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Commentary

Peritoneal Imaging may be the Last Piece of the Puzzle for Precision Evaluation of Peritoneal Function

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Due to changes in end-stage renal disease (ESRD) policies in many countries and the impact of COVID-19, the importance and demand for peritoneal dialysis (PD) as a home dialysis treatment modality is growing prominently [1]. However, peritoneal membrane dysfunction remains a bottleneck restricting the application of PD. Therefore, there is an urgent need to develop new methods to accurately assess peritoneal function. The newly published "Recommendations for the evaluation of peritoneal membrane dysfunction in adults" by the International Society of Peritoneal Dialysis (ISPD) classifies peritoneal membrane dysfunction into fast peritoneal solute transfer rate (PSTR) and low peritoneal osmotic conductance to glucose (low OCG) [2]. It is recommended that standard or modified peritoneal equilibration test (PET) should be used to assess peritoneal function. However, PET is a semi-quantitative test for indirect assessment of peritoneal transport function, and the accuracy of its results is influenced by the skill of the operator, as well as the conditions of patients and laboratory instruments. In addition, an evaluation method that accurately predicts the velocity and extent of peritoneal membrane dysfunction after long-term PD is clinically desirable. PET is still far away from that target. It is generally acknowledged that long-term PD not only causes functional changes to the peritoneum but also structural changes [3]. A structurally and functionally stable peritoneum is the key to dialysis adequacy and survival in PD patients [3]. In recent years, rapid advances appear in imaging technology which allowed us not only to clearly observe the morphology of the organs, but also to quantitatively detect the texture, vascularity and other changes of the tissues. Advances in imaging techniques are gradually being applied to the field of PD. Peritoneal morphological changes revealed by imaging are found to be relevant to peritoneal function, and are expected to be an important complement to the evaluation of peritoneal function, as exemplified recently by the study reported by Zhang *et al.* [4]. This commentary summarizes previous applications of peritoneal imaging in the assessment of peritoneal function and provides a prospect on the future of an accurate evaluation of peritoneal function.

The use of CT in the diagnosis of Encapsulating Peritoneal Sclerosis (EPS) is a typical example of how peritoneal imaging combined with peritoneal function examinations can reflect changes to the peritoneum. EPS is a rare and severe long-term complication of PD. It is a chronic progressive inflammation of the peritoneum caused by various factors, manifesting as impaired intestinal absorption and motility, as well as decreased peritoneal function and structural modifications such as peritoneum thickening, intestinal adhesion and obstruction, and calcification [5]. In 1988, Korzets *et al.* first reported the CT features of two PD patients with EPS [6]. The main CT features of EPS patients can be divided into the following four aspects: (1) peritoneal changes: e.g. thickening, calcification and marked enhancement (in case of contrast application); (2) small bowel abnormalities: thickening, encapsulation or dilatation of the intestine, which in severe cases can form a "cocoon" appearance; (3) fluid collections: local fluid accumulation and recurrent blood ascites; And (4) calcifications: intestinal, mesenteric and parietal peritoneal calcification [7]. Stafford-Johnson *et al.* [8] first compared CT scans of patients with EPS with other PD patients (vintage ranging from 1 month to 7 years) and concluded that peritoneal calcification, peritoneal thickening, localized fluid collections, and bowel tethering were diagnostic of EPS. The next two case-control reports established the important role of CT in aiding the diagnosis of EPS. Tarzi *et al.* [9] studied abdominopelvic CT scans in

27 patients with EPS and compared them with CT scans in 15 hemodialysis patients and 20 non-EPS PD patients. They scored the patients' abdominal CT manifestations according to the following six aspects: peritoneal calcification, peritoneal thickening, loculation, bowel dilatation, bowel tethering, and bowel wall thickening. The EPS patients had a median score of 9, significantly higher than non-EPS PD patients (a median score of 1) and hemodialysis patients (a median score of 0). Vlijm *et al.* [10] compared EPS patients with long-term (at least 4 years) PD patients without EPS. They found that when three of the following six parameters were present: peritoneal enhancement, peritoneal thickening, peritoneal calcification, bowel tethering, bowel dilatation, and fluid loculation (two of the five if no intravenous contrast agent was used). The sensitivity of diagnosing EPS was 100% and the specificity was 94%. They also suggested that enhanced CT helped improve the diagnostic accuracy for EPS. In 2017, Sam Stuart *et al*. [11] performed prospective abdominal CT scans on PD patients and matched patients with EPS to control patients with similar PD durations. They used a simplified scoring system based on the presence or absence of the manifestations such as peritoneal thickening, peritoneal calcification, intestinal tethering, intestinal thickening, and intestinal dilatation. When the score was ≥ 3, the sensitivity of diagnosing EPS was 78% and the specificity was 85%. They concluded that CT could distinguish EPS from peritoneal changes related to long-term PD and the severity of abnormal CT presentations was associated with patients' clinical outcomes. After realizing that CT can assist in the diagnosis of EPS, researchers turn their attention to whether CT can detect early EPS. In the study reported by Catriona Goodlad *et al.* [12], 20 patients with EPS underwent at least two CT scans, one at least 3 months before the onset of EPS and one at the time of diagnosis. The control group was 20 non-EPS patients. The scan scores at the time of EPS diagnosis were significantly higher than those before diagnosis or in the control group (median 9, 2 and 1; $P<0.001$). Twelve of the patients with EPS who were asymptomatic before diagnosis had a median 1.75 CT score before their EPS diagnosis, similar to the control group; the other eight EPS patients who had abdominal symptoms before diagnosis (7 required hospitalization) had a median 4.5 CT score before the onset of EPS. They concluded that CT screening of asymptomatic PD patients is not meaningful and EPS may occur within a year or less after a normal CT scan. In contrast, in symptomatic patients, CT scans may be useful in assessing future EPS risk. In addition to the application in EPS, there are other studies focusing on the relationship between CT peritoneal manifestations and peritoneal function. Huang *et al.* [13] included 183 PD patients with a mean duration of 41 months and found a 27% ratio of peritoneal calcification. It was suggested that peritoneal calcification was associated with high peritoneal KT/V and peritonitis. In 2021, Atas *et al.* [14] summarized 94 PD patients' abdominal CT presentations and suggested that peritoneal thickness was significantly associated with PD duration and C-reaction protein. Besides, increased peritoneal thickness was an independent predictor of reduced Kt/V.

Zhang *et al.* [4] retrospectively included patients who had been converted to hemodialysis with less than 5 years on continuous ambulatory peritoneal dialysis (CAPD) and patients with CAPD for more than 10 years. They found extensive thickening of the parietal peritoneum, severe calcification of the parietal peritoneum, the mesentery and the free margin of the small intestine wall were adverse factors for long-term PD by analyzing their non-enhanced abdominal CT imaging features. They established a simple and practical scoring method that can assist physicians in objectively evaluating the efficiency of PD. This is another example and extension of how and why peritoneal imaging can be applied in the evaluation of peritoneal function.

As mentioned earlier, imaging techniques are constantly evolving and no longer should only be used to detect morphological abnormalities. The continuous application of new techniques has made it possible to detect changes in the morphology, texture, and blood flow of tissues and organs with greater precision [15]. Recently, nuclear imaging has been introduced and broadened the imaging application in the field of PD [16]. In addition to advances in imaging, significant progress has been made recently in molecular biology related to peritoneal function. Mehrotra *et al.* [17] collected blood samples from 2850 PD patients in different regions for Genome-wide association study (GWAS) analysis, and found that genetic variation was an important factor influencing inter-individual variation of PSTR. Morelle *et al.* [18] performed Aquaporin 1 (AQP1) genotyping in 1851 PD patients and found that the AQP1 rs2075574 genotype was associated with ultrafiltration and prognosis in PD patients: T allele of rs2075574 carriers had a lower mean net ultrafiltration than C allele carriers and had a higher risk of all-cause mortality and technique failure. Further basic studies confirmed that this locus was associated with AQP1 promoter activity and AQP1 expression.

In the future, more basic researches are needed to elucidate the pathogenesis of peritoneal membrane dysfunction. Besides, the combined application of molecular biology, imaging technology and traditional methods is expected to provide accurate methods for the evaluation of peritoneal function. On this basis, the establishment of a standard process for the early diagnosis and prevention of peritoneal membrane dysfunction could benefit more patients with maintenance PD.

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