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## P-041 Elevated beta-defensin 119 level is associated with seminal microbiome dysbiosis in male infertility

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**Study question:** What is the correlation between a reproductive-tract specific beta-defensin DEFB119 and seminal microbiome and their involvement in male infertility?

**Summary answer:** A subpopulation of male-factor infertile patients demonstrated an elevated level of DEFB119 that is associated with decreased bacterial diversity and differentially regulated bacterial taxa.

**What is known already:** Beta-defensins are small (2-6kDa) cationic peptides with antimicrobial and immunomodulatory functions. A group of beta-defensins are specifically expressed in the male reproductive tract (MRT) and modulate sperm functions and fertility. Accumulating evidence suggests an association between seminal microbiome and semen quality. Specific bacterial taxa are involved in the development and maturation of the sperm, while dysbiosis contributes to infertility. However, despite the antimicrobial nature of beta-defensins, whether these small peptides interact with the seminal microbiome remain elusive.

**Study design, size, duration:** 93 semen samples were collected from the Prince of Wales Hospital (Hong Kong). The seminal DEFB119 level was determined by ELISA and the seminal microbiome was examined by 16S rRNA sequencing. The effect of DEFB119 on the seminal microbiome was validated in a subgroup of 5 samples by comparing total bacterial load ($n = 5$) and the abundance of selected genera ($n = 4$) after incubating with recombinant DEFB119 (2ug/ml) or vehicle for 1hr at 37°C.

**Participants/materials, setting, methods:** The patients were grouped according to seminal DEFB119 level and the spermiogram. Samples with DEFB119 levels below the threshold (900ng/ml, median of the cohort) were in G1/2 ($n = 30/53$) based on the absence/presence of abnormal sperm parameters. Samples with elevated levels of DEFB119 and abnormal sperm parameters were in G3 ($n = 5$). The seminal microbiome in G1-3 was analyzed by Quantitative Insights into Microbial Ecology (2021.2) and R package microeco.

**Main results and the role of chance:** Seminal DEFB119 level in G3 was significantly higher than that in G1 and 2 ($p < 0.001$). Microbiome alpha and beta diversity were comparable in G1 and G2 ($p > 0.1$) but was significantly lower in G3 ($p < 0.05$). Taxonomic analysis showed the dominance of different bacterial taxa in the three groups, including Prevotella in G1 and 2, and Streptococcus in G3. The dysbiosis of seminal microbiome in patients with an elevated level of DEFB119 demonstrated a marked reduction in the complexity of functional networks. In validation experiments, recombinant DEFB119 treatment in G1 or G2 seminal plasma samples decreased the total bacterial load. Of note, the abundance of Prevotella and Streptococcus was differentially regulated by rDEFB119 treatment.

**Limitations, reasons for caution:** Our study is a single-center study with a relatively small sample size, which makes interpretation of the analysis susceptible to individual variations. As a result, G3-specific abundant taxa identified in 16S rRNA analysis may not be representative.

**Wider implications of the findings:** Our work has provided novel insight into the host-microbiome interaction via reproductive-tract-specific antimicrobial peptides, which shed light on the aetiology of male-factor infertility.

**Trial registration number:** Not applicable