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Short Communication

The Relationship Between Chronic Prostatitis and the Male Factor of Infertility in the Context of Changes in the Taxonomic Structure of the Microbiota of the Prostate Gland

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Male infertility is a global problem of public health. There are about 48.5 million couples suffering from infertility worldwide. In 50 % of cases, the male factor is the cause of infertility in a couple [1-3]. In addition, male infertility is increasingly seen as a "canary in the coal mine" for future male health disorders [4]. Male infertility is a multifactorial disease, so the cause could be: acquired and congenital urogenital abnormalities, endocrine disorders, toxic and medicinal effects, genetic abnormalities, ideopathic and immunological causes, malignant neoplasms, sexual dysfunction, as well as infections of the urogenital tract [5]. With aging, men have an increase of the case of genitourinary infections, during their lifetime from 13,000 to 14,000 men out of 100,000 experienced symptoms which associated with genitourinary infection [6]. Several studies state that from 6 to 18% of infertile men suffer from urogenital tract infections [7]. It is also worth to note the general decrease in male fertility. Carlsen E and co-authors investigated changes in seminal fluid parameters between 1940 and 1990 using the Accumulated Index Medicus and Current List (1930-1965) and the MEDLINE Silver Platter database (1966-August 1991). The authors revealed a significant decrease in the average number of spermatozoa from 113 x 10(6)/ml in 1940 to 66 x 10(6)/ml in 1990 ($p < 0.0001$), as well as a decrease in the volume of seminal fluid from 3.40 ml to 2.75 ml ($p = 0.027$) [8]. Fainberg and co-authors in 2019 published the same results demonstrating a decrease in sperm concentrations both in the United States and around the world [9]. Currently, more and more studies are being published describing the relationship between microorganisms and male infertility. Male infertility caused by microbial and viral infection is mainly achieved due to an immune response, while microorganisms induce the accumulation of immune cells and pro-inflammatory cytokines and chemokines. Also the formation of antisperm antibodies and biofilms can also damage germ cells, reducing man's reproductive potential [10]. The Lancet journal published review which summarizes some common factors that can cause male infertility, one of such factors is prostatitis [11]. Approximately 10% of men in the world experienced symptoms

of prostatitis [12]. The U.S. National Institutes of Health classifies prostatitis into four categories: acute bacterial prostatitis, chronic bacterial prostatitis, chronic non-bacterial prostatitis/chronic pelvic pain syndrome, and asymptomatic inflammatory prostatitis [13]. Epidemiological studies have shown that the global prevalence of chronic prostatitis ranges from 9% to 16% [14]. Moreover, abacterial prostatitis makes up 90-95% of cases [15]. It is worth to note that the etiology of bacterial prostatitis is a widely discussing today. The main causative agents of bacterial prostatitis are E. coli and enterococcus [16].

Chronic prostatitis in clinical practice is considered as a syndrome of chronic pelvic pain with a wide range of clinical manifestations, on the basis of this manifestations Shoskes and co-authors in 2009 [17] formed the diagnostic/therapeutic system UPOINT (urinary tract symptoms [U], psychosocial dysfunction [P], organ-specific symptoms [O], symptoms associated with infection [I], neurological/systemic conditions [N], skeletal muscle soreness [T]. This system summarizes various factors of chronic prostatitis [18]. It should be noted that spermatozoa make up about 2-5% of the volume of the ejaculate, [19] the proportion of secretions of the accessory glands (prostate and seminal vesicles) in the ejaculate varies widely. Thus, the secret of the seminal vesicles can be from 50 to 80% of the ejaculate, and the secret of the prostate gland from 25 to 35% of the ejaculate [20]. The prostate gland secretes the hormone-like substance spermin, which ensures sperm motility [21], as well as the secret of the prostate gland contains Zn 2+, citrate and kallikreins, which is crucial the importance for molecular synchronization of the functional cascade which being launched by ejaculatory stimuli [22]. Taking into consideration the contribution of the prostate gland to the volume of seminal fluid, also the possibility of a negative effect of prostate inflammation on the quality of seminal fluid and on the fertilizing ability of spermatozoa in particular should not be ruled out. Traditionally, the seeding of prostate secretions plays an essential role in the diagnosis of CP. According to some authors, the existing methods of detection microorganisms do not meet modern requirements, because of cultural method could detects about ten types of aerobic microorganisms and does not detecting anaerobic microorganisms and viruses. The use of the polymerase chain reaction (PCR) method in real time also has drawbacks due to the limited determination of the number of microorganisms due to primers. In addition, the existence of biofilms in chronic infections requires completely new approaches to their diagnosis and treatment. Modern molecular methods allow the identification of microorganisms in biofilms: gel electrophoresis, high-performance liquid chromatography with fluorescence in situ hybridization, PCR with reverse transcriptase, as well as a more available for the practice method of gas chromatography-mass spectrometry (GC MS) of biotopes. Modern diagnostic techniques for the study of biomaterial in men (PCR, immunotests and McCoy cells cell culture technologies, 16s rRNA/DNA sequencing) allow to identify different taxa of microorganisms, in this case, some authors in their publications notice about the possible role of unverified infection in CP. That is why, the actual frequency of bacterial forms of CP is unknown. Underestimation of intracellular pathogens and viruses as an etiological factor leads to the chronization of the disease and treatment failures.

The above contributes of changing in the methodology of conducting such studies and the search for new, more advanced techniques. In particular, some authors deviate from classical bacteriological techniques and use of an expanded set of nutrient medium with special cultivation conditions, mass spectrometry and the method of nucleic acid amplification [23]. Next-generation sequencing technology (NGS) has opened a new era of understanding the human microbiome, allowing the detection of previously unknown commensal and pathogenic microorganisms [24]. Friedrich Sanger, the creator of the revolutionary method of DNA detection, wrote: knowledge of sequences will make a great contribution to the understanding of living matter [25]. Indeed, this is what has happened, today, sequencing methods have undergone a certain evolution, the application of NGS technology and its various methodological variants now allows the simultaneous detection of different types of microorganisms present in a microbial sample, using of a culture-independent approach and in one sequential run [26]. One of the sequencing techniques is based on targeting of amplicon sequencing and is a widely used approach to characterize microbial communities. Here, DNA is extracted from a clinical sample and subjected to PCR amplification using of PCR set primers that targets a taxonomically informative gene that is common to either prokaryotes (bacteria and archaea) or common to microbial eukaryotes (fungi or opponents) - there is no universal target gene present in both prokaryotic and in the eukaryotic microorganisms. After amplification, the resulting amplicon is sequenced and then characterized using bioinformatics tools that search databases of reference sequences

to determine which microorganisms are present in the sample and at what relative quantity. Advances in NGS technology now mean that the latest amplicon-based NGS protocols enable extensive sample multiplexing, allowing researchers to process hundreds of samples and analyze millions of PCR amplicons in a single NGS run [27]. Recent developments in molecular biology and cultivation methods have made possible the detection of specific microbiome associated with areas that were previously considered sterile, including the urogenital tract [28]. The human microbiome is an ecosystem consisting of many types of microorganisms. It is a relatively balanced condition, not completely sterile, and mainly exists in external cavities such as the reproductive tract, oral cavity, and gastrointestinal tract. External bacteria, viruses, fungi, mycoplasma and chlamydia infections or opportunistic bacterial infection cause the occurrence and development of various diseases, including diseases of the male reproductive system [29]. The Human Microbiome project of the National Institutes of Health was one of the first large-scale initiatives aimed at solving the issue of the influence of the microbiome on various pathological conditions, as well as studying its dynamics [30]. Launched in 2007 [31], the first phase of the program was aimed at determining the presence of common elements in "healthy" microbiomes in the absence of obvious diseases. Studies of populations with specific diseases have established typical ranges (for some populations) of microbial affiliation and enzymatic repertoire in the human organism, combinations of metabolic functions that were either prevailing or strain-specific and some host factors (such as race or ethnicity) that determine this variation [32]. Thus, the first phase of HMP identified: nucleotide sequences of microorganisms and communities from a large number of isolates, individuals and populations [33-36], protocols for reproducible sampling of the microbiome of any locus, computational methods for analyzing the results of the microbiological landscape [37]. However, the loci of research in this project were: vagina, intestines, respiratory tract and skin [38]. This makes the microbiome of the urogenital tract a potential target for research by the entire scientific community. The sperm microbiome has been studied in more detail, as there are a number of microorganisms associated with a decrease in male fertility. Thus, the genus Prevotella has always been associated with a decrease in the quality of seminal fluid, mainly due to a decrease in sperm motility [39] The genera Proteobacteria and Actinobacteria are also associated with increased viscosity of seminal fluid, oligoastenotheratozoospermia and azoospermia [40]. However, there are catastrophically few references to the microbiota of the prostate gland in the scientific literature, which does not allow us to assess its contribution to the microbiome of seminal fluid and draw a conclusion about the influence of prostate microbiota to the man fertile potential, relying solely on literary data. It is worth mentioning that the providence of such studies would be impossible with the use of standard cultural techniques, as well as PCR diagnostics. Okada K. and the co-authors [41] revealed the presence of the own microbiota of the prostate gland, using metagenomic analysis methods 16S, as well as FISH and ISH methods, the main localization of microbiological communities inhabiting the prostate gland according to the authors are the ducts of the prostate gland. However, to date, based on scientific literature data, there are no identified microorganisms associated with male infertility. Despite many studies, the relationship between chronic prostatitis and infertility remains as unknown as it was many years ago, which, in our opinion, is due to the fact that to date there are discrepancies and limitations in the diagnostic approach and verification of diagnosis. This issue requires further research, which will subsequently shed light on the relationship between prostatitis and male infertility.

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