Biomarkers for Evaluation of Clinical Outcomes of Hemodiafiltration

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Key Words

β_2 -Microglobulin · α_1 -Microglobulin · Hemodiafiltration · Uremic toxins · Removal rate · Restless legs syndrome

Abstract

β_2 -Microglobulin (β_2 -MG) is the substance that causes dialysis amyloidosis, and its predialysis value is useful for evaluating the quality of dialysis therapy itself. In addition, β_2 -MG is also an important biomarker for evaluating the removal performance of hemodialysis and hemodiafiltration (HDF). However, since β_2 -MG has a molecular weight of 11.8 kDa and can be efficiently removed by diffusion with existing high-performance dialyzers, a higher molecular weight substance should be used for evaluating removal performance of HDF, in which diffusion and convection are performed simultaneously. α_1 -Microglobulin (α_1 -MG) has a molecular weight of 33 kDa, and it is removed by convection during dialysis. When we used α_1 -MG to evaluate the removal performance of HDF in a study based on our own cases, we were able to describe the distinctive features and benefits of HDF with precision. α_1 -MG removal rate exactly paralleled the changes in symptoms. Kt/V and the β_2 -MG removal rate, however, did not undergo significant changes as the symptoms fluctuated. α_1 -MG should be used as a biomarker for evaluation of clinical outcomes of HDF.

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Introduction

Hemodiafiltration (HDF) can efficiently remove uremic toxins, from low-molecular-weight to large-molecular-weight substances, by using a combination of diffusion and convection [1–3]. More specifically, the benefits of HDF can be best utilized and good therapeutic efficacy achieved in the treatment of insomnia, pruritus, irritability, restless legs syndrome (RLS), anemia, dialysis amyloidosis (DA), etc., when removal performance of low-molecular-weight protein (LMWP) is improved [4–7].

However, if the conditions under which HDF is performed are unsuitable, the removal performance of HDF is not as high as expected, and it is difficult to differentiate from hemodialysis (HD) with a high-performance dialyzer.

β_2 -Microglobulin (β_2 -MG) is the substance that causes DA, and it is widely accepted that its predialysis value is useful for evaluating the quality of dialysis therapy (quality of water purification, dialysis membrane, dialysis time, dialysis frequency, presence or absence of inflammation) [8–11]. In addition, β_2 -MG is also an important biomarker for evaluating the dialysis efficiency of HD and HDF [12].

However, β_2 -MG has a molecular weight of 11.8 kDa, which is toward the lower end of the molecular weight range of LMWPs (MW: 10–55 kDa), and since it can be efficiently removed by diffusion with existing high-per-

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formance dialyzers, a higher molecular weight substance should be used to evaluate removal efficiency in evaluations of the performance of HDF, in which diffusion and convection are performed simultaneously.

In this paper, we state based on our own cases what kind of marker should be used and how conditions for HDF should be set up in order to make the best use of the distinctive features and benefits of HDF.

What Is a Suitable Biomarker for Evaluation of Clinical Outcomes of HDF?

On-line HDF became formally covered by the Japanese National Health Insurance system (JNHAS) in 2010. However, four conditions were stipulated for performing it: (1) use of approved dedicated HDF equipment, (2) use of an approved hemodiafilter, (3) guarantee of dialysis water purification by each institution, and (4) DA and dialysis difficulty as indications.

We changed the dialysis conditions at our own institution to conform to the conditions stipulated for coverage by JNHAS in 17 cases that had become stable on HDF with a super high-flux dialyzer, and the result was that by one month after changing the dialysis conditions, the symptoms in 13 of the 17 cases had become worse. In 6 of these 13 cases, the dialysis method had been changed to HD with a super high-flux dialyzer, and in the other 7 cases it had been changed to HDF with a hemodiafilter that had been approved.

We then changed the dialysis conditions again in the 13 cases in which the symptoms had become worse. More specifically, we attempted to improve removal performance of dialysis by performing HDF with the super high-flux dialyzer that had been used before or performed HD with a higher performance super high-flux dialyzer, etc. The result was that one month later ADL had improved in 11 of the 13 cases, and their QOL had returned to its previous level. An improvement in QOL was also noted in the other 2 cases.

α_1 -Microglobulin (α_1 -MG) removal rates in the 13 cases whose symptoms changed from 'stable' to 'worse' and then to 'improved' changed significantly almost exactly in tandem with the changes in symptoms from 35.5 ± 7.7 to $23.2 \pm 4.9\%$ and then to $32.3 \pm 5.6\%$ ($n = 13$, all $p < 0.01$). However, the corresponding changes in Kt/V from 1.59 to 1.65 and then to 1.56 and in the β_2 -MG removal rate from 78.2 to 75.2% and then to 77.3% only fluctuated within narrow ranges. These changes show that the symptom worsening occurred because the α_1 -MG removal rate

Fig. 1. Relationship between IRLS score and α_1 -MG removal rate. The α_1 -MG removal rate and IRLS score during the course of treatment of 7 cases of RLS are shown. Although the symptoms were alleviated up to α_1 -MG removal rates of 35%, RLS was not cured, and an α_1 -MG removal rate of 38% or more was needed to cure RLS.

had decreased, i.e. they occurred because of insufficient removal of uremic toxins having a molecular weight of 30 kDa or more, and the improvement in symptoms occurred because the removal of uremic toxins having a molecular weight of 30 kDa or more had increased. They also showed that it is impossible to infer associations between changes in symptoms and LMWPs by assessing only Kt/V and β_2 -MG removal rates.

The symptoms that occurred were either the development or aggravation of bone and/or joint pain (10/13 cases), reduced activity (7/13 cases), pruritus (4/13 cases), RLS (3/13 cases), irritability (2/13 cases), etc. Dialysis vintage in these 13 cases was 21.0 ± 10.1 years, and dialysis vintage in the group that developed or experienced aggravation of bone and/or joint pain was 24.3 ± 9.0 years (group without these changes: 8.4 ± 4.1 years). When the dialysis vintages and the symptoms that developed were reviewed together, these episodes showed that continuing HDF at an α_1 -MG removal rate of 35% is advisable to prevent the onset of DA or mitigate these symptoms.

RLS symptoms have been classified into four stages by International Restless Legs Syndrome score (IRLS score): 1–10, mild; 11–20, moderate; 21–30, severe; 31–40, very severe [13]. Even a review of the IRLS score and α_1 -MG removal rate together in the 7 cases in which RLS developed as a complication revealed that while the symptoms were alleviated up to an α_1 -MG removal rate of 35%, the patients' RLS was not cured, and that an α_1 -MG removal rate of 38% or more was necessary in order to cure their RLS (fig. 1). This shows that it is impossible to hope for a cure of RLS even by increasing removal of uremic toxins

Fig. 2. Relationship between predialysis α_1 -MG and β_2 -MG values and dialysis vintage. There were no correlations between the predialysis values of α_1 -MG or β_2 -MG and dialysis vintage. Their mean values were: α_1 -MG 117.0 ± 19.9 mg/l and β_2 -MG 26.5 ± 5.3 mg/l ($n = 126$, tested August 2012).

from a molecular weight of 10–20 kDa, and that aggressively removing uremic toxins having molecular weights of 30 kDa or more leads to a cure of RLS [14].

These assessments showed that α_1 -MG should be used to correctly evaluate the distinctive features and benefits of HDF.

What Is α_1 -MG?

α_1 -MG has a molecular weight of 33 kDa and a Stokes radius of 28.4 Å. Its predialysis values are not correlated with dialysis vintage, and no associations between predialysis values and dialysis complications have been found in any studies conducted thus far (fig. 2). The predialysis α_1 -MG values of dialysis patients in our institution were 117.0 ± 19.9 mg/l ($n = 126$), and the mean value of healthy subjects was 12.5 ± 2.3 mg/l ($n = 31$).

β_2 -MG is known to be the substance that causes DA, and many studies have been conducted regarding its etiology and β_2 -MG. β_2 -MG has a molecular weight of 11.8 kDa and a Stokes radius of 16 Å. The β_2 -MG predialysis values of dialysis patients in our institution were 26.5 ± 5.3 mg/l ($n = 126$), and the mean value of healthy subjects was 1.4 ± 0.3 mg/l ($n = 31$).

The changes in α_1 -MG and β_2 -MG values between August 2011 and August 2012 in all of the cases as a whole ($n = 126$) were: α_1 -MG, $119.8 \rightarrow 117.0$ mg/l, and β_2 -MG, $27.4 \rightarrow 26.5$ mg/l, and thus there was hardly any change in either of them. In an assessment of the HDF group ($n = 11$) alone, the changes were: α_1 -MG, $119.1 \rightarrow 120.3$

mg/l, and β_2 -MG, $24.0 \rightarrow 22.9$ mg/l, and a tendency for the β_2 -MG values to decrease was observed, but the difference was not significant.

Many studies have been conducted in this field since the Gejyo study in which β_2 -MG was identified as the precursor protein of DA, but no correlations have been reported between predialysis β_2 -MG values and the onset of DA or the severity of the symptoms [8, 9, 15–17]. Nor have there been any reports of studies that investigated the relationship between α_1 -MG and dialysis complications. Based on our study as well, at present predialysis α_1 -MG values have not been found to indicate the severity of the pathology or the appropriateness of the dialysis conditions, etc., but further study is needed.

Uremic toxins whose molecular weights are greater than that of β_2 -MG may be involved in the development of clinical manifestations such as insomnia, pruritus, irritability, RLS, anemia, and osteoarticular pain. For that reason, it has been said that it will be necessary to remove a wider range of LMWPs than β_2 -MG and to remove protein-bound toxins in order to treat these symptoms, and the same appeared to be true in the present study of our own cases.

We wish to emphasize that the reason for removing α_1 -MG is not because α_1 -MG itself is toxic, but because α_1 -MG has a molecular weight of 33 kDa and should be used as a biomarker for evaluation of clinical outcomes of HDF. We also concluded that an increase in therapeutic efficacy, an increase in patient QOL, and a higher survival rate can be expected when the distinctive features and advantages of HDF are best utilized by setting the HDF performance conditions with an α_1 -MG rate of 35% as the goal.

When HDF is performed under these conditions, a β_2 -MG removal rate of 80% can be easily achieved. On the other hand, even if the replacement fluid volume is increased, a β_2 -MG removal rate of 80% and α_1 -MG removal rate of 15% are likely to be achieved by HDF with a small-pore size dialyzer or hemodiafilter.

Difference in Removal Characteristic between β_2 -MG and α_1 -MG

We used two high-flux dialyzer models (FX, Fresenius Medical Care; FDX, Nikkiso Co., Ltd.) and one super-high dialyzer model (FDY, Nikkiso) having a dialysis area of 1.8 m² and assessed the relationship between β_2 -MG and α_1 -MG removal rates and the amount of albumin loss when HD, predilution on-line HDF, and postdilution on-

Fig. 3. Relationship between removal rate of β_2 -MG and α_1 -MG and amount of albumin loss. We investigated the relationship between β_2 -MG and α_1 -MG removal rate by HD, predilution on-line HDF, and post-dilution on-line HDF, with two high-flux dialyzer models (FX and FDX) and one super-high dialyzer model (FDY), and the amount of albumin leakage in 6 cases. Q_B 300 ml/min, Q_D total 500 ml/min, Q_F 6–21 ml/min, pre-HDF; FX and FDX: 50 l/session, FDY: 40 l/session, post-HDF; FX and FDX: 15 l/session, FDY: 8 l/session.

Fig. 4. Comparison of removal rates of three hemodiafilters. 50-liter predilution on-line HDF (4 h) was performed at Q_B 250 ml/min (Q_D total 500 ml/min) with TDF-20H, ABH-21P, and MFX-21U hemodiafilters, and LMWP (β_2 -MG, prolactin, α_1 -MG) removal rate and the amount of albumin loss were assessed ($n = 7$, mean $\pm$ SD).

line HDF were performed (fig. 3). Although there was a large amount of albumin loss when we performed HDF with each of the dialyzers, β_2 -MG removal rate was almost constant. This means that β_2 -MG is mainly removed by diffusion.

There is a twofold difference between the molecular weight of albumin (MW: 66 kDa, Stokes radius: 35.5 Å) and α_1 -MG, but there is a mere 20% difference in their Stokes radius. Because of the difference in their Stokes radius, it is impossible to differentially remove α_1 -MG and albumin with the dialysis membranes currently in use, and a correlation exists between the amount of α_1 -MG removed and the amount of albumin loss [18]. There is a strong likelihood that a certain degree of albumin loss has a positive impact on the body from the standpoint of removing uremic toxins that fall into the category of protein-bound solutes and of removing albumin that has lost its antioxidant capacity [19–21].

Evaluation of Hemodiafilter Performance

We performed 50-liter predilution online HDF (for 4 h) at Q_B 250 ml/min (Q_D total 500 ml/min) with TDF-20H (Toray Medical Co., Ltd), ABH-21P (Asahi Kasei Medical Co., Ltd), and MFX-21U (Nipro Co.), and assessed removal performance (fig. 4). These three products can be described as high-performance versions of hemodiafilters that are currently on the market in Japan.

Under these assessment conditions, all three models yielded a good β_2 -MG removal rate of 80% [amount removed (mg): TDF, 186; ABH, 169; MFX, 190], but there were large differences in their α_1 -MG removal rates: TDF, 18.2% (amount removed: 93 mg), ABH, 25.9% (amount removed: 126 mg), and MFX, 37.5% (amount removed: 179 mg), respectively. Thus, differences between the performance of the hemodiafilters became in-

creasingly marked as molecular weight increased from the 11.8 kDa for β_2 -MG, to 23 kDa for prolactin, and to 33 kDa for α_1 -MG. If the removal performance of the hemodiafilters had been evaluated on the basis of β_2 -MG alone, the results for all three hemodiafilter models would have been the same. In other words, to make the best use of the distinctive features and benefits of HDF, it is important to use α_1 -MG as the biomarker to evaluate the removal performance of HDF, and to choose a hemodiafilter that provides an α_1 -MG removal rate of 35%. An improvement in clinical manifestations can be expected by doing so, and it increases patients' QOL and, in turn, their survival rate.

Conclusion

The removal performance of HDF should be assessed by using α_1 -MG as a biomarker. Further, the distinctive features and benefits of HDF are best utilized by selecting a suitable hemodiafilter and setting an α_1 -MG removal rate of 35% as the target value.

Disclosure Statement

I have no relationship with the industry or financial associations that might pose a conflict of interest in connection with the submitted article.

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