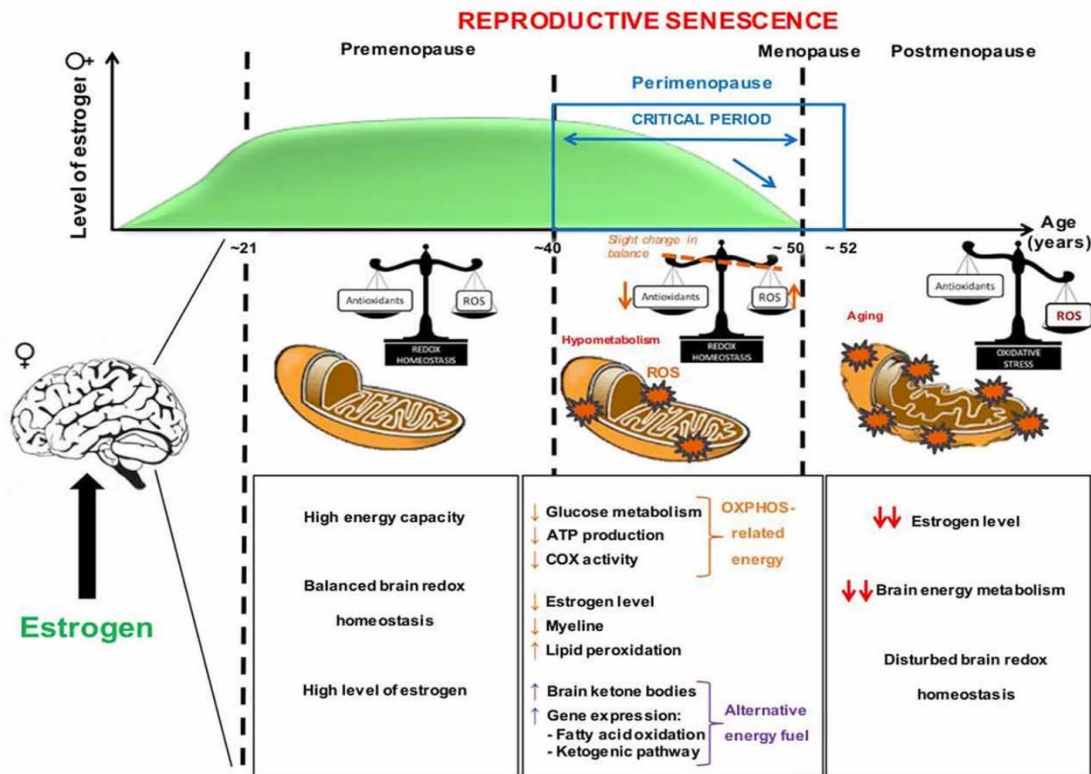
# Menopause: a metabolic transition

## Menopause: a cardiometabolic transition

Prof Rossella E Nappi, MD • Prof Peter Chedraui, MD • Prof Irene Lambrinoudaki, MD •

Prof Tommaso Simoncini, MD

Published: May 05, 2022 • DOI: [https://doi.org/10.1016/S2213-8587\(22\)00076-6](https://doi.org/10.1016/S2213-8587(22)00076-6) • Check for updates



## 'EARLY' PERIMENOPAUSE



### Hormones\*

↔ E<sub>2</sub> (relatively unchanged)

↑ FSH \*

### CVD Risk Factors

↑ C-IMT and vascular remodeling

↓ Endothelial function (FMD)

**NOTE:** Few studies of women in *early perimenopause* have been conducted due to the inherent difficulty in categorizing women in this earlier stage. As a result, the cardiometabolic changes that occur during *early perimenopause* have yet to be fully elucidated.

## 'LATE' PERIMENOPAUSE



### Hormones\*

↓ E<sub>2</sub> \* and AMH

↑ FSH \*

### Body Composition

↑ Fat mass (abdominal fat)

↓ Fat-free (lean) mass

### Energy Intake & Expenditure



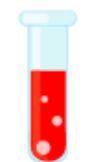
24-h, Sleep, & Physical Activity EE

Resting EE (?)

Fat oxidation

Energy Intake

### Cardiovascular Risk Factors



↑ Dyslipidemia  
(mostly within 1-year of FMP)

↑ C-IMT, Aortic PWV, and  
vascular remodeling

↓ Endothelial function (FMD)  
and cardiac health

↑ Insulin resistance

↑ Sleep disturbances



# Myo-inositol

## Inositols in Midlife

Kalra, Sanjay; Kalra, Bharti<sup>1</sup>

[Author Information](#) ✓

*Journal of Mid-life Health* 9(1):p 36-38, Jan-Mar 2018. | DOI: 10.4103/jmh.JMH\_52\_16

This review describes the mechanistic, animal, and clinical data related to the use of inositols in midlife. It covers studies related to the mechanism of action of myo-inositol and D-chiro-inositol and randomized controlled trials conducted in postmenopausal women with metabolic syndrome and supports these data with the results of *in vitro* and animal studies on inositol in nephropathy and other related conditions. Recent advances related to biochemistry, pharmaceutical science, and genetics are discussed. It concludes that inositols have a potential role to play in maintaining metabolic health in postmenopausal women.

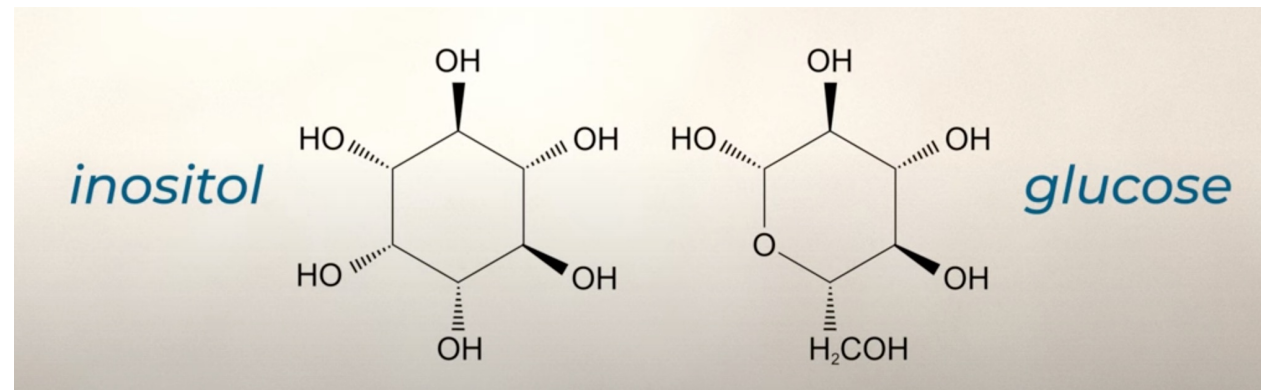


# Myo-inositol



*Inositols are small molecules similar to sugar*

- myo-inositol is the most abundant isomer makes up 95% in the body
- myo-inositol is an intracellular 2<sup>nd</sup> messenger for hormones, especially insulin , FSH and TSH
- Being a 2<sup>nd</sup> messenger for insulin facilitates a normal response to insulin and thereby improving insulin sensitivity



# Inositol

## Combination of inositol and alpha lipoic acid in metabolic syndrome-affected women: a randomized placebo-controlled trial

**Myo-inositol** 2g BD- 6mths

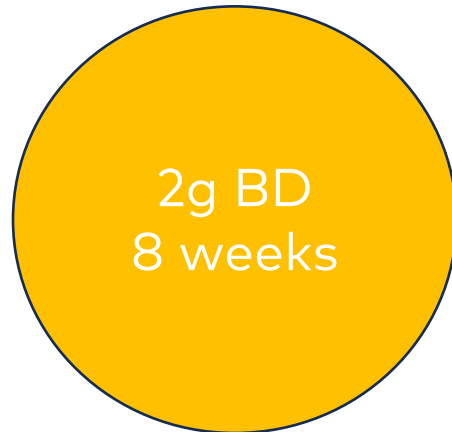
"A significant HOMA-IR reduction of more than 20% was evidenced in 66.7% ( $P < 0.0001$ ) of patients, associated with a serum insulin level decrease in 89.3% ( $P < 0.0000$ ). A decrease in triglycerides was evidenced in 43.2% of patients consuming the supplement ( $P < 0.0001$ ). An increase in HDL cholesterol (48.6%) was found in the group consuming inositol with respect to the placebo group. A reduction in waist circumference and waist-hip ratio was found in the treated group with respect to the placebo group".

### Significant results observed in:

- Reduction of more than 20% of the HOMA-IR index
- Reduction of triglycerides
- Improvement of HDL-C levels
- Reduction of anthropometric features such as BMI, WHR

# Myo-inositol supplementation improves cardiometabolic factors, anthropometric measures, and liver function in obese patients with non-alcoholic fatty liver disease

Sara Arefhosseini<sup>1</sup>, Neda Roshanravan<sup>2</sup>, Helda Tutunchi<sup>3</sup>, Somayyeh Rostami<sup>1</sup>, Manuchehr Khoshbaten<sup>4</sup> and Mehrangiz Ebrahimi-Mameghani<sup>5\*</sup>



- Anthropometric measures decreased significantly
- Weight reduction (P=0.049)
- Systolic blood pressure (P=0.006)
- Reductions in serum fasting insulin (p=0.008)
- Reductions in HOMA-IR (P=0.046)
- Significant improvements in lipid profile, liver enzymes, AST, ALT and serum ferritin

# Myo-Inositol Thyroid & BMI

## Specifically, myo-inositol may help with weight loss in several ways:

- By supporting and balancing thyroid function
- By Improving sensitivity to thyroid hormone
- By reducing insulin resistance and lowering blood sugar levels
- By reducing the increases in insulin after glucose intake

## Body Mass Index

Obesity Science and Practice  
Open Access



REVIEW | [Open Access](#) |

## Inositol supplementation and body mass index: A systematic review and meta-analysis of randomized clinical trials

Meysam Zarezadeh , Azadeh Dehghani, Amir Hossein Faghfour, Nima Radkhah, Mohammad Naemi Kermanshahi, Fatemeh Hamed Kalajahi ... [See all authors](#)

First published: 10 October 2021 | <https://doi.org/10.1002/osp4.569> | Citations: 3

## Thyroid Dysfunction

frontiers  
in Endocrinology

REVIEW  
published: 10 May 2021  
doi: 10.3389/fendo.2021.662582



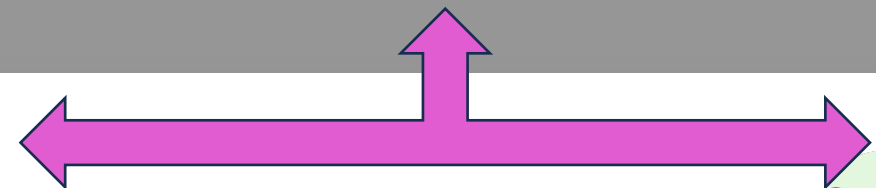
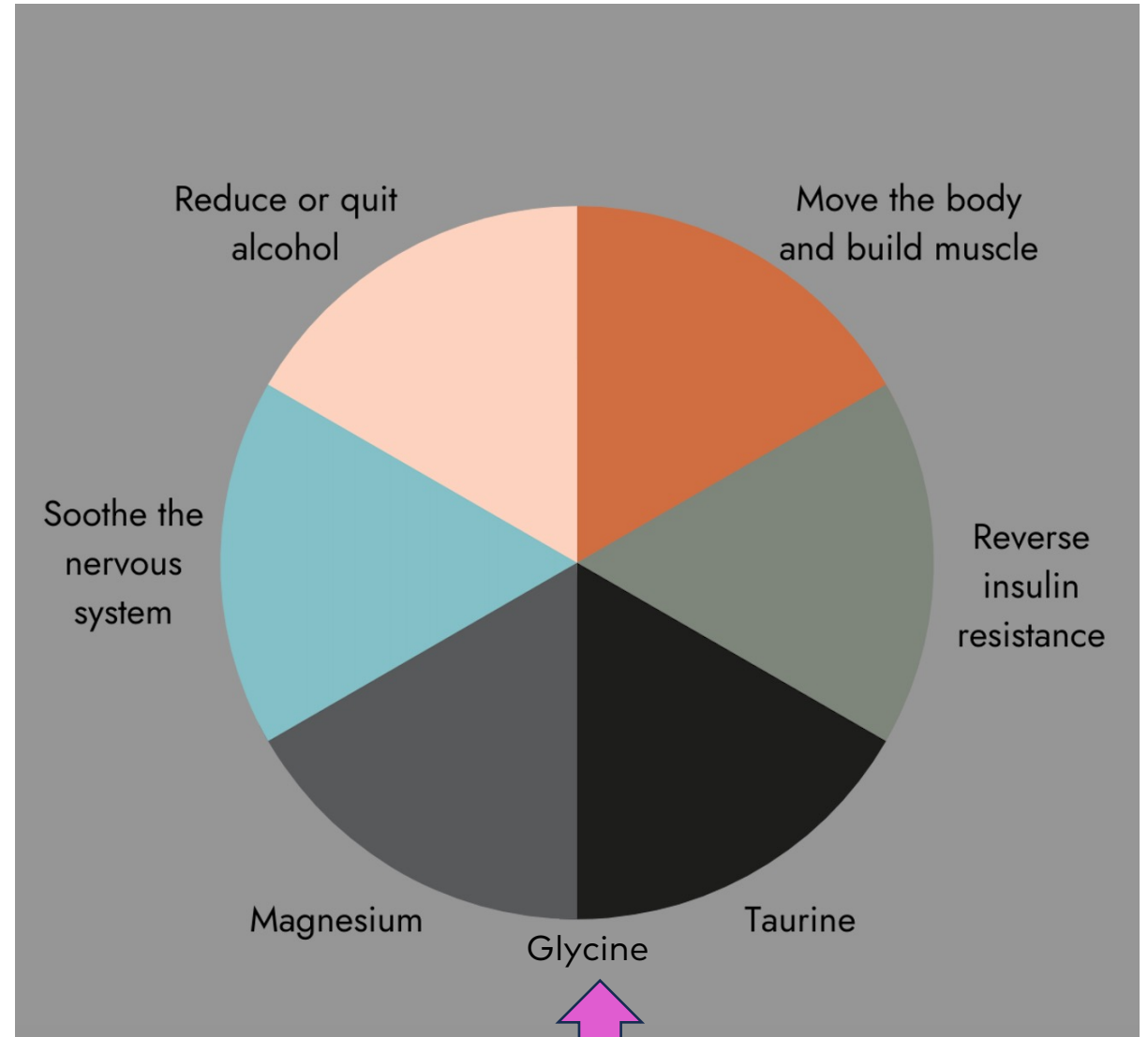
## The Role of Inositol in Thyroid Physiology and in Subclinical Hypothyroidism Management

Salvatore Benvenga<sup>1,2</sup>, Maurizio Nordio<sup>2,3</sup>, Antonio Simone Laganà<sup>2,4</sup> and Vittorio Unfer<sup>2,5\*</sup>

amrita

# The Perimenopause Essentials

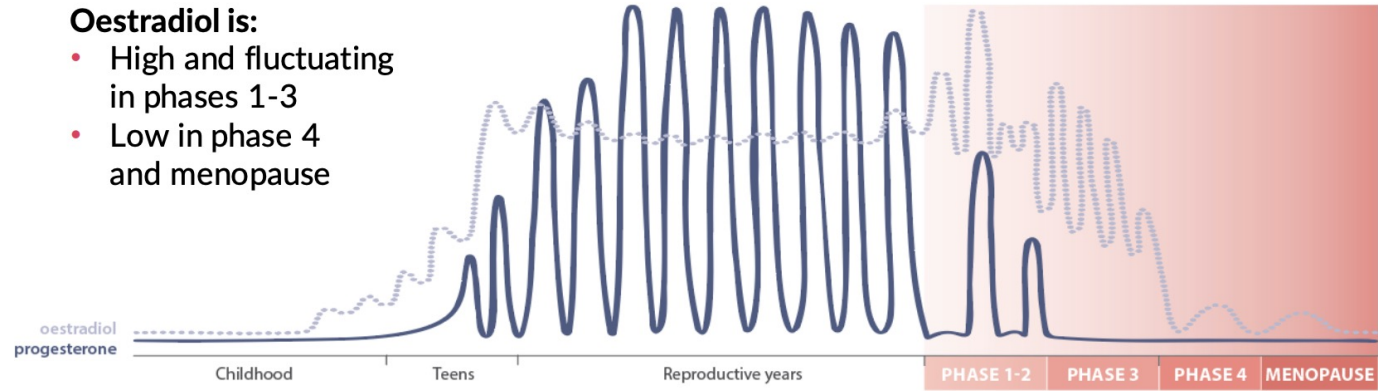
- Magnesium
- Glycine
- Taurine



# Resilience & Perimenopause

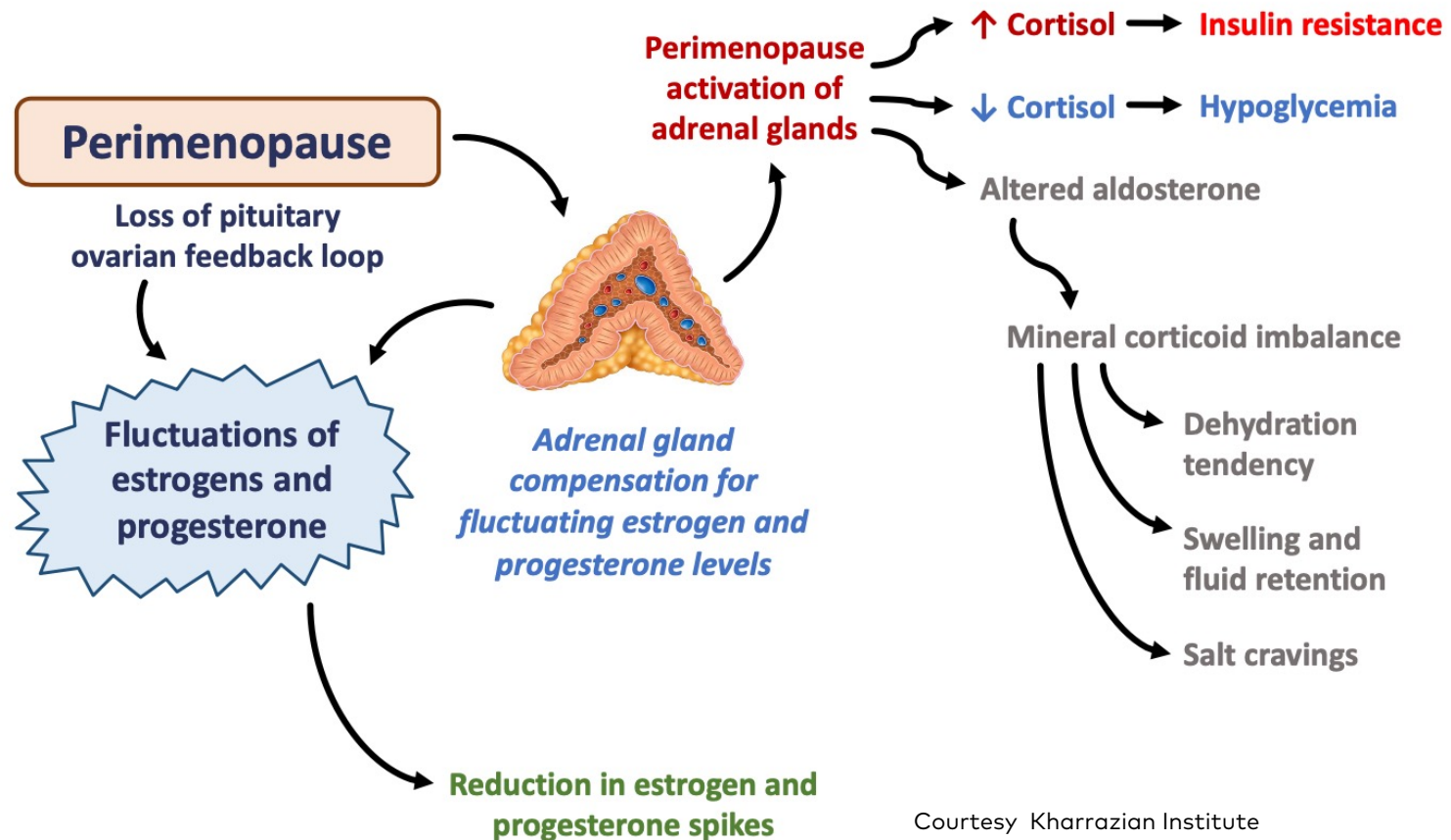
Oestradiol is:

- High and fluctuating in phases 1-3
- Low in phase 4 and menopause



Ovarian hormones through the lifespan

(Lara Briden, 2021)

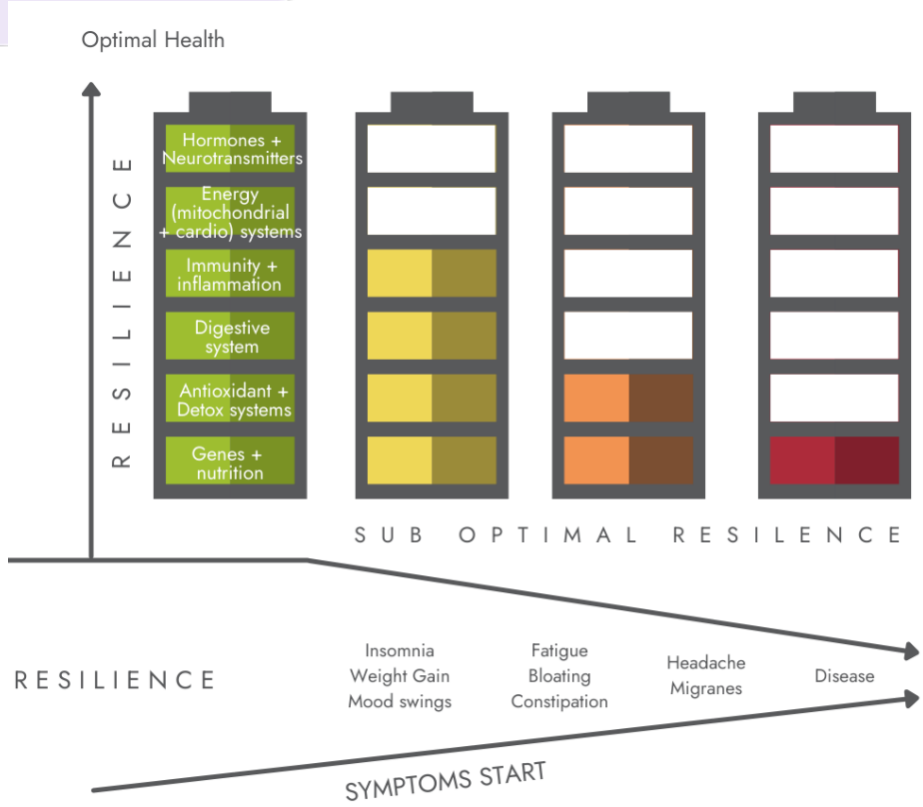


# Nutraceuticals to support Stress



- Rhodiola
- Holy basil
- Panax ginseng
- Ashwagandha
- Relora (Magnolia & phellodendron )
- L-Theanine
- Phosphatidylserine

BUT..... Nothing without **METABOLIC RESERVE**  
And **resilience**





# Magnesium

- ✓ Improves metabolic markers
- ✓ Fuels mitochondria- ATP production
- ✓ Improves glucose homeostasis and insulin sensitivity
- ✓ Supports oestrogen detoxification
- ✓ Supports thyroid health
- ✓ Stabilises the HPA axis
- ✓ Increases vitamin D uptake
- ✓ Calms the nervous system

300-600mg  
glycinate  
daily



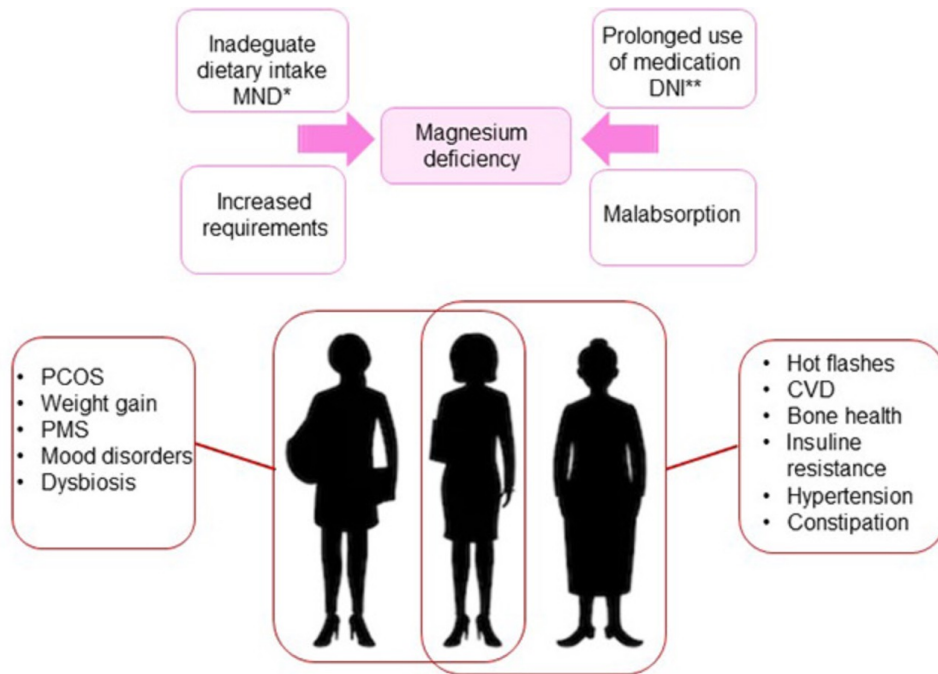
# Magnesium Research



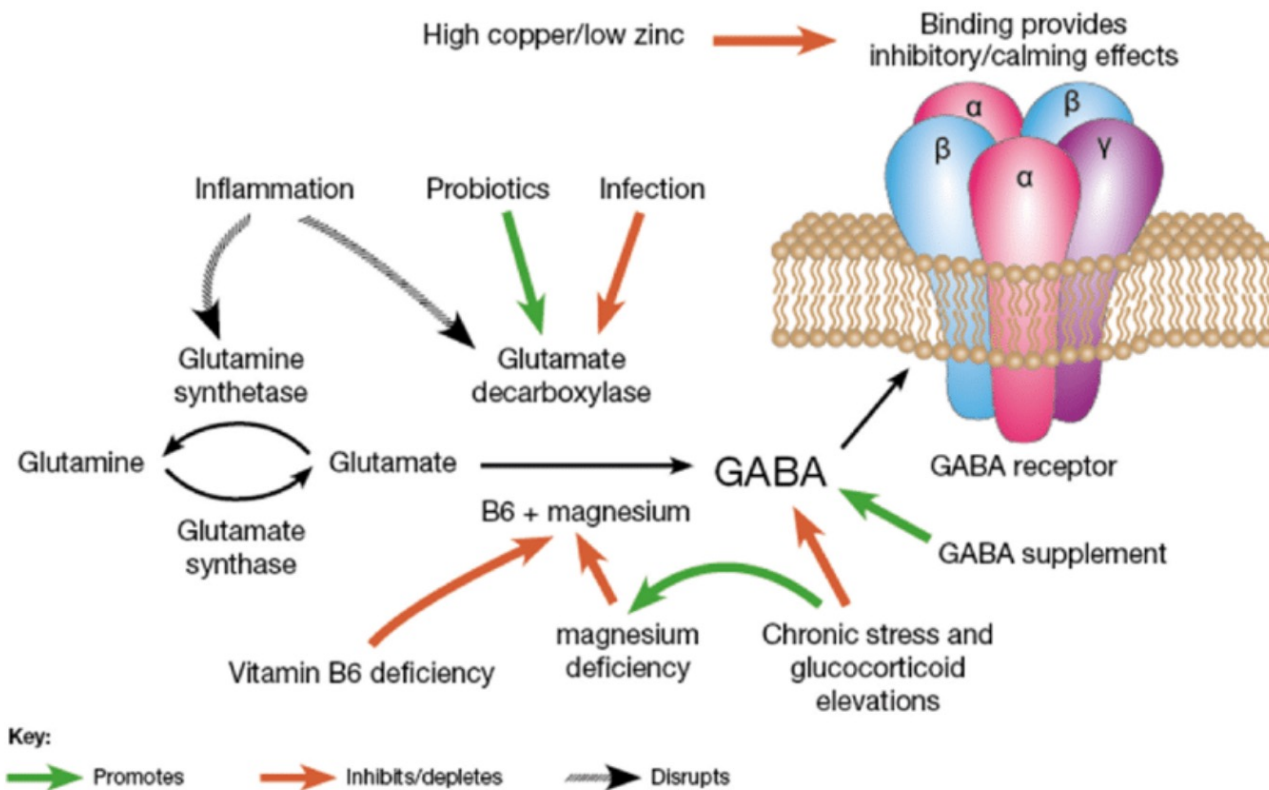
## Effect of magnesium supplementation on women's health and well-being

Debora Porri <sup>a,\*</sup>, Hans K. Biesalski <sup>b</sup>, Antonio Limitone <sup>c</sup>, Laura Bertuzzo <sup>c</sup>, Hellas Cena <sup>a,d</sup>

<sup>a</sup> Laboratory of Dietetics and Clinical Nutrition, Department of Public Health, Experimental and Forensic Medicine, University of Pavia, 27100 Pavia, Italy



# Magnesium Research



# Taurine

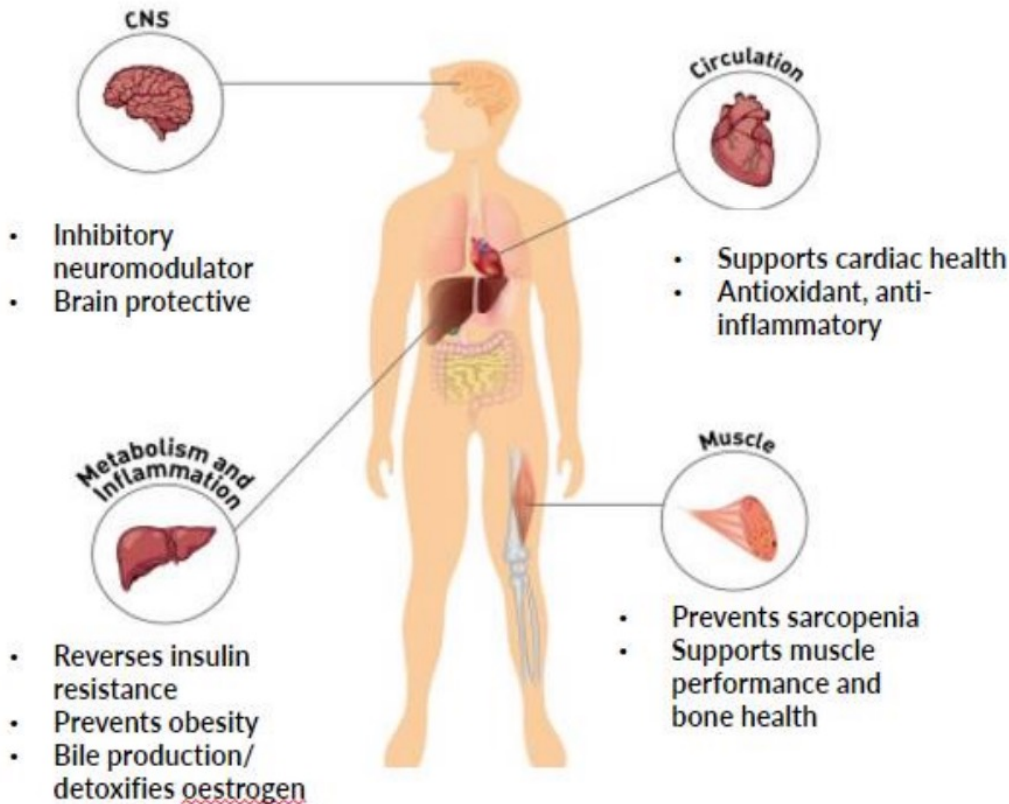
- ✓ Promotes oestrogen detoxification
- ✓ Supports mitochondrial function; inhibits ROS
- ✓ Improves insulin sensitivity
- ✓ Anti-inflammatory, quenches oxidative stress
  - ✓ Counteracts bone mineral density loss



2-4g daily

**amrita**

# Taurine Research



Amino Acids  
<https://doi.org/10.1007/s00726-020-02859-8>

ORIGINAL ARTICLE



The effects of taurine supplementation on glycemic control and serum lipid profile in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial

Vahid Maleki<sup>1,2</sup> · Mohammad Alizadeh<sup>3</sup> · Fatemeh Esmaeili<sup>2</sup> · Reza Mahdavi<sup>3</sup>

Received: 6 October 2019 / Accepted: 18 May 2020  
© Springer-Verlag GmbH Austria, part of Springer Nature 2020

## After 8 weeks:

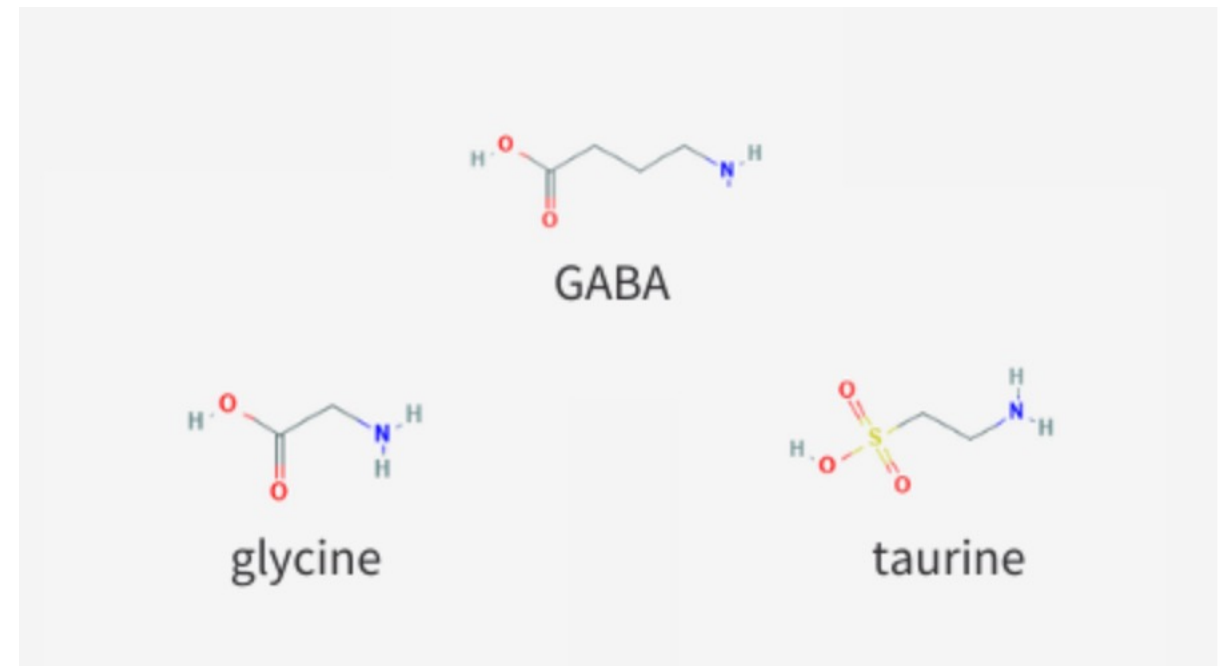
- ✓ Fasting blood sugar (p=0.01)
- ✓ Insulin (p=0.01)
- ✓ HOMA-IR (p=0.003)
- ✓ Total cholesterol (p=0.013)
- ✓ LDL-C (p=0.041)

# Taurine Research




Taurine is a "calming" neurotransmitter similar in structure to GABA (gamma-aminobutyric acid) & Glycine — the brain's other two calming neurotransmitters.

By interacting with GABA receptors, taurine helps to support beneficial "GABAergic" tone or overall GABA activity, thereby improving sleep, preventing migraines & relieving perimenopausal mood symptoms.



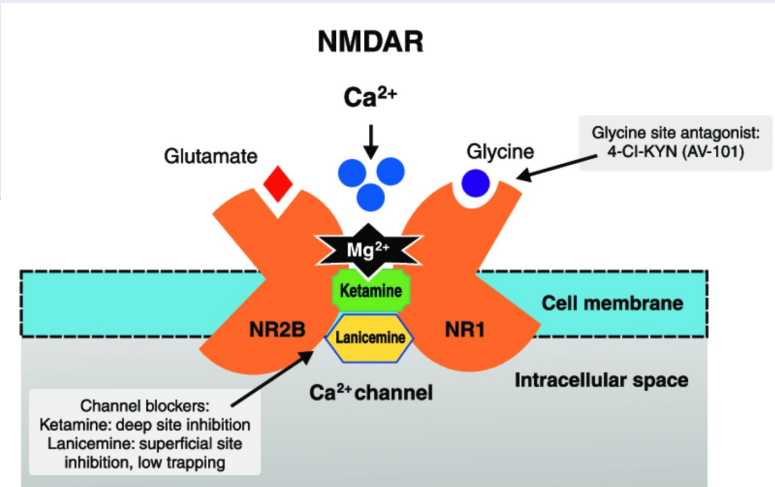
# Glycine

- ✓ Induces deeper REM restorative sleep
- ✓ Deficiency is associated with obesity and NAFLD
- ✓ Lowers markers of oxidative stress
- ✓ Improves liver detoxification- glutathione synthesis
- ✓ Calms the brain by inhibiting glutamate
  - ✓ May control food intake



2-6g daily in  
divided doses.  
3g to promote  
sleep

# Glycine Research

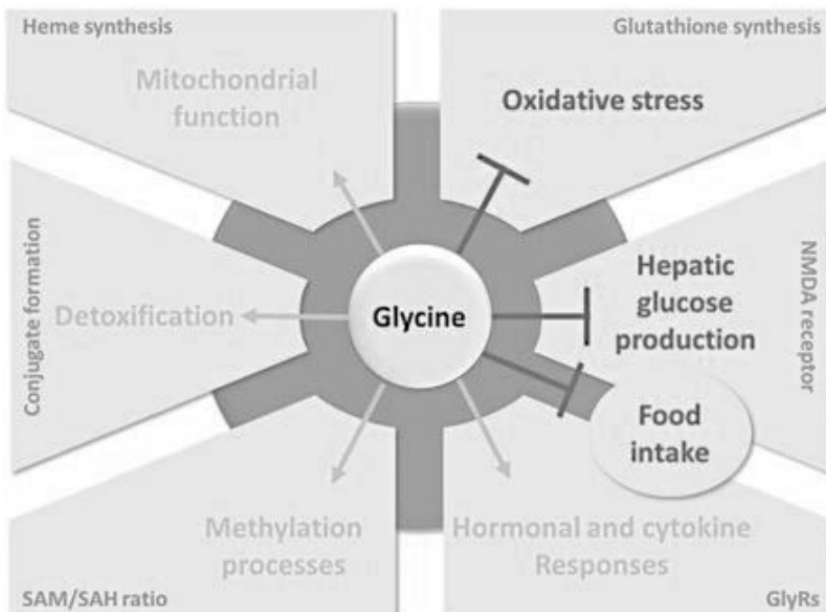


Review

## Glycine Metabolism and Its Alterations in Obesity and Metabolic Diseases

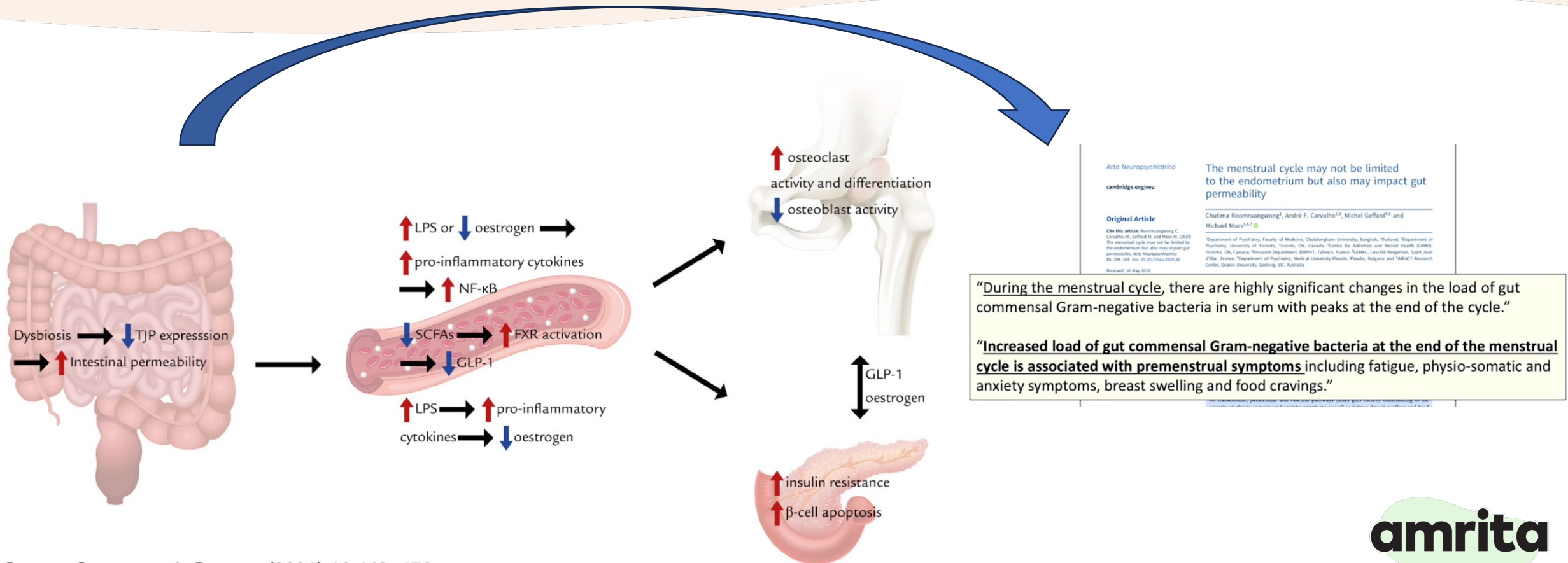
Anaïs Alves <sup>1</sup>, Arthur Bassot <sup>1</sup>, Anne-Laure Bulteau <sup>2</sup>, Luciano Pirola <sup>1</sup> and Béatrice Morio <sup>1,3,\*</sup>

The study also suggested that decreased plasma glycine concentration was associated with hepatic insulin resistance. This finding is supported by a recent meta-analysis, which showed that plasma glycine concentration is consistently lower in patients with obesity and T2DM compared to healthy individuals (-11 and -15%, respectively) [72]. Another meta-analysis showed that plasma glycine concentration has a very significant inverse association with the risk of developing T2DM [8]. In addition





# Gut Dysbiois – Insulin Resistance & Bone loss



Acta Neuropsychiatrica  
cambridge.org/neu

The menstrual cycle may not be limited to the endometrium but also may impact gut permeability

Original Article

Cite this article: Roomruangwong C, Carvalho AF, Geffard M, and Maes M. (2020) The menstrual cycle may not be limited to the endometrium but also may impact gut permeability. *Acta Neuropsychiatrica* 33: 294–304. doi: 10.1017/neu.2019.30

Received: 05 May 2019

Chutima Roomruangwong<sup>1</sup>, André F. Carvalho<sup>2,3</sup>, Michel Geffard<sup>4,5</sup> and Michael Maes<sup>1,4,7</sup>

<sup>1</sup>Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; <sup>2</sup>Department of Psychiatry, University of Toronto, Toronto, ON, Canada; <sup>3</sup>Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada; <sup>4</sup>Research Department, IDePH1, Talence, France; <sup>5</sup>SEMME, Lou-Dit-Bergeron, Saint-Jean d'Illac, France; <sup>6</sup>Department of Psychiatry, Medical University Plovdiv, Plovdiv, Bulgaria and <sup>7</sup>IMPACT Research Centre, Deakin University, Geelong, VIC, Australia

“During the menstrual cycle, there are highly significant changes in the load of gut commensal Gram-negative bacteria in serum with peaks at the end of the cycle.”

“Increased load of gut commensal Gram-negative bacteria at the end of the menstrual cycle is associated with premenstrual symptoms including fatigue, physio-somatic and anxiety symptoms, breast swelling and food cravings.”

# Research



ORIGINAL RESEARCH article

Front. Microbiol., 12 January 2022

Sec. Microorganisms in Vertebrate Digestive Systems

Volume 12 - 2021 | <https://doi.org/10.3389/fmicb.2021.752512>

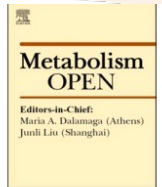
## Berberine Relieves Metabolic Syndrome in Mice by Inhibiting Liver Inflammation Caused by a High-Fat Diet and Potential Association With Gut Microbiota



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Metabolism Open

journal homepage: [www.sciencedirect.com/journal/metabolism-open](https://www.sciencedirect.com/journal/metabolism-open)



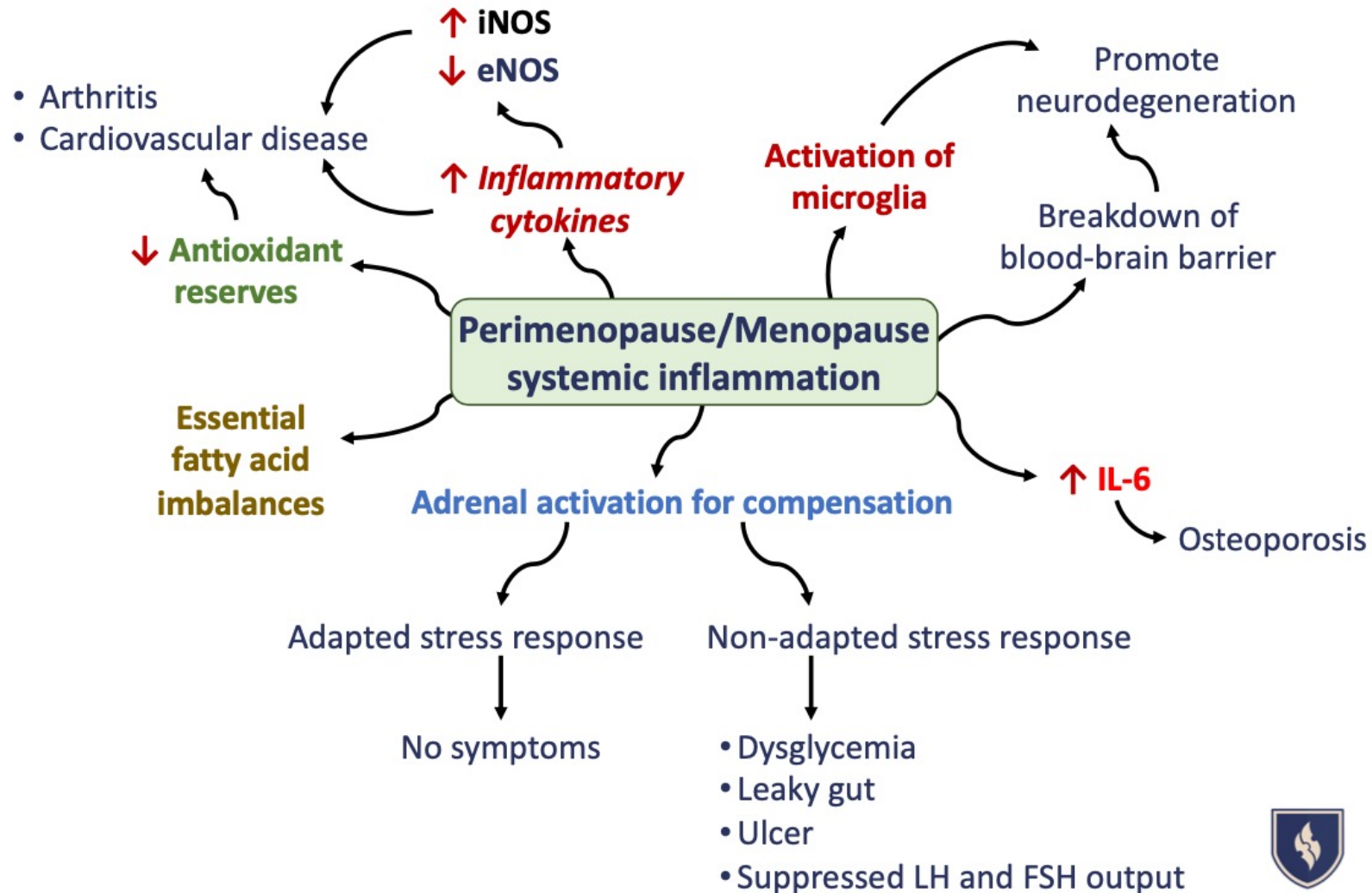
Effect of 8 Weeks milk thistle powder (silymarin extract) supplementation on fatty liver disease in patients candidates for bariatric surgery

Seyed Hadi Mirhashemi<sup>a</sup>, Azadeh Hakakzadeh<sup>b,c</sup>, Farbod Emami Yeganeh<sup>a</sup>, Bahador Oshidari<sup>a</sup>, Seyed Parviz Rezaee<sup>a,d,\*</sup>

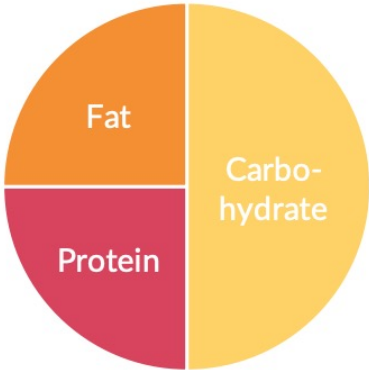
<sup>a</sup> Department of the General Surgery, Loahman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran



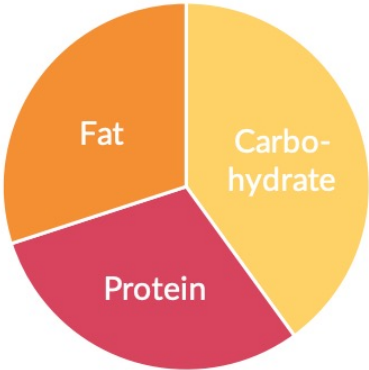
# Impact Systemic Inflammation in Perimenopause



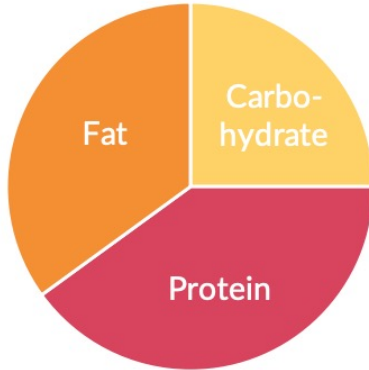
# Eating for body type with Mediterranean principles



Ectomorph



Mesomorph



Endomorph

# Eating for body type with Mediterranean principles

Hormones

Ideal protein intake:  $\text{Bodyweight (lb.)} \times 0.36 \text{ to } 1.0 = \text{grams of protein per day}$

Minimal dietary fat should be at least 30% of total calories.

Peptide hormones

Steroid hormones

Require dietary protein for synthesis

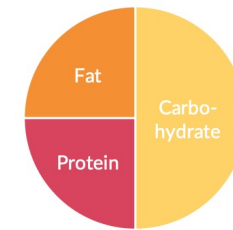
Require dietary fat for synthesis



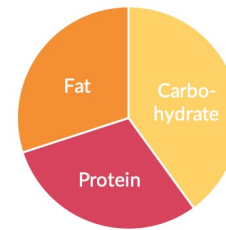
TSH  
LH  
FSH  
ACTH  
PTH  
TRH  
Epinephrine  
Prolactin



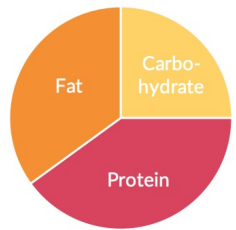
Testosterone  
Progesterone  
Estradiol  
DHEA  
Androstenedione  
Cortisol  
Aldosterone



Ectomorph

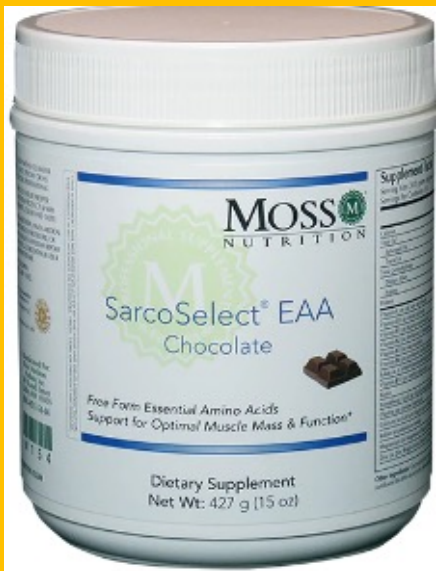


Mesomorph



Endomorph

# Nutraceuticals



# Nutraceuticals

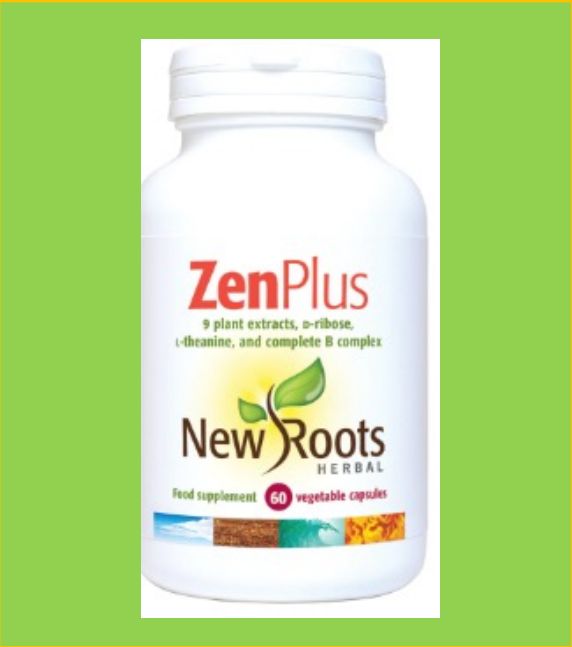


# Nutraceuticals





# Nutraceuticals



# References

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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5879846/>

[Slide 30](#) <https://doi.org/10.3390/ijms24010223>  
<https://doi.org/10.3390/ijms20061351>  
<https://www.sciencedirect.com/science/article/pii/S0891584922000752>  
<https://doi.org/10.7556/jaoa.2018.037>

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[Slide 34](#)  
[https://www.sciencedirect.com/science/article/pii/S0022316622010161#:~:text=The%20present%20study%20revealed%20that,with%20Alzheimer%20disease%20\(52\).](https://www.sciencedirect.com/science/article/pii/S0022316622010161#:~:text=The%20present%20study%20revealed%20that,with%20Alzheimer%20disease%20(52).)  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7982985/>