



The role of gut microbiome in women health

*Importance of the intestinal
microbiome in the diagnosis and
treatment of endometriosis and
polycystic ovary syndrome*

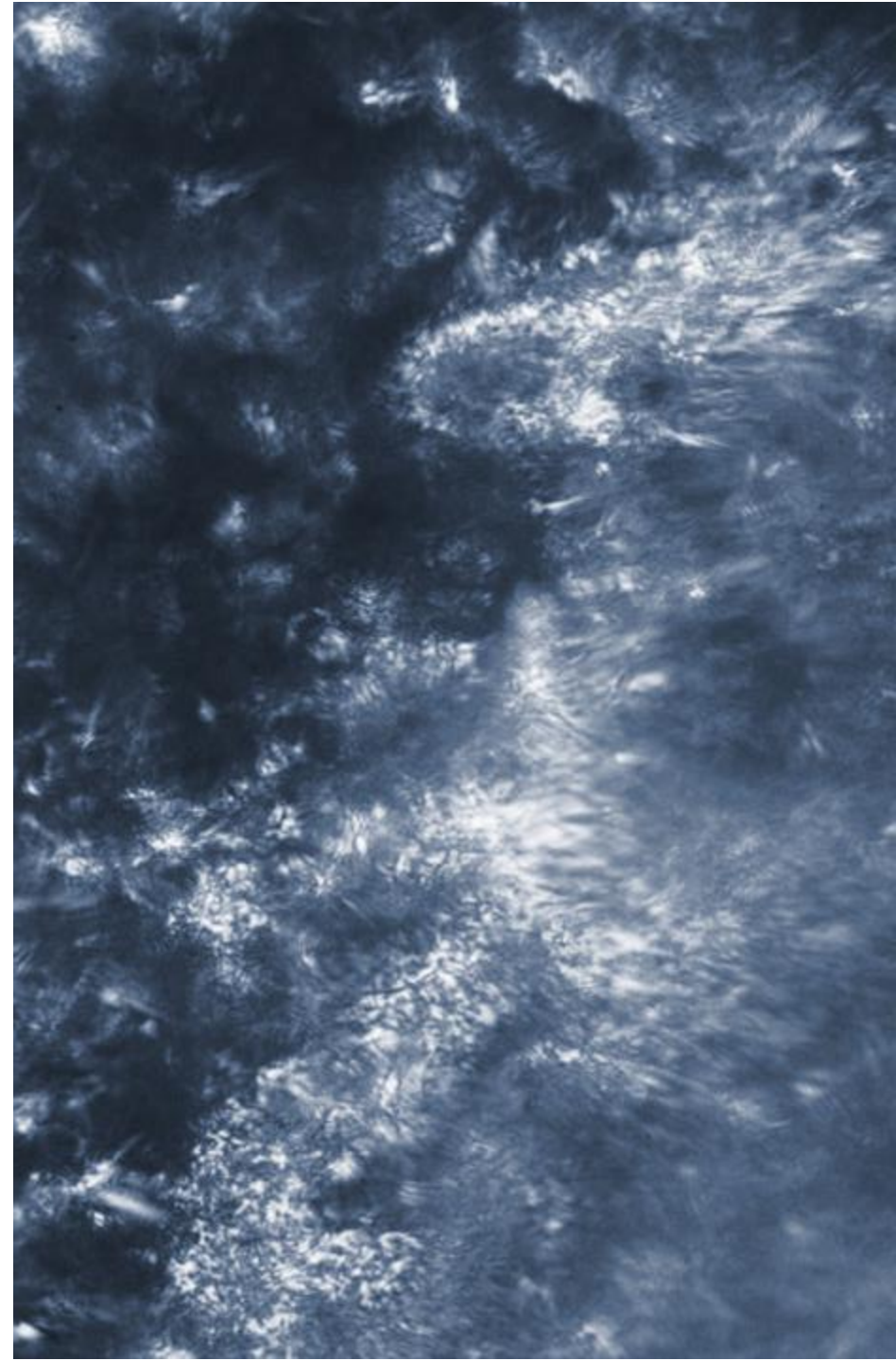
Ira Renko, [univ.mag.ing.biotechn](mailto:univ.mag.ing.biotechn@ccm.hr)
Center for the Gut Microbiome, info@ccm.hr

- Master of Engineering in Molecular Biotechnology
- Project Manager at the Center for the Gut Microbiome (CCM)
- Author of numerous works in the field of: microbiome, women's health and skin health, nutrition and oncology, personalized medicine
- Contact: info@ccm.hr



ABOUT CENTER FOR GUT MICROBIOME

- first Croatian institution for gut microbiome analysis and interpretation
- leading research institution dedicated to exploring the complex ecosystem of microorganisms within the human digestive system
- focus on:
microbiome & health, personalized medicine, research & innovation



OUR TEAM



**Andrija
Karačić**

dr. med.



**Anđela
Đinđić**

dr. sc.



**Domagoj
Lisica**

mag. cin.



**Sandra
Krstev Barać**

mag. nutr.



**Jagoda
Šušković**

prof. dr. sc.



**Donatella
Verbanac**

prof. dr. sc.

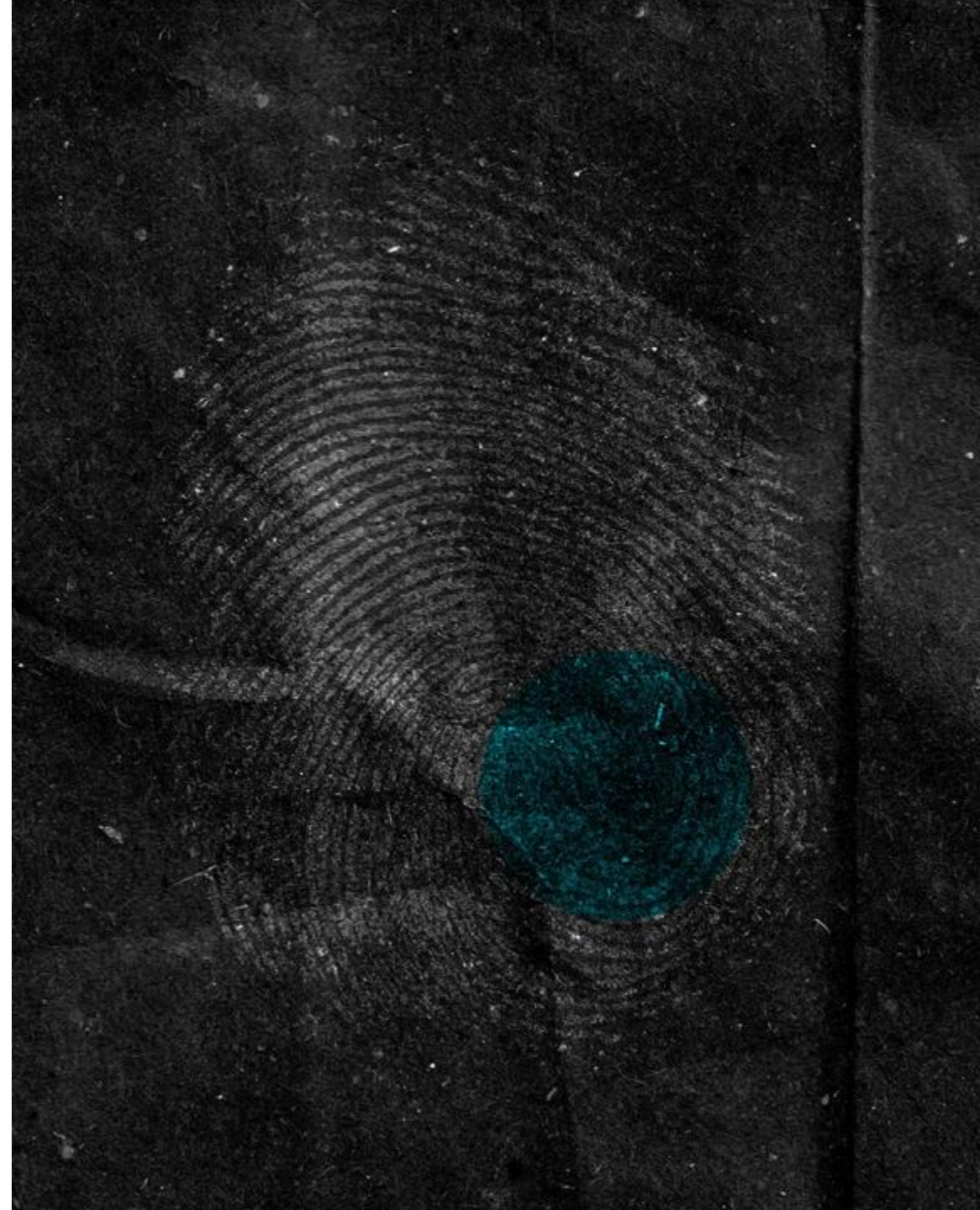


**Ana-Marija
Liberati Pršo**

dr. sc. dr. med.

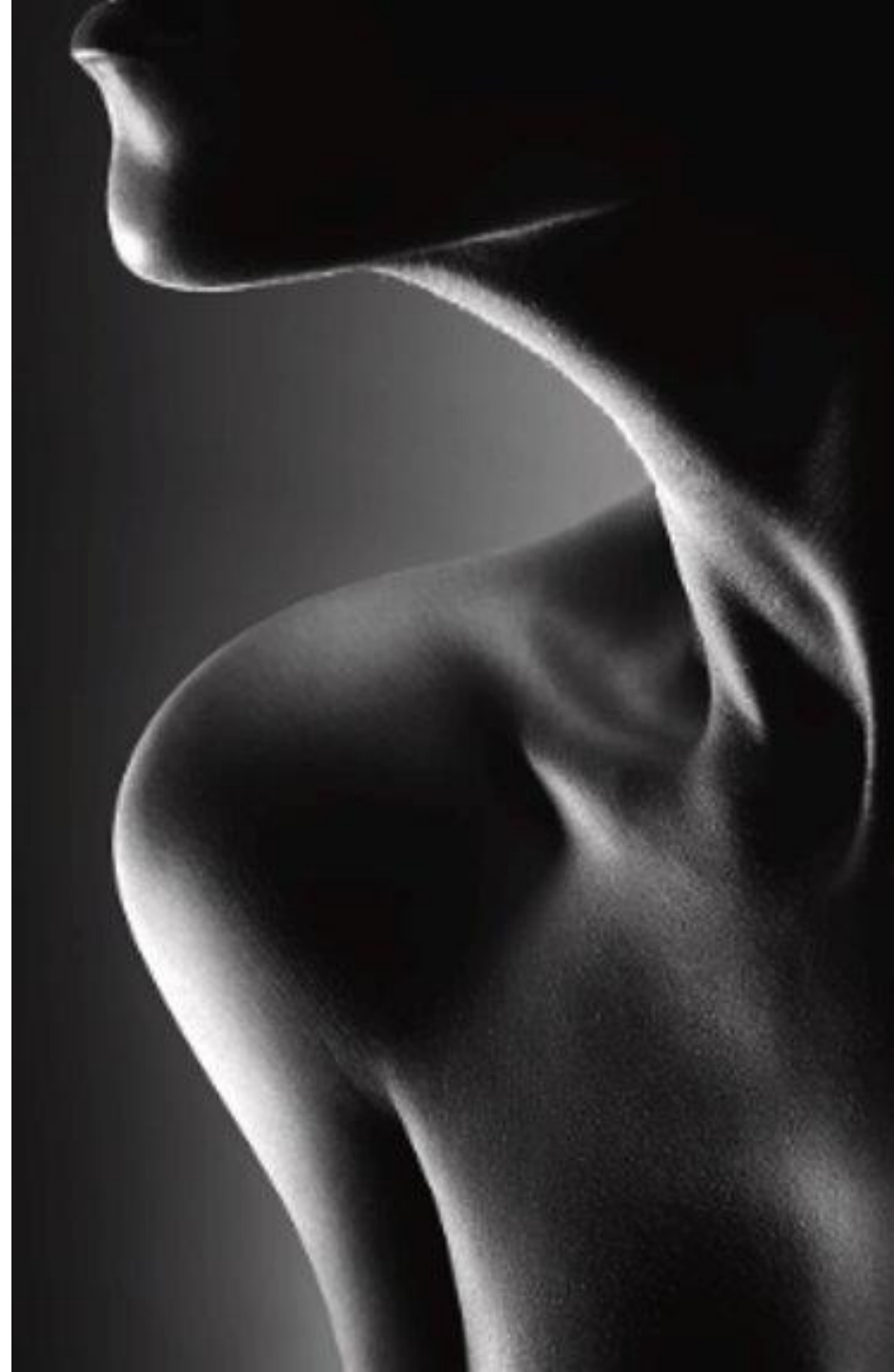
OUR SERVICE

- gut microbiome analysis
- gut microbiome interpretation
- consultation with members of research team
- GYNOBIOM
- microbiome in the service of health modulation



INTESTINAL MICROBIOME 101

- a new concept of intestinal flora
- "gut-brain axis, "gut-vaginal axis",...
- human-environment interface
- 100 trillion- intestines
- an almost equal ratio of human and bacterial cells
- subject to change



FACTORS AFFECTING DESIGN

- external and internal factors
- lifestyle and eating habits
- exposure to stress
- diseases of the female reproductive system (gonadectomy, PCOS, endometriosis)
- hormone therapy, antibiotics, ...



REGULATION

- metabolism
 - immunity
 - nervous system
 - epigenetics
 - hormone status
-
- short-chain fatty acids (lactate, butyrate,...)



INTESTINAL MICROBIOME OF WOMEN

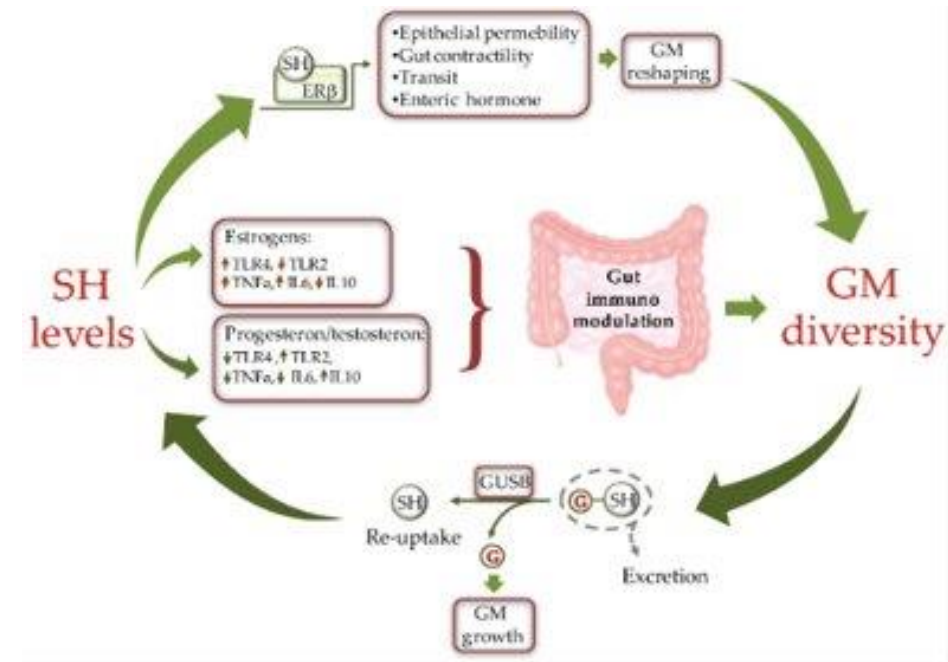
SPECIAL FEATURES OF THE "FEMALE INTESTINAL MICROBIOME"

- richer, more diverse, but also a different composition compared to the "male" intestinal microbiome
- changes occur during puberty
- bidirectional communication of the microbiome and sex hormones
- connection with diseases of the female reproductive system, pregnancy, menopause,...



BIDIRECTIONAL COMMUNICATION OF THE INTESTINAL MICROBIOME AND SEX HORMONES

- estrogen and testosterone are responsible for the sexual dysmorphism of the intestinal microbiome
- communication: bile salts, phytoestrogens, enzymatic activity



Talwar C, Singh V, Kommagani R. The gut microbiota: a double-edged sword in endometriosis†. *Biology of Reproduction*. 2022 Oct;107(4):881-901. DOI: 10.1093/biolre/ioac147. PMID: 35878972; PMCID: PMC9562115.

HOW THESE CHANGES ARE REFLECTED IN THE FEMALE ORGANISM?

- hormonal changes (menopause)-**fat redistribution in** the body
- diabetes type 2/insulin resistance - high testosterone levels
- frequent urinary **infections**-pathogen migration
- vaginal microbiome disorder (*Candida albicans*, Döderlein bacteria).
- **fertility**, pregnancy complications - reduced number of mucin-producing bacteria, adequate estrogen levels (secretion of β -glucuronidase)

INTESTINAL MICROBIOME AND ENDOMETRIOSIS/PCOS

INTESTINAL MICROBIOME AND ENDOMETRIOSIS

ENDOMETRIOSIS

- chronic gynecological hormonal disease
- uterine endometrial-like tissue lesions outside the uterus
- Problems:
 - 30% of patients suffer from infertility
 - chronic pain
- Cause: genetic-epigenetic theory of development (intestinal microbiome dysbiosis?)
- Treatment methods:
 - operation
 - estrogen/progestin hormone therapy



INTESTINAL MICROBIOME - ESTROGEN

- **estrogen**-a hormone responsible for the development and regulation of the female reproductive system
- influence on brain functions, health of the digestive system - female reproductive system
- regulation of estrogen levels by β -glucuronidase
- lower microbial diversity = lower β -glucuronidase activity



ESTRABOLOME

= microorganisms of the intestinal microbiome whose products can metabolize estrogen

- main forms: estradiol (E2), estrone (E2) and estriol (E3) - free in the blood, the presence of the form depends on the stage of life
- conversion of estrogen in the liver and excretion into bile (conjugated estrogen)
- deconjugation by bacteria with β -glucuronidase and β -glucosidase activity to return to circulation
- *Bacteroides, Bifidobacterium, Lactobacillus...*



MECHANISM OF ACTION

- immune function
- endocrine organ
- regulation of sex hormones (estrogen, androgenic hormones, insulin)
- SCFA- reduced growth of lesions



SPECIFIC PROFILE OF THE INTESTINAL MICROBIOME

HIGH ENDO-score (> 60%)

- phylum: Bacteroidetes(↓) and Firmicutes(↑)
- genus: *Turicibacter*, *Odoribacter*, *Adlecreutzia*(↓)
- genus: *E.coli*, *Pseudomonas*, *Fusobacteria*(↑)



THE ROLE OF THE INTESTINAL MICROBIOME IN THE TREATMENT OF ENDOMETRIOSIS

- PROBIOTICS

- *Lactobacillus gasseri* OLL 2809 (Itoh et al., 2011; Uchida and Kobayashi, 2013)
- *Lactobacillus rhamnosus* BPL005 (Chennoll et al., 2019)
- *Lactobacillus acidophilus*, *L. plantarum*, *L. fermentum*, *L. gasseri* (Khodaverd et al., 2019)

- NUTRITION

- fermented milk drinks (yogurt, kefir)
- fermented vegetables (sauerkraut, kimchi,...)
- seafood
- nuts and seeds
- increased intake of plants

- SUPPLEMENTS

vitamin D, zinc omega-3 fatty acids, N-acetylcysteine, diindolylmethane

- EXERCISE

- acupuncture, yoga, aerobic training

INTESTINAL MICROBIOME AND PCOS

POLYCYSTIC OVARY SYNDROME

- hormonal gynecological endocrine and disorder
- Entities:
 - menstrual cycle disorder
 - elevated levels of male sex hormones (hyperandrogenemia),
 - polycystic ovarian appearance
 - infertility, acne, increased hair growth, obesity, depression and anxiety
 - precursor of metabolic diseases - obesity, dyslipidemia, and diabetes
- Causes:
 - insulin resistance
 - genetic predisposition
 - inflammatory processes
 - poor health of the digestive system
- Treatment methods:
 - contraceptive pills
 - antiandrogens, metformin,...



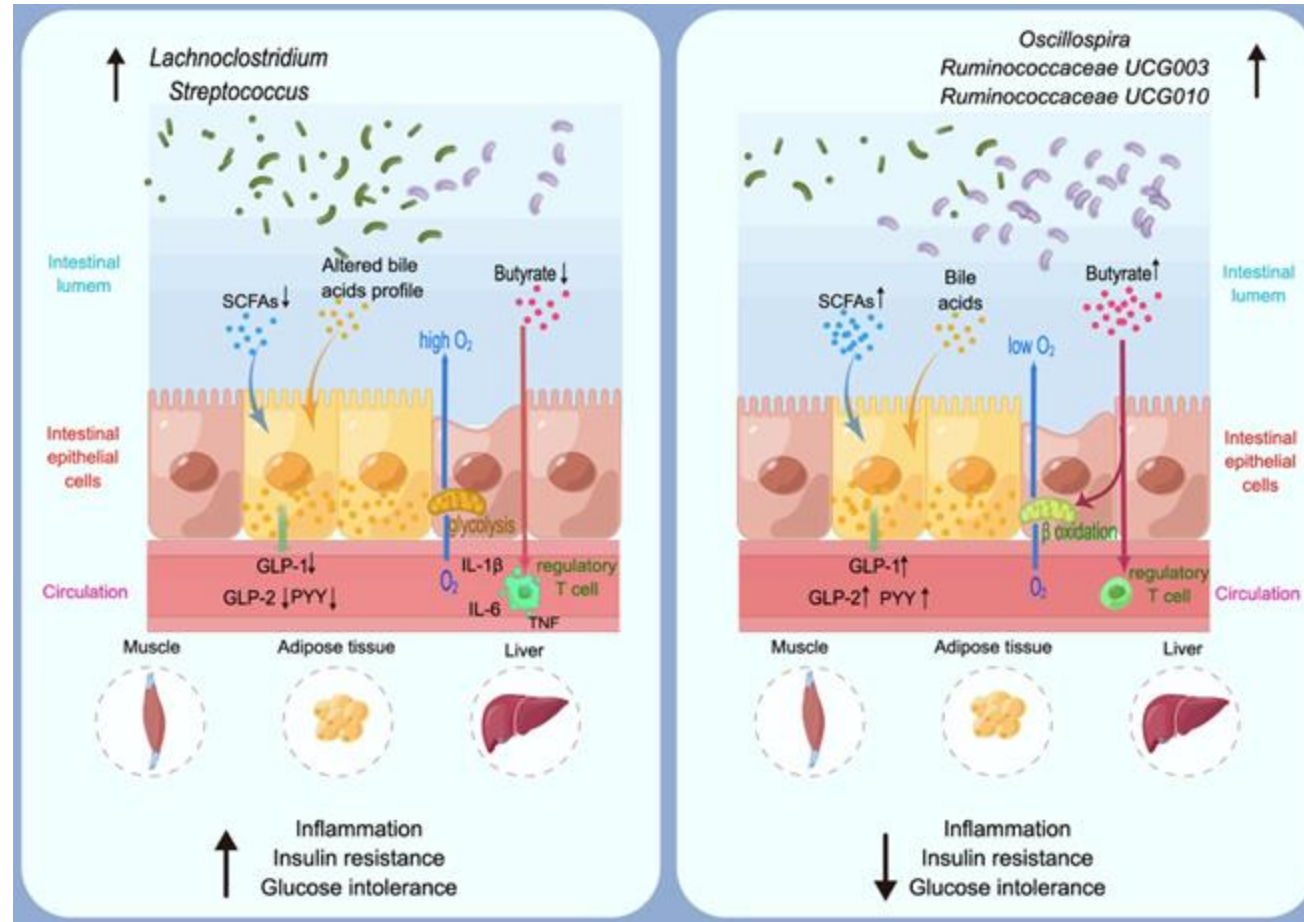
INSULIN

- insulin - thyroid hormone
- enables the use of blood sugar as an energy source
- necessary for metabolism
- imbalance of the intestinal microbiome - disorder in the secretion of digestive hormones ghrelin and peptide YY, bile acids, IL-22
- greater representation *Coprococcus*- greater insulin sensitivity
- diabetes type 2- high levels of testosterone, insulin resistance
- greater representation Flavonifractor- lower insulin sensitivity (insulin resistance)



MECHANISM OF ACTION

insulin resistance



insulin sensitivity

Reference: Li, Hanjing & Li, Candong. (2023). Causal relationship between gut microbiota and type 2 diabetes: a two-sample Mendelian randomization study. *Frontiers in Microbiology*. 14. 10.3389/fmicb.2023.1184734.

SPECIFIC PROFILE OF THE INTESTINAL MICROBIOME

HIGH PCOS score (> 60%)

- phylum: Firmicutes(↓), Bacteroidetes(↓), Actinobacteria (↑)
- genus: *Faecalibacterium*, *Ruminococcus*, *Akkermansia*(↓)
- genus: *Catenibacterium*, *Streptococcus*, *Klebsiella* (↑)



THE ROLE OF THE INTESTINAL MICROBIOME IN THE TREATMENT OF PCOS

- PROBIOTICS

- *Lactobacillus*, *Bacillus*, *Bifidobacterium*, *Streptococcus*, and *Enterococcus* (Bhalla i sur., 2022)
- *L. acidophilus* UBLA-34, *L. rhamnosus* UBLR-58, *L. reuteri* UBLRu-87, *L. plantarum* UBLP-40, *L. casei* UBLC-42, *L. fermentum* UBLF-31, *B. bifidum* UBBB-55, (Kaur i sur., 2022)
- *Bifidobacterium lactis*, *Lactobacillus acidophilus*, *L. paracasei*, *L. plantarum*, *Lactobacillus salivarius*, and *L. lactis* (Chudzika i sur., 2021)

- NUTRITION

- vetch
- plant-based alternatives to meat
- whole grains

- SUPPLEMENTS

inositol, zinc, berberine, vitamin D, magnesium, fish oil,...

EXERCISE

- exercise for "body and spirit" (yoga, meditation, ...)

CONCLUSION

- women gut microbiome is significantly different compared to men
- specific gut microbiome profile in women with PCOS and endometriosis
- regulation via nutrition, exercise, supplements
- probiotics and prebiotics as a treatment for PCOS and endometriosis?
- novel approach in treatment in these diseases

REFERENCE

- Santos-Marcos, JA, Mora-Ortiz, M., Tena-Sempere, M.*et al.* Interaction between gut microbiota and sex hormones and their relation to sexual dimorphism in metabolic diseases.*Biol Sex Differ*14, 4 (2023).<https://doi.org/10.1186/s13293-023-00490-2>
- Maffei, S.; Forini, F.; Canale, P.; Nicolini, G.; Guiducci, L. Gut Microbiota and Sex Hormones: Crosstalking Players in Cardiometabolic and Cardiovascular Disease.*Int. J. Mol. Sci.*2022,23, 7154.<https://doi.org/10.3390/ijms23137154>
- James M. Baker, Layla Al-Nakkash, Melissa M. Herbst-Kralovetz, Estrogen–gut microbiome axis: Physiological and clinical implications, *Maturitas*, Volume 103, 2017, 45-53.<https://doi.org/10.1016/j.maturitas.2017.06.025>.
- Kwa M, Plottel CS, Blaser MJ, Adams S. The Intestinal Microbiome and Estrogen Receptor-Positive Female Breast Cancer. *J Natl Cancer Inst.* 2016 Apr 22;108(8):djw029. doi: 10.1093/jnci/djw029.
- Jinrui Cui, Gautam Ramesh, Martin Wu, Elizabeth T. Jensen, Osa Crago, Alain G. Bertoni, Chunxu Gao, Kristi L. Hoffman, Patricia A. Sheridan, Kari E. Wong, Alexis C. Wood, Yii-Der I. Chen, Jerome I. Rotter, Joseph F. Petrosino, Stephen S. Rich, Mark O. Goodarzi; Butyrate-Producing Bacteria and Insulin Homeostasis: The Microbiome and Insulin Longitudinal Evaluation Study (MILES).*Diabetes*1 November 2022; 71 (11): 2438–2446.<https://doi.org/10.2337/db22-0168>
- Lee CJ, Sears CL, Maruthur N. Gut microbiome and its role in obesity and insulin resistance. *Ann NY Acad Sci.* 2020 Feb;1461(1):37-52. doi: 10.1111/nyas.14107. Epub 2019 May 14
- Li Hanjing, Li Candong, Causal relationship between gut microbiota and type 2 diabetes: a two-sample Mendelian randomization study, *Frontiers in Microbiology*, 14, 2023, doi:10.3389/fmicb.2023.1184734
- Takeuchi, T., Kubota, T., Nakanishi, Y.*et al.* Gut microbial carbohydrate metabolism contributes to insulin resistance.*Nature*621, 389–395 (2023).<https://doi.org/10.1038/s41586-023-06466-x>
- Legro RS. Insulin resistance in women's health: why it matters and how to identify it. *Curr Opin Obstet Gynecol.* 2009 Aug;21(4):301-5. doi: 10.1097/GCO.0b013e32832e07d5
- Khodaverdi S., Mohammadbeigi R., Khaledi M., Mesdaghinia L., Sharifzadeh F., Nasiripour S., Gorginzadeh M. Beneficial Effects of Oral Lactobacillus on Pain Severity in Women Suffering from Endometriosis: A Pilot Placebo-Controlled Randomized Clinical Trial.*Int. J. Fertil. Sterile.*2019;13:178–183. doi: 10.22074/ijfs.2019.5584
- Talwar C, Singh V, Kommagani R. The gut microbiota: a double-edged sword in endometriosis†. *Biology of Reproduction.* 2022 Oct;107(4):881-901. DOI: 10.1093/biolre/ioac147. PMID: 35878972; PMCID: PMC9562115.



**Thanks for your
attention!**

info@ccm.hr