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Review

# Microbiome impact on metabolism and function of sex, thyroid, growth and parathyroid hormones

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**Commensal bacteria and their genes associated with host are known as microbiome. In recent years, microbial influence on host endocrine system has been under detailed investigation. The role of microbiome in the pathogenesis of insulin resistance and obesity, the function of hypothalamic-pituitary-adrenal axis and secretion of hormones regulating appetite is well described in world literature. In this article we discuss poorly reviewed issues: the microbiome role in modulation of non-peptide (sex and thyroid) and peptide (growth hormone and parathyroid hormone) functions. Understanding complex bidirectional relations between host endocrine system and bacteria is of fundamental importance to understanding microbial impact on host reproduction, risk of endocrine-related cancers, pathogenesis of non-thyroidal illness syndrome, growth failure in children and hormonal changes during chronic kidney disease. This article also highlights effects of dietary compounds on microbiome composition and bacterial enzymes activity, and thus host hormonal status.**

**Key words:** microbiome, lipopolysaccharide, estrogens, thyroid hormones, growth hormone

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## INTRODUCTION

By definition microbiome is the catalog of commensal bacteria (microbiota) and their genes associated with host (Ursell *et al.*, 2012). Human microbiome is strongly associated with the number of processes, which occur in host organism, affecting its immunological, nutritional and metabolic functions. That is why in recent years the conception of human-microbiome superorganism was proposed (Dietert & Dietert, 2012). The microbial composition is established in early life and is mainly dependent on mode of delivery and diet. After infancy the main factors which affect microbiome are diet, antibiotic treatment, obesity, sex and geography. There are complex bidirectional relations between host-endocrine system and bacteria, which justifies the use of term "human-microbiome superorganism" also in hormonal system. Microbes sense and react for example to host adrenaline, noradrenaline, triiodothyronine and sex hormones, which changes their metabolism, growth and virulence (Sperandio *et al.*, 2003; Hughes & Sperandio, 2008; García-Gómez *et al.*, 2013). In turn, many reviews and original papers analyzing the influence of microbiota on hormones regulating appetite, insulin sensitivity, pathogenesis of diabetes and obesity and hypothalamic–pituitary-adrenal axis have been published (Sudo *et al.*, 2004; Gao *et al.*, 2009; Vrieze *et al.*, 2010; Burcelin *et al.*, 2011; Zimomra *et al.*, 2011; Holzer *et al.*, 2012; Norris *et al.*, 2013). In this review, we focus on less well described issues: the microbiome role in modulation of non-peptide (sex and thyroid) and peptide (growth hormone - GH and parathyroid hormone — PTH) functions.

In animals, bacteria influence their endocrine system *via* various mechanism, i.e. intestinal metabolism of bile-excreted hormones, intestinal conversion of exogenous molecules to endocrine-active derivatives, production/release of endocrine-active molecules like short chain fatty acids (SCFAs) and lipopolysaccharide (LPS). The first way concerns steroid and thyroid hormones, which are metabolized in the liver and excreted with bile. A large number of intestine bacteria are capable of hydrolysis of hormone conjugates and afterward modify chemical structure of free molecules. Another important aspect concerns the ability of microorganisms associated with plants to produce phytohormones and hormone-like substances, which may modify host metabolism (Tsavkelova *et al.*, 2006).

## SEX HORMONES AND REPRODUCTION

Steroid sex hormones such as estradiol (E2), testosterone (T) and progesterone (P4) modulate a number of physiological processes, both related and unrelated to reproduction. They are produced in endocrine glands such as adrenal cortex, ovaries and testes as well as in peripheral tissues like skin. They act through intracellular and extracellular receptors and affect e.g. host blood pressure, energy homeostasis and metabolism, bone remodeling, mood, erythropoiesis and cells growth. Then they are metabolized in the liver and excreted with the bile. Thus, liver metabolism of steroid hormones includes: reduction of the sterol ring A, conjugation with sulfate or glucuronide, and excretion in the bile. Afterward these compounds are deconjugated by bacterial sulfatases (Van Eldere *et al.*, 1988) and glucuronidases synthesized both in the intestinal wall and by bacteria (Macdonald *et al.*, 1983). Moreover steroids undergo enterohepatic circulation (EHC).

Large number of species found in human intestinal or other microbiomes, such as *Eubacterium lentum*, *Bac-*

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**Abbreviations**: E2, estradiol; EHC, enterohepatic circulation; GH, growth hormone; hCG, human chorionic gonadotropin ; hPL, human placental lactogen ; HSD, hydroxysteroid dehydrogenase; IL, interleukin; LBP, LPS-binding protein; LPS, lipopolysaccharide; P4, progesterone; PAH, polycyclic aromatic hydrocarbons; PTH, parathyroid hormone; SCFA, short chain fatty acid; T, testosterone; TLR, Toll-like receptor

*teroides sp., Bifidobacterium sp., Streptococcus sp.* posses enzymes which are involved in degradation of unconjugated steroids, like 21-dehydroxylase, 17,20-desmolase, 16-dehydratase and various dehydrogenases (Macdonald *et al.*, 1983). Interestingly, hydroxysteroid dehydrogenases (HSDs) which are involved in the production of steroid hormones and regulation of their receptor-active and receptor-inactive derivative levels in host cells, were found in bacteria. Accumulating evidence indicates that members of the normal human gastro-intestinal flora (especially members of *Actinobacteria*, *Proteobacteria* and *Firmicutes*), possess HSDs, which are active on keto- or hydroxyl-groups at positions C3, 7, 12, 17 and 20 of steroid compounds (Kisiela *et al.*, 2012). It follows that bacterial HSDs may influence concentration of active steroid derivatives which return to blood throughout EHC. Furthermore, bacterial steroid metabolism has its local long-term effects, since it is known that increased number of bacterial strains capable of steroid degradation in colon is associated with higher risk of colon cancer (Debas, 1981).

Except of direct metabolism of steroid hormones, bacteria may change expression of host genes involved in steroid hormones metabolism and function. Some studies highlight the effects of oral probiotic supplementation on sex hormones metabolism and function. Research conducted on female zebrafish fed with *Lactobacillus rhamnosus* revealed an increase of transcription of aromatase cytochrome p 19 (cyp19a), vitellogenin (vtg), α isoform of the estrogen receptor (erα), luteinizing hormone receptor (lhr), 20-β hydroxysteroid dehydrogenase (20β-hsd), membrane progesterone receptors α and β and activin βA1 genes. These changes of respective genes' expression affect sex differentiation during larval development and improve fertility in adults (Carnevali *et al.*, 2013). In turn metabolomic analysis with use of murine typhoid infection model revealed that during *Salmonella typhimurium* infection the 3β-HSD2 and 17β-HSD2 gene expression in the liver is repressed (Antunes *et al.*, 2011). During acute shigellosis in human volunteers, significant reduction in fecal steroid metabolites was observed (Huang *et al.*, 1976). Changes in steroid metabolism during infection may diminish the HPA axis function and thus hinder proper reaction to pathogen invasion.

## LPS-DEPENDENT EFFECTS

Not to be underestimated is bacterial impact on host steroid hormone metabolism and function which is exerted *via* LPS (endotoxin). LPS is a part of Gram-negative bacteria cell wall and is a trigger of septic shock. Nevertheless, Marshall stated that LPS is "not less an endotoxin than an exohormone" (Marshall, 2005). He pointed out some LPS features similar to human hormones: 1. its exposure arises from endogenous stores (commensal, Gram-negative bacteria of the gastrointestinal tract), 2. it has a dedicated carrier protein, 3. it interacts with specific cellular receptor, 4. its signaling is specifically modulated by endogenous mechanisms and in turn LPS downstream signal interferes with endogenous hormones pathways. Endotoxemia and thus increased LPS influence on host occur under various conditions, such as major vascular surgery (Roumen *et al.*, 1993), cigarette smoking (Hasday *et al.*, 1999), mechanical ventilation (Nahum *et al.*, 1997), laparoscopic abdominal surgery (Schietroma *et al.*, 2006, 2013), colorectal carcinoma (Iarŭmov *et al.*, 2004), high-fat diet (Erridge *et al.*, 2007), inflammatory bowel disease (Aoki, 1978), intensive care (Guidet *et al.*, 1994), stomatological intervention and tooth-brushing (Jacob *et al.*, 2012). Increased translocation of LPS in leaky gut syndrome may cause chronic dysfunction of some elements of endocrine and other systems (Maes *et al.*, 2008). LPS is composed of three parts: lipid A, a core oligosaccharide, and an O side chain (Pålsson-McDermott & O'Neill, 2004). In bloodstream LPS is recognized by LPS-binding protein (LBP), an acute phase protein produced in the liver. Afterward, LBP facilitates LPS binding to CD14, which enables transfer of LPS to the TLR4/MD-2 receptor complex. LPS causes TLR4/MD-2 homodimerization, thus aids interactions between intracellular domains of TLR-4 and Toll/IL-1R (TIR) domains of adaptor proteins. Subsequent signals activated by TLR4 have been divided into MyD88-dependent and MyD88-independent (TRIF-dependent) pathways. MyD88-dependent pathway leads to the activation of IRAKs/TRAF6 and in consequence NF-ϰB, AP-1 and IRF-5 transcription factors. In turn TRIF signals recruit TRAF3 and RIP1, thus induce Type I interferons by activation of IRF3, NF-ϰB and AP-1.

Signaling pathways of human hormones are regulated by various negative feedback loops. Similarly, LPS action is inhibited by circulating inhibitors and factors causing acceleration of LPS degradation, inhibition of TLR4 signaling or enhancement of TLR4 degradation (Lu *et al.*, 2008).

LPS intravenous injection activates HPA and leads to increased secretion of CRH and AVP into hypophyseal portal blood (HPB), which is mediated by EP1 and EP3 pathway activation in periventricular nucleus (PVN) (Dadoun *et al.*, 1998; Matsuoka *et al.*, 2003). This effect was even observed in tilapia, which may reflects evolutionary preservation of hypothalamic response to LPS (Pepels *et al.*, 2004). Simultaneously, LPS suppresses GnRH pulsatile release into HPB and indirectly LH concentrations and pulse amplitude thus inhibits reproduction (Battaglia *et al.*, 1997, 1998). LPS elevates the E2/P4 ratio and alters the function of FSHR and LHR in uterus during the preimplantation days of pregnancy in mouse leading to the failure of implantation (Agrawal *et al.*, 2011, 2012). Furthermore, after implantation LPS decreases placental endocrine function, reducing amounts of trophoblast-released human chorionic gonadotropin (hCG), human placental lactogen (hPL), and P4 and hence leading to preterm delivery (Okada *et al.*, 1997). LPS is known to be a direct suppressor of E2 secretion by ovarian granulosa cells in bovine, which could explain a mechanism of infertility in pelvic inflammatory disease (Williams *et al.*, 2008). Ovarian follicles do not contain immune cells, however granulosa cells express the TLR4 and via this receptor LPS down-regulates transcripts for aromatase (Herath *et al.*, 2007). Similar effects were observed after primary bovine granulosa cells exposure to the Pam3CSK4 and peptidoglycan that bind TLR2 (Shimizu *et al.*, 1998; Price *et al.*, 2013). LPS or peptidoglycan treatment of theca cells under LH exposure results in suppressed P4 and androstenedione (A4) production (Magata *et al.*, 2014b, 2014a). It follows that in cows uterine infections may lead to ovarian dysfunction. In humans, high expression of TLR1, 2, 4, 5, 6 and COX2 gene in follicular cells was observed in patients with poor ovarian response to gonadotropin stimulation (Taghavi *et al.*, 2014). It suggests that increased TLR pathways activity may be associated with declining fertility rates.

Testicular functions, both spermatogenesis and steroidogenesis, are also disrupted after LPS treatment. Leydig cells (LC) and Sertoli cells (SC) — the key

players in the hormonal function of testes — express TLR-2 and TLR-4, similarly as testicular macrophages (Winnall *et al.*, 2011). In the response to LPS, these latter cells start to produce reactive oxygen species (ROS) and nitric oxide, which alter the function of LC mitochondria (Pomerantz & Pitelka, 1998; Allen *et al.*, 2004). Furthermore, LPS increases NF-ϰB pathway activity in LC, hence reducing testicular Cyp11a, StAR and 3β-HSD protein levels. In consequence, plasma T level decreases. This effect is partially dependent on LH secretion reduction and inflammatory cytokine level elevation caused by LPS. In SC, LPS acts *via* MyD88 pathway and activates expression of IL1, IL6 and activin A. In turn, FSH increases cAMP level and promotes lactate, transferrin, stem cell factor (SCF) and inhibin B expression. Intriguingly, these two pathways have probably reciprocal inhibitory effects (Hedger, 2011). It is well established that acute and chronic bacterial infections may be associated with temporary or constant infertility. Vitamin K may contribute to inhibition of inflammatory pathways in testis and may help maintain steady levels of T (Takumi *et al.*, 2011).

## NON-LPS-DEPENDENT EFFECTS

### Estrogens

Apart from LPS-dependent influence on estrogen function, bacteria may also directly metabolize them and similar particles, like phytoestrogens. To better understand these processess we describe host estrogen metabolism first.

Before excretion with bile, estrogens are metabolized in several steps in the liver (Fig. 1). First of all, interconvertible primary estrogens estrone (E1) and estradiol (E2) are hydroxylated by cytochrome P450 enzymes, yielding catechol estrogens: either 2-hydroxy (2-OH) or 4-hydroxy (4-OH) metabolites. Another derivative is made by hydroxylation at C-16α position yielding 16α-hydroxy (16α-OH) derivative. Both 16α-OH and produced in small portion 4-OH derivatives have greater estrogenic activity compared to 2-OH, thus domination of C-16α pathway has been hypothesized as a potential risk factor of breast cancer. However, recent studies do not support this hypothesis (Eliassen *et al.*, 2008). Catechol estrogens might be oxidized into harmful derivatives- quinones-

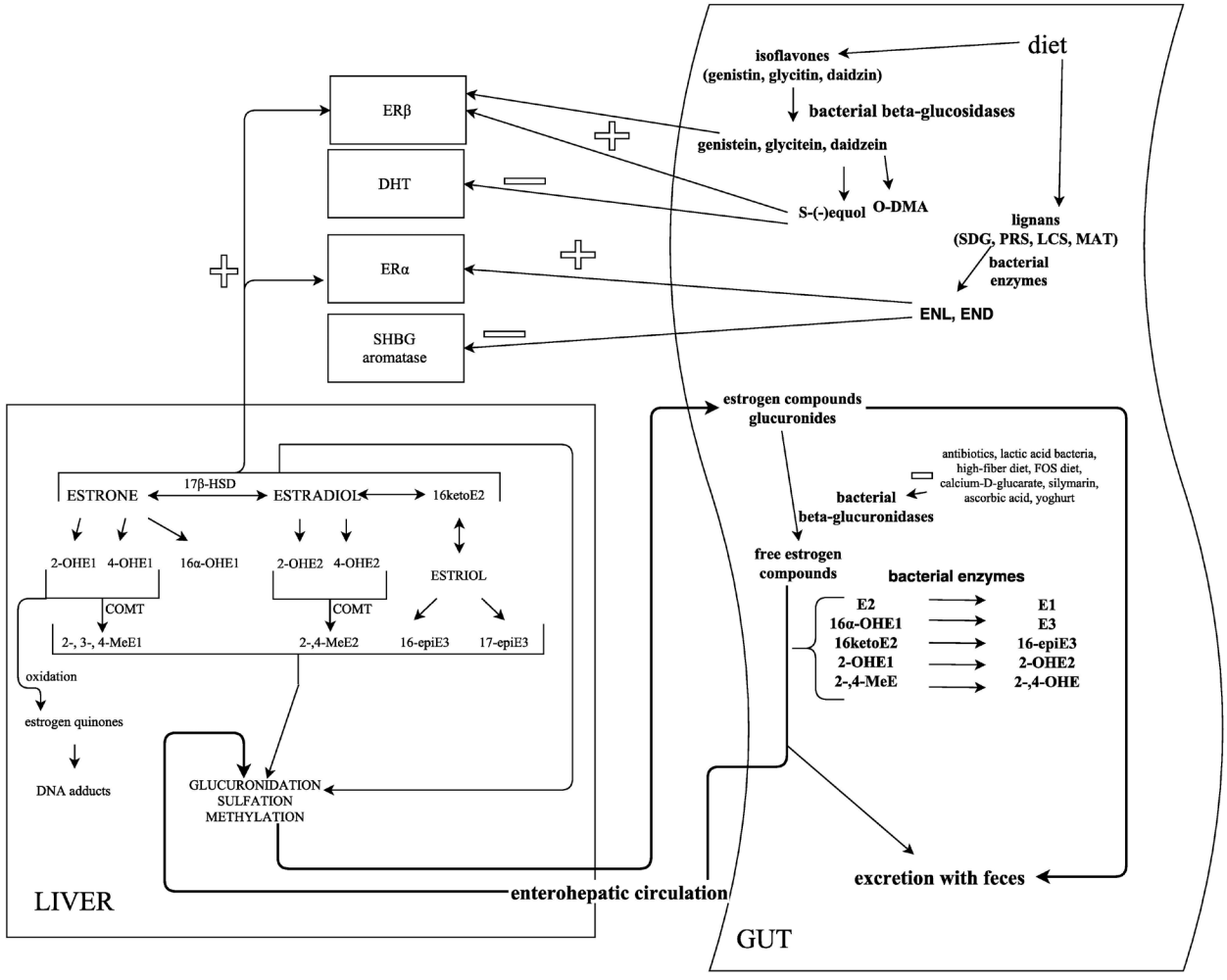


**Figure 1. Metabolism of estrogens and estrogenic compounds.**
The bold font denotes the metabolic pathways dependent on bacterial activity. Details, see main text. COMT, catechol-O-methyl transferase; DHT, dihydrotestosterone; ER, estrogen receptor; E, estrogens; E1, estrone; E2, estradiol; E3, estriol; FOS, fructooligosaccharides; LCS, lariciresinol; MAT, matairesinol; O-DMA, O-desmethylangolensin; PRS, pinoresinol; SDG, secoisolariciresinol diglucoside; SHBG, sex hormone binding protein

that can react with DNA to form depurinating adducts, thus are potential breast cancer initiatiors (Cavalieri *et al.*, 2006). Methylation of 2-OH and 4-OH estrogens by catechol-O-methyltransferase (COMT) prevents the formation of estrogen quinones, therefore the metoxy and catechol estrogen proportions may influence the cancer risk. Another metabolic pathway includes E2 conversion to 16-ketoE2 and further epimerization to 16-epi-E3 and 17-epi-E3 (Jobe *et al.*, 2013). This latter steroid is very interesting, since it has an anti-inflammatory, but not glycogenic activity (Latman *et al.*, 1994). The phase II of estrogen metabolism includes either glucuronidation or sulfation or methylation, which facilitates its elimination from the organism via bile in feces and with urine.

Plottel and coworkers proposed the term "estrobolome" to define the aggregate of enteric bacterial genes whose products are capable of metabolizing estrogens (Plottel & Blaser, 2011). Every individual has its own, unique estrobolome, which influences EHC of estrogens. Bacterial β-glucuronidases hydrolyze glucuronides which are excreted via bile, thus promotes recycling of aglycone forms through enterohepatic cycle. Excess of β-glucuronidase activity may be associated with higher estrogen-dependent cancers risk. Most species with β-glucuronidase expression are members of Firmicutes phylum and Enterobacteriaceae family (*Lactobacillus, Streptococcus, Clostridium, Ruminococcus, Roseburia, Faecalibacterium, Eubacterium* and *Escherichia*), however bacteria capable of β-glucuronidase production are also among Actinobacteria (i.e. *Bifidobacterium dentium*) (Gloux *et al.*, 2011). Administration of oral oxytetracyclin diminished urinary excretion and increased losses of conjugated estrogen metabolites in feces in men, probably by destruction of β-glucuronidase-producing microflora and the interruption of the estrogen recycling (Hämäläinen *et al.*, 1987). In one study fecal β-glucuronidase activity and diversity of fecal microbiome were found to be directly associated with higher concentrations of systemic estrogens (Flores *et al.*, 2012*a*). Lactic acid bacteria supplements and high-fiber diet (like vegetarian) decrease fecal bacterial β-glucuronidase, which leads to increased fecal excretion and a decreased plasma concentration of estrogen (Goldin *et al.*, 1980, 1982; Goldin & Gorbach, 1984; Han *et al.*, 2005). Other factors which diminish β-glucuronidase activity include oral antibiotic treatment (Hämäläinen *et al.*, 1987), lactic acid bacteria probiotics (Goldin & Gorbach, 1984), high-fiber diet (Gorbach, 1984), cellulose-fructooligosaccharides (FOS) diet (Gudiel-Urbano & Goñi, 2002), cabbage and sweet pepper pectin protein complexes (Borisenkov *et al.*, 2011), calcium-D-glucarate (Zóltaszek *et al.*, 2008), silymarin (Kim *et al.*, 1994), ascorbic acid (Young *et al.*, 1990) and yoghurt (de Moreno de LeBlanc & Perdigón, 2005). In turn bile salts enhance β-glucuronidase activity (Fujisawa & Mori, 1996), while weight loss elevates its fecal level (Flores *et al.*, 2012*b*). Advanced age and childhood are associated with higher β-glucuronidase activity than middle age, probably due to microflora composition changes throughout life (Goldin & Gorbach, 1977; Mroczyńska & Libudzisz, 2010).

In addition to the ability of deconjugation of steroid hormone glucuronides, intestinal bacteria are also able to interconvert steroid derivatives. *Alcatigenes faecalis*, *Pseudomonas aeruginosa, Staphylococcus aureus* and *Bacteroides fragilis* interconvert E2 to E1 and participate in regulation of E2 concentration (Järvenpää *et al.*, 1980). Other reactions performed by intestinal bacteria include: E1 formation from E1-3-sulfate, estriol (E3) from 16α-OHE1, 16-ketoE2 reduction to 16-epiE3 (Macdonald *et al.*, 1983). Ampicillin treatment diminishes reductive metabolism of estrogens in intestine, thus increases E1/E2 and E2/E3 ratio in both urine and feces (Adlercreutz *et al.*, 1984). Catechol estrogens 2-OHE1 and 2-OHE2 are interconverted by human fecal bacteria in anaerobic and aerobic conditions (Järvenpää *et al.*, 1980). Fecal flora is capable of formation of catechol estrogens from metoxyestrogens. It follows that bacteria are able to convert biologically inactive estrogens into active forms (Axelson & Sjövall, 1983).

Gingival bacteria, similarly to the intestinal ones are capable to metabolize sex hormones (García-Gómez *et al.*, 2013). During the pubertal period gingivitis rate significantly increases and this effect is thought to be related with higher concentration of steroids in saliva, which may be the carbon source for gingivitis-related bacteria as *Prevotella intermedia*. This species uptakes estrogens and P4, when its important growth factor, vitamin K, is unavailable (Kornman & Loesche, 1982).

Bacterial colonization of germ-free mice led to the normalization of estrous cycles and increase of reproduction, probably due to direct influence on intravaginal epithelial cells and indirect effect *via* EHC of estrogen metabolites (Shimizu *et al.*, 1998). The bidirectional connection between vaginal microflora and estrous cycle was also the conclusion of other studies (Minami *et al.*, 1987).

Van Wiele et al. showed that colon microbiota are able to bioactivate ingested polycyclic aromatic hydrocarbons (PAHs) like naphthalene, phenanthrene, pyrene, and benzo(a)pyrene to estrogenic hydroxylated metabolites (Van de Wiele *et al.*, 2005). That conversion can exacerbate cancerogenic effect of PAHs and affect endocrine system; nevertheless the real role of estrogenic PAHs is still unclear (Gozgit *et al.*, 2004).

Another group of exogenous molecules with estrogenic activity are plant-derived phytoestrogens. Lignans and isoflavones are the best studied groups of phytoestrogens and are of interest of this article, because their activity is partly dependent on bacteria.

Flaxseeds, sesame seeds, soybean, berries and nuts are known lignan-rich foods. Lignans are classified as phytoestrogens, despite their lack of biological activity per se. Intestinal bacteria in the upper part of the large bowel convert lignans (secoisolariciresinol, pinoresinol, matairesinol, lariciresinol) to compounds with estrogenic activity called enterolignans: enterolacton (ENL) and enterodiol (END). Enterolignans induce the production of sex hormone-binding globulin (SHBG) in the liver and inhibit aromatase activity, therefore reduce the levels of free and total estrogens in circulation (Hall, 2001). Both ENL and END act as ERα agonist, however they have weaker agonist activity than endogenous estrogens (Carreau *et al.*, 2008). When endogenous estrogens level is low, ENL and END increase total systemic estrogenic effect, whereas when estrogens level is high they prevent estrogen from exerting its effects. Flaxseed-derived enterolignans decrease proliferation fraction in prostate cancer (Azrad *et al.*, 2013) and risk of colorectal adenoma (Kuijsten *et al.*, 2006). They may increase survival of postmenopausal breast cancer patients (Buck *et al.*, 2011) and lower risk of ER+/PR+ breast cancer (Touillaud *et al.*, 2007). However, other studies did not show associations between enterolignans and lower breast cancer risk (Peeters *et al.*, 2003; Zaineddin *et al.*, 2012). The main lignan, secoisolariciresinol (SECO) and its diglucoside (SDG), pinoresinol (PRS) and lariciresinol (LCS) are converted into enterolignans via multistage route to END, whereas matairesinol undergoes direct conversion to ENL (Wang *et al.*, 2010). END may then be irreversibly converted to ENL. The final ENL

to END ratio depends on type of food and individual composition of gut microflora (Bartkiene *et al*., 2011). In one study the subdominance of ENL-producing bacteria in gastrointestinal tract was found (Eeckhaut *et al*., 2008). High colon concentrations of *Peptostreptococcus productus, Eggerthella lenta* and *Clostridium coccoides,* which are able to demethylase and dehydroxylate SECO are associated with higher serum enterolignans level (Clavel *et al*., 2005). To conclude, microflora composition affects bioavailability of enterolignans and therefore its action.

Human intestinal flora metabolizes also another class of phytoestrogens, isoflavones in similar to lignans way. *Fabaceae* is the plant family, which members (e.g. soybean) almost exclusively produce isoflavones. Dietary isoflavones occur in the form of glycosides: genistin, daidzin and glycitin, which are bioactivated by bacterial β-glucosidases in colon to aglycones: genistein, daidzein and glycitein. Daidzein is further metabolized to S-(-)equol and O-desmethylangolensin (O-DMA). Interestingly, not all people are able to produce these derivatives - the first can be found only in 20–60% (so called "equol-producers") and the latter in 80–90% of the population (Atkinson *et al*., 2005). Some studies indicate that ability to produce these metabolites, especially equol, is associated with lower risk of breast and prostate cancer, acne and male-pattern baldness (Lund *et al*., 2004). Intestine-derived S-(-)equol is a selective ERβ agonist and antiandrogen. Mechanism of its antiandrogenic effect is associated neither with 5α-reductase inhibition nor with binding to androgen receptor, but rather with direct binding to dihydrotestosterone (DHT) (Setchell *et al*., 2005). Equol non-producers have probably higher risk of some diseases (e.g. prostate cancer) than equol-producers (Akaza, 2012). It was demonstrated that supplementation of equol-producing bacteria may convert non-equol producer into an equol-producer (Decroos *et al*., 2006). *Lactococcus garvieae* is used to produce S-(-)equol rich substance, called SE5-OH (Yee *et al*., 2008). Supplementation with this food ingredient improved mood in perimenopausal/postmenopausal equol non-producers (Ishiwata *et al*., 2009). There are some differences in estrogen metabolism by fecal bacteria between equol-producers and non-producers. The latter are more likely than former to convert E1 to E2, and l6α-OHE1 to E3 (Atkinson, 2004). Increased E2 and E3 formation may have mutually exclusive effects in evaluation of breast cancer risk.

Interestingly, amongst species capable of soy milk isoflavone bioconversion are lactic acid bacteria which are also potentially able to influence the renin-angiotensin hormonal system (Yeo & Liong, 2010). These bacteria have special proteolytic enzymes and produce angiotensin-I-converting enzyme (ACE) inhibitory peptides from milk proteins. Inhibitory peptide mixtures are resistant to digestive enzymes and dairy processing (Gobbetti *et al*., 2000). Significantly lower pressor effect after intravenous angiotensin I injection, was observed in rats which were pre-fed with milk fermented using certain strains of *Lactobacillus helveticus* (Fuglsang *et al*., 2003).

## Androgens

*B. fragilis* reversibly reduces 17-keto group of A4 to a 17β-hydroxy derivative — T (Winter *et al*., 1984*b*), whereas a steroid-inducible 17α-HSD, capable of converting T to epitestosterone (epiT) was isolated from *Eubacterium sp*. VPI 12708 (de Prada *et al*., 1994). It is possible that intestinal microbiota are capable of epimerizing T to epiT, when both activities are present. EpiT is a hormone which regulates some androgen-dependent action and inhibits 5α-reductase (Stárka, 2003). Pathways which contribute in T-epiT interconversion were not conclusively identified in human, so one cannot exclude significant role of microbiota in this process (Bellemare *et al*., 2005). These findings suggest possible role of microbiota in the regulation of T level and release of excessive androgens in humans (Donova *et al*., 2005).

*Clostridium scindens* belongs to the small number of intestinal bacterial species capable of bile acid 7α/β dehydroxylation, which leads to formation of secondary bile acids (Winter *et al*., 1984*a*). Furthermore, *C. scindens* possess steroid-17,20-desmolase which converts corticosteroids to androgens (Bokkenheuser *et al*., 1986; Krafft *et al*., 1987). In this process cortisol is transformed into 11-β-hydroxyandrostendione (11-OHA4), which is reabsorbed into the bloodstream and excreted in the urine (Ridlon *et al*., 2013). Since its discovery in 1953, 11-OHA4 has been a molecule of unknown biological significance. 11-OHA4 has insignificant androgen activity, nevertheless, in accordance with last studies, its derivatives are important metabolites in formation of novel androgens (Bloem *et al*., 2013). The main source of 11-OHA4 in humans is adrenal cortex, but intestine-derived 11-OHA4 may be also the important source of androgens precursors.

Studies conducted in nonobese diabetic (NOD) mouse model of type 1 diabetes (T1D) showed that in germ free (GF) environment gender bias in T1D had diminished (Markle *et al*., 2013). Relative to GF males, specific pathogen free (SPF) males had significantly higher levels of T. Interestingly, after transplantation of microbiome from SPF males to females, recipient T levels had elevated and T1D morbidity had decreased. Similar results were observed in another study (Yurkovetskiy *et al*., 2013). These findings indicate a key role of microbiome in determining host T level and sex differences in susceptibility to autoimmune diseases. *Lactobacillus reuteri* in drinking water prevents aging male mice from age-related testicular atrophy and elevates theirs T level, probably acting on hypothalamic-pituitary level (Poutahidis *et al*., 2014). Authors of this study theorize that microbial impact on host T level may favor evolutionary success for the microbe and mammalian host. In general, GF compared to conventional mice have significantly lower weights of testis, epididymis, ductus deferens, kidneys, and adrenals (Fujiwara *et al*., 1990).

Gingival pathogens, *Aggregatibacter actinomycetemcomitans*, *P. intermedius* and *Porphyromonas gingivalis* are capable of reducing T to DHT and increase DHT synthesis by fibroblasts (Soory, 1995). *Bacillus cereus* and *Streptococcus mutans* also possess 5α-steroid reductase activity and moreover, 3β-, 17β- and 20α-HSDs, which allows them to metabolize T and P4 within easy reach in the gingival tissues. During inflammatory periodontal disease, local elevated DHT level foster fibroblast metabolism and matrix production, thus has an impact on inflammatory repair. On the other hand, DHT influence bacterial metabolism, promoting gene expression which facilitates survival and dissemination of bacteria (Markou *et al*., 2009).

Thus, we propose a new term, analogous to estrobolome, the "androbolome". Detailed analysis of bacterial genes involved in androgens metabolism is necessary to understand a role of microbiome in androgen-dependent conditions like baldness, acne and prostate cancer.

## Progestins

*C. innocuum* synthesize the 3α-5β-reductase and *C. paraputrificum* the 3β-5β-reductase which are involved in in-

activation of natural and synthethic progestins by reduction in the ring A (Bokkenheuser *et al.*, 1983). Nevertheless, synthetic progestins, which are used as contraceptives, are much more resistant to reducing enzymes than natural analogs.

Reports on the impact of concomitant use of oral contraceptives and antibiotics on contraception effectiveness are contradictory (Weisberg, 1999; Dickinson *et al.*, 2001; DeRossi & Hersh, 2002; Toh *et al.*, 2011). Rifampicin induces hepatic microsomal enzymes, thus facilitates oral contraceptive (OC) inactivation, whereas other commonly used antibiotics have neither pharmacokinetic nor pharmacodynamic interactions with OC. Probably rare cases of failure of OC associated with antibiotic use are caused by reduction of some microbial populations with β-glucuronidase activity and substantial loss of EHC of hormones.

As mentioned before, LPS reduces placental endocrine function. LPS administration to pregnant mice and ascending intrauterine infection in pregnant rabbits results in rapid P4 decrease and preterm parturition (Fidel *et al.*, 1998).

## THYROID HORMONES

The very first hypothesis concerning the role of intestinal bacteria in thyroid function appeared in early 1900s (Smith, 1982). Sir Arbuthnot Lane theorized that chronic constipation may lead to systemic dysfunction, including "exopthalmic goitre" (Graves disease) due to toxin absorption from intestine. Basing on this theory D. J. Harries concluded that intestinal bacteria unbalance leads to Graves disease due to an excessive absorption of tryptophan from the intestine, whereas parenchymatous goiter — from an excessive destruction of tryptophan (Harries, 1923). Current studies suggest that sir Lane was not completely wrong, because LPS actually influences thyroid function.

Nonthyroidal illness syndrome (NTIS, euthyroid sick syndrome) is a condition characterized by clinical euthyroidism with low triiodothyronine (T3), total thyroxine (T4), and normal or low thyroid stimulating hormone (TSH) concentration (McIver & Gorman, 1997). NTIS is usually associated with serious disease (either infectious or non-infectious) or wasting. The Gram-negative bacterial LPS exposure may participate in pathogenesis of this condition in several ways. Endotoxin directly and by induced cytokines inhibits hepatic type I iodothyronine deiodinase (D1), that converts T4 to T3 (Yu & Koenig, 2000) and induces the type II iodothyronine deiodinase (D2) in the mediobasal hypothalamus and anterior pituitary gland (Baur *et al.*, 2000; Fekete *et al.*, 2004). Induction of D2, that converts T4 to T3, in the central nervous system may cause suppression of TRH and TSH release. These effects are partly dependent on competition for limiting amounts of coactivators caused by the surplus of cytokines. IL-1, IL-6, TNFα signaling pathways include NF-ϰB and AP-1, which interact with SRC-1 thus decreasing its availability for other pathways. SRC-1 in healthy individual increases the expression of hepatic D1 gene and its deficit decreases D1 activity (Yu & Koenig, 2000; Boelen *et al.*, 2004). It is worth pointing out that thyroid changes observed after combined administration of IL-1α, TNFα, IL-6 and IFNγ are smaller than after administration of LPS (Boelen *et al.*, 1995). Another mechanism responsible for NTIS during infection is LPS influence on thyroid hormone receptor (TR) in the liver. LPS decreases RXR and TR expression in hepatic extracts, reducing RXR/TR DNA binding (Beigneux *et al.*, 2003).

$Na^+/I^-$ symporter (NIS) plays a crucial role in thyroid physiology by participating in iodide uptake which is the main rate-limiting step in thyroid hormonogenesis. TSH induces NIS expression and stimulates its transport to basolateral membrane of thyrocytes. In turn, iodide inhibits NIS expression and increases NIS protein turnover, which contributes to the reduction of thyroid hormones' levels after treatment with large amounts of iodine (Wolff-Chaikoff effect) (Bizhanova & Kopp, 2009). Studies conducted on Fisher rat thyroid cell line FRTL-5 revealed that LPS binding to TLR-4 on thyroid cells activates NF-ϰB pathway, which leads to the p65 subunit of NF-ϰB interaction with a specific ϰB site at the NIS enhancer (Nicola *et al.*, 2010). Consequently, TSH-induced NIS expression and iodide uptake are stimulated (Nicola *et al.*, 2009). Thyroglobulin (TG) gene expression is also enhanced by LPS, which acts with the involvement of Pax8 and TTF-1(Vélez *et al.*, 2006). Apart from transcriptional level, LPS modifies TG expression also at posttranscriptional and posttranslational levels.

The exact role of these changes in thyroid hormone metabolism is unclear. Some authors postulate that NTIS should be treated with levothyroxine, despite clinical euthyroidism (Warner & Beckett, 2010). On the other hand, low T3 concentration may be associated with lower energy expenditure and be beneficial in serious infection. Then, reaction of thyroid gland to bacterial LPS could be an adaptive change and proper physiological reaction to bacterial invasion.

Gut condition is strongly associated with thyroid function (Ebert, 2010). Hypothyroidism may lead to heartburn, dysphagia, vomiting, dyspepsia, intestine motility disorder and constipation. In turn, hyperthyroidism may be associated with diarrhea. Thyroid hormones' influence on gut condition is dependent on their direct action in enterocytes. T3 induces intestinal alkaline phosphatase (IAP) and represses lactase gene transcription in these cells, thus regulates their differentiation and function (Meng, 2001). SCFAs produced by the resident microbiota in the intestine lumen may accompany T3 in these processes. SCFAs (butyrate, propionate, acetate) are used by enterocytes as an energy source and are involved in regulation of host appetite and glucose level. They are mainly produced by *Clostridium sp.,* which belong to the Gram-positive phylum of bacteria, *Firmicutes*. Most of their effects is exerted via free fatty acid receptors (FFAR) 2 and 3 (former G-protein coupled receptors (GPR) 43 and 41), locally in colon (Lin *et al.*, 2012). They stimulate release of incretins, GLP-1 and PYY by intestinal cells L (Tolhurst *et al.*, 2012). Nevertheless SCFAs are absorbed into bloodstream and SCFAs sensing receptors are expressed also in immune cells, adipose tissue and peripheral nervous system (Georgiadi & Kersten, 2012). Main effects of SCFAs on endocrine system seem to be related to energy homeostasis - insulin sensitivity increases after SCFAs treatment, while in adipose tissue the SCFAs improve leptin secretion. These molecules are considered beneficial, improving colon function and carbohydrate metabolism. However, studies performed in vitro suggest that SCFAs may modulate hormonal system function in various locations, such as anterior pituitary gland, where they suppress GH secretion (Ishiwata *et al.*, 2000, 2005) and enhance T3-induced stimulation of prolactin expression (Stanley & Samuels, 1984).

SCFAs inhibit histone deacetylase HDAC-1 activity and activate the Mitogen-Activated Protein Kinase (MAPK) signaling pathway, which leads to hyperacetyl-

ation of some histones and hyperphosphorylation of nuclear receptors (NR) coactivators, which in turn increases transcription of various NR, such as TR (Meng *et al.*, 1999; Jansen *et al.*, 2004). This leads to the enhancement of TRβ-1 function and increases the T3-dependent IAP induction. IAP is a marker of crypt-villus differentiation, so we can conclude that bacterial SCFAs and host T3 cooperate in maintaining the proper intestinal epithelial development and homeostasis (Malo *et al.*, 2013).

Varian et al. showed that *L. reuteri* supplementation improve function of thyroid gland in mice. *L. reuteri* consuming mice had higher fT4 levels, higher mass of thyroid gland tissue and increased height of the thyroid glandular epithelia as compared with their untreated counterpart (Varian *et al.*, 2014). Mice treated with *L. reuteri* were also slimmer, more active and had healthier skin than control mice, which correlated with fT4 levels. These bacteria induce interleukin-10 production in the intestine, which stimulates host immune tolerance, triggered by anti-inflammatory CD25+ regulatory T cells. In CD25+-depleted mice, *L. reuteri* supplementation was not beneficial for the thyroid function. Positive effects of bacteria on the thyroid function were also observed in other animals. For instance, female GF rats have smaller thyroids than CV (Vought *et al.*, 1972). Moreover, lactic acid bacteria supplementation in the broiler chicken diets increased the blood plasma thyroid hormone level (Sohail *et al.*, 2010; Chotinski & Mihaylov, 2013). It is suggested that positive impact of probiotics on testicles, thyroid and probably ovaries in animals, inducing changes in GI microbiome composition may affect both the endocrine and immunological systems, thus influencing aging course (Varian *et al.*, 2014).

Sulfation of T4 and T3 in the liver significantly facilitates deiodination by D1 to inactive derivatives rT3 and T2 (Wu *et al.*, 2005). Under some conditions like prophylthiouracyl treatment, fetal development, selenium deficiency, or NTIS when D1 activity is low, sulfoconjugates may be hydrolyzed to bioactive T4 and T3 due to expression of sulfatases in different tissues and by intestinal bacteria (Kester *et al.*, 2002). However, the significance of gut microflora in maintaining T3 level under conditions of reduced D1 activity is disputed (Veronikis *et al.*, 1996). Physiologically about 20% of serum T3 is of intestine origin and T3-sulfate (T3S) is a reservoir, which can be recovered by sulfatases. Similarly, major billiary-excreted T3 metabolite — T3 glucuronide — may be hydrolyzed by microflora, which enables EHC of thyroid hormones (de Herder *et al.*, 1989; Rutgers *et al.*, 1989). Gut may be an important site in production of bioactive thyroid hormones and intestinal dysbiosis may lead to reduced T3S to T3 conversion and to T3 enterohepatic cycle dysfunction. One study suggests that intestinal bacteria are even capable of deiodination of thyroid hormones (DiStefano *et al.*, 1993). However, this finding remains unconfirmed.

7α-dehydroxylation of primary bile acids by intestinal microbiota results in formation of secondary bile acids: lithocholic and deoxycholic. Main 7α-dehydroxylating species isolated from human feces include *Clostridium* and *Eubacterium* (Wells & Hylemon, 2000). Taurine-conjugated secondary bile acids, taurolithocholic acid and taurodeoxycholic acid are the most potent TGR5 ligands. In response to these compounds, the G-protein-coupled receptor TGR5 activates and subsequently intracellular cAMP level raises. Afterward, in brown adipocytes and human skeletal myocytes induction of the cAMP-dependent D2 occurs, which promotes energy expenditure (Watanabe *et al.*, 2006). Paradoxically, some studies show that GF rats have significantly higher T3 to T4 ratio in the blood plasma than conventional animals (Ukai & Mitsuma, 1978). It is possible that greater reabsorption of bile acids in these animals may lead to enhanced T3 producing enzymes expression (Wostmann, 1973).

## GROWTH HORMONE

GH is secreted by anterior pituitary gland in a pulsatile manner dependent on the action of GH releasing hormone (GHRH) and ghrelin, which stimulates GH secretion, and somatostatin which inhibits GH secretion (Vijayakumar *et al.*, 2010). The physiological effects of GH results from direct by interacting with a specific receptor on the surface of cells and stimulation of insulin growth factor 1 and 2 (IGF-1 and -2) secretion by liver.

*Lactobacillus plantarum* may promote *Drosophila* systemic growth by affecting the TOR-dependent host nutrient sensing system controlling hormonal growth signaling (Storelli *et al.*, 2011). Similarly, *L. rhamnosus* administration to zebrafish cause elevation of IGF-I, IGF-II, thus accelerates backbone calcification (Avella *et al.*, 2012). It has been hypothesized that intestinal microbiota may also influence growth of mammals. For instance, in rabbits fed with probiotics, GH level elevates (Ghoneim & Moselhy, 2013), whereas human infants fed with formula enriched with *L. rhamnosus* GG grew better compared to their control counterpart (Vendt *et al.*, 2006).

LPS is a known exogenous factor which affects GH secretion and action (Figure 2). Studies performed on rats and domestic fowls revealed that LPS causes GH release inhibition (Curtis *et al.*, 1980; Kasting & Martin, 1982), whereas in human and sheep transitionally enhances GH secretion, probably acting on pituitary level (Lang *et al.*, 1997; Briard *et al.*, 1998; Daniel *et al.*, 2002). Despite sustained increase in GH concentration, LPS injection results in a state of resistance to GH. LPS increases the production of proinflammatory cytokines like TNF-α, interleukin-1β (IL-1b), and interleukin-6 (IL-6). TNF-α suppresses GH receptor (GHR) expression by reduction of transactivators Sp1/Sp3 binding to a GHR promotor (Denson *et al.*, 2001), IL-6 up-regulates strong inhibitor of GH intracellular signal transduction, SOCS-3 (Wang *et al.*, 2002*a*; Denson *et al.*, 2003). Other mechanisms of LPS-dependent GH resistance are: decrease in IGF-1 concentration caused by liver cyclooxyganase-2 activation (Briard *et al.*, 2000; Wang *et al.*, 2002*b*; Martín *et al.*, 2008), direct suppression of GHR expression by MyD88-dependent and -independent TLR4 signaling pathways (Dejkhamron *et al.*, 2007) and promotion of proteolytic GHR cleavage (Wang *et al.*, 2008). Moreover, the ability of GH to promote phosphorylation of signal transducer and activator of transcription (STAT) in the liver is reduced during sepsis (Hong-Brown *et al.*, 2003). Furthermore, LPS administration alters IGFBP serum concentrations. In normal condition, IGFBP-3 forms a stable ternary complex with IGF and the acid labile subunit (ALS), so that IGF half-life is extended, IGFBP-1 serves as an inhibitor of IGF bioactivity, whereas IGFBP-2 is an optional IGF carrier in condition of low IGFBP-3 level (Donaghy & Baxter, 1996). LPS administration promotes increased IGFBP-3 proteolysis in serum and/or its decreased synthesis in the liver (Priego *et al.*, 2003), while IGFBP-1 accumulates in certain tissues, like skeletal muscles and blocks IGF-dependent protein synthesis (Frost & Lang, 2004).

These studies may be crucial to understanding the mechanism of growth failure in children with inflamma-

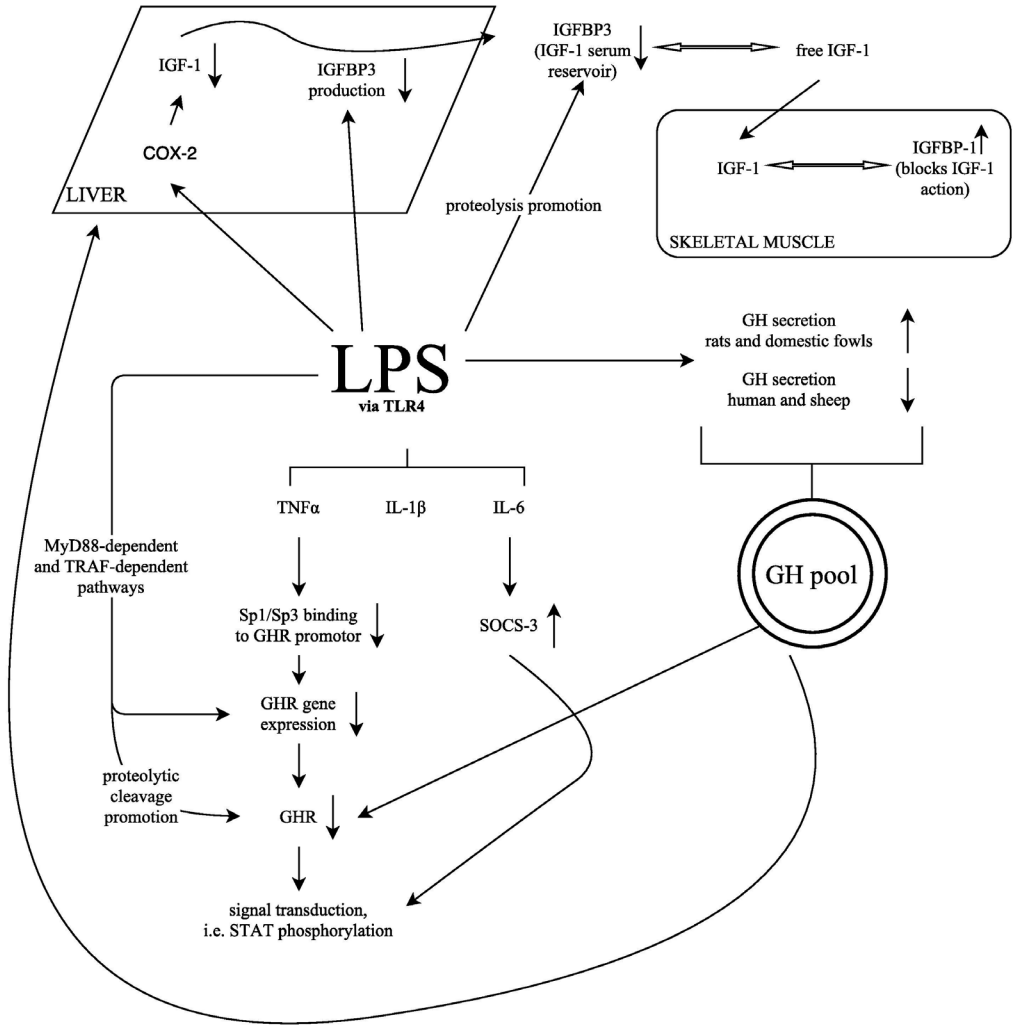


**Figure 2. LPS influence on GH action.**
Details, see main text. COX-2, cyclooxygenase-2; IGF-1, insulin like growth factor 1; IGFBP3, IGF binding protein 3; GH, growth hormone; GHR, GH receptor; LPS, lipopolysaccharide

tory bowel diseases (IBD). Due to increased intestinal permeability, systemic endotoxemia is a common finding in these patients and may underpin extra-intestinal complications. Chronic elevation of LPS binding protein (LBP) serum level has been proposed as a potentially useful marker of high refractory growth failure risk in pediatric IBD (Pasternak *et al.*, 2010). During chronic infection or after sepsis, GH resistance develops in peripheral tissues, that may result for instance in muscle mass loss. Thus, LPS-dependent pathways leading to GH resistance may become the future therapy targets.

Another mechanism of bacteria-associated growth failure in children is observed in *Helicobacter pylori* carriers. An assessment of the anti-*H. pylori* antibodies in GH deficient short stature group, an idiopathic short stature group and control group, revealed that in children with idiopathic short stature the antibody positivity rate was significantly higher than in other groups (Takahashi *et al.*, 2002). Possible explanation of this effect is decreased ghrelin production by enteroendocrine cells in the gastric mucosa. Ghrelin is a GH releasing peptide as a GH secretagogue type 1A receptor (GHSR) ligand and has an important role in maintaining energy homeostasis and regulation of hunger. Chronic damage of gastric ghrelin-positive cells during *H. pylori* infection leads to decreased GH secretion, impaired hunger signals and in consequence growth retardation. Importantly, body composition improves in children after therapy (Osawa *et al.*, 2006). Surprisingly, in some patients after *H. pylori* eradication, plasma ghrelin concentrations decrease and BMI increases (Pacifico *et al.*, 2008). These variances may be dependent on the strain of bacteria: type I (producing the *cag*) is associated with lower ghrelin concentration than type II (without virulence factors), so eradication of different strains may lead to different effects (Deng *et al.*, 2012).

Maternal oral *Campylobacter rectus* or *P. gingivalis* infection may cause intrauterine growth restriction (IUGR). These bacteria may invade placental tissues and promote hypermethylation in the promoter region-P0 of the Igf2 gene (Bobetsis *et al.*, 2007). TLR-4 knockout mice do not develop IUGR phenotypes after systemic *C. rectus* infection, which emphasizes the crucial role of this receptor in placental immunity (Arce *et al.*, 2012).

## PARATHYROID HORMONE AND GUT-KIDNEY AXIS

Due to the deterioration of renal clearance during chronic kidney disease (CKD), many compounds accumulate and contribute to the uremic syndrome. These

molecules, called uremic toxins are classified as: small water-soluble compounds (urea, guanidines, oxalate, phosphorus, polyamines), protein-bound compounds (p-cresol and p-cresylsulfate, indoles, homocysteine, furanpropionic acid) and middle molecules (β2-microglobulin, PTH) (Duranton *et al.*, 2012). The originator of some uremic toxin is colon microbiome, which changes its composition during CKD. Low dietary fiber intake and impaired protein assimilation in the small intestine decreases carbohydrate to protein ratio in colon, thus promoting proteolytic bacterial species over saccharolytic ones. SCFA production by Lactobacillaceae and Prevotellaceae families decreases, whereas Bacteroides family overgrows and generates toxic solutes (Poesen *et al.*, 2013). Gut bacteria convert tryptophan to indole, which is hydroxylated and sulfonated to indoxyl sulfate (IS) in the liver, whereas p-cresyl sulfate (PCS) is the product of bacterial tyrosine degradation followed by sulfate conjugation. Bone mineralization deficiency in CKD is called renal osteodystrophy. Endocrine changes which cause this condition are secondary hyperparathyroidism (SHP) and low vitamin D activation rate in kidneys. SHP in CKD may be a result of phosphate retention, hypocalcemia, decreased production of or resistance to calcitriol, abnormal sensitivity to calcium, direct effects of phosphate and skeletal resistance to PTH (Fukagawa *et al.*, 2002). The mechanism of the latter stimulus, skeletal resistance to PTH, is related to IS and PCS produced by anaerobic bacteria. IS is taken up by osteoblasts via organic anion transporter 3 (OAT3) and afterward increases intracellular free radical production. Furthermore, IS down-regulates PTHR gene and decreases PTH-induced cAMP production in osteoblasts, that might lead to skeletal resistance to PTH (Nii-Kono *et al.*, 2007; Goto *et al.*, 2010).

Uremic toxins produced by bacteria might have an impact on function of other hormones. For instance, PCS activates ERK1/2 in mice skeletal muscle, thus promoting insulin resistance (Koppe *et al.*, 2013). Also, uremic patients usually have low total T3 level, which may be caused by inhibition of T4 hepatocyte transport and subsequent T4 deiodination by IS (Lim *et al.*, 1993).

## CONCLUSIONS

Bacterial influence on endocrine system is difficult to understand and investigate, however new metabolomics and bioinformatics research provide information about bidirectional cross-talk between host hormones and microbiome. This knowledge is necessary to comprehend hormonal changes during a bacterial infection, antibiotic or probiotic treatment and diet modifications. Rational modifications of intestinal flora may decrease some hormone-dependent diseases risk, like breast and prostate cancer.

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