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Stromal Vascular Fraction and Autologous Activated Platelet-Rich Plasma Combination in Treatment of Type 2 Diabetes: A Single Center Retrospective Study

ABSTRACT

Objective: A cutting edge potential treatment of type 2 diabetes (T2D) is the use of cellular therapy. One recent method is the use of combination of stromal vascular fraction (SVF) and autologous activated platelet-rich plasma (aaPRP). This study is aimed to evaluate the efficacy of SVF combined with aaPRP to treat T2D.

Materials and methods: Patients with T2D who underwent SVF and aaPRP treatment were recruited in this study. The lipoaspirate was digested by H-Remedy enzyme and centrifuged to isolate SVF. Blood was drawn from the patients and the aaPRP was isolated. The combination of autologous SVF and aaPRP was administered intravenously to each patient. Patients' 1-month and 3-month post-therapy HbA1c level were statistically analyzed to their baseline level.

Results: A total of 39 patients, 28 male and 11 female, with T2D with mean age of 59±11 years and baseline HbA1c of 8.31 g/dL were included in this study. Combination of SVF and aaPRP treatment in T2D resulted in a statistically significant decrease in HbA1c level to 7.58 g/dL at 1 month and to 7.63 g/dL at 3 months post-therapy, while a decrease in HbA1c was still observed at 6 and 12 months after therapy.

Conclusions: SVF combined with aaPRP may have potential to reduce HbA1c levels in patients with T2D. Further research is needed to confirm the findings of our research. (Clin Diabetol 2023; 12; 4: 247–252)

Clinical trial registration number: NCT05925829

Keywords: glycated hemoglobin A1c, platelet-rich plasma, stromal vascular fraction, type 2 diabetes

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder and a worldwide health problem that has not been solved since ancient times. The cases are steadily increasing; therefore, it becomes an epidemic in many countries. Furthermore, multiple organ system complications worsen the condition of patients with DM and may cause premature death. Most of the cases of DM are type 2 diabetes mellitus (T2D) which is characterized by insulin resistance, chronic inflammation, and the dysfunction of insulin-producing pancreatic beta cells [1–4]. The treatments of T2D include lifestyle changes and therapeutic regimens. Various therapeutic regimens used to treat T2D include oral antidiabetic

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drugs and insulin. However, therapeutic regimens and lifestyle changes are only able to ameliorate hyperglycemia which does not solve the main problem of T2D, peripheral insulin resistance and beta cell dysfunction. Therefore, strategies to solve the main problem of T2D lies on solving peripheral insulin resistance and beta cell dysfunction in producing insulin [2, 3].

One of the most promising options to solve peripheral insulin resistance and beta cell dysfunction is to use mesenchymal stem cells (MSCs). MSCs are known for their regenerative potential and have been studied for the treatment of T2D. The ability of MSCs to treat T2D lies on their potential to regenerate pancreatic islet beta cells, prevent apoptosis of endogenous pancreatic islet beta cells through amelioration of inflammation, and provide a supportive niche microenvironment through their ability to secrete paracrine factors or deposit extracellular matrix which ameliorates peripheral insulin resistance [3, 5]. Another advantage of utilizing MSCs to treat T2D is that MSCs can be used autologously, so the patient does not need a donor and further assure the safety of MSCs therapy without the risk of allogenic immunological reactions [5]. However, autologous MSCs from T2D patients are found to have low number of cells and poor quality. It makes their MSCs difficult to culture which lowers the clinical efficacy of MSCs to treat T2D especially when it is administered intravenously [2, 6–8]. Furthermore, the use of allogenic MSCs is risky due to the potential of immunogenic reactions which may worsen the course of T2D [9].

The solution to the problem is to use the combination of stromal vascular fraction (SVF) and autologous activated platelet-rich plasma (aaPRP), a similar cell-based therapy. SVF which is extracted from the adipose tissue contains preadipocytes, pericytes, fibroblasts, endothelial cells, macrophages, and MSCs. SVF is a suitable option to treat T2D because these combination of cells are able to exert beneficial effects including amelioration of inflammation and oxidative stress, regeneration of pancreatic islet beta cells, and promotion of angiogenesis [10]. Furthermore, SVF is able to yield billions of cells when processed through a certain processing method, such as H-Remedy. This large number of cells will be able to reach the target tissue with a sufficient amount to compensate for the reduced biological functions due to the T2D [11, 12]. In addition to that, SVF treatment is often combined with aaPRP which enhances the regenerative potential of SVF, hence making it a more suitable option for the treatment of T2D over MSCs [13].

Although the combination of SVF and aaPRP shows a promising potential to treat T2D, there were only limited studies exploring this topic. Most of the previously reported studies were conducted to evaluate their potential in osteoarthritis, fat grafting, vascular diseases, and improving wound healing [13]. Therefore, this study was conducted to elaborate the therapeutic potential of SVF and aaPRP in T2D patients.

Materials and methods

This study was a retrospective study on T2D patients that were treated with autologous SVF and aaPRP. The lipoaspiration procedures were performed by a single operator. Ethical approval clearance was obtained from Health Research Ethics Committee of University of Indonesia and Cipto Mangunkusumo Hospital (HREC-FMUI/CMH) with letter of approval No. 0249/UN2.F1/ETIK/2018. The data was collected from the medical records documented by the clinics or hospitals with informed consent obtained from each patient enrolled in this study.

This study has been registered in clinicaltrials.gov with trial registration number NCT05925829.

Patient recruitment criteria

The inclusion criteria for the patients in this study were: (1) patients who were diagnosed with T2D for at least 2 years; (2) patients who have undergone standard oral anti-hyperglycemic therapy with metformin and had not been able to reach normal HbA1c level with the medication; and (3) patients who underwent autologous SVF-aaPRP therapy between April until December 2017. The diagnosis of T2D and treatment with oral anti-hyperglycemic therapy with metformin were in accordance with the guideline for management and prevention of T2D by the Indonesian Society of Endocrinology. The exclusion criteria were: (1) patients who were pregnant; (2) patients who were below 18 years of age; and (3) patients who were on insulin therapy.

Stromal vascular fraction (SVF) preparation

The preparation of SVF used the H-Remedy (Jakarta, Indonesia) method invented by HayandraLab. Manual liposuction was performed to collect the lipoaspirate. The lipoaspirate was put into 10 tubes with a volume of 50 ml each. Six tubes were processed immediately while the remaining tubes were preserved in 2–8°C temperature for the subsequent therapy sessions. Lipoaspirate was then digested by H-Remedy enzyme and incubated for 1 hour at 37°C. Afterwards, they were centrifuged at 300 ×g centrifugation speed. Digested lipoaspirate was then added to low-glucose (1 g/L) Dulbecco's modified Eagle medium (DMEM) containing 4 mM L-glutamine (Gibco, USA) to inactivate the enzyme, continued by 5 min of centrifugation at 600 ×g. The supernatant was then discarded and the

SVF pellet was diluted in saline solution. Calculation of live cells used the following formula:

$$\text{Number of cells} = \frac{\textit{Average live or dead cells}}{\textit{4 (chambers)}} \times \textit{Df} \times 10^4$$

Df = dilution factor.

To calculate cell viability, the following formula was used:

$$\textit{Cell viability} = \frac{\textit{Average live cells}}{\textit{Average live + dead cells}}$$

Some of the SVF was cultured as part of the quality control protocol. The cultured cells expressed CD73, CD90, and CD105 with less expression or without the expression of CD34/CD45/CD11b/CD19/HLA-DR. The cells were also able to differentiate into chondrocyte, osteocyte, and adipocyte. Therefore, the SVF contained fraction of cells that met the criteria of MSCs in accordance to the International Society of Cellular Therapy's standard [12].

The lipoaspirate allocated for the subsequent therapy sessions was stored by two different methods. Lipoaspirate that would be processed within 2 weeks period were stored in 2–8oC temperature. The pellet of lipoaspirate that needed to be stored more than 2 weeks was mixed with 2 mL of KM banker II and moved into cryopreservation tubes. The tubes were then incubated in –80°C for 1 night in Mr. Frosty Freezing Container (Sigma-Aldrich, USA). The tubes were then cryopreserved in liquid nitrogen for up to 4 weeks.

Autologous activated platelet-rich plasma (aaPRP) preparation

The aaPRP was prepared using an in-house method of HayandraLab. A 24 mL sample of whole blood was collected from each patient in a sodium citrate tube and centrifuged at low speed for 10 minutes until the plasma layer was separated from the red blood cell (RBC) layer. The plasma was aspirated and subjected to a high-speed centrifugation for another 10 minutes until the platelets were concentrated at the lower part of the plasma. The upper part of the plasma was then removed until the remaining volume in the tube was 2.5 ml. The pellets of platelets were resuspended in the remaining plasma. This product was considered as an inactivated PRP. Activation was done by calcium activator until a clot was formed. The clot was removed and the PRP underwent a light activation process (AdiLight-1, AdiStem Ltd., Hong Kong). The final product of this technique was called autologous activated Platelet-rich Plasma (aaPRP). The aaPRP was used to treat T2D patients in combination with the SVF [12].

SVF and aaPRP administration

The SVF pellet was resuspended in 0.9% normal saline, resulting in a total of 22 mL SVF suspension. 7 mL of cell suspension was used for quality control. A total of 15 mL SVF suspension was mixed with 3 mL aaPRP. A total of 20 mL of SVF and aaPRP suspension was injected into an infusion bag which contained 250 ml of 0.9% normal saline. The mixture of SVF and aaPRP was then infused intravenously to each patient for a duration of around 30 minutes. The infusion was given on the day of the patient's lipoaspiration procedure. The patients underwent three subsequent infusions of SVF and aaPRP combination, followed by four aaPRP infusions. These therapy sessions were scheduled with a 2-weeks interval [12].

HbA1c test

Serum HbA1c levels were measured by an independent laboratory using the boronate affinity high-performance liquid chromatography method. The Wondfo HbA1c Rapid Quantitative Test (Wondfo, Guangzhou, China) was used to measure HbA1c level. Results were expressed in g/dL using the Wondfo FIA Meter Plus (Wondfo, Guangzhou, China) fluorescence immunochromatographic analysis. HbA1c level measurement was done at baseline before therapy, 1 month, and 3 months after the first therapy. The reference value for the HbA1c was as follow : normal (< 5.7 g/dL), prediabetic (5.7–6.5 g/dL), and diabetes (≥ 6.5 g/dL).

Statistical analysis

Baseline, 1-month post-therapy, and 3-month post-therapy HbA1c level of patients recruited in this study was analyzed statistically. The Shapiro-Wilk normality test was done in this study due to the small sample size. The non-parametric Wilcoxon test was done in this study as the data were not normally distributed with $p < 0.05$ indicated a significant difference.

Results

Patient demographics and SVF combined with aaPRP treatment

In this study, 39 patients diagnosed with T2D were included. Figure 1 shows the flowchart of patient recruitment. Among 39 patients, 28 patients were male (71.8%) and 11 patients were female (28.2%). The mean age was 59 years old. The youngest patient in this study was 38 years old and the oldest was 85 years old. Table 1 shows the patients' baseline demographics.

The mean lipoaspirate volume of SVF, re-SVF 1, and re-SVF 2 were 250 mL, 136 mL, and 0 mL, respectively. The mean fat volume of SVF, re-SVF 1, and re-SVF 2 were 114 mL, 54 mL, and 0 mL, respectively. The mean total cells of SVF, re-SVF 1, and re-SVF 2 were 2.68 × × 109, 1.67 × 109, and 0.74 x 109 cells, respectively.

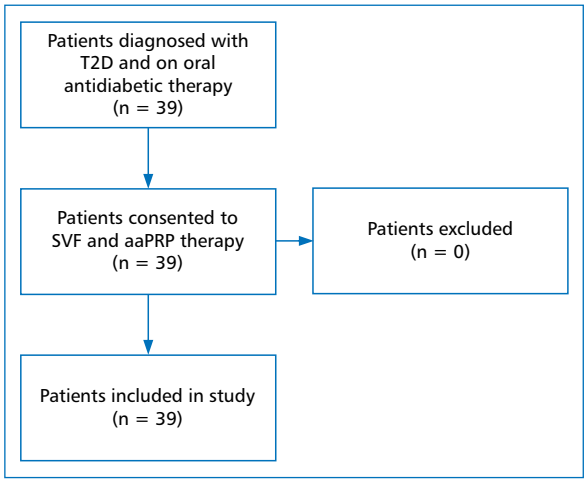

Figure 1. Flowchart of Patient Recruitment
SVF — stromal vascular fraction; T2D — type 2 diabetes

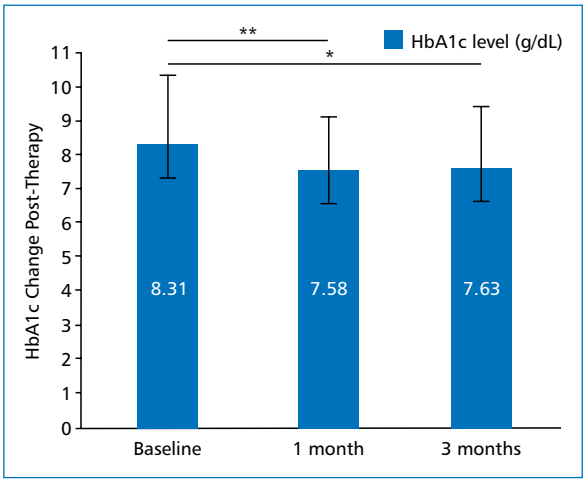

Figure 2. HbA1c Change in T2D Patients Post-Therapy with SVF and aaPRP after 1 Month and 3 Months
*p < 0.05; **p < 0.001; aaPRP — autologous activated platelet-rich plasma; HbA1c — glycated hemoglobin; SVF — stromal vascular fraction

The mean viability were 98.71% for SVF, 97.7% for re-SVF 1, and 96.98% for re-SVF 2.

Efficacy of SVF and aaPRP in T2D patients

The mean baseline HbA1c level of all 39 patients was 8.31 g/dL. Of all 39 patients diagnosed with T2D, the combination of SVF and aaPRP in T2D patients (Fig. 2) resulted in a statistically significant decrease in HbA1c level after 1 month ($p < 0.001$) and 3 months ($p < 0.05$). At 1 month after treatment with SVF and aaPRP, a statistically significant decrease in HbA1c level from 8.31 g/dL to 7.58 g/dL was observed. At 3 months after treatment with SVF and aaPRP, a statistically significant decrease in HbA1c level from 8.31 g/dL to 7.63 g/dL was also observed. Meanwhile, no statistically significant decrease was observed between 1 month and 3 months after treatment.

Out of 39 patients that participated in the study, 4 patients were still observed at 6 months and 12 months after treatment with SVF and aaPRP. A decrease in HbA1c level was still observed from baseline HbA1c level of 7.95 g/dL to 7.5 g/dL at 6 months and to 7.825 g/dL at 12 months after therapy.

Safety analysis of SVF and aaPRP combination in T2D patients

Among all patients that participated in the study, no SVF- and aaPRP-related adverse events, such as immunologic reactions and other complications, were observed in the study.

Discussion

Our study is the first to report the efficacy and safety of combination of SVF and aaPRP to treat T2D patients via intravenous administration. A significant decrease in HbA1c level after therapy for 1 month from 8.31 g/dL to 7.58 g/dL and 3 months from 8.31 g/dL to 7.63 g/dL and decrease in HbA1c level after 6 months and 1 year of SVF and aaPRP treatment was observed in this study. Our finding shows that initial

Table 1. Baseline Demographics of T2D Patients

	Male (n = 28)	Female (n = 11)	Both gender (n = 29)
Age (mean ± SD) [years]	56 ± 9	68 ± 11	59 ± 11
Baseline HbA1c level [g/dL]	8.36	8.18	8.31
Diabetes duration [years]	5	4	5
Diabetes therapy duration pre-therapy [years]	5	4	5
Comorbidities	CAD (4), CKD (2), hypertension (3), stroke (1)	CAD (2), hypertension (1), stroke (1)	CAD (6), CKD (2), hypertension (4), stroke (2)

CAD — coronary artery disease; CKD — chronic kidney disease; HbA1c — glycated hemoglobin; SD — standard deviation; T2D — type 2 diabetes

3-month treatment with SVF and aaPRP is useful to significantly decrease HbA1c level, which may help prevent comorbidities to occur. The decrease in HbA1c after 6 months and 1 year of treatment with SVF and aaPRP implies that this treatment might be beneficial in long-term HbA1c control, but it should be confirmed with further studies [14]. To date, the efficacy of SVF as diabetic therapy has been reported in type 1 diabetes by Vanikar et al. using allogenic SVF. The study showed the potential efficacy of SVF through the significant decrease in mean HbA1c level of the 11 patients from 8.47 g/dL to 7.39 g/dL over a mean follow-up of 7 months. Although a significant decrease in HbA1c level was reported, the study used allogenic SVF from healthy donors which has better viability than autologous SVF [15]. Meanwhile, our study showed similar significant decrease in HbA1c level through the use of autologous SVF combined with aaPRP. The use of aaPRP is necessary in patients with diabetes to improve SVF viability and efficacy, as patients with diabetes tend to have lower SVF cell viability [16].

The decrease in the HbA1c levels in patients after the treatment with SVF and aaPRP was due to the exerted effects by the variety of cells in SVF, the enhanced regenerative capability of SVF by aaPRP, and the anti-inflammatory effect of aaPRP. MSCs found in the SVF are known to regenerate insulin-producing pancreatic islet beta cells, ameliorate inflammation, and oxidative stress which prevent endogenous pancreatic islet beta cells apoptosis, and provide a supportive microenvironment niche which enhances the production of insulin and ameliorates the peripheral insulin resistance [3, 5].

It has been revealed that inflammation is associated with an increase in HbA1c level in patients with diabetes [17]. MSCs are known to modulate the immune responses and inflammation. One of the identified mechanisms is that MSCs are able to promote type 2 macrophage polarization which produces an anti-inflammatory response [18]. Besides MSCs, fibroblasts found in the SVF are also known to modulate the immune response [19]. SVF also contains macrophages with the majority of M2 macrophages. M2 macrophages are known to secrete various anti-inflammatory factors such as interleukin 4 (IL-4), IL-10, and transforming growth factor beta (TGF-ß). The various anti-inflammatory factors produced by M2 macrophages are useful to modulate the chronic inflammation present in T2D. All of aforementioned mechanisms could explain the decrease in HbA1c level that was observed in our patients [10].

It has been avowed that aaPRP is able to suppress the cytokine release and limit the inflammation [20]. This explains the therapeutic potential of aaPRP to treat the chronic inflammation present in T2D. Similar to MSCs, aaPRP also enhances the proliferation of fibroblasts which further ameliorates the inflammation in T2D [21]. aaPRP promotes the attenuation of excessive inflammation through the induction of IL-10 that suppresses the pro-inflammatory cytokines such as TNF-α [22]. Furthermore, the addition of aaPRP, enhances MSCs regenerative capabilities. It is due to the ability of aaPRP to improve MSCs proliferation and delay the senescence of MSCs which prolonged the regenerative capabilities [23].

The advantage of SVF for being able to yield billions of cells also enables repeated administration of SVF to prolong the efficacy to treat T2D. In addition, it has also been found that SVF contains MSCs and other various cells able to promote micro-vessel formation together with endothelial cells which creates a stable vascular network system. The promotion of angiogenesis is by way of the differentiation of MSCs and the secretion of pro-angiogenic and anti-apoptotic factors, such as hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), placental growth factor B (PGF-B), and TGF-ß, in large number by MSCs and other components in SVF cells. This may be beneficial for T2D patients who suffer from microvascular complications that may lead to ischemia-related complications [10]. Moreover, the use of SVF and aaPRP combination has been proven to be more effective in promoting angiogenesis for wound healing which explains the advantage of SVF and aaPRP used in our study [13].

Unlike allogenic MSCs which may induce immunological reactions and cause adverse events [9], the use of autologous SVF and aaPRP combination with dose of around 2.5 billion cells in our study did not show any immunogenic reactions nor any complications. Our study reported similar safety outcome along with previous result by Karina et al. that also found no SVF- and aaPRP-related adverse events in T2D patients [12].

However, there were still some limitations of our study: (1) our study was not a randomized controlled trial and the HbA1c result of our study may be affected by confounding factors such as medications, lifestyle, age, and other comorbidities such as obesity; (2) our study was a retrospective pilot study with only small sample size and short duration of study; and (3) our study only measured HbA1c level as our parameter and did not measure other parameters such as C-peptide level.

Despite its limitations, this study could serve as a preliminary study showing the efficacy and safety of SVF and aaPRP therapy. Therefore, further studies with larger sample size, control group, and longer follow-up

period of patients are required to confirm these preliminary findings.

Conclusion

In summary, SVF and aaPRP could be used as adjuvant treatment to help fulfill the current recommendation of maintaining HbA1c level below 7% by significantly decreasing HbA1c level for the first 3 months of administration and maintaining HbA1c level after 3 months of administration. The mechanisms of SVF and PRP to lower HbA1c level of T2D patients are through the various beneficial effects exerted by the cells present in SVF, enhanced regenerative capability of SVF by PRP, and the anti-inflammatory effects of PRP. Furthermore, no SVF- and aaPRP-related adverse events was found in our study. The efficacy and safety showed promising therapeutic potential of SVF and aaPRP to be an adjuvant treatment in treating and preventing comorbidities in T2D patients.

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Conflicts of interest

The authors declare no conflicts of interest.

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