RESEARCH ARTICLE

Autologous Dendritic Cell Immunotherapy Modulates Renal Perfusion and Hemodynamics in Diabetic Kidney

Adi Soekardi[1], Linda Chiuman[2], Chrismis Novalinda Ginting[3,*]

[1]Departmetment of Radiology, Faculty of Medicine, Dentistry, and Health Science, Universitas Prima Indonesia, Jl. Ayahanda No.68a, Medan, Indonesia
[2]Departmetment of Physiology, Faculty of Medicine, Dentistry, and Health Science, Universitas Prima Indonesia, Jl. Ayahanda No.68a, Medan, Indonesia
[3]Departmetment of Medicine, Faculty of Medicine, Dentistry, and Health Science, Universitas Prima Indonesia, Jl. Ayahanda No.68a, Medan, Indonesia

*Corresponding author. Email: chrismisnovalindaginting@unprimdn.ac.id

Received date: Oct 21, 2025; Revised date: Jan 13, 2026; Accepted date: Jan 19, 2026

Abstract

BACKGROUND: Diabetic kidney disease (DKD) is driven by chronic inflammation and endothelial dysfunction, which often persist despite standard pharmacological treatments. Autologous dendritic cell (DC) immunotherapy offers a novel approach to restore immune homeostasis and improve renal vascular function. While the use of autologous DC for immune homeostasis has been previously discussed, not many studies have explicitly reported on the modulation of renal perfusion parameters, such as peak systolic velocity (PSV) and resistive index (RI), following DC immunotherapy. Therefore, this study was conducted to evaluate the effect of autologous DC administration on renal hemodynamics, including PSV and RI, as well as inflammatory biomarkers, including tumor necrosis factor (TNF)-α and vascular cell adhesion molecule (VCAM-1) in DKD patients.

METHODS: Thirty-one DKD patients were selected via simple random sampling. All subjects underwent autologous DC therapy, which was administered via intravenous infusion at a concentration of approximately 1×10^7 cells suspended in 100 mL of normal saline. PSV and RI were measured using Renal Doppler Ultrasonography, while TNF-α and VCAM-1 were quantified using the Enzyme-Linked Immunosorbent Assay (ELISA) method. All measurements were conducted before intervention and 60 days after intervention to evaluate the therapeutic efficacy.

RESULTS: DC therapy led to significant alterations in renal hemodynamic parameters. The mean PSV decreased from 52.74 to 38.21 cm/s (p=0.016), while RI showed a modest increase from 0.7350 to 0.7550 (p=0.028). Greater hemodynamic effects were observed in patients with well-controlled glycemia, lower serum urea, and microalbuminuria. In contrast, no significant changes were detected in TNF-α and VCAM-1 levels.

CONCLUSION: Autologous DC therapy delivers measurable, statistically significant benefits in renal vascular parameters for DKD, particularly in early-stage disease and metabolically stable patients. These findings may support DC therapy as a promising adjunctive strategy to improve renal microcirculation in DKD.

KEYWORDS: diabetic kidney disease, dendritic cell therapy, TNF-α, VCAM-1, PSV, RI

Indones Biomed J. 2026; 18(1): 45-57

Introduction

Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease (CKD) and end-stage renal disease worldwide, accounting for 25–45% of all CKD cases.(1–3) The increasing global prevalence of diabetes directly drives the rising burden of DKD.(4,5) In Indonesia, diabetes affects approximately 2% of adults, contributes to 6% of total mortality, and underscores the urgent need for improved strategies to manage its complications, particularly DKD.(6–8) DKD is characterized by persistent albuminuria, declining glomerular filtration rate, and histopathological changes including glomerulosclerosis and interstitial fibrosis.(9,10)

Its pathogenesis involves chronic hyperglycemia, endothelial dysfunction, and sustained inflammation. Key inflammatory mediators such as including tumor necrosis factor (TNF)-α and vascular cell adhesion molecule (VCAM)-1 promote renal injury by enhancing leukocyte infiltration and fibrosis.(11,12) Elevated levels of these biomarkers correlate with disease severity and progression. The pathogenesis of DKD involves hyperglycemia-induced oxidative stress, endothelial dysfunction, and persistent inflammation. Among the inflammatory mediators, TNF-α and VCAM-1 play pivotal roles in promoting renal inflammation and fibrosis. TNF-α induces endothelial permeability, leukocyte infiltration, and tubular injury (13), while VCAM-1 mediates adhesion and transmigration of inflammatory cells into renal tissue. Elevated circulating VCAM-1 correlates with albuminuria and inversely with glomerular filtration rate (GFR).(14) Thus, both TNF-α and VCAM-1 serve as key biomarkers reflecting the inflammatory and endothelial status of DKD.

Renal imaging techniques, particularly ultrasonography, provide non-invasive insight into renal structure and hemodynamics. Doppler parameters such as peak systolic velocity (PSV) and resistive index (RI) reflect renal blood flow and microvascular resistance, serving as potential indicators of renal fibrosis and functional impairment.(15) While renal biopsy remains the gold standard for assessing fibrosis, its invasive nature limits its use; therefore, ultrasonography offers a safer and reproducible alternative for clinical evaluation. Current standard therapies for DKD, such as renin-angiotensin-aldosterone system (RAAS) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors, primarily target hemodynamic and metabolic pathways. While these agents slow disease progression, many patients experience residual inflammation and gradual renal function decline once fibrosis is established.(16,17) This highlights a critical therapeutic gap that most available treatments do not adequately address the underlying immune dysregulation that perpetuates chronic inflammation and vascular injury in DKD. To bridge this gap, novel immunomodulatory approaches are being explored. Recent advances in immunology have revealed the critical role of dendritic cells (DCs) in mediating renal inflammation. DCs are antigen-presenting cells that bridge innate and adaptive immunity by regulating T-cell responses.(18,19) Under inflammatory conditions, DCs can acquire either proinflammatory or tolerogenic phenotypes. Autologous DC therapy, which is generated by differentiating patient-derived monocytes *ex vivo*, has been successfully applied in cancer, autoimmune diseases, allergies, and fibrotic disorders, showing favourable safety and immunomodulatory profiles.(16,17,20) Although current therapie such as renin-angiotensin inhibitors and SGLT2 inhibitors can slow kidney damage, DKD often continues to progress once inflammation and fibrosis have developed. Most treatments control blood sugar and blood pressure but do not address the immune imbalance driving chronic inflammation. DCs are known to influence these immune pathways, yet clinical evidence on their therapeutic role in DKD is still limited. Therefore, this study was conducted to fill that gap by evaluating the effects of autologous DC therapy on both inflammatory markers, including TNF-α and VCAM-1, as well as renal blood flow inclusing PSV and RI. Compared with earlier studies, this work combines biochemical and vascular parameters to provide a more comprehensive view of the immunomodulatory effects of DC therapy in DKD. This investigation seeks to explore DC therapy as a novel immunomodulatory approach for mitigating renal inflammation and improving vascular function in diabetic kidney disease.

Methods

Study Design and Subjects Recruitment

This study employed a quasi-experimental, one-group pretest–posttest design to evaluate the effects of DC therapy in patients with DKD. Each subjects underwent pre-intervention and post-intervention evaluations of inflammatory biomarkers (TNF-α, VCAM-1) and renal ultrasonographic parameters (PSV and RI). No control group was included due to ethical and practical considerations in this preliminary exploratory study; all eligible patients were offered the investigational therapy as an add-on to standard care. The study was conducted between January and October 2024 at Gatot Soebroto Army Central Hospital, Jakarta, Indonesia.

Sampling was performed using simple random sampling among eligible outpatients. Inclusion criteria were patients with: Diagnosis of type 2 diabetes mellitus (T2DM) according to PERKENI (2021), age ≥18 years, estimated GFR (eGFR) ≥30 mL/min/1.73 m², urinary albumin–creatinine ratio (UACR) ≥30 mg/g, clinically stable condition, able and willing to comply with study procedures. The exclusion criteria encompassed the use of immunosuppressive drugs within four weeks prior to enrollment; the presence of other renal disorders such as lupus nephritis or polycystic kidney disease; active infections including HIV, HBV, or HCV; malignancy under

treatment; pregnancy; uncontrolled hypertension (blood pressure >180/100 mmHg); severe obesity with a BMI greater than 40 kg/m²; and any psychiatric or physical condition that could interfere with study participation. The sample size was calculated using G*Power software (effect size=0.7, α=0.05, power=0.95, two-tailed), resulting in a minimum of 29 subjects. The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Universitas Prima Indonesia, Medan (No. 039/KEPK/UNPRI/III/2025). All subjects provided written informed consent prior to enrollment, in accordance with the principles of the Declaration of Helsinki.

Preparation of Autologous DCs

As much as 40–50 mL peripheral venous blood was collected aseptically from each subjects. Mononuclear cells were isolated by density gradient centrifugation using Ficoll-Paque Plus (Cytiva, Uppsala, Sweden). Monocytes were then cultured in RPMI-1640 medium (Gibco-Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS) (Gibco), recombinant human GM-CSF (50 ng/mL) (PeproTech, Cranbury, NJ, USA), and recombinant human IL-4 (20 ng/mL) (PeproTech) to generate DCs, following established protocols.(18,19) All cell processing was performed under aseptic conditions in a certified Good Manufacturing Practice (GMP)-compliant cleanroom facility at the Cell Therapy Laboratory, Gatot Soebroto Army Central Hospital, Jakarta, Indonesia. Cells were incubated for five days at 37°C in a humidified 5% CO_2 atmosphere. On Day-6, cells were harvested, washed, and resuspended in sterile saline (B. Braun, Melsungen, Germany) at a final concentration of 1×10^6 cells in 2 mL. Quality control of autologous DCs was performed by flow cytometric analysis. Mature DCs were identified based on the expression of CD11c, CD80, CD86, and HLA-DR, confirming appropriate differentiation and maturation.

Hematological and Biochemical Assessments

Baseline hematological and biochemical parameters were measured using standardized automated analyzers. Complete blood count was performed using a Sysmex XN-1000 hematology analyzer (Sysmex Corporation, Kobe, Japan). Fasting plasma glucose, 2-hour postprandial glucose, serum creatinine, lipid profile, and uric acid were quantified using a Cobas c501 analyzer (Roche Diagnostics, Basel, Switzerland). Hemoglobin A1c (HbA1c) was measured by high-performance liquid chromatography (HPLC) using a Bio-Rad D-100 system (Bio-Rad Laboratories, Hercules, CA, USA). The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. UACR was determined from a spot urine sample, with albumin measured by immunoturbidimetry and creatinine by the Jaffe method on a Cobas c501 analyzer.

Inflammatory Biomarker Measurement

Serum concentrations of TNF-α and VCAM-1 were measured using commercially available Enzyme-linked Immunosorbent Assay (ELISA) kits. Specifically, TNF-α was quantified using the Human TNF-α Quantikine ELISA Kit (Catalog #DTA00D, R&D Systems, Minneapolis, MN, USA), and VCAM-1 was measured using the Human CD106/VCAM-1 Quantikine ELISA Kit (Catalog #DVC00, R&D Systems). Assays were performed according to the manufacturer's instructions. Briefly, standards and samples were incubated in antibody-coated microwells, followed by detection with a horseradish peroxidase-conjugated secondary antibody and colorimetric substrate. Absorbance was read at 450 nm with wavelength correction at 570 nm using a microplate reader (BioTek Instruments, Winooski, VT, USA). All samples were analyzed in duplicate, and the mean concentration was calculated based on a standard curve. Intra-assay and inter-assay coefficients of variation were less than 10%.

Renal Doppler Ultrasonography

Renal hemodynamic parameters were assessed by color Doppler ultrasonography using a Philips Affiniti 70 ultrasound system (Philips Healthcare, Amsterdam, The Netherlands) equipped with a convex array transducer (C5-1). The peak systolic velocity (PSV) and resistive index (RI) were measured in the interlobar arteries of both kidneys according to standard protocols. After obtaining a clear spectral waveform, PSV was recorded as the maximum systolic velocity, and RI was calculated using the formula: RI = (peak systolic velocity - end-diastolic velocity) / peak systolic velocity. Three consecutive measurements were taken for each kidney, and the average value was used for analysis. All ultrasonographic examinations were performed by the same experienced radiologist who was blinded to the treatment status of the participants to minimize operator bias.

Follow-up and Safety Monitoring

Participants were followed for 60 days post-therapy. Scheduled assessments were conducted at three time points: Day-7 (evaluating UACR and eGFR for early renal response), Day-30 (measuring TNF-α, VCAM-1, PSV, and RI as the primary study endpoints), and Day-60 (final

safety and clinical evaluation). The Day-60 visit focused on documenting adverse events, clinical symptoms, vital signs, and overall tolerability. Laboratory and ultrasonographic parameters were not repeated at Day-60 because the study was designed to evaluate the 30 days immunomodulatory and hemodynamic effects, consistent with previous DC therapy protocols. Adverse events were monitored through direct clinical examination and structured telecommunication follow-ups. All events were documented and graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. No serious or life-threatening adverse reactions were observed during the study period.

Statistical Analysis

Data were processed using SPSS 23.0 (IBM Corporation, Armonk, NY, USA). The Shapiro–Wilk test evaluated data normality. Paired t-tests were applied for normally distributed variables, and the Wilcoxon signed-rank test was used for nonparametric data. Quantitative data were expressed as mean±standard deviation (SD). A p-value<0.05 was considered statistically significant.

Results

The Internal Medicine Polyclinic at Gatot Soebroto Army Hospital recorded a total of 10,930 patient visits from April to May 2024. Of these, 648 patients visited the Endocrine Metabolic Diabetes Internal Medicine Sub-Department, while 1,280 other patients visited the Kidney Hypertension Internal Medicine Sub-Department. Of all these visits, 312 patients were diagnosed with diabetes mellitus and proteinuria. After going through a selection process, 80 subjects agreed to participate and undergo further screening. However, after further examination, 4 subjects met the exclusion criteria: 1 subject was detected HBsAg positive, 1 subject was severely obese (BMI >40), and 2 other subjects had uncontrolled hypertension (systolic blood pressure >180 mmHg, diastolic blood pressure >100 mmHg). Thus, 76 subjects continued the study. Subsequently, 31 subjects underwent PSV RI examination, so that only 31 subjects completed the study and their data could be analyzed.

Quality Assurance of the Autologus DC

The quality assurance results showed that the prepared cell suspension contained a high purity of dendritic cells, with more than 92.70% of cells expressing CD11c, 93.83 of cells expressing CD86 and 93.83% expressing maturation markers CD80/HLA-DR (Figure 1). This confirms that the infusion consisted of viable, mature DCs ready for immunotherapy.

Light micrograph showing adherent cells after 5 days of culture in the presence of recombinant human GM-CSF and IL-4 (Figure 2). The cells exhibit the characteristic morphology of immature DCs, including an irregular, stellate shape and the development of numerous cytoplasmic projections (veils or dendrites). This morphological assessment, together with flow cytometric analysis in Figure 1, confirms the successful differentiation of monocytes into functional DCs for autologous immunotherapy.

Clinical Profile of DKD Subjects Receiving DC Therapy

Among the 31 subjects, the mean body weight was 69.00±15.46 kg, mean height was 160.42±7.60 cm, and mean

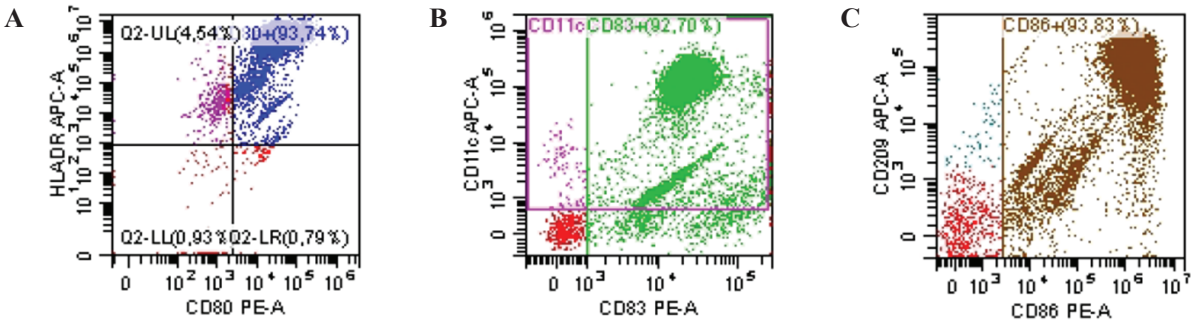

Figure 2. Flow cytometric analysis of autologous DC quality assurance. Peripheral blood mononuclear cells were isolated from DKD patients, differentiated into DCs *in vitro* with GM-CSF and IL-4, and analyzed by flow cytometry after 5 days of culture. The prepared DC suspension demonstrated high purity, confirming the successful generation of viable, mature DCs suitable for immunotherapy. Representative histograms show the expression of key surface marker; A: Expression of CD80 and HLA-DR, indicating DC maturation and antigen-presenting capability (>93.83% co-expressing CD80/HLA-DR); B: Expression of CD11c, a pan-DC marker confirming dendritic lineage (>92.70% of cells expressing high CD11c); C: Expression of CD86, a co-stimulatory molecule essential for T-cell activation (>93.83% expressing CD86).

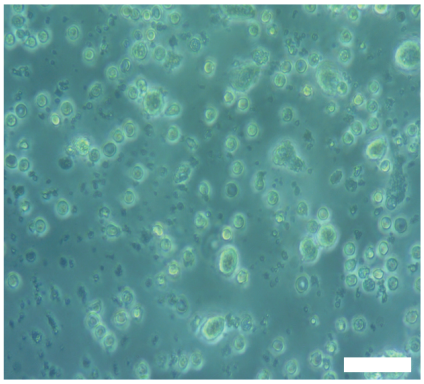

Figure 1. Morphology of *in vitro*-generated autologous DCs. Light showing adherent monocyte-derived cells after 5 days of culture in the presence of recombinant human GM-CSF and IL-4. The cells exhibit characteristic dendritic morphology, including an irregular, stellate shape with numerous cytoplasmic projections (veils or dendrites, indicated by arrows), which are typical of immature DCs. This morphological assessment confirms the successful differentiation of monocytes into functional DCs for autologous immunotherapy. White bar: 50 µm.

BMI was 26.69±4.97 kg/m², indicating that most subjects were within the overweight to obese category. Based on BMI classification, 22.6% of subjects had a normal BMI, 6.5% were underweight, 41.9% were classified as Obesity Class I, and 29.0% as Obesity Class II, suggesting a predominance of excessive body weight among the study subjects. In terms of glycemic control, 61.3% of subjects had HbA1c levels <8%, indicating relatively well-controlled diabetes, while 38.7% had HbA1c ≥8%, reflecting suboptimal glycemic control consistent with the clinical characteristics often observed in patients with DKD. Renal function assessment showed that 83.9% of participants had ureum levels below 50 mg/dL, and 74.2% had creatinine levels <1.5 mg/dL, suggesting that the majority maintained near-normal renal biochemical parameters. However, based on the eGFR, 45.2% were classified as Grade 1 (normal renal function), 22.6% as Grade 2 (mild impairment), and 32.3% as Grade 3 (moderate impairment), indicating a notable proportion with early to moderate renal dysfunction (Table 1).

Comorbidities and Disease History of Study Subjects

The majority of subjects in this study (96.8%) had a history of hypertension, reflecting a strong coexistence of elevated blood pressure among patients with diabetes and kidney-related disorders. Only 3.2% of participants reported no history of hypertension. Regarding cardiac comorbidities, 64.5% of subjects had no heart disease, while 16.1% were diagnosed with hypertensive heart disease (HHD) and another 16.1% with coronary heart disease. A smaller proportion had arrhythmia (3.2%) or other unspecified cardiac conditions. These findings highlight that cardiovascular involvement was a common complication in this population, consistent with the known association between diabetes, hypertension, and cardiac morbidity. A history of stroke was present in 16.1% of respondents, predominantly ischemic infarction, indicating the presence of cerebrovascular complications. Neuropathy was observed in 51.6% of participants, suggesting that more than half of the study population had peripheral nerve involvement, which is a frequent chronic complication of diabetes (Table 2).

Retinopathy was identified in 12.9% of subjetcs, indicating a lower proportion of ocular complications compared to neuropathy. In addition, osteoarthritis was found in 19.4% of participants, which may reflect age-related degenerative changes common in this older population. Other comorbid conditions included tuberculosis (3.2%), ischemic heart disease (3.2%), benign prostatic hyperplasia (3.2%), anemia (3.2%), low back pain (6.5%), and hypertensive metabolic problems (16.1%), demonstrating a wide range of systemic health issues in this cohort (Table 2). Overall, these results indicate that the study subjects

Table 1. Clinical profile of DKD subjects receiving DC therapy.

Variables	Value
Age (years), Mean±SD	64.19±8.24
Body Weight (kg), Mean±SD	69.00±15.46
Height (cm), Mean±SD	160.42±7.60
BMI (kg/m²), Mean±SD	26.69±4.970
Gender, n (%)	
Male	18 (58.1)
Female	13 (41.9)
BMI, n (%)	
Normal BMI	7 (22.6)
Underweight	2 (6.5)
Obesity Class I	13 (41.9)
Obesity Class II	9 (29.0)
HbA1c, n (%)	
HbA1c <8%	19 (61.3)
HbA1c ≥8%	12 (38.7)
Ureum, n (%)	
Ureum <50 mg/dL	26 (83.9)
Ureum ≥50 mg/dL	5 (16.1)
Creatinine, n (%)	
Creatinine <1.5 mg/dL	23 (74.2)
Creatinine ≥1.5 mg/dL	8 (25.8)
eGFR, n (%)	
Grade 1	14 (45.2)
Grade 2	7 (22.6)
Grade 3	10 (32.3)

Table 2. The high prevalence of the cardiometabolic comorbidities in study subjects.

Diseases	n (%)
Hypertension	
No	1 (3.2)
Yes	30 (96.8)
Heart Disease	
No	20 (64.5)
Hypertensive Heart Disease (HHD)	5 (16.1)
Coronary Heart Disease	5 (16.1)
Arrhythmia	1 (3.2)
Stroke	
No	26 (83.9)
Infarction	5 (16.1)
Neuropathy	
No	15 (48.4)
Yes	16 (51.6)
Retinopathy	
No	27 (87.1)
Yes	4 (12.9)
Osteoarthritis	
No	25 (80.6)
Yes	6 (19.4)
Other Diseases	
None	17 (54.8)
Tuberculosis (TB)	1 (3.2)
IHD	1 (3.2)
HMP	5 (16.1)
Benign Prostatic Hyperplasia (BPH)	1 (3.2)
Anemia	1 (3.2)
Low Back Pain (LBP)	2 (6.5)

were predominantly composed of older adults with multiple comorbidities, particularly hypertension, cardiac disease, and diabetic neuropathy, which were recognized as key contributors to increased morbidity and mortality in patients with metabolic and renal disorders.

Medication Patterns Reflecting Standard DKD Management

The distribution of medication used among study subjects demonstrated a therapeutic pattern consistent with the multifactorial management of DKD, encompassing both antihypertensive and glucose-lowering regimens. A predominance of angiotensin receptor blocker use (74.2%) highlights adherence to evidence-based nephroprotective strategies aimed at reducing intraglomerular hypertension and albuminuria. Only a small proportion received angiotensin-converting enzyme inhibitors (ACE-i) (3.2%), possibly reflecting clinical substitution due to adverse reactions such as cough or hyperkalemia. Furthermore, calcium channel blockers (DHP type, 54.8%) were the second most commonly prescribed antihypertensive agents, underscoring their complementary role in blood pressure control and vascular protection in DKD patients. The minimal use of diuretics (6.5%), beta blockers (25.8%), and alpha blockers (3.2%) suggested a selective approach to minimize metabolic and hemodynamic side effects. Regarding glycemic management, the data indicated that insulin (64.5%) and sulphonylureas (45.2%) were the most frequently used agents, suggesting that a substantial subset of patients had advanced diabetes or impaired renal function necessitating insulin therapy (Table 3). Collectively, these findings illustrate that the majority of DKD patients in this cohort were managed using a dual-target pharmacologic strategy emphasizing renoprotection through RAAS blockade and glycemic control through insulin-based therapy.

DC Therapy Significantly Improved Renal Hemodynamic Parameters

Figure 3A presented a representative Doppler ultrasonography image from a DKD subject, showing interlobar arterial blood flow measurement with calculated PSV and RI. The pre-treatment scan revealed elevated RI values, indicating increased renal vascular resistance, while the post-treatment scan following autologous DC therapy demonstrates reduced PSV and mild normalization of RI, suggesting improved renal microcirculation. Accompanying color Doppler imaging revealed minimal vascularization in the pre-treatment kidney (shown in red, representing arterial flow), consistent with impaired renal perfusion. Figure 3B displayed an abdominal ultrasonography image of the same patient after DC therapy, illustrating normal hepatic, pancreatic, gallbladder, splenic, and gastric morphology without focal lesions, biliary dilatation, ascites, or pleural effusion. Both kidneys appear reduced in size with irregular contours and cortical thinning, indicative of chronic kidney disease, and a simple left renal cyst (Bosniak I, 1.4 cm) was noted. Post-treatment color Doppler revealed increased renal vascularization, with enhanced red signals indicating arterial flow and blue signals representing venous flow, supporting improved perfusion and macrovascular preservation following DC intervention.

Spectral Doppler ultrasonography performed prior to DC administration demonstrated reduced intrarenal perfusion, characterized by a PSV of 44.1 cm/s and an RI of 0.65 in the left kidney. Thirty days after the intervention, repeat ultrasonographic evaluation revealed an increase in both parameters, with the PSV rising to 49.9 cm/s and the

Table 3. Medication patterns reflecting standard DKD management.

Medication Type	Consumption Status	
	Yes n (%)	No n (%)
ARB		
Angiotensin Receptor Blocker (ARB)	23 (74.2)	8 (25.8)
Angiotensin-Converting Enzyme Inhibitor (ACE-i)	1 (3.2)	30 (96.8)
Beta Blocker (β-Blocker)	8 (25.8)	22 (71.0)
Calcium Channel Blocker (CCB) – DHP type	17 (54.8)	14 (45.2)*
Calcium Channel Blocker (CCB) – Non-DHP type	9 (29.0)	22 (71.0)*
Alpha Blocker	1 (3.2)	30 (96.8)
Diuretic (Hydrochlorothiazide)	2 (6.5)	29 (93.5)
Central Alpha Agonist	0 (0.0)	31 (100.0)
Antidiabetic Drugs		
Sulphonylurea	14 (45.2)	17 (54.8)
Biguanide (Metformin)	9 (29.0)	22 (71.0)
Thiazolidinedione	0 (0.0)	31 (100.0)
Glinide	0 (0.0)	31 (100.0)
α-Glucosidase Inhibitor	4 (12.9)	27 (87.1)
DPP-4 Inhibitor (Gliptin)	7 (22.6)	24 (77.4)
GLP-1 Agonist	0 (0.0)	31 (100.0)
SGLT2 Inhibitor	4 (12.9)	27 (87.1)
Insulin	20 (64.5)	11 (35.5)

*Significantly different between Yes and No with $p<0.05$, tested with Paired t-tests.

RI increasing to 0.74. Although the numerical changes were relatively small, the upward trend in PSV and RI suggests an improvement in renal vascular resistance and blood flow following DC therapy. To quantify these observations, statistical comparisons of PSV, RI, TNF-α, and VCAM-1 levels before and after therapy were performed across subgroups based on RI classification, serum creatinine, and eGFR (Table 4).

The comparative analysis of pre- and post-administration of DC on PSV, TNF-α, and VCAM-1 parameters was carried out according to the RI classification. The results indicated significant variations in some parameters depending on RI category. For PSV, the normal RI group showed a notable decrease after DC administration, with a *p*-value of 0.069, suggesting a clear difference between pre- and post-treatment values. In the elevated RI group, PSV also decreased significantly ($p=0.046$), indicating that DC administration had a meaningful effect in reducing PSV in this subgroup. There was no significant difference between pre- and post-administration in either RI group, with *p*-values of 0.929 for normal RI and 0.985 for elevated RI. This suggested that DC treatment did not significantly alter TNF-α concentrations. Similarly, for VCAM-1, although mean values changed slightly, the differences between pre- and post-treatment were not statistically significant in either RI category ($p=0.859$ for normal RI; $p=0.621$ for elevated RI). Overall, DC administration produced a significant reduction in PSV in both normal and elevated RI groups, while no significant effects were observed on TNF-α or VCAM levels across RI classifications.

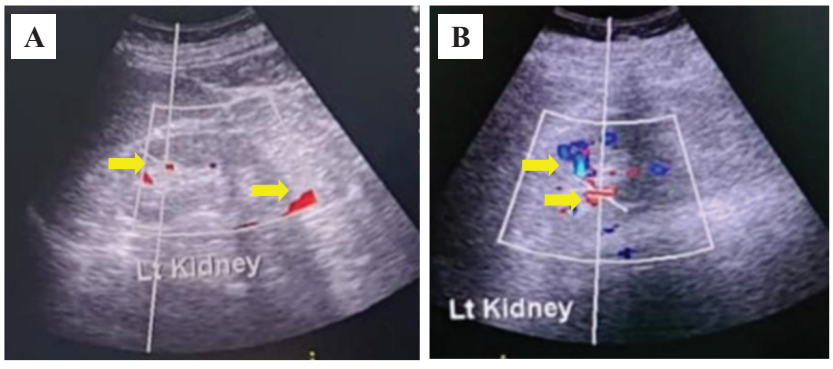

Figure 3. Renal Doppler ultrasonography imaging of a DKD subject. A: before therapy; B: after therapy. The yellow arrow points to the interlobar artery where the hemodynamic measurements were taken. The blue and red colors represent the directional blood flow (venous and arterial, respectively), which appeared to increase in intensity following the administration of DCs, indicating improved renal vascular perfusion.

Table 4. Comparison of PSV, TNF-α, RI and VCAM levels before and after autologous DCs administration based on RI classification, creatinine, and eGFR grade.

Variables	Before (Mean±SD)	After (Mean±SD)	*p*-value
PSV (cm/s)			
Normal RI	43.0750±19.64256	31.3000±16.71926	0.069
Increased RI	56.1065±22.53370	40.6196±22.64338	0.046*
TNF-α (ng/mL)			
Normal RI	1.9275±0.96000	1.9138±0.61188	0.929
Increased RI	2.1296±0.91424	2.1137±0.72837	0.985
VCAM-1 (ng/mL)			
Normal RI	1416.1250±482.05318	1395.2500±434.79412	0.859
Increased RI	1474.9565±474.00024	1454.3913±452.86239	0.621
PSV (cm/s)			
Creatinine <1.5 mg/dL	47.6630±19.37673	37.3000±18.70570	0.066
Creatinine ≥1.5 mg/dL	60.1500±24.83992	48.6000±29.22932	0.093
RI			
Creatinine <1.5 mg/dL	0.7272±0.06810	0.7450±0.07540	0.116
Creatinine ≥1.5 mg/dL	0.7575±0.05363	0.7450±0.05478	0.135
TNF-α (ng/mL)			
Creatinine <1.5 mg/dL	1.9609±0.90394	1.9493±0.90410	0.895
Creatinine ≥1.5 mg/dL	2.4150±0.56330	2.4562±0.47878	0.781
VCAM-1 (ng/mL)			
Creatinine <1.5 mg/dL	1411.3916±510.4223	1377.3180±486.4867	0.831
Creatinine ≥1.5 mg/dL	1598.8750±295.9959	1616.6250±224.3197	0.879
PSV (cm/s)			
Grade 1	50.2429±20.90739	42.4286±21.84233	0.268
Grade 2	40.4643±15.17934	30.0286±18.79293	0.216
Grade 3	64.8400±24.05641	43.8405±26.61409	0.053
RI			
Grade 1	0.7275±0.05377	0.7418±0.05419	0.150
Grade 2	0.7071±0.07039	0.7286±0.05633	0.457
Grade 3	0.7650±0.07576	0.7930±0.05111	0.122
TNF-α (ng/mL)			
Grade 1	1.8657±1.07467	1.9179±0.64691	0.748
Grade 2	2.2043±0.98249	2.2026±0.89109	0.462
Grade 3	2.2850±0.57560	2.3290±0.69087	0.878
VCAM-1 (ng/mL)			
Grade 1	1327.7857±511.5928	1229.5000±358.3008	0.172
Grade 2	1541.1429±593.07207	1532.7143±667.85994	0.936
Grade 3	1587.6000±517.6000	1605.6000±285.21828	0.857

*Significantly different with $p<0.05$, tested Paired T-Test (for normally distributed data) or the Wilcoxon Signed-Rank Test (for non-normally distributed data).

The comparative analysis of pre- and post-administration of DC on the parameters PSV, RI, TNF-α, and VCAM was conducted based on creatinine level classifications. The results showed variations in response to DC administration between groups with creatinine levels <1.5 and ≥ 1.5 mg/dL. For the PSV parameter, in the group with creatinine levels <1.5 mg/dL, a significant decrease was observed after DC administration, with a *p*-value of 0.066, indicating that DC administration had an effect on reducing PSV. Meanwhile, in the group with creatinine levels ≥1.5 mg/dL, the reduction in PSV after DC administration was not statistically significant. For the RI parameter, no significant differences were found between pre- and post-DC administration in either the <1.5 or ≥1.5 mg/dL creatinine groups, suggesting that DC administration did not significantly affect RI values. Similarly, for TNF-α, no significant changes were observed between pre- and post-DC administration in either group. In the group with creatinine levels <1.5 mg/dL, the *p*-value was 0.885, while in the group with creatinine levels ≥1.5 mg/dL, the *p*-value was 0.639, indicating that DC administration did not have a significant effect on TNF-α levels. For the VCAM parameter, in the group with creatinine levels <1.5 mg/dL, a decrease was observed but was not statistically significant. In the

group with creatinine levels ≥1.5 mg/dL, no significant changes were observed after DC administration. Overall, DC administration showed a more notable effect on PSV in the group with creatinine levels <1.5 mg/dL, while no significant impact was found on the other parameters (RI, TNF-α, and VCAM) in either creatinine classification group.

A comparative analysis was conducted to evaluate the effects of DC administration on PSV, RI, TNF-α, and VCAM parameters according to eGFR classifications. For the PSV parameter, a reduction in mean PSV values was observed across all eGFR groups following DC administration. In the Grade 1 group, the decrease yielded a *p*-value of 0.268, indicating no statistically significant change. A similar pattern was seen in the Grade 2 group (p=0.216), suggesting that the intervention did not produce a meaningful difference. Interestingly, in the Grade 3 group, a more pronounced decline in PSV was observed, with a *p*-value of 0.053, indicating a trend toward statistical significance and suggesting a potential effect of DC therapy in participants with moderate renal impairment. For the RI parameter, no significant changes were detected across all eGFR groups neither for Grades 1, 2, and 3. These findings suggest that DC administration did not exert a measurable influence on vascular resistance as reflected by RI values. Regarding TNF-α, no significant pre- to post-treatment differences were observed in any eGFR category (Grade 1: p=0.748; Grade 2: p=0.462; Grade 3: p=0.680). This indicated that DC administration did not significantly alter systemic inflammatory status as measured by TNF-α levels. The VCAM parameter, although minor fluctuations were noted, none reached statistical significance, suggesting that DC therapy did not significantly affect endothelial adhesion activity. DC administration was associated with a non-significant downward trend in PSV, particularly among participants with reduced renal function (Grade 3), while no significant changes were detected in RI, TNF-α, or VCAM parameters across all eGFR classifications (Table 5). These findings imply that the biological response to DC therapy may vary with the degree of renal function impairment.

Analysis of the comparison between pre- and post-administration of DCs on the parameters PSV, RI, TNF-α, and VCAM based on HbA1c classification. For the PSV parameter, in the HbA1c <8% group, there was a significant decrease after DC administration, with a *p*-value of 0.008, indicating a significant change in the PSV parameter. Conversely, in the HbA1c ≥8% group, there was no significant change, suggesting that DC administration did not affect the PSV parameter in this group. For the RI parameter, in the HbA1c <8% group, there was a significant change after DC administration, with a *p*-value of 0.019, indicating that DC administration had an effect on increasing RI. However, in the HbA1c ≥8% group, there was no significant change in RI, indicating that DC administration had no effect in this group. For the TNF-α parameter, no significant differences were found in either group. The HbA1c <8% group had a *p*-value of 0.497, and the HbA1c ≥8% group had a *p*-value of 0.485, indicating that DC administration did not affect TNF-α levels in either group. The VCAM parameter showed there were no significant changes after DC administration in either group. The HbA1c <8% group had a *p*-value of 0.403, and the HbA1c ≥8% group had a *p*-value of 0.791, indicating that DC administration did not affect VCAM levels in either group. Overall, these results show that DC administration had a significant effect on the PSV and RI parameters in the HbA1c <8% group, but did not affect TNF-α and VCAM, and had no significant impact in HbA1c ≥8% (Table 5).

In the microalbuminuria group, the PSV parameter showed a significant reduction after DC administration (p=0.004), indicating that the treatment effectively lowered PSV values. Conversely, in the macroalbuminuria group, the difference before and after treatment was not significant, suggesting that the intervention had a limited influence on this group. Regarding the RI parameter, no statistically significant change was detected in either group. This implies that while minor variations occurred, DC administration did not meaningfully alter RI values. When assessing TNF-α, both groups exhibited stable levels following treatment, with p=0.862 and p=0.929, respectively. These results demonstrate that the intervention did not produce measurable effects on TNF-α concentrations. As for VCAM, the microalbuminuria group experienced a slight decline in mean levels, though it was not statistically significant. Similarly, in the macroalbuminuria group, the change remained insignificant. DC therapy showed a marked impact only on PSV within the microalbuminuria group, whereas RI, TNF-α, and VCAM parameters remained largely unaffected across both albuminuria classifications (Table 5).

An analysis was conducted to compare pre- and post-administration of DC on several physiological parameters, including PSV, RI, TNF-α, and VCAM, based on urea classification (<50 and ≥50 mg/dL). In terms of the PSV parameter, the urea <50 mg/dL group exhibited a significant decrease following DC administration (p=0.037), indicating a positive response to the intervention. Meanwhile, in the urea ≥50 mg/dL group, although a reduction in PSV values was observed, the change was not statistically significant,

Table 5. Comparison of PSV, TNF-α, RI and VCAM levels before and after autologous DC administration based on HbA1c, UACR status, and ureum.

Variables	Before (Mean±SD)	After (Mean±SD)	*p*-value
PSV (cm/s)			
HbA1c <8%	52.25±24.73	32.34±20.75	0.008*
HbA1c ≥8%	55.53±18.61	47.50±26.99	0.483
RI			
HbA1c <8%	0.7187±0.08187	0.7489±0.06192	0.109
HbA1c ≥8%	0.7875±0.05940	0.7575±0.06073	0.285
VCAM-1 (ng/mL)			
HbA1c <8%	1461.95±498.51	1359.13±300.68	0.043*
HbA1c ≥8%	1472.17±438.36	1509.58±557.50	0.791
TNF-α (ng/mL)			
HbA1c <8%	2.0863±0.86642	2.0095±0.8777	0.497
HbA1c ≥8%	2.0344±1.02215	2.0813±0.8083	0.959
PSV (cm/s)			
Microalbuminuria	58.48±24.38	35.11±20.63	0.003*
Macroalbuminuria	46.80±16.74	19.56±23.87	0.083
RI			
Microalbuminuria	0.7353±0.06349	0.7400±0.07122	0.108
Macroalbuminuria	0.7375±0.08397	0.7575±0.04656	0.208
TNF-α (ng/mL)			
Microalbuminuria	1.9911±0.8639	2.0063±0.8025	0.808
Macroalbuminuria	2.4875±0.8799	2.4375±0.9396	0.902
VCAM (ng/mL)			
Microalbuminuria	1405.44±533.80	1302.44±404.64	0.194
Macroalbuminuria	1535.00±367.35	1564.00±435.77	0.611
PSV (cm/s)			
Ureum <50 mg/dL	50.3096±25.4472	38.6904±21.65079	0.037*
Ureum ≥50 mg/dL	65.4000±28.87523	35.7400±22.34240	
RI			
Ureum <50 mg/dL	0.6753±0.06377	0.7049±0.05768	0.049*
Ureum ≥50 mg/dL	0.7030±0.07813	0.7390±0.05964	
TNF-α (ng/mL)			
Ureum <50 mg/dL	2.0550±0.21940	2.0677±0.21106	0.558
Ureum ≥50 mg/dL	2.1940±0.74844	2.1920±0.79751	
VCAM (ng/mL)			
Ureum <50 mg/dL	1380.5535±441.90463	1346.9615±374.48302	0.489
Ureum ≥50 mg/dL	1871.8000±417.13901	1763.0000±495.83046	

*Significantly different with $p<0.05$, tested Paired T-Test (for normally distributed data) or the Wilcoxon Signed-Rank Test (for non-normally distributed data).

suggesting that the treatment effect in this group was less pronounced. For the RI parameter, the urea <50 mg/dL group demonstrated a significant increase after treatment (p=0.049), whereas the urea ≥50 mg/dL group showed no significant change. These findings might imply that DC administration had a more notable influence on vascular resistance among subjects with lower urea levels. Regarding TNF-α, no significant changes were detected in either group. This indicates that DC administration did not substantially affect inflammatory marker levels. As for VCAM, the urea <50 mg/dL group showed a mild reduction in mean VCAM levels post-treatment, though the difference was not statistically. Similarly, the urea ≥50 mg/dL group exhibited only minor, non-significant changes. In summary, DC therapy produced clearer and more meaningful effects on PSV and RI in participants with urea <50 mg/dL, while its impact on TNF-α and VCAM remained minimal across both urea classifications (Table 5).

Autologous DC administration resulted in statistically significant changes in renal vascular parameters. As shown in Table 6, the mean PSV decreased significantly (p=0.016), while the mean RI increased significantly (p=0.028). In contrast, no significant changes were observed in inflammatory biomarkers TNF-α and VCAM-1. Subgroup

Table 6. Bivariate analysis of PSV, RI, TNF-α, and VCAM.

Biomarker	Before Autologous DC Administration (Mean±SD)	After Autologous DC Administration (Mean±SD)	*p*-value
PSV (cm/s)	52.7435±22.27081	38.2145±21.41040	0.016*
RI	0.7350±0.06891	0.7550±0.05324	0.028*
TNF-α (ng/mL)	2.0774±0.91303	2.0755±0.69661	0.983
VCAM-1 (ng/mL)	1459.7742±468.68779	1439.1290±441.81208	0.608

*Significantly different with $p<0.05$, tested Paired T-Test (for normally distributed data) or the Wilcoxon Signed-Rank Test (for non-normally distributed data).

analyses revealed that the reduction in PSV was more pronounced in patients with well-controlled glycemia (HbA1c <8%: $p=0.008$), microalbuminuria ($p=0.003$), and lower serum urea levels (<50 mg/dL: $p=0.037$). Similarly, the increase in RI was more evident in patients with lower urea levels ($p=0.049$). These findings suggest that patients with earlier stages of DKD and better metabolic control may derive greater hemodynamic benefit from DC therapy.

Discussion

This quasi-experimental study presents novel clinical data indicating that a single administration of DCs can significantly modulate renal hemodynamic parameters in patients with DKD. The core findings reveal a statistically significant reduction in PSV and a concurrent increase in RI within 60 days post-intervention, while systemic levels of the inflammatory biomarkers TNF-α and VCAM-1 remained unchanged. This apparent dissociation between vascular and systemic inflammatory responses provides a compelling platform for hypothesizing the site-specific immunomodulatory mechanisms of DC therapy and delineating its potential therapeutic niche in DKD management.(21–23)

The observation that PSV significantly decreased from 52.74 to 38.21 cm/s following DC administration is a salient outcome. In the pathophysiology of early DKD, renal hyperfiltration and glomerular hypertension are driven by afferent arteriolar vasodilation, leading to increased intrarenal blood flow velocity. A reduction in PSV may therefore reflect a beneficial attenuation of this hyperdynamic state, potentially lowering glomerular capillary pressure and mitigating mechanical stress on the filtration barrier. This interpretation is reinforced by the more pronounced PSV reduction in subgroups with better-preserved renal status (microalbuminuria, lower urea) and glycemic control (HbA1c <8%), suggesting greater vascular responsiveness in earlier disease stages. The concomitant increase significantly in RI from 0.735 to 0.755 presents a more nuanced finding. Traditionally, an elevated RI is associated with heightened vascular resistance from interstitial fibrosis and arteriolosclerosis, correlating with poor renal outcomes. However, in this interventional context, the slight RI elevation may paradoxically indicate an improvement in vascular regulatory tone. In diabetic vasculopathy, impaired autoregulation and deficient endothelial nitric oxide activity can blunt the normal diastolic flow.(24) A therapeutic intervention that improves endothelial function could restore some vasoconstrictive capacity of efferent arterioles or reduce pathological systolic overflow, thereby altering the (PSV-EDV)/PSV ratio. Thus, the observed RI shift might represent a move toward normalized flow dynamics rather than progressive vasculopathy, a hypothesis supported by its association with favorable clinical subgroups.

TNF-α and VCAM-1 are known for its relation with metabolic including T2DM and obesity.(25,26) However, in this study, the absence of significant changes in circulating TNF-α and VCAM-1 levels, despite clear hemodynamic effects, forms the central paradox of this study. This discordance challenges a simplistic anti-inflammatory mechanism but opens several plausible explanatory avenues that are not mutually exclusive. The primary mechanism may involve compartmentalized immunoregulation within the renal compartment.(27–29) Intravenously administered tolerogenic DCs (tolDCs) are known to traffic to secondary lymphoid organs and potentially to sites of inflammation. Their action may not be to systemically suppress cytokine production but to re-educate the local renal immune landscape. By promoting regulatory T-cell (Treg) induction or anergy of effector T-cells in the renal interstitium and perivascular areas, tolDCs could dampen locoregional inflammation and leukocyte-endothelial interactions. This would improve microvascular function and perfusion without immediately altering steady-state levels of systemic cytokines.(30) Furthermore, hemodynamic parameters,

influenced by neural and endothelial tone, can change rapidly, whereas circulating biomarkers like VCAM-1, with longer half-lives, may require a longer period of sustained immunomodulation to exhibit measurable decline. Additionally, DC therapy may confer renal benefits through inflammation-independent pathways, such as directly enhancing endothelial nitric oxide synthase (eNOS) activity or reducing oxidative stress, thereby improving vasodilation and autoregulation independently of systemic cytokine networks.(27,31,32)

The stratified analyses provide critical insight for future clinical translation. The consistent trend wherein patients with earlier-stage DKD (microalbuminuria, lower urea, HbA1c <8%) exhibited more robust hemodynamic responses is highly informative. This suggests that DC therapy predominantly benefits patients with a "responsive vasculature", where functional disturbances like hyperfiltration and endothelial dysfunction are still dominant over irreversible structural damage like extensive glomerulosclerosis. In advanced disease, the fibrotic remodeling may limit the capacity for hemodynamic improvement. This identifies a potential window of opportunity for DC immunotherapy as an adjunct to standard care in early to moderate DKD, targeting the residual vascular risk not fully addressed by RAAS or inhibition alone.(33,34)

These findings position autologous DC therapy as a novel, pathophysiology-driven adjunctive strategy. Its potential role is not to replace foundational therapies but to address the component of immune and vascular dysregulation that persists despite optimal conventional treatment. The favorable safety profile observed supports further investigation. Methodologically, this study underscores the value of renal Doppler ultrasonography as a sensitive, non-invasive tool for detecting early functional changes in interventional trials for DKD, potentially more responsive than systemic biomarkers in the short term. The promising results must be contextualized within the study's design limitations. The lack of a control group is the principal constraint, as it precludes definitive attribution of the observed changes to the DC intervention versus natural variation or placebo effects.(35,36) The modest sample size limits the statistical power of subgroup analyses and generalizability. The 60-day follow-up is inadequate to assess long-term safety, durability of effect, or hard renal outcomes like eGFR decline. Future research must progress to rigorous, controlled trials. A logical next step is a randomized, placebo-controlled, double-blind phase II study with a larger cohort, longer follow-up, integrated immunophenotyping, and exploration of urinary biomarkers of renal-specific inflammation to bridge the systemic-tissue gap.

Conclusion

This study provides initial evidence that autologous DC therapy may modulate renal hemodynamics in patients with DKD, particularly those with well-controlled glycemia and early-stage disease. The significant reduction in PSV and concomitant increase in RI may reflect normalization of hyperdynamic renal blood flow, though the clinical implications of these changes require further investigation. Notably, these hemodynamic alterations occurred without significant changes in systemic inflammatory biomarkers, suggesting potential tissue-specific effects.

Acknowledgments

The authors sincerely acknowledge Universitas Prima Indonesia and RSPAD Gatot Soebroto for their valuable support and partnership.

Authors Contribution

AS designed the study and collected ultrasonography data; LC conducted laboratory and statistical analyses; and CNG supervised, reviewed, and finalized the manuscript. All authors approved the final version and are responsible for its content.

Conflict of Interest

There are no conflicts of interest.

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