

# THE HUMAN MICROBIOME

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The symbiotic relationship with the microbial flora inhabiting our bodies plays an immense role in maintaining our vitality. The microbiota protects us from pathogens, hardwires our immunity, and engages in the production of essential micronutrient components. The human microbiota encompasses several thousands of fungi, eubacteria, archaea and viruses, with eubacterial cells alone totaling over 10 trillion and outnumbering our body cells 100 to 1. Next generation sequencing has allowed researchers to comprehensively assess the diversity of microbial species in the human microbiota and to estimate their proportions with stunning accuracy. This has led to a breakthrough in our understanding of associations between human health and the microbiota. This review focuses on the current state of research on key microbial communities inhabiting the human body: those of the gastrointestinal and genitourinary systems. Less studied microbial communities colonizing the nose, nasopharynx, auditory canal, eye, and skin, as well as some others, are not included in the review.

**Keywords:** microbial community, gut flora, genitourinary, periodontal, metagenome, next generation sequencing

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# МИКРОБИОМ ЧЕЛОВЕКА

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Симбиотическая микрофлора играет огромную роль в обеспечении здорового состояния нашего организма. Она защищает от патогенов, поддерживает иммунитет, обеспечивает производство важных компонентов питания. Микробиота человека включает, по всей видимости, несколько тысяч видов грибов, эубактерий, архей и вирусов. Суммарное количество клеток только зубактерий в составе микробиоты превышает десять триллионов, что в сто раз больше числа собственных клеток организма человека. С появлением методов высокопроизводительного секвенирования исследователи получили возможность очень точной и комплексной оценки всего микробного сообщества с глубиной до тысячных долей процента (по содержанию микроба). Это позволило выйти на новый уровень понимания взаимосвязи здоровья человека и состояния его микробиома. В данном обзоре представлено современное состояние исследований ключевых микробных биоценозов человека — пищеварительного и урогенитального трактов. Менее изученные биоценозы носа и носоглотки, слухового канала, глаз, кожи и ряд других в обзор не вошли.

**Ключевые слова:** микробный биоценоз, микрофлора кишечника, урогенитальный, пародонтальный, метагеном, высокопроизводительное секвенирование

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## The gut microbiome

The human gut microbiota is one of the most actively studied microbial communities. It is incredibly complex in composition and interacts extensively with the human host. The role of the gut microbiota in pathology has been increasingly hypothesized, and the evidence to support those theories is still growing.

The human gut microbiota goes through a number of development stages until it is finally shaped. First, the fetus is colonized *in utero* by the bacteria coming from maternal sources, including the intestines, oral cavity and vagina [1]. Second, when going through the birth canal, the baby picks up another lot of its mother's microbes [1]. Besides, breast milk is not sterile and contains substantial amounts of bacteria,

such as *Streptococcus*, *Staphylococcus*, *Propionibacterium*, and *Bifidobacterium* [2]. The early postnatal gut microbiota is abundant with *Bifidobacterium* species [3] that thrive on human milk oligosaccharides. By the age of two, *Bifidobacterium* species become less abundant and the gut microbiota of the child starts to resemble that of an adult [3]. In infants born by caesarian section the composition of the gut microbiota in the first few months after birth is different from that of vaginally born children, which may be explained by the lack of contact with the vaginal microbiota of the mother, her exposure to antibiotics or the delayed onset of breastfeeding [3, 4].

The gut microbiota of adults encompasses over 600 microbial genera [5]. The *Firmicutes* and *Bacteroidetes* phyla together make up about 90 % of the microbial community, in which they are mainly represented by poorly culturable obligate anaerobes. In the European population *Firmicutes* are normally represented by *Faecalibacterium prausnitzii*, *Blautia*, *Dorea*, *Roseburia*, and *Coprococcus*. Intestinal *Bacteroidetes* are usually represented by *Bacteroides*, *Parabacteroides*, *Prevotella*, *Odoribacter*, *Barnesiella*, and *Alistipes* [5, 6]. A few percent of the gut microbiota of adult humans are made up of *Actinobacteria* and *Proteobacteria* [5, 7], the proportion of *Fusobacteria*, *Verrucomicrobia*, and methanogenic archaea *Euryarchaeota* is even smaller [5, 8].

Members of the gut microbiota have complex symbiotic and antagonistic relationship influencing the abundance of each group. Therefore, some of the compositional patterns - discrete and stable clusters called enterotypes - will occur more frequently in the population than their gradient forms. Researchers distinguish between three major enterotypes depending on whether the latter are rich in *Bacteriodes*, *Prevotella*, or *Ruminococcaceae*, respectively [5, 9]. Unfortunately, this classification cannot describe the real diversity of qualitative and quantitative characteristics of intestinal microbial communities. Gut microbiota composition is affected by dietary and smoking habits, age, body mass index, levels of hemoglobin and red blood cells in the blood, and exposure to antibiotics [5]. Diet has also been speculated to be a source of marked interpopulation differences in the microbiota composition [7, 8]. Although the term "dysbiosis" is readily used to describe the state of the microbial community that contributes to pathology, the "normality" of the gut microbiota composition is a matter of controversy.

The gut microbiome profusely synthesizes substances capable of entering the bloodstream and affecting distal organs and systems. Some researchers even called the gut microbiome a "virtual endocrine organ" [10, 11]. Members of the gut microbiota can secrete into the blood stream such agents as serotonin, gamma-aminobutyric acid, histamine, acetylcholine, dopamine, and noradrenaline [11]. They also produce a number of ligands that bind to the receptors of the innate and adaptive immune systems, such as flagellin, formyl methionine-containing peptides, lipopolysaccharides, and capsular polysaccharides (polysaccharide A of *Bacteroides fragilis*) [12].

There has been considerable focus on short-chain fatty acids, the end-products of carbohydrate fermentation carried out by microbial communities under anaerobic conditions of the intestines. These are usually acetic, propionic and butyric acids produced at a molar ratio of 3 : 1 : 1 [11, 13]. They are rapidly and efficiently absorbed in the intestines, with only 5 to 10 % excreted in feces [13].

Short-chain fatty acids exert their functions through a variety of mechanisms. First, they can be used by our body cells to harvest energy produced during oxidative phosphorylation.

Butyric acid alone can cover 60 to 70 % of colonocytes' energy needs [13]. Second, short-chain fatty acids inhibit histone deacetylase and thus down-regulate inflammation: they modulate transcriptional activity of NF- $\kappa$ B factors, reduce production of TNF- $\alpha$  and induce maturation of FoxP3<sup>+</sup> T<sub>reg</sub>-cells [12]. Third, short-chain fatty acids can specifically bind to a few G-protein-coupled receptors, namely GPR41, GPR43 and GPR109A [12, 13]. These receptors are involved in regulating the growth and activities of microglia, dendritic cells and Tregs [12].

The range of short-chain fatty acids' activities is not limited to their effect on the immune system. They also induce proliferation of intestinal goblet cells and stimulate mucin production [12]. Being a substrate for gluconeogenesis and lipogenesis, they participate in the regulation of carbohydrate and lipid metabolism in the liver [13]. They also have been shown to suppress appetite by stimulating secretion of leptin in adipocytes and inducing production of YY peptide and glucagon-like peptide-1 in the L-cells of the gastro-enteropancreatic endocrine system [13]. Indeed, one of the most important functions of the gut microbiome is to produce short-chain fatty acids essential for human health

The gut microbiota is also responsible for protecting the intestine from pathogen dissemination which can be controlled through competition for nutrients [14]. Another mechanism of colonization resistance is mediated by special antimicrobial proteins and peptides, the so-called bacteriocins, produced by the gut microbiota [15]. Antimicrobial activity is also conferred on secondary bile acids, products of dehydroxylation of primary bile acids by members of the gut microbial community, such as *Clostridium scindens* [16].

Among all human diseases *Clostridium difficile*-associated disease is most obviously linked to shifts in the gut microbiota composition. Its clinical signs may vary from mild diarrhea to lethal systemic inflammatory response syndrome [17]. *Clostridium difficile* is often present in the microbiota of healthy individuals; however, intake of broad-spectrum antibiotics that disrupt colonization resistance mechanisms prompts this species to proliferate uncontrollably producing toxins that glycosylate Rho GTPase [16, 17]. There is evidence that oral intake of live probiotic cultures can be effective in preventing *Clostridium difficile*-associated disease in both children and adults [18]. One of the most effective treatments for this condition is fecal microbial transplantation. A microbial suspension prepared from the gut microbiota of a healthy donor is infused into the patient's intestines by enema, colonoscopy, nasogastric or nasoduodenal tubes [19]. There are plans to create donor banks of the intestinal microbiota that could be used for autologous fecal transplantation should it be necessary (Fig. 1). Unlike probiotic-based therapies, this technique makes it possible to transplant the entire microbial community including its poorly cultured members.

One of the most dangerous diseases typically seen in premature infants is necrotizing enterocolitis, the acute inflammatory condition of the bowel complicated by necrosis of the intestinal wall, perforation and diffuse peritonitis. According to the most recent studies, necrotizing enterocolitis is associated with hyperresponsiveness of the innate immunity to microbial colonization of the bowel [21]. The inadequate immune response can be caused by the interaction between overexpressed Toll-like receptors 4 and lipopolysaccharides found in the cell wall of gram-negative bacteria [21]. Numerous studies have described compositional changes in the gut microbiota of infants observed prior to the onset of necrotizing enterocolitis: increased abundance of *Proteobacteria* and low

levels of *Firmicutes* and *Bacteroidetes* [22]. At the moment there are reasons to believe that some probiotics can reduce incidence of severe necrotizing enterocolitis and improve survival [21, 23].

A few residents of the gut microbiota are involved in the development of colorectal cancer and are frequently detected in tumor tissues [24]. For example, *Fusobacterium nucleatum* can promote tumor growth through direct or inflammation-mediated mechanisms. In particular, interaction between the FadA adhesin produced by this species and the surface protein E-cadherin triggers a cascade of  $\beta$ -catenin-dependent oncogenic and proinflammatory signaling pathways [24]. Some strains of *Escherichia coli* are also potentially oncogenic since they produce genotoxic pathogenic factors, such as low molecular weight colibactin and protein toxin CDT [24, 25].

There has been growing evidence that the gut microbiota is involved in the pathogenesis of many other diseases, such as type 1 diabetes [26], obesity [27] and autism [28], which encourages us to believe that our knowledge about the intestinal microbiome and its role in human health will continue to expand.

### The microbiome of the oral cavity and periodontium

The oral cavity of humans teems with eubacteria, archaea, fungi and viruses — over 1000 different species in total. Residents of the oral microbiota have been linked to a wide range of conditions, including diseases of the oral cavity (caries and periodontal diseases), diabetes mellitus, cardio-vascular diseases, cancer, etc. It has been established that it is not the presence of a particular microbe that triggers disease progression but a combination of microorganisms inhabiting the oral cavity.

To study microbial communities of the oral cavity, the following types of samples are normally collected: saliva, soft deposits, sub- or supra gingival calculus, and periodontal pocket contents. In terms of composition, these communities,

except that of the periodontal pocket, are highly unstable and largely depend on dental care intensity and type. For example, one of the studies in which next-generation sequencing techniques were used allowed the researchers to estimate relative abundance of microbial residents of the subgingival plaques: 1.0–13.5 % for *Actinobacteria*, 21.4–63.5 % for *Bacteroidetes*, 14.6–30.8 % for *Firmicutes*, 4.7–12.1 % for *Fusobacteria*, 2.6–22.9 % for *Proteobacteria*, 0.04–12.9 % for *Spirochaetes*, and 0.0004–0.84 % for *Synergistetes* [29].

One of the most stable ecological niches of the oral cavity is the periodontal pocket. It is isolated from the external environment and is hardly affected by regular dental care (Fig. 2).

There has been a lot of research indicating the connection between the composition of the periodontal pocket microbiota and caries or periodontitis [30, 31]. A few authors have demonstrated the connection between periodontal microbiota composition and conditions of the lower digestive tract [32, 33]. An association between the periodontal pocket microbiota and patient's sex has been established. For example, hypercolonization of periodontal tissues by *Porphyromonas gingivalis* correlates with the severity of chronic periodontitis in women, but not in men. In contrast, *Tannerella forsythensis* alone or together with *Treponema denticola* is the only periodontal pathogen whose predominance is statistically associated with chronic periodontitis in men [34].

In their work Zorina et al. [35] analyzed the abundance of bacterial species and genera in the periodontal microbiota of patients with aggressive periodontitis and healthy individuals. It was discovered that of all studied genera 6 were potentially capable of protecting the periodontium and 8 were potentially pathogenic and associated with the risk of aggressive (but not chronic) periodontitis. The researchers demonstrated significantly increased abundance of *Porphyromonas*, *Treponema*, *Synergistes*, *Tannerella*, *Fillifactor*, *Ruminococcus*, *Parvimonas*, and *Mycoplasma*, of which three (*Porphyromonas*, *Treponema* and *Tannerella*) are conventionally considered periodontal pathogens. Interestingly, *Veillonella* was found

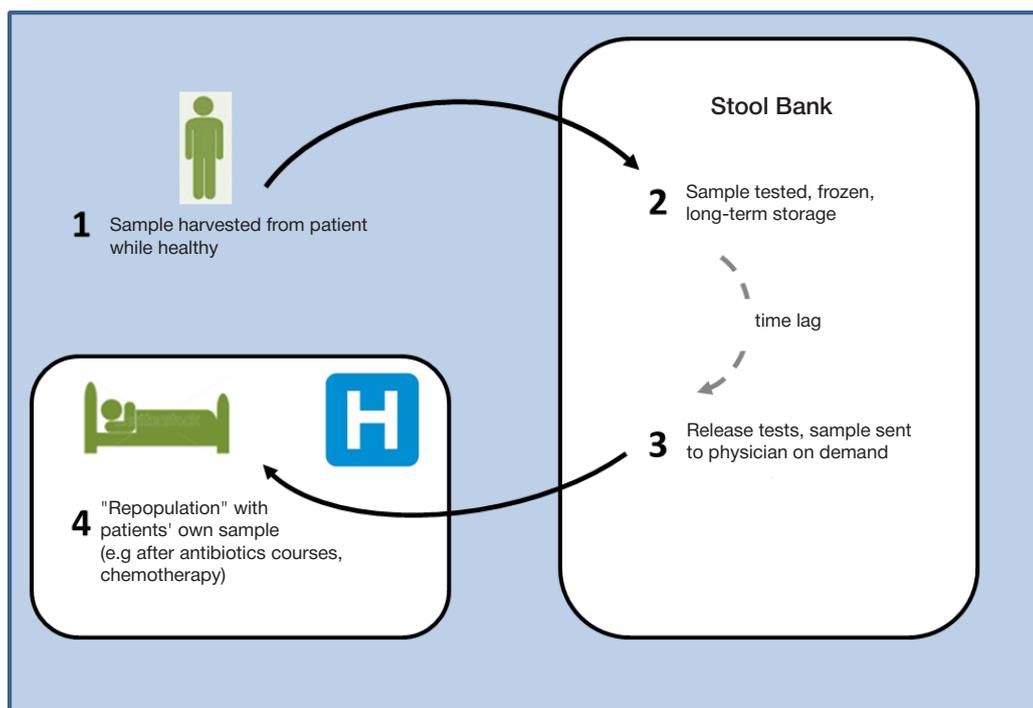


Fig. 1. Autologous stool banking for microbiota transplants (Olle, [20])

to dominate other microbiota residents in the control group, therefore it may be used as a criterion of periodontal health. The researchers also proposed to include *Streptococcus*, *Bergeyella*, *Granulicatella*, *Kingella* and *Corynebacterium* in the list of potential periodontal protectors [35].

### The microbiome of the reproductive system

It has been long known that the microbiota of the female reproductive system is very diverse. Traditionally the focus was on the vaginal microbiota, but over the past few decades sufficient evidence was obtained to prove that other parts of the female reproductive tract, including the uterine cavity, are not sterile as well [36]. It is becoming clear that the microbiota extends up and over the endometrial cavity. According to some researchers, bacteria can also be found in the fallopian tubes of healthy women.

Studies of associations between the microbiota of the reproductive tract and successful fertilization/normal pregnancy are starting only now. So far, the association has been established between clinically manifested infection, inflammation and defective reproductive function. Inflammation triggers secretion of proinflammatory cytokines and growth factors produced by immune cells that are activated in response to pathogen invasion. Even small changes in the microbiome can entail changes in the surrounding tissue that are normally less evident but can be clinically significant [37].

The normal vaginal microbiota is dominated by lactobacilli [38] that have probiotic properties and inhibit growth of other bacteria. *Lactobacilli* produce large amounts of  $H_2O_2$  and are believed to be highly beneficial. This leads us to understand that direct interaction between microbes and the surrounding tissues is possible but does not have to be the rule, and that perhaps the primary function of certain microbiome components is to inhibit expansion of other microbiota residents.

The microbiota of the reproductive system is not a mere aggregation of free-floating bacteria. In many cases these bacteria produce complex 3D biofilm structures, sometimes multilayered, consisting of polysaccharides, nucleic acids and proteins, serving as a protective coat. Sometimes these biofilms prevent the immune system from detecting a pathogen and diminish positive effects of antimicrobial treatment [39].

Biofilms usually occur in the vagina but can extend into the endometrial cavity [39] or even further upwards into the fallopian tubes. Although no definite conclusions have

been made so far about the role of such biofilms in the pathology of the reproductive system, one should have a clear understanding that the connection between the microbiome and the reproductive system may not be determined solely by the abundance or the lack of certain bacterial species.

The microbiome can affect gametogenesis. It was found that some bacteria can undermine follicular development and suppress follicular response to gonadotropin [36]. Similarly, some bacteria produce a negative effect on the reproductive system of men. Even slight changes in the microbiome can impact semen quality. The microbiome of the male reproductive system turns out to be more complex than it was thought before. As our knowledge about the microbiomes of female and male reproductive systems is expanding, we are discovering new therapeutic targets.

### The vaginal microbiome

Studies of healthy vaginal microbiota were carried out under the Human Microbiome Project [38]. Samples of 113 healthy female volunteers were used to characterize three microbial communities of the vagina: those inhabiting the vaginal introitus, the midpoint, and the posterior fornix. The samples were analyzed using 16S rRNA pyrosequencing. Alpha and beta diversities (i. e., in one individual and between different individuals, respectively) of vaginal microbial communities were described. Interestingly, the study yielded unexpected results. It was established that in comparison with other body parts, such as mouth or skin, the reproductive system harbors a microbiota with the lowest alpha and a very low beta diversities in terms of bacterial phyla [38]. Besides, the samples obtained from different regions of the vagina did not vary much in bacteria species and were dominated by *Lactobacillus*. Samples of the same donor collected at different time points varied less than samples of different individuals, indicating that the vaginal microbiota is stable over time. Vaginal microbial communities of healthy women are relatively simple in composition compared to communities inhabiting other body parts, which means that health and pathology may be associated with certain shifts in the microbiota [39].

The Human Microbiome project recruited healthy women to explore “healthy” microbiomes. There were other projects in which the association between the vaginal microbiota and infertility in women was studied. In one of such studies, a bacterial culture method was applied to prospectively analyze 152 patients who had undergone In Vitro Fertilization (IVF) treatment [40]. Samples of 133 (87.5 %) women were positive for one or more microorganisms; 19 (12.5 %) samples were negative for any microbial contamination. The most common bacteria detected in the samples were *Lactobacillus spp.*, *Staphylococcus spp.* and *Enterobacteriaceae*, including *E. coli*, *Klebsiella* and *Proteus*. Successful fertilization was observed in 12.4 % of patients positive for one or more bacterial species and in 14 % of women tested negative for any bacteria ( $p < 0.001$ ). Besides, patients who tested positive for *Enterobacteriaceae* and *Staphylococcus* were found to have lower pregnancy rates than those tested negative. Though this study provides some insight into the microbiota composition during IVF treatment, it also points out limitations of culture methods in microbiota assessment. The fact that 12.5 % of patients tested absolutely negative for bacterial contamination indicates that methods based on culture isolation seriously underestimate the abundance and diversity of microbiota residents during IVF.

Using 16S RNA sequencing, the researchers described the vaginal microbiota of the infertile patient who had undergone



**Fig. 2.** Collecting a periodontal pocket sample [Photo courtesy of Nelly Aimadinova of Central Research Institute of Dental and Maxillofacial Surgery, Moscow, Russia]

IVF treatment [40]. Poor bacterial diversity was shown to be associated with higher probability of live birth. To date, there are effective molecular and biological techniques that facilitate studies of the vaginal microbiome [41]. Robust data have been obtained on the quality of vaginal microbiota in pathology [42, 43], but research of the microbiome still goes on.

#### *The microbiome of the uterus*

Until recently it was believed that microbial colonization of the upper genital tract occurring by the ascending pathway from the vagina through the cervix could be related only to a pathological condition. Cervical mucus contains high levels of proinflammatory cytokines, immunoglobulins and antimicrobial peptides and acts as a protective barrier, which is why the uterine cavity of healthy women was long considered sterile [44–48]. However, upward transport is quite possible in a healthy reproductive tract. For example, 2 minutes after 1–2 ml radiolabeled sperm-sized macroaggregates of human serum albumin were placed into the posterior vaginal fornix, they were observed in the uterus [49].

Early studies of the uterine microbiota were carried out using culture methods, which have certain limitations described above (See *The vaginal microbiome*). In a recent study, samples of 58 women undergoing hysterectomy were tested for 12 bacterial species using quantitative PCR assays [50]. Vaginal swabs were collected before hysterectomy, while uterine swabs were collected after the surgery. Colonization of the upper genital tract by at least one bacterial species was confirmed in 95 % of cases. The most frequently observed species were *Lactobacillus* and *Prevotella*. Of note, the average number of bacteria in the upper genital tract was lower than in the vagina, by 2–4 log<sub>10</sub> RNA gene copies per swab. This means that either the cervix acts as a filter for ascending microorganisms or the immune system suppresses their upward transport; a combination of both mechanisms is also possible.

#### *The microbiome of ovarian follicles*

Human follicular fluids are readily culturable and are inhabited by microbes in many patients, as shown by a number of studies. In those studies, some of the samples were collected from the follicular aspirate during transvaginal oocyte retrieval, others were obtained through laparoscopy [51–54]. It is unclear whether the bacteria cultured from the collected samples were in the follicles prior to oocyte retrieval or the follicular fluid was contaminated during follicular aspiration [52, 54]. Some authors believe that microbes can be classified as colonizing or contaminating based on the comparison of microbiota composition of the sample with the bacteria detected on the surface of the puncture needle [54, 55]; if the follicle contains unique species, they should be considered colonizing. This approach to classification, however, does not account for the cases when a potential pathogen moves upwards from the uterus to the upper genital tract colonizing this region. The follicular fluid was found to contain microbes typical for the healthy microbiota of the vagina (*Lactobacillus spp.*), gastrointestinal tract (*Bifidobacterium spp.*, *Enterobacteriaceae*, *Streptococcus agalactiae*), skin (*Staphylococcus spp.*) and oral

mucosa (*Streptococcus spp.*), which supports the hypothesis that the follicular fluid does not always get contaminated during oocyte retrieval and can be colonized before this procedure [56]. So far, there has been no research to assess the vaginal, cervical, endometrial, fallopian, follicular and peritoneal microbiomes in parallel.

#### *The microbiome of the reproductive system of men*

Because of small sample sizes, there are only scanty data on the composition of the healthy urethral microbiota of men. For example, in a group of 33 men without urethritis, only the presence of *Staphylococcus epidermidis*, *Corynebacterium spp.*, *Lactobacilli*, *Haemophilus vaginalis*, and *alpha-hemolytic streptococci* was detected by a standard culture method [57]. In another study 16S rRNA gene sequencing was used to analyze 9 samples of first pass urine of men who had no clinical signs of urethritis or sexually transmitted infections; the most frequently detected bacteria were *Corynebacterium*, *Lactobacilli* and *Streptococci* [58]. In the coronal sulcus of uncircumcised men, whose sexual partners had no bacterial vaginosis, non-culture methods revealed the presence of *Corynebacterium*, *Lactobacillus* and *Staphylococcus* [59]. Thus, unlike women of reproductive age whose microbiota is dominated by *Lactobacillus* [60], men's microbiota of the urethra is not dominated by any particular species, and bacterial communities are usually complex [58].

Traditionally, research of semen microbiota was carried out using the culture method. It was successfully applied to discover associations between acute or chronic prostatitis and some infections, including gonorrhea and chlamydia. But recently metagenomics was introduced to describe semen microbiomes and conduct the traditional semen analysis. Hou et al. analyzed 77 samples collected from 58 infertile men and 19 healthy sperm donors [61]. Patients were divided into 6 groups based on the similarities of microbiota composition and diversity of taxa. It was shown, however, that their semen had very similar characteristics. Further analysis showed that only *Anaerococcus* was significantly associated with compromised sperm quality. Recently Weng et al. have conducted a similar research using 96 samples [62], of which 60 had one or more defects in semen parameters. The rest 36 samples were normal and used as control. *Pseudomonas*, *Lactobacillus* and *Prevotella* were prevailing microorganisms. The most interesting association was established among these taxa and the quality of corresponding sperm samples. In the samples dominated by *Lactobacillus* the proportion of healthy sperm cells was very high. It indicates that some *Lactobacillus* species inhabiting the male reproductive tract can exert probiotic activities protecting the host from pathogens, as is the case with the female reproductive system.

The conducted studies raise questions rather than answer them. They demonstrate the associations between the clinical signs of the pathology and microbiota composition. It is unknown what does harm to sperm cells: shifts in the microbiome that shape the environment or differences in semen properties that create favorable conditions for various bacteria. However, these first results are very important and urge us to collect more data. Some authors indicate that similar studies are being carried out at the moment.

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