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Sitagliptin treatment for peritoneal mesothelial cell tight junction proteins and function in peritoneal dialysis

Chor Ho Jo[1], Sua Kim[1], Eun-Joo Oh[4], Duk-Hee Kang[3], Gheun-Ho Kim[2]
[1]Department of Institute of Biomedical Science, Hanyang University College of Medicine, Korea, Republic of
[2]Department of Internal Medicine-Nephrology, Hanyang University College of Medicine, Korea, Republic of
[3]Department of Internal Medicine-G-I/Hepatology, Ewha Womans University School of Medicine, Korea, Republic of
[4]Department of Internal Medicine-Nephrology, Kyungpook National University Hospital, Korea, Republic of

Objectives: The integrity of peritoneal mesothelial cells is important to maintain peritoneal membrane transport in peritoneal dialysis (PD). We previously isolated tight junction (TJ) proteins occludin, ZO-1, claudin-1, and claudin-15 from PD effluent, and the dipeptidyl peptidase-4 (DPP4) activity was reported to be correlated with peritoneal dysfunction. This study was undertaken to test whether the DPP4 inhibition may restore peritoneal mesothelial cell TJ proteins and function in peritoneal dialysis.

Methods: Human peritoneal mesothelial cells (HPMCs) were isolated and cultured from omentum obtained during the abdominal surgery, and the effects of sitagliptin (5 mg/kg BW/d) were tested by measuring transepithelial resistance (TER) and dextran flux. The 4.25% peritoneal dialysate was daily infused to Sprague-Dawley rats with and without sitagliptin administration for eight weeks. At the end of the animal experiment, peritoneal equilibration test (PET) was done over two hours. Peritoneum was obtained from each rat for light microscopy and isolation of the rat peritoneal mesothelial cells (RPMCs) to evaluate TJ protein expression.

Results: In HPMCs, the protein expression of claudin-1, claudin-15, occludin, and E-cadherin were decreased by transforming growth factor-beta (TGF-ß) treatment but reversed by sitagliptin cotreatment. TER was decreased by TGF-ß but improved by sitagliptin cotreatment. Consistent with this, dextran flux was increased by TGF-ß and reversed by sitagliptin cotreatment. In the animal experiment, sitagliptin-treated rats had a lower D2/D0 glucose and a higher D2/P2 creatinine than PD controls during the PET. The protein expression of claudin-1, claudin-15, and E-cadherin were decreased in RPMCs from PD controls but improved in those from sitagliptin-treated rats. Peritoneal fibrosis was induced in PD controls but improved in sitagliptin-treated rats.

Conclusions: In our rat model of PD, sitagliptin preserved peritoneal mesothelial cell TJ proteins and function and prevented peritoneal fibrosis. Clinical trials are necessary to demonstrate the effects of sitagliptin in patients undergoing PD.