Renal Replacement Therapy

REVIEW

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Hemodiafiltration in Japan: current status and future directions

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Abstract

Hemodiafiltration (HDF) therapy has become standard treatment in Japan and Europe, but evidence from Europe is not directly applicable to HDF in Japan because HDF therapy differs greatly in the two regions. Japanese dialysis membranes vary widely, including use of protein-leaking and non-leaking membranes, and the molecular weight of solutes that can be removed is generally larger in Japan than in Europe. Given the characteristics of pre-dilution, the volume of replacement fluid itself cannot be used as a marker for solute removal, and the relationship of this volume to life prognosis is still unknown. Under these circumstances, the JAMREDS, a multicenter study led by the Japanese Society for Hemodiafiltration, was started in April 2020. The goal of the study is to determine whether α1-microglobulin reduction rate can be used as a marker for the prognosis of hemodialysis patients, including life prognosis and cardiovascular event onset. The JAMREDS is being performed from a new perspective of solute removal by HDF. This research design is reasonable and highly original for HDF in Japan, in view of the wide variety of membrane types and treatment modes, and the results of the study will be of particular interest.

Keywords α1-Microglobulin (α1MG), Hemodiafiltration (HDF), Prognosis, JAMREDS

Introduction

The molecular weight range of solutes removed by blood purification therapies has changed over time, and a dialyzer with clearance of β2-microglobulin (β2-MG; molecular weight 11,800) exceeding 70 ml/min has now been developed. The principle of diffusion is now sufficient for managing β2-MG removal. After β2-MG, removal of substances with a molecular weight close to albumin (67,000) and large-middle molecular weight uremic toxins has been targeted. In Japan, removal of α1-microglobulin (α1-MG; molecular weight 33,000) has been achieved by hemodiafiltration (HDF) and it has become clear that α1-MG removal improves several clinical symptoms [1–4]. However, the effects of α1-MG reduction rate on survival and prognosis are still unknown. To examine the effects of this rate on prognosis of hemodialysis (HD) patients, three academic societies, the Japanese Society for Hemodiafiltration, the Japanese Society of High Performance Membranes for Blood Purification, and the Japanese Society of Intermittent Infusion Hemodiafiltration started the JAMREDS (https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000043823), as a multicenter prospective observational study, in April 2020.

HDF as standard treatment

An advantage of HDF is that it can efficiently remove middle molecular weight solutes that are difficult to remove using conventional HD. At a time when performance of membranes was not as good as it is today, HDF was developed mainly for removal of small-middle-sized molecules (i.e., β2-MG) by filtration.

To date, various clinical effects have been reported, such as 1) improvement of β2-MG removal, dialysis

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amyloidosis, pruritus, irritability, restless leg syndrome, bone/joint pain, loss of appetite, and other general malaise, 2) improvement of anemia, 3) improvement of inflammation, and 4) improvement of dialysis related hypotension [1–10]. Recent reports showing improvement of life prognosis have established the effectiveness of HDF in dialysis treatment [11–17].

HDF has always been widely recognized as a useful treatment modality in Japan, but its widespread use was initially limited because it was not covered by national health insurance. In 2010, online HDF equipment was approved and coverage of online HDF was included in national health insurance. However, the low coverage rate still limited use of HDF. In 2012, insurance reimbursement was set at a higher rate, leading to a rapid increase in clinical use and making HDF a standard treatment as a form of dialysis therapy. A national survey by the Japanese Society for Dialysis Therapy (https://docs.jsdt.or.jp/overview/index.html) showed that the percentage of HDF patients among all dialysis patients has increased rapidly, reaching 47.1% at the end of 2020.

α1-MG as a marker for solute removal in HDF

Once it was shown that β2-MG can be removed with conventional HD therapy, the next removal target for HDF in Japan was in the region of α1-MG, which is a large-middle molecular weight of 33,000, and the α1-MG reduction rate has become a target value for improving various clinical symptoms. A recent HDF treatment standard has been proposed with reduction rates of β2-MG of ≥ 80% and α1-MG of ≥ 35%, with 3–5 g of albumin leakage [2, 4]. Albumin leakage is unavoidable under HDF conditions that give high α1-MG removal, since the Stokes radius of α1-MG is about 80% that of albumin, but this is relatively well tolerated in Japan based on our experience of the clinical effects. For example, the symptoms of restless leg syndrome, which is a particularly clinically intractable complaint, can be improved with an α1-MG reduction rate of ≥ 40% and albumin leakage of ≥ 5 g [3].

α1-MG as a bioactive substance

α1-MG has been regarded as a marker for removal of uremic toxins in the α1-MG size range, as a so-called surrogate marker. However, recently, the physiological functions of α1-MG itself have been recognized and its role in disease has gained attention [18–21]. α1-MG is a low molecular weight glycoprotein that is mainly produced in the liver [22]. A free form of α1-MG and a form bound to IgA are present in the blood at approximately the same level in healthy subjects [23]. The physiological activity of α1-MG as a strong radical scavenger has become of particular interest in recent years [18–21]. The reduced form of α1-MG is relatively low in dialysis patients with high oxidative stress, while the degraded oxidized form of α1-MG is higher, indicating that the original function of α1-MG as a radical scavenger may be reduced, despite its higher blood concentration [4]. α1-MG has a much faster metabolic turnover than albumin, taking only a few hours, and a large reserve capacity for liver production that exceeds the amount removed [4]. Therefore, even if α1-MG is removed by HDF or other methods, its concentration will not decrease to normal after treatment [4]. Regardless, one of the reasons why the high α1-MG reduction rate contributes to the improvement of clinical symptoms may be to promote the turnover of α1-MG and increases the amount of the reduced form, which restores the original function of α1-MG as a radical scavenger and brings about various clinical benefits.

Research on life prognosis of HDF and the JAMREDS (Fig. 1)

In the first part of the 2010s, several overseas randomized controlled trials (RCTs) [13–16] demonstrated positive effects of post-dilution online HDF on life prognosis and suggested a relationship with convection volume, but the mechanism has yet to be determined. From the perspective of solute removal, HDF in European countries uses non-protein leaking membranes, and thus, the convection volume is thought to reflect removal of solutes with a molecular weight of < 20 kDa, which is a smaller target than that used in Japan. It can be inferred that removal of uremic toxins of this size improves life prognosis. In 2019, a Japanese observational study of the effects of pre-diluted online HDF on life prognosis using propensity score matching (a quasi-RCT) suggested the significance of a high replacement fluid volume on life prognosis [17]. However, protein-leakage and non-leakage membranes are used in HDF in Japan, and the removable molecular weight is likely to be larger. Given the characteristics of pre-dilution, the volume of replacement fluid is not likely to be a direct marker of solute removal, and a clear answer on how this volume is related to life prognosis has not been obtained.

The results of the recent 2018 Euro-DOPPS 4–5 real-world data study did not show superiority of HDF [24], and the weakness of the study design in previous RCTs has been pointed out [25, 26]. In these circumstances, in the 2020s, new RCTs such as CONVINCE [26] and H4RT [25] are being performed for further verification in Europe. In Japan, the JAMREDS (https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000043823), a multicenter study led by the Japanese Society for Hemodiafiltration, was started in April 2020, with the goal of determining whether α1-MG reduction rate is a marker of prognosis, including life prognosis and cardiovascular events. The abbreviation "JAMREDS" was coined by Dr. Kenji

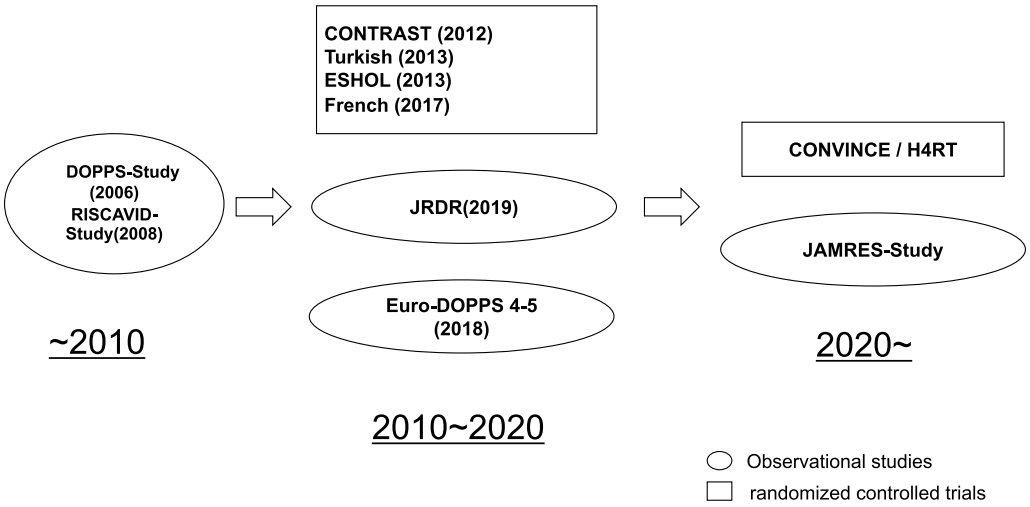

Fig. 1 Development of research on life prognosis after treatment with HDF

Sakurai from the "Japanese study of the effects of AMG (α1-microglobulin) reduction rates on survival, complications and prognosis in dialysis patients." The observation period of the JAMREDS will continue until the end of 2023, after which the data will be cleaned and confirmed before moving to analysis.

Conclusion

HDF is a standard treatment in Europe and Japan, but differs between these regions, and evidence from Europe cannot be used directly for HDF in Japan. The JAMREDS is a clinical study designed from the new perspective of examining solute removal by HDF. This approach is reasonable and innovative for HDF in Japan, due to the use of a wide variety of membrane types and treatment modes, and the results of this study are highly anticipated.

Abbreviations

HDF	Hemodiafiltration
β2-MG	β2-Microglobulin
α1-MG	α1-Microglobulin
RCTs	Randomized controlled trials

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Not applicable.

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T.N. (corresponding author) contributed to the concept and writing. Y.T., N.K. and H.K. reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
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Competing interests
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