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Research Progress on Blood Sugar Management in Diabetic Patients Undergoing Maintenance Hemodialysis

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Abstract

Maintenance hemodialysis (MHD) has a long treatment cycle, and the process is accompanied by complex metabolic changes. Blood glucose management has become a significant factor affecting treatment outcomes. During dialysis, diabetic patients are more prone to blood glucose fluctuations compared to non-diabetic patients. Optimizing blood glucose management in diabetic patients undergoing maintenance hemodialysis can reduce the occurrence of dialysis-related hypoglycemic events, improve metabolic disorders, lower the risk of diabetic complications, and enhance patients' quality of life. This is particularly important for the long-term prognosis of patients with concomitant cardiovascular diseases. Currently, there is a lack of standardized blood glucose management protocols for diabetic patients on MHD. Future research should focus on optimizing more individualized blood glucose management plans to improve patient prognosis and reduce the risk of complications.

Keywords

Maintenance Hemodialysis, Diabetes, Blood Glucose Management

1. Introduction

Diabetes mellitus is a systemic metabolic disorder characterized by hyperglycemia. The prevalence of diabetes mellitus among people over 18 years old in China is 12.4% [1]-[3], about 129.8 million people, and the overall incidence has been on the rise in recent years [4]. With the increasing incidence of DM in China year by year, about 32.5% of patients will progress to chronic kidney disease, and the number of patients with chronic kidney disease progressing to end-stage renal disease is also gradually increasing [5]. Maintenance hemodialysis (MHD) can replace renal function and prolong the survival time of patients and is one of the main treatment methods for patients with end-stage renal disease. About 40% of dialysis patients are complicated with diabetes [6], and high medical expenditure and high disability will bring a heavy burden to individuals and society. Diabetic patients have metabolic disorders, hemodynamic changes during dialysis, decreased renal insulin clearance rate, glucose loss and transfer, malnutrition, decreased gluconeogenesis, and reduced muscle and liver glycogen stores, which lead to a significant increase in the risk of blood glucose fluctuations during maintenance hemodialysis in diabetic patients. They are especially prone to asymptomatic hypoglycemia, and its incidence is much higher than that of non-diabetic people [6]. Frequent episodes of hypoglycemia may lead to hypotension, anemia, and brain damage. Even serious consequences such as severe cognitive impairment may occur, increasing the risk of death of patients [7]. Therefore, optimizing blood glucose management during dialysis is very important to improve the prognosis and survival rate of patients. This article reviews the particularities and challenges of blood glucose management in diabetic patients on MHD and discusses the research progress of blood glucose monitoring, drug intervention, dialysate optimization, and nutritional support.

2. Particularity and Challenges of Blood Glucose Management in Diabetic Patients on MHD

2.1. Renal Failure Becomes Specific to Glucose Management

The kidney is one of the main organs for insulin degradation, and about one-third of insulin is metabolized through the kidney. Under physiological conditions, the kidney generates glucose through gluconeogenesis and can take glucose from the blood, and at the same time, it can reabsorb glucose from the glomerular filtrate into the body [8]. During fasting, 75% - 80% of glucose comes from the liver, and the remaining 20% - 25% comes from the kidney [9]. With the increase in fasting time, the proportion of renal gluconeogenesis in total glucose release also increases, and after 48 hours, almost all glucose in circulation comes from gluconeogenesis. Influenced by insulin and glucagon levels, renal gluconeogenesis actually increases approximately twofold in postprandial patients, accounting for about 60% of postprandial endogenous glucose release [10] [11]. In the diabetic state, the glucose release from the kidney into the blood circulation increases during fasting, and the relative increase of renal gluconeogenesis is much greater than that of hepatic gluconeogenesis. Postprandial glucose uptake by the kidneys increases in diabetic patients compared with non-diabetic patients, while glucose uptake by muscle does not change significantly [10] [11]. As a key organ for insulin degradation and glucose metabolism, kidney dysfunction can cause multiple metabolic disorders. In renal failure, reduced clearance of insulin prolongs its half-life, which increases the risk of hypoglycemia. In addition, because the kidney is involved in both gluconeogenesis and glucose reabsorption, its impaired function can directly destroy the body's glucose homeostasis mechanism. Therefore, for MHD patients with diabetes, it is necessary not only to prevent the risk of hypoglycemia caused by exogenous insulin accumulation and decreased endogenous glucose production during fasting, but also to cope with hyperglycemia caused by insulin resistance associated with uremia.

2.2. The Difficulty of Blood Glucose Assessment and Monitoring Has Become a Challenge for Blood Glucose Management

Glycosylated hemoglobin (HbA1c) is a commonly used clinical indicator to reflect the blood glucose level of patients, which can effectively evaluate the average blood glucose control of patients in the past 2 - 3 months, but the accuracy of HbA1c in dialysis patients may be affected [12]. Hemodialysis may damage red blood cells and shorten their lifespan, resulting in lower HbA1c values. At the same time, patients may be treated with erythropoietin or iron during dialysis treatment, which can stimulate the generation of new red blood cells. Because young red blood cells exist for a short time and have a low degree of glycation, HbA1c values can also be underestimated. However, if patients are iron deficient, the turnover of red blood cells will be slowed down, resulting in high HbA1c. After iron supplementation, the proportion of young red blood cells will increase, which may reduce HbA1c. These changes can indirectly affect the blood glucose control of patients [13]. For such patients, simply relying on HbA1c to evaluate blood glucose may not be accurate enough. Comprehensive evaluation can be performed by combining patients' fingertip blood glucose detection, continuous glucose monitoring system (CGM) detection and other blood glucose monitoring methods, or other indicators reflecting blood glucose control such as fructosamine and glycated albumin can be selected to assist judgment [14].

2.3. The Multiple Metabolic Regulations of Blood Glucose by Hemodialysis Become a Challenge

The effect of hemodialysis on insulin is mainly manifested in two aspects: hormone clearance and substance exchange. The dialysis process can remove glucose regulatory hormones such as insulin and glucagon, and improve metabolic abnormalities such as uremia, hyperphosphatemia, and acidosis, thereby regulating insulin secretion and sensitivity [15]. Glucose concentration in dialysate also has an impact on blood glucose management. There is a concentration gradient between dialysate and blood. Glucose, a relatively small molecule, can be removed or obtained by diffusion according to the concentration gradient of blood and dialysate, so the hemodialysis process can directly affect blood glucose concentration [16]. Glucose-free dialysate is widely used in most blood purification centers in China due to its low economic cost, difficulty in breeding bacteria, and convenient storage. When using glucose-free dialysate, patients lose about 5.5 g of glucose per hour, and this continuous glucose loss is an important cause of dialysis-related hypoglycemia [17]. The blood glucose fluctuation of MHD diabetic patients on dialysis days is greater than that on non-dialysis days, especially from the beginning to 2 hours after the end of hemodialysis [18]. On the other hand, patients may be at increased risk of developing hyperglycemia due to insulin resistance, secretion of counterregulatory hormones such as glucagon and cortisol, and reduced renal glucose clearance [16]. At present, the mechanism of insulin resistance in dialysis patients is not fully understood, but some studies have shown that inflammation and uremic toxins may be its promoting factors [19]. In addition, secondary hyperparathyroidism and vitamin D deficiency affect insulin secretion, and vitamin D supplementation has been shown to improve insulin secretion [20].

2.4. The Imbalance of Nutritional Metabolism Has Become a Challenge for Blood Glucose Management

The imbalance of nutritional metabolism in hemodialysis patients is closely related to the risk of hypoglycemia. Long-term dialysis can cause manifestations of malnutrition such as protein-energy wasting (PEW) and hypoalbuminemia. About 28% - 54% of maintenance hemodialysis patients have PEW, and hypoalbuminemia, as a key nutritional indicator, is directly related to poor prognosis. Disorders of nutritional metabolism can reduce the supply of gluconeogenic substrates and impair the compensatory function for hypoglycemia, while anemia and electrolyte disturbances further impair tissue oxygen supply and insulin sensitivity. Hypoalbuminemia, as a key indicator to evaluate nutritional status, is closely related to poor prognosis of patients [21]. Studies have shown that the mortality rate decreased by 35% in one year and 20% in five years for every unit increase in the Prognostic Nutrition Index (PNI) score [22]. The short-term and long-term follow-up showed that 10.7% of cases died in less than one year, and the mortality rate reached 32.8% in five years. The incidence of malnutrition in dialysis patients is as high as 55.9% [23]. This abnormal nutritional metabolism not only reduces the immune function of the body and increases the risk of infection, but also significantly increases the incidence of cardiovascular complications, thus affecting the clinical treatment effect [24]. The anemia and electrolyte disturbances that accompany a malnourished state further disrupt tissue oxygen delivery and insulin sensitivity, creating a vicious cycle of metabolic regulation. Chronic inflammatory responses also play an important role in this process, while promoting protein catabolism and glucose regulation disorders. Clinical practice shows that dialysis patients with deteriorating nutritional status are more likely to have glucose fluctuations and hypoglycemic events. Therefore, in the blood glucose management of dialysis patients, the improvement of nutritional status must be taken as an important link, and the nutritional support strategy should be optimized to maintain blood glucose stability.

2.5. The Dilemma of Patients' Blood Sugar Self-Management

For diabetic patients who rely on hemodialysis, blood glucose management not only faces complex physiological challenges, but also comes with a heavy treatment burden and far-reaching psychological impact [25]. Frequent blood glucose monitoring, strict dietary restrictions, insulin dose adjustment and dialysis treatment superposition make patients have to deal with tedious medical tasks every day, which can easily lead to "treatment burnout". At the same time, dialysis itself can cause violent fluctuations in blood sugar—a sudden increase in insulin sensitivity after dialysis may induce hypoglycemia, and uremia-related insulin resistance exacerbates the risk of hyperglycemia [26]. Therefore, individualized patient education becomes the key to improving prognosis. The multidisciplinary medical team needs to help patients understand the bidirectional impact of dialysis on blood sugar, guide them to identify early warning symptoms of hypoglycemia, develop flexible insulin adjustment strategies, and reduce the fear of blood sugar fluctuations through cognitive behavioral interventions, and reduce the burden of self-management with the help of CGM and other tools, helping patients find a balance between controlling blood sugar and maintaining quality of life, so that patients can gain a sense of control over disease management.

3. Goals and Strategies for Glycemic Management

3.1. Blood Glucose Monitoring and Management Goals

As a key link in diabetes treatment, blood glucose monitoring plays a fundamental role in disease management [27]. At present, clinical blood glucose monitoring methods mainly include self-monitoring of blood glucose (SMBG), hemoglobin A1c (HbA1c), and glycated albumin (glycated albumin, GA), and so on. Among them, HbA1c is still the gold standard for assessing the level of long-term blood glucose control in diabetic MHD patients [28]. Continuous glucose monitoring (CGM) has significant advantages over traditional methods, as it can show the characteristics of blood glucose fluctuations in real time and dynamically, and is especially suitable for patients with unstable blood glucose control and a high risk of hypoglycemia [29]. By providing parameters such as time in range (TIR), this technology can more accurately evaluate the quality of blood glucose control and is not affected by complications such as anemia. Theoretically, TIR has better monitoring performance, but due to the limitations of technology popularity and equipment accessibility, TIR cannot completely replace HbA1c in clinical practice at present. Studies showed that HbA1c decreased from 8.4% at baseline to 7.6% after adjusting insulin therapy under the guidance of CGMS in diabetic patients receiving MHD treatment, and the incidence of hypoglycemia was also significantly reduced [30]. The KDIGO guideline clearly states that CGM can avoid further kidney damage caused by high or low blood glucose in patients with diabetes and chronic kidney disease (CKD), especially those with large blood glucose fluctuations and difficulty in effectively controlling blood glucose by traditional blood glucose monitoring methods [31]. Continuous glucose monitoring (CGM) technology provides an important basis for clinical blood glucose management by obtaining dynamic blood glucose data in real time, which helps to guide the timely adjustment of treatment plans and reduce the risk of hypoglycemia while improving the effect of blood glucose control [32]. For specific patient groups, capillary blood glucose monitoring (SMBG) still has irreplaceable clinical value, especially at key time points in the treatment process. Due to the high risk of hypoglycemia in diabetic hemodialysis patients, blood glucose control targets should be individualized, and it is generally recommended that glycosylated hemoglobin (HbA1c) be controlled between 7.0% and 8.0% [33], so as to balance the risks of hyperglycemia and hypoglycemia and reduce the occurrence of cardiovascular events. In young patients with no apparent complications and a long life expectancy, appropriately tight glycemic control can be used to reduce the risk of long-term complications. For high-risk patients, such as elderly patients or those with cardiovascular disease, glycemic control targets can be appropriately relaxed to HbA1c < 8.5% [34].

3.2. Glucose Management Strategies

3.2.1. Pharmacological Interventions

For patients with diabetes mellitus combined with maintenance hemodialysis (MHD), due to the high risk of disease progression and the fact that oral antidiabetic drugs may aggravate kidney damage and cause other adverse reactions, clinical guidelines recommend insulin as the preferred hypoglycemic treatment for such patients [33]. In recent years, new hypoglycemic drugs such as SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors have shown renal protective effects in addition to hypoglycemic effects. Currently, SGLT2 inhibitors approved in China include dapagliflozin, empagliflozin, and canagliflozin. These drugs have clear cardiorenal benefits in patients who are not entering the dialysis stage, but their therapeutic effect is significantly reduced when eGFR < 30 $mL \cdot min^{-1}$ (1.73 $m^2)^{-1}$. Therefore, some guidelines do not recommend the use of such drugs at this stage [35]. Common drugs of GLP-1 receptor agonists include liraglutide, lixisenatide, exenatide, and somalutide, etc. According to the guideline information of the Chinese Guidelines for the Clinical Diagnosis and Treatment of Diabetic Kidney Disease [36], the use of these drugs in patients with chronic kidney disease (CKD) needs to be evaluated according to the specific situation, and the applicability of different drugs may be different. Exenatide and lixisenatide are indicated for patients with renal function stages G1-3, whereas liraglutide and duraglutide can be extended to patients with stage G1-4 but are not recommended for patients with end-stage renal disease. DPP-4 inhibitors commonly used in domestic clinical practice play a hypoglycemic effect by delaying the degradation of GLP-1 [37]. Among them, linagliptin has a unique hepatobiliary metabolic pathway, which makes it advantageous in patients with renal insufficiency, while the other drugs mainly rely on renal clearance. In clinical application, for patients with moderate to severe renal impairment, except linagliptin, the dose of other DPP-4 inhibitors should be adjusted according to the level of renal function [38].

Due to the complete loss of renal function and metabolic disorders, the pharmacokinetics of maintenance hemodialysis diabetic patients are significantly altered, and some water-soluble drugs may be removed during the dialysis process, while the uremic state will affect the drug protein binding rate and distribution volume, increasing the risk of poisoning. Its blood glucose tube control is particularly complex, and it is necessary to control both hyperglycemia and prevent dialysis-related hypoglycemia, which requires fine adjustment of the use of insulin and oral hypoglycemic drugs. At the same time, phosphorus binders commonly used in therapy may interfere with the absorption of other drugs, and the metabolic interactions between multiple drugs also require special attention. These patients often require multiple medications to cope with diabetic complications and uremia symptoms, and the heavy medication burden significantly affects treatment adherence. More complicatedly, there are often conflicts between different treatment goals, such as correcting anemia may exacerbate hypertension, and controlling blood phosphorus may affect bone metabolism. Therefore, it is necessary to adjust insulin doses through multidisciplinary collaboration, regular evaluation of medication regimens, priority selection of drugs with less impact on dialysis, and combination of CGM and other methods. Clinical observations found that the average blood glucose level of patients was significantly reduced after the use of CGM-guided insulin dose adjustment [38].

3.2.2. Dialysis Process Intervention

Dialysate is a key factor in the treatment of maintenance hemodialysis. The various components and their ratios of dialysate can significantly affect glucose metabolism, blood pressure regulation, electrolyte homeostasis, and other important physiological indicators of patients. Due to the significant clinical heterogeneity of patients receiving long-term dialysis treatment, individualized dialysate formulations must be developed according to the specific metabolic characteristics of patients in the actual treatment process to achieve the best treatment effect [39] [40]. For hemodialysis patients with diabetes mellitus, the complexity of metabolic disorders and cardiovascular complications makes the choice of dialysate particularly critical [41]. Studies have shown that the glucose metabolism rate of such patients can reach 5.5 g/h during dialysis. Although the glucose-free dialysate, which is widely used in clinical practice, has the advantages of easy storage and low contamination, it may lead to a sharp drop in blood glucose levels. It is worth noting that hypoglycemia and hypotension during dialysis often interact and occur at the same time, leading to serious cardiovascular adverse events [41] [42], which not only reduce the efficacy of dialysis, but also significantly increase the mortality of patients. Therefore, it is very important to choose an appropriate concentration of glucose-containing dialysate to reduce the occurrence of intradialytic hypoglycemia. For patients with normal blood glucose during dialysis, glucose-containing dialysate can help stabilize blood glucose levels and improve heart rate variability [17], but glucose-free dialysate is more common in clinical practice in our country. Therefore, the choice of glucose concentration in dialysate should be individualized. Although glucose-free dialysate reduces caloric load, it may increase the risk of hypoglycemia, while glucose-containing dialysate is more suitable for diabetic patients, and blood glucose changes should be closely monitored.

3.2.3. Lifestyle Interventions

In the comprehensive management of diabetic patients, lifestyle intervention plays an important role in the prognosis of MHD diabetic patients. The literature included in this study mainly involved diet and exercise for life intervention. In current medical practice, although dietary guidance is included in routine nursing, fragmented health education is often carried out based on disease status, and systematic nutrition management plans are lacking [43]. The incidence of malnutrition in maintenance hemodialysis patients in China is as high as 30% - 66.7% [44], among which patients with diabetic nephropathy are at more prominent nutritional risk due to multiple pathological factors. These patients often have multiple system problems such as renal insufficiency, gastrointestinal dysfunction, and metabolic abnormalities at the same time, which significantly increases the probability of malnutrition. In addition, patients with maintenance hemodialysis generally have a chronic microinflammatory state, and persistent inflammatory response can promote muscle protein catabolism and inhibit the protein synthesis pathway. It further aggravates malnutrition in patients under dual mechanisms [45]. Therefore, improving nutritional status is of great clinical significance for improving the prognosis and quality of life of patients.

In terms of diet management, first of all, it is recommended that smoking patients quit smoking, eat in divided meals, strictly control total calorie intake, and ensure balanced nutrition. The daily calorie intake is about 35 kcal/kg, but for elderly patients over 60 years old, if there is reduced activity or good nutritional status, it can be appropriately reduced to 30 - 35 kcal/kg [45]. Fat < 30% and protein > 15% (1.0 - 1.2 g/kg/d) are recommended. For patients with high risk of hypoglycemia, an appropriate amount of low glycemic index carbohydrates can be considered before and after dialysis, but the clinical value of eating during dialysis is still controversial [46]. For example, while nutritional interventions restricting phosphorus, sodium, and fluid intake in maintenance hemodialysis patients have been shown to improve clinical outcomes, strict dietary management requires both adequate energy and protein intake to meet patients' nutritional needs and must comply with multiple restrictive requirements, making it difficult for patients to adhere to them in the long term. In addition, it is necessary to focus on controlling electrolyte intake, optimizing the ratio of the three major nutrients, and establishing a regular dietary pattern to avoid the adverse effects caused by an irregular diet [47]. Eating during dialysis may also lead to an increased incidence of symptomatic hypotension and other symptoms (nausea, vomiting, gastrointestinal reactions, muscle cramps, etc.) [46]. Therefore, whether or not to allow patients to eat during hemodialysis should be individualized based on nutritional needs, hemodynamic changes during dialysis, and the risk characteristics of adverse events during hemodialysis.

Regular exercise has a positive effect on blood glucose management in diabetic patients with maintenance hemodialysis. Studies have shown that a comprehensive exercise program combining aerobic exercise and resistance training can enhance skeletal muscle glucose metabolism and improve insulin sensitivity, thereby helping to maintain blood glucose homeostasis [48]. In the development of exercise programs, special attention should be paid to the synergistic regulation of exercise intensity with diet and hypoglycemic drugs to prevent the occurrence of exercise-related hypoglycemia. Moderate-intensity aerobic and resistance training programs are recommended in clinical practice, and moderate-intensity physical activity or exercise at a level compatible with cardiovascular and physical tolerance is recommended for at least 150 min per week [49]. The application of high-intensity interval training should be cautious. Although existing studies have confirmed the clinical value of exercise intervention, there are still limitations such as limited research samples and insufficient long-term efficacy data. In the future, more studies are needed to establish individualized exercise treatment programs [50].

4. Comprehensive Strategic Recommendations

Multi-dimensional and individualized strategies should be adopted for blood glucose management in dialysis patients. CGM is recommended for blood glucose monitoring for patients who have the conditions, and CGM's continuous glucose monitoring and hyperglycemia and hypoglycemia alerts enable patients to identify changes in blood glucose in time and thus adjust insulin doses in a timely manner [50]. Special attention should be paid to the changes in blood glucose before, during, and after dialysis. Hemoglobin A1c may be low in patients with anemia, which should be comprehensively evaluated in combination with other indicators. With the advancement of technology, researchers are actively exploring the integration of insulin pumps with continuous glucose monitoring (CGM) systems to achieve automatic regulation of insulin infusion through intelligent control algorithms. This closed-loop system can dynamically adjust insulin doses based on real-time glucose data, allowing for more precise and stable blood sugar control [51] [52]. Although CGM is recommended by clinical experts as a more accurate means of blood glucose monitoring, the interpretation of CGM data relies on professional guidance, coupled with the high price of the device and the more complex operation than traditional blood glucose monitoring, all of which limit its popularity in clinical practice. In clinical trials, the application of CGM is also subject to multiple constraints: long-term wear may affect the design of the trial protocol and increase the uncertainty of the research results; extending the monitoring time will significantly increase the cost of research and may affect the accuracy of the data. In addition, there are differences in CGM devices and models used in different studies, making it difficult to compare the results horizontally. These factors collectively restrict the widespread application of CGM in clinical research [53].

Insulin should be the first choice for drug treatment, and the dose should be adjusted flexibly according to real-time blood glucose monitoring on dialysis days, rather than simply stopping. Oral antidiabetic drugs with high renal safety, such as linagliptin, should be selected, and contraindicated drugs such as metformin are strictly prohibited. If rapid-acting insulin is used and the basal dose is reduced by 30%, the morning dose on the day of dialysis should be reduced by 20% - 30%. The integration of CGM data with artificial intelligence in diabetes management is currently a research hotspot [54]. These AI-based CGM models provide dynamic blood glucose data by interpreting large datasets and build blood glucose prediction models to adjust the dosage of hypoglycemic drugs or insulin in a timely manner. The ability of AI-based algorithms to predict blood glucose levels based on CGM data can help provide early warning of potential hypoglycemia or hyperglycemia episodes in patients. Studies have shown that machine learning-based models can significantly facilitate accurate glucose predictions, promoting more personalized optimal diabetes glucose management, especially for those patients receiving multidrug combination therapy [55].

The dialysis program should be customized according to the characteristics of blood glucose. Glucose-containing dialysate is recommended for patients who are prone to hypoglycemia, and glucose-free dialysate is recommended for patients with hyperglycemia. The ultrafiltration rate should be controlled, and low-temperature dialysis or increased dialysis frequency should be used if necessary. When using glucose-free dialysate, it is recommended to eat small amounts multiple times after dialysis, and eating during dialysis should be performed cautiously to prevent hypotension.

It is suggested to establish a multidisciplinary diagnosis and treatment team consisting of nephrology, endocrinology, nutrition, and nursing teams for regular consultation and evaluation. Patient education should be strengthened, focusing on coping with hypoglycemia, dialysis day management, and medication rules. The efficacy should be comprehensively evaluated every 1 - 2 months, focusing on hypoglycemic events, blood glucose fluctuations, nutritional status, and complications, and the treatment plan should be optimized in time.

5. Conclusion

In summary, although progress has been made in the management of blood glucose in diabetic patients with maintenance hemodialysis in terms of monitoring technology, drug therapy, dialysate modification, and lifestyle intervention, further research is still needed. In the future, we should focus on exploring individualized treatment options, including precise adjustment of dialysate composition, optimization of drug selection, and personalized nutrition and exercise guidance. At the same time, long-term follow-up studies with large samples are needed to comprehensively evaluate the clinical benefits and safety of existing interventions, so as to provide an evidence-based basis for improving the prognosis and quality of life of patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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