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Gut Microbiome Structure and Metabolic Analysis in the Obese PCOS Patients After The Treatment of Exenatide Combined with Metformin and Metformin Only

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SUMMARY. **Emerging evidence has linked the gut microbiome to obese/overweight PCOS patients. Since GLP-1Ras and/or exenatide could alleviate the phenotype of PCOS patients, we tend to identify their differences in the mechanism through a metagenome-wide association study and serum metabolomics profiling in a cohort of obese/overweight PCOS women. Obese patients with PCOS were distributed to two groups: one received exenatide combined with metformin (COM group, n=28) and the other used metformin alone (MF group, n=22) received metabolomic profiling. Fresh fecal specimens from the participants, including 29 PCOS patients and 6 healthy controls, were collected for metagenome analysis. In the Post_MF group, the enrichment of M58_7XD, AM30_15AC and AF42_9BH of R. gnavus were negatively correlated with 3b,16a-Dihydroxyandrostenone sulfate (3b,16a-DHEAS) and 8,11,14-Nonadecatriynoic acid. Dorea longicatena in the MF_Post group and is positively correlated with 10-hydroxy-2E-decenoic id (10HDA). Interestingly,** *Megamona funiformis***, *Clostridium* sp CAG _226,** *Firmicutes* **bacterium CAG_341,** *Pseudoflavonifractor* **sp MSJ 30, unclassified g** *Turicibacter* **in the COM group were positively associated with 3b,16a-DHEAS and 8,11,14-Nonadecatriynoic acid. Besides,** *Megamonas_funiformis* **was negatively correlated with Coriandrone B and** *Clostridium*_**sp_CAG_226,** *Firmicutebacterium*_**CAG_341 and** *Pseudoflavonifractor*_**sp_MSJ_30 were positively associated with the increase of 1alpha,21-dihydroxy-20-oxo-22,23,24,25,26,27-hexanorvitamin D3. Exenatide combined with metformin increased the abundance of** *M. funiformis, Clostridium_sp, Firmicutes_bacterium Pseudoflavonifractor*_**sp and reduce certain** *Ruminococcus*_**spp better than the impact of metformin on the gut flora of obese PCOS patients and these changes were associated with the reduction of the derivatives of DHEA and 8,11,14-Nonadecatriynoic acid, resultantly alleviating PCOS-like phenotype like hyperandrogenemia and insulin resistance. In the MF group, the enrichment of** *Dorea longicatena* **was related to the production of 10HDA to improve the clinical phenotype of PCOS.**

RESUMEN. Evidencia emergente ha relacionado el microbioma intestinal con pacientes con SOP obesos/sobrepeso. Dado que GLP-1Ras y/o exenatida podrían aliviar el fenotipo de las pacientes con SOP, tendemos a identificar sus diferencias en el mecanismo a través de un estudio de asociación de todo el metagenoma y un perfil de metabolómica sérica en una cohorte de mujeres con SOP obesas/con sobrepeso. Los pacientes obesos con SOP se distribuyeron en dos grupos: uno recibió exenatida combinada con metformina (grupo COM, n=28) y el otro que usó metformina sola (grupo MF, n=22) recibió un perfil metabolómico. Se recolectaron muestras fecales frescas de los participantes, incluidos 29 pacientes con SOP y 6 controles sanos, para el análisis del metagenoma. En el grupo Post_MF, el enriquecimiento de M58_7XD, AM30_15AC y AF42_9BH de R. gnavus se correlacionó negativamente con el sulfato de 3b,16a-dihidroxiandrostenona (3b,16a-DHEAS) y el ácido 8,11,14-nonadecatriinoico. Dorea longicatena en el grupo MF_Post y se correlaciona positivamente con 10-hidroxi-2E-decenoico id (10HDA). Curiosamente, *Megamona funiformis, Clostridium* sp CAG _226, *Firmicutes* bacteria CAG_341, *Pseudoflavonifractor* sp MSJ 30, g *Turicibacter* no clasificado en el grupo COM se asociaron positivamente con 3b,16a-DHEAS y 8,11,14-Nonadecatriynoic acid.

KEY WORDS: exenatide, metformin, metagenomic and metabolomic analyses, obese/overweight PCOS.

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Además, *Megamonas_funiformis* se correlacionó negativamente con Coriandrone B y *Clostridium*_sp_CAG_226, *Firmicutebacterium*_CAG_341 y Pseudoflavonifractor_sp_MSJ_30 se asociaron positivamente con el aumento de 1alfa,21-dihidroxi-20-oxo-22,23,24,25,26,27-hexano o vitamina D3. La exenatida combinada con metformina aumentó la abundancia de *M. funiformis*, *Clostridium*_sp, *Firmicutes*_bacterium Pseudoflavonifractor_sp y redujo ciertas Ruminococcus_spp mejor que el impacto de la metformina en la flora intestinal de pacientes con SOP obesos y estos cambios se asociaron con la reducción de los derivados de DHEA y 8, Ácido 11,14-nonadecatriinoico, lo que alivia el fenotipo similar al síndrome de ovario poliquístico, como la hiperandrogenemia y la resistencia a la insulina. En el grupo MF, el enriquecimiento de *Dorea longicatena* se relacionó con la producción de 10HDA para mejorar el fenotipo clínico del SOP.