

# Autologous bone marrow-derived mesenchymal stem cells and endothelial progenitor cells transplantation showed potential benefits for type 2 diabetes mellitus Filipino patients: a case series

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## ABSTRACT

**Introduction:** Type 2 diabetes mellitus (T2DM) is a serious metabolic disorder characterized by hyperglycemia and insulin resistance. Long-standing T2DM may lead to various macro- and microvascular complications such as diabetic nephropathy, neuropathy, and retinopathy. Currently available treatments for T2DM target high plasma glucose levels but do not address T2DM-associated complications. In this report, the therapeutic application of mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs) transplantation in improving diabetic blood monitoring parameters among selected T2DM patients was investigated. **Methods:** Five Filipino patients with T2DM diagnosed for more than five years agreed to participate in the autologous bone marrow-derived stem cell transplantation. Five milliliters (mL) per kilogram (kg) of bone marrow was collected from the patients following standard procedures, and bone marrow-derived stem cells underwent quantification, genetic typing, microbial analysis, and quality control before being infused into the patients. MSCs and EPCs were intravenously transfused into the patients once a month for 6 months. Fasting blood glucose (FBG), blood urea nitrogen (BUN), glycated hemoglobin (HbA1c), and creatinine (CREA) levels were recorded pre- and post-stem cell transplantation. **Results:** The findings of the study revealed that the administration of autologous bone marrow-derived stem cells showed no adverse effects and improved or controlled the blood monitoring levels in most patients. Four out of five patients showed a reduction in their BUN (mean reduction = 2.246) and HbA1c (mean reduction = 0.74%) and maintained their creatinine levels within the normal range following the 6 months of infusion. Meanwhile, three out of five patients showed a decrease in FBG levels (mean reduction = 1.484 mmol/L). **Conclusion:** This preliminary report suggests the potential of autologous bone marrow-derived stem cell transplantation for the treatment and management of T2DM. Future studies may focus on examining other parameters such as C-peptide levels and evaluate the efficacy and safety of autologous MSCs and EPCs in the long-term management of T2DM.

**Key words:** type-2 diabetes, stem cell therapy, bone marrow-derived stem cell, HbA1c

## INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder caused by beta cell dysfunction, a failed response of insulin-sensitive tissues to insulin, and uncompensated insulin resistance<sup>1</sup>. It affects primarily adults aged 45 years old or older and is often characterized by a high body fat percentage in the abdominal region and/or obesity. Risk factors include a sedentary lifestyle, age, population aging, family history, and a high-caloric diet<sup>2</sup>. T2DM may present with multiple-systemic complications, both microvascular (diabetic retinopathy, neuropathy, and nephropathy) and macrovascular (cardiovascular diseases, peripheral vascular disease, etc.), primarily caused by a chronic and unregulated hyperglycemic state<sup>3</sup>. Diagnosis of T2DM includes laboratory testing (fasting

blood glucose level, glycated hemoglobin percentage, and oral glucose tolerance test), assessment of risk factors (BMI, race, family history, lifestyle), and clinical symptoms<sup>4</sup>. The management of T2DM is aimed at maintaining good metabolic and glycemic control as well as near-normal levels of glycated hemoglobin to reduce the development or progression of diabetes complications<sup>5</sup>.

T2DM affected 536.6 million people globally in 2021 and is expected to rise to about 783.2 million people by 2045<sup>6</sup>. In the Western Pacific, the Philippines ranks fifth—behind China, Indonesia, Japan, and Thailand—in the number of diabetic patients. With the current population of over 100 million, local experts estimate that the Philippines has more than 5 million diagnosed diabetics. A similar number

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will likely remain undiagnosed or have prediabetes<sup>7</sup>. T2DM is the most common type of diabetes in the Philippines, with the highest prevalence rate found among the richest in the wealth index, those living in urban areas, and within the 60- to 69-year age group in both sexes. It also continues to be the fourth leading cause of mortality in the Philippines, following ischemic heart disease, cerebrovascular diseases, and neoplasms<sup>8</sup>. Continuing efforts are made to develop anti-diabetic drugs, which help to delay the various complications. However, due to the progressive nature of the disease, most patients eventually respond less to these drugs<sup>9</sup>.

Recent progress in regenerative medicine, especially stem cell therapy, has suggested several novel and potential cures for T2DM. Various sources of stem cells exist, with mesenchymal stem cells (MSCs) being the most common. MSCs have been determined to be efficacious in reducing fasting blood sugar and glycated hemoglobin levels among T2DM patients<sup>10</sup>. They also showed potential in mitigating insulin resistance and dependence observed in diabetic patients<sup>11</sup>. Another cell type used for T2DM management is the endothelial progenitor cells (EPCs). EPCs are used to alleviate vascular complications observed in T2DM patients<sup>12</sup>. However, there are limited studies exploring the synergistic effects of stem cell therapy in combination with other cell-based therapies. In this report, we present the application of autologous MSCs with endothelial progenitor cell (EPC) therapy in treating Filipino T2DM patients at the Lung Center of the Philippines, Quezon City, Philippines.

## CASE PRESENTATION

### Patient Enrollment

Five T2DM Filipino patients aged 53-68 years old, diagnosed according to American Diabetes Association<sup>13</sup> criteria, were enrolled in the study. The inclusion criteria were: (1) must be Filipino diabetic patients over 45 years old; (2) diagnosed with T2DM for at least the past 10 years; and (3) may have an existing diabetic complication that is stable and non-progressive. Patients with malignancies, acute or chronic infections, hematological illnesses or coagulopathies, or immunosuppressive diseases were excluded from the trial. Patients were clinically assessed by a physician, and clinical clearances were obtained prior to their enrollment in the trial. All patients had an HbA1c over 5.0% for the year preceding the enrollment, with stable hepatic, renal, and cardiopulmonary status. The summary of the baseline characteristics is shown in **Table 1**.

## Ethical Considerations

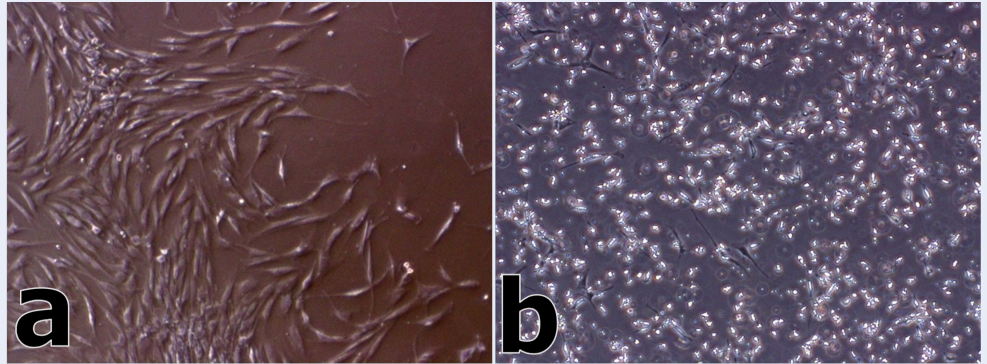
The study protocol was approved by the Technical Review Board Committee of the Lung Center of the Philippines. Patient cases were assessed by the Stem Cell Ethics Committee of the Lung Center of the Philippines to determine the eligibility of patients who would benefit from the cellular therapy. All patients were informed of the risks, potential benefits, and formulations of the stem cell therapy to be administered, provided written informed consent, and confirmed their willingness to be treated by autologous bone marrow-derived stem cell transplantation.

## Stem Cell Collection, Expansion, Identification, and Quality Check

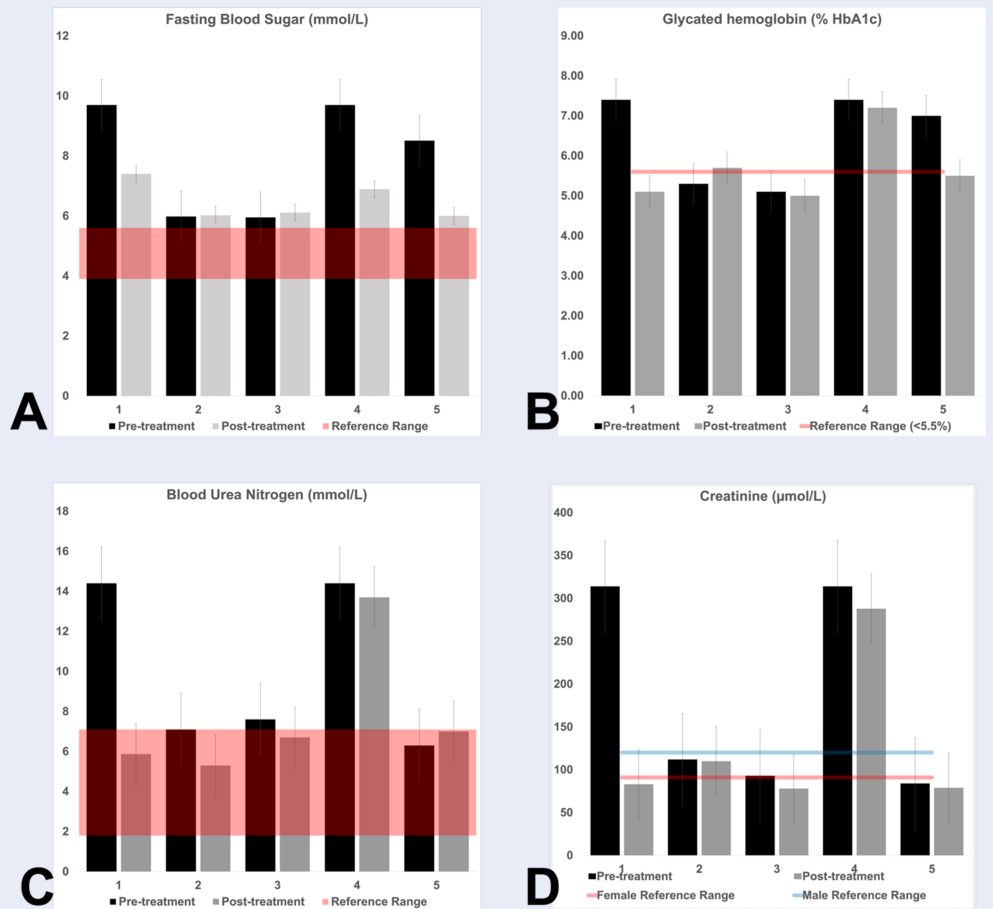
Bone marrow samples were collected from each patient under general anesthesia in a sterile environment. Approximately 70 – 75 mL of bone marrow was collected from the posterior iliac crests using Jamshidi biopsy needles (gauge 8) into a syringe containing 10% sodium heparin. For the isolation of bone marrow-derived stem cells, the Ficoll-Paque density gradient centrifugation method was used following the protocol of Gudleviciene and colleagues (2015)<sup>14</sup>. Mesenchymal stem cells were expanded in MesenPRO RS<sup>TM</sup> medium (Thermo Fisher Scientific), while Iscove's modified Dulbecco's medium (Sigma-Aldrich) supplemented with fibroblast growth factors (FGFs) and vascular endothelial growth factors (VEGFs) was used for endothelial progenitor cell (EPC) expansion.

Cells were characterized based on their morphology fourteen (14) days following the cell expansion (**Figure 1**). Cellular identities were confirmed through detection of expressed cluster of differentiation (CD) markers using the flow cytometer (BD FACSCalibur<sup>TM</sup>). MSCs were positive for CD90 and CD105 markers, while EPCs were positive for the CD133 marker. Both cell cultures were negative for the CD45 marker. Finally, microbiologic control testing revealed that all cells were negative for mycoplasma, endotoxins, bacterial, and fungal infections.

Immune Cell Therapy Infusion and Monitoring Expanded cells were washed, transferred to a syringe, and reconstituted in 10 milliliters of lactated Ringer's solution for cell therapy infusion. The cell count for each cell therapy was set at approximately 5 million MSCs and 1 million EPCs. The patients were given cell infusion under the supervision of the cell therapy physician, anesthesiologist, and cardiologist to ensure



**Figure 1: Cell appearance after 14 days in culture (40x).** (a) Mesenchymal stem cells; characterized by fibroblast-like appearance and spindle-shaped cells. (b) Endothelial progenitor cells; characterized by spindle-shaped cells. Cells were confirmed through flow cytometry to detect expressed CD markers specific to each cells.



**Figure 2: Summary of the baseline and post-treatment glucose metabolism panel results of the five patients who received autologous mesenchymal stem cells and endothelial progenitor cells.** (A) Fasting Blood Sugar; (B) Glycated hemoglobin; (C) Blood Urea Nitrogen; (D) Creatinine.

**Table 1: Baseline characteristics of the patients enrolled in the cellular therapy**

	Fasting blood sugar (mmol/L)	HbA1c (%)	Blood urea nitrogen (mmol/L)	Creatinine ( $\mu\text{mol/L}$ )
Patient 1	9.7	7.40	14.4	314
Patient 2	5.98	5.30	7.1	112
Patient 3	5.95	5.1	7.6	93
Patient 4	9.7	7.4	14.4	314
Patient 5	8.51	7	6.3	84

the safety of the treated patients. Each patient received a total of 30 to 35 million MSCs and 6 to 7 million EPCs. All patients underwent one cell therapy intravenous infusion per month for six (6) months. No adverse effects were observed in the patients receiving the therapy. Peripheral blood samples were collected from patients before cell therapy and after the 6<sup>th</sup> cell infusion for close monitoring of hemoglobin A1c (HbA1c), fasting blood sugar (FBS), blood urea nitrogen (BUN), and creatinine levels. It is important to note that some patients continued with their prescribed or herbal medication when they received the cells.

### Case Studies

#### Patient 1

A 70-year-old female Filipino patient has been diagnosed with type-2 diabetes since 2003. She presented with numbness in her fingers to the Lung Center of the Philippines in 2013. Her recent medical examination revealed increased blood sugar levels. The patient has a family history of liver disease and hypertension. The patient was referred to a cardiologist to manage her hypertension. At the time of consultation, the patient was taking only herbal medicines for a year to manage her diabetes and hypertension.

The patient received a total of 6 monthly intravenous infusions of EPCs ( $1.0 \times 10^6$  cells) and MSCs ( $5.0 \times 10^6$  cells) at the Lung Center of the Philippines. Cellular therapy response monitoring was performed following the 6th infusion treatment and compared against her baseline blood chemistry results (Table 1). Findings showed improvements in FBS and HbA1c (Figure 2A-B), with a significant impact on her BUN and creatinine levels (Figure 2C-D).

#### Patient 2

In 2008, a 74-year-old male Filipino businessman was diagnosed with T2DM at the Lung Center of the Philippines. He presented elevated blood sugar accompanied by muscular spasms. He has been treated

with metformin (an antihyperglycemic drug; 500 mg) and tamsulosin (an  $\alpha$ -1 adrenoreceptor antagonist; 400 mg) for the past 5 years. Medical evaluation prior to therapy revealed that his FBS level was 5.98 mmol/L and his HbA1c was 5.30%. His BUN level was 7.1 mmol/L, and he had a creatinine level of 112  $\mu\text{mol/L}$  (Table 1).

He received a total of 6 monthly intravenous infusions of EPC and MSC cellular therapy at the Lung Center of the Philippines. Following post-treatment monitoring after 6 months, the patient's FBS and HbA1c levels unfortunately showed no improvements (Figure 2 A-B).

#### Patient 3

A 66-year-old male Filipino patient was admitted to the Lung Center of the Philippines and was diagnosed with T2DM in 2013. Medical evaluation prior to his enrollment in the study revealed that his FBS level was 5.95 mmol/L and his HbA1c was 5.1%. Besides this, his BUN levels pre-treatment were 7.6 mmol/L, and his creatinine level was 93  $\mu\text{mol/L}$ . The patient presented some diabetic complications such as renal function impairment and hypertension.

A total of 6 monthly intravenous infusions of EPC ( $1.0 \times 10^6$  cells) and MSC ( $5.0 \times 10^6$  cells) were given to the patient. All of the patient's tested blood parameters showed slight improvements (Figure 2B-D) except for the FBS levels (Figure 2 A).

#### Patient 4

A 69-year-old male Filipino working as an ophthalmologist presented with an elevated blood sugar level to the Lung Center of the Philippines in 2013. Aside from hypertension, which is one of the common diabetic complications, the patient also presented with chronic kidney disease. The patient was then referred to a cardiologist and nephrologist to manage his hypertension and CKD. His past medical history revealed an increase in blood sugar level, BUN, and creatinine. The patient did not mention any medications for managing his preexisting conditions.

He received a total of 6 infusions intravenously of EPC ( $1.0 \times 10^6$  cells) and MSC ( $5.0 \times 10^6$  cells) every month at the Lung Center of the Philippines (LCP). All cellular therapy products were tested and cleared for any fungal, bacterial, Mycoplasma, and endotoxin contamination.

Cellular therapy response monitoring was performed pre-treatment and post-6<sup>th</sup> treatment. Results showed a decrease in blood parameters such as FBS, HbA1c, BUN, and creatinine (Figure 2). The patient expired due to T2DM and CKD complications.

### Patient 5

A 71-year-old male Filipino patient was diagnosed with T2DM in 1980. In 2017, he was also diagnosed with hepatocellular carcinoma and was treated with chemotherapy. Furthermore, his past medical history revealed an increase in blood sugar level. He has a family history of cancer and diabetes mellitus. His initial symptoms include frequent urination with high blood sugar levels. The patient was then referred to an oncologist to manage his hepatocellular carcinoma.

The patient received 6 infusions intravenously of EPC ( $1.0 \times 10^6$  cells) and MSC ( $5.0 \times 10^6$  cells) every month at LCP. All cellular therapy products underwent quality assurance procedures to avoid any complications associated with contaminated blood products. Cellular therapy response monitoring was performed pre-treatment and post-6<sup>th</sup> treatment. Findings suggest decreased levels in tested blood parameters such as FBS, HbA1c, and creatinine (Figure 2 A, B, D) with the exception of the BUN (Figure 2 C).

## DISCUSSION

Type 2 diabetes mellitus (T2DM) represents a significant public health concern, particularly given the prevalence of individuals exhibiting resistance to the conventional therapies available<sup>15</sup>. Moreover, these conventional therapies were not designed to prevent the diabetic complications that are often chronic and difficult to manage. The development of cellular-based therapies offers an alternative approach in the management of T2DM and the prevention of its known complications. Over the years, cellular-based therapies have been explored as treatments for some of the known DM complications, such as diabetic foot ulcers and retinopathy, among others<sup>16</sup>.

Diabetic patients exhibit impaired mobilization of adult stem cells from the bone marrow, along with dysfunctional circulating progenitor cells. A growing body of evidence has demonstrated that DM is associated with a generalized reduction in circulating endothelial progenitor cells (EPC), and that this decline

is linearly correlated with the severity of DM, in terms of HbA1c and blood glucose levels. It can be inferred that an increased number of circulating mesenchymal stem cells (MSC) and EPC in the system can directly correlate with improvements in glycated hemoglobin and fasting blood glucose levels<sup>17</sup>. In this case series, most of the patients demonstrated improved glucose parameters following the treatment. Although there is little or no clear evidence of in vivo stem cell differentiation into pancreatic beta cells, other potential mechanisms to explain this improvement include neovascularization, endothelial repair, modulation of the inflammatory environment, and stimulation of endogenous stem cells through paracrine mediators<sup>18</sup>. Additionally, this case series has presented the capability of autologous MSC and EPC therapy in improving creatinine levels in patients following six monthly infusions, supporting current studies regarding the feasibility of autologous combined MSC and EPC therapy in the management of diabetic kidney disease<sup>19</sup>.

Combined stem cell therapy for T2DM management has been performed in recent years. Most of these studies were conducted in vivo using murine models, and its application in humans led to the discovery of its actual efficacy and associated safety<sup>10</sup>. Some literature has investigated the synergistic effects of growth factors with MSC therapy in managing T2DM microvascular complications<sup>20</sup>. Other studies on the combinatory application of different cellular types, such as hematopoietic and MSCs, were applied to type-1 diabetes mellitus (T1DM)<sup>21</sup>. This study demonstrates the safe and effective application of combined MSC and EPC therapy in managing T2DM.

In the Philippines, bone marrow aspiration (BMA) is the primary method used for harvesting stem cells. BMA has been found to yield a sufficient quantity of cells required for cellular therapy infusion, though the quality varies according to the patient's age<sup>22</sup>. Proper cellular processing of bone marrow-derived MSCs must be achieved to counteract its significant reduction in proliferative capacity, differentiation potential, and clonal expandability with age, gender, and seeding density. This case series has demonstrated a standardized protocol for immune cell therapy conducted solely for research purposes, in accordance with national health guidelines on cellular-based therapies<sup>23</sup>. While attempts have been made to establish a bioethics advisory board to regulate cellular-based therapies in the Philippines<sup>24</sup>, there have been no updates regarding the establishment of laws regulating and supporting cellular-based therapies for clinical

and research applications. This case series elucidates the potential of autologous cellular-based therapies for disease management and alternative medicine. Future studies might explore its application for long-term stem cell therapy, safety monitoring, and T2DM management on a larger sample size and the integration of controls. Statistical treatment could also be applied to describe its therapeutic value and dosing.

## CONCLUSION

The six-monthly infusions of combined autologous mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs) therapy through the intravenous route in this case series were safe and well-tolerated in patients with T2DM. This case series provides clear preliminary evidence of the potential benefits of autologous immune cell therapy in controlling T2DM, while the optimal dosage, administration, and cell types are yet to be determined.

This case series has observed that both MSCs and EPCs obtained from bone marrow aspiration (BMA) are easy to prepare, generally economical, and readily available in most tertiary hospitals in the country. The methodology for stem cell preparation adapted in this case series has demonstrated a safe and humane procedure aligned with the current standardized procedures for stem cell collection and infusion. Likewise, this can also serve as a framework for designing large-scale randomized studies to determine the optimal stem cell type and corresponding cell dosage. Subsequent studies related to this case series may investigate the most effective intervention time for treatment and explore other routes of cell infusion administration. Application of this intervention on a larger sample size, along with statistical treatment and the incorporation of controls, could further maximize the potential of combined stem cell therapy for T2DM. Finally, prolonged cellular infusion, patient monitoring, and follow-up interventions can be applied to further elucidate the potential of combined cellular therapy in T2DM management.

## ABBREVIATIONS

**BMA:** Bone Marrow Aspiration, **BUN:** Blood Urea Nitrogen, **CD:** Cluster of Differentiation, **CKD:** Chronic Kidney Disease, **CREA:** Creatinine, **EPCs:** Endothelial Progenitor Cells, **FBG:** Fasting Blood Glucose, **FBS:** Fasting Blood Sugar, **FGFs:** Fibroblast Growth Factors, **HbA1c:** Hemoglobin A1c, **kg:** Kilogram, **LCP:** Lung Center of the Philippines, **mL:**

Milliliters, **MSCs:** Mesenchymal Stem Cells, **T2DM:** Type 2 Diabetes Mellitus, **VEGFs:** Vascular Endothelial Growth Factors

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## AUTHOR'S CONTRIBUTIONS

**M. S. A. De Guzman, M. P. B. Apellido, and J. P. Panuelos** designed the experiment and performed the bone marrow collection, extraction of stem cells and quality control; **M. S. A. De Guzman, M. P. B. Apellido, J. P. Panuelos, F. M. Heralde, III, P. R. Relacion, N. S. Tan-Liu, and M. T. A. Barzaga** performed the analysis of the data and manuscript writing; **M. S. A. De Guzman, M. P. B. Apellido, J. P. Panuelos, A. B. Bilbao** performed the patient recruitment, infusion of autologous bone marrow-derived stem cells to the patients and monitored the patients during the transplantation. All of the authors read and approved the final version of the manuscript.

## FUNDING

None.

## AVAILABILITY OF DATA AND MATERIALS

None.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the technical review Board Committee of the Lung Center of the Philippines. Patient cases were assessed by the Stem Cell Ethics Committee, Lung Center of the Philippines to determine the eligibility of the patients that would benefit from the cellular therapy.

## CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## COMPETING INTERESTS

The authors declare no competing interests.

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