The Role of Adipose Derived Mesenchymal Stem Cell (MSCs) to Control Autoimmune Disease

by Sumorejo Purwati

The Role of Adipose Derived Mesenchymal Stem Cells (MSCs) to Control Autoimmune Disease

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Abstract: There are 80 types of autoimmune diseases (ADs) with some of the same symptoms, but causes are still unclear. The major treatment of ADs is immunosuppressive drugs but these are not effective and associated with substantial toxicities. Stem cell has demonstrated remarkable effectiveness in halting destructive immune response and restoring the body to level of normal function by providing cellular level repair of damage, increasing blood flow, and reducing inflammation. Adipose tissue is one of the most potent and concentrated source of mesenchymal stem cells (MSCs) as an anti-inflammatory and tissue protecting agent which is promote healing and minimal invasive. This study conducted in 20 patients with ADs (11 women and 9 men) in various age between 22 to 70 years old. Patients treated with autologous adipose-derived MSCs implantation through catheterization. The laboratory analysis result of patients before and after MSCs application in 6 months were measured, include haemoglobin (Hb), leukocytes, erythrocyte sedimentation rate (ESR), protein and blood levels in urine, high sensitivity c-reactive protein (hsCRP), C3 and C4 complement, anti-nuclear antibodies (ANA) and anti-double stranded DNA (anti-dsDNA). MSCs are able to improve the performance of hemoglobin which statistically significant increased (p=0.002). MSCs are able to reduce the inflammatory as shown in the number of leukocytes (p=0.015) and ESR (p=0.031) which statistically significant decreased. MSCs can repair the renal function as shown in no presences of protein and blood in patient's urine. MSCs are also able to augment the immune response as shown in hsCRP which statistically significant decreased (p≤0.001), while C3 and C4 complements statistically significant increased (p≤0.001). ANA and anti-dsDNA showed a negative result which means MSCs therapy may give a good response to heal the ADs.

Introduction

Autoimmune Diseases (ADs) represent a heterogeneous group of disorders with genetic, environmental, and individual etiological factors [1]. Autoimmune is defined as the immune response to the tissue antigen itself caused by loss of tolerance, so that it normally can not maintain self-tolerance of B-cells or T-cells, and/or both. Noted there are 80 types of autoimmune diseases with some of the same symptoms. However, the causes of autoimmune diseases are still unclear. Autoimmune diseases affect organs and tissues such as blood vessels, connective tissues, thyroid, pancreas, joints, muscles, and skin [2]. Some of the most common autoimmune diseases are Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Multiple Sclerosis (MS), Spondyloarthropathy, and Behcet's Diseases.

Autoimmune diseases are the third most common disease in the United States after cancer and cardiovascular, affecting 5 to 8% of population or 14.7 to 23.5 million people [3] with the highest

prevalence in Rheumatoid Arthritis relatively constant between 1 to 2%, approximately 5 million SLE patients spread across the world with an annual increase of 100,000 new patients, worldwide prevalence of spondyloarthropathy is approximately 1.9%, and Behcet's Diseases prevalence of 5.2 per 100,000 population [4,5,6]. ADs are more common in women at 2.7 times greater risk than men, about 78% of total patients in the world with the largest age group at 25 to 34 years old (45%). Studies of the differences in immune response in men and women show that women respond to infection, vaccination, and trauma with increased antibody production, whereas inflammation is usually more severe in men resulting in an increased mortality in men and protection against infection in women [7].

Basically there are many factors affect to the development of autoimmune diseases (multifactor). Predisposing factors contributing to ADs include genetic, gender, infection, autoantigen properties, medications, and age. Antibody deficiency is responsible for about 50 to 60% of all ADs cases [8]. A genetic predisposition, T-cell defects, B-cell hyperactivity, hormonal alterations, and environmental trigger likely result in the disordered immune response that typifies the disease [9]. Delay in diagnosis and improper handling can lead to serious morbidity and mortality rapidly. The goals of treatments for ADs are to 1) reduce symptoms, 2) control the autoimmune process and 3) maintain the body's ability to fight the disease [2]. The major immunosuppressive drugs in treatment of ADs are corticosteroids, cyclophosphamide, azathioprine, and methotrexate. However, these drugs are not effective and associated with substantial toxicities [10].

Stem cell that has homing and plasticity has demonstrated remarkable effectiveness in halting destructive immune response and restoring the body to a level of normal function by providing cellular level repair of damage, increasing blood flow, and reducing inflammation [11]. Some in vitro studies have reported that mesenchymal stem cells (MSCs) have immunomodulatory properties and immunosuppressive effects on MHC-mismatched lymphocytes proliferation by inhibiting naïve, memory and activated T-cells, B-cells, NK-cells and dendritic cells [10]. Adipose tissue is one of the most potent and concentrated source of MSCs as an anti-inflammatory and tissue protecting agent which is promote healing and also minimal invasive [10,12]. Adipose tissues are abundant, easily accessible and obtainable with little patient discomfort.

This study conducted in 20 patients with autoimmune diseases include Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Spondyloarthropathy, and Behcet's Diseases using autologous adipose-derived mesenchymal stem cells (MSCs). In a research, stem cell therapy has been seen to give RA patients an improvement in tender or swollen joints as well as less pain and better function [13]. Meanwhile, adipose-derived mesenchymal stem cells improve the cells function already damaged by diabetes [14]. In another study, the implantation of stem cell cells from normal mice to W/BF1 mice was found to prevent and cure the lupus nephritis, thrombocytopenia and anti-phospholopid Ab syndrome. Moreover, the platelet counts were normalized and circulating antiplatelet Ab levels as well as anti-phospholipid levels were reduced [15].

Materials and Methods

Subjects

Twenty patients with autoimmune diseases (11 women and 9 men) in various age between 22 to 70 years old (Table 1) treated with autologous adipose-derived mesenchymal stem cells implantation. MSCs injected into patients through catheterization. The laboratory analysis result of patients before and after MSCs application in 6 months were measured, include: 1) hematology: haemoglobin (Hb), leukocytes/white blood cell (WBC), erythrocyte sedimentation rate (ESR); 2) urinalysis: protein and blood levels; 3) inflammatory: high sensitivity c-reactive protein (hsCRP), C3 complement, C4 complement; 4) immunology: anti-nuclear antibodies (ANA) and anti-double stranded DNA (anti-dsDNA). The results between pre-injection and post-injection then compared.

Table 1. Frequency of ADs patient's age

Age	Frequency
20-29	3
30-39	4
40-49	5
50-59	4
>=60	3
Mean = 44.4000	
Std. Deviation = 14.00902	

Adipose-derived Mesenchymal Stem Cells Isolation and Culture

Mesenchymal stem cells were derived from adipose tissue using aspiration and separation on Histopaque-1.077 (Sigma). Harvested cells were cultured in Dulbecco's Modified Eagles Medium containing 1.0 g/L glucose. MSCs characterization were performed by analyzing the expression of 90+, CD34- and CD105+ by using DAB immunostaining and FACS (BD).

Statistical Analysis

Data analysis include descriptive analysis and hypothesis testing were performed using IBS SPSS Statistics version 23. Data in ratio expressed in mean, standard deviation, frequency distribution, and percent on descriptive analysis and frequency. Data normality test performed by Kolmogorov-Smirnov Z statistics. Variable paired comparison performed by T-test if data were normally distributed or two related samples (Chi-Square test) if data distribution was abnormal. Anova or variance analysis was used to compare three average or more. Significance limit is that if $p < 0.05$ with 95% confidence interval [14].

Results

After the application of stem cells three times with injection every month period, we compared the laboratory results of patients before and after injection include hematology, urinalysis, inflammatory, and immunology.

In the hematology examination, the average of hemoglobin of the patients increased after stem cell injection with $p = 0.002$, where statistically was a significant different between pre-injection and post-injection of MSCs ($p < 0.05$). Meanwhile, the average of white blood cells (WBC) and erythrocyte sedimentation rate (ESR) of the patients decreased after stem cell injection with $p = 0.015$ and $p = 0.031$. This also indicates a statistically significant different between pre and post-injection of MSCs ($p < 0.05$) as shown in Figures 1 and Table 2.
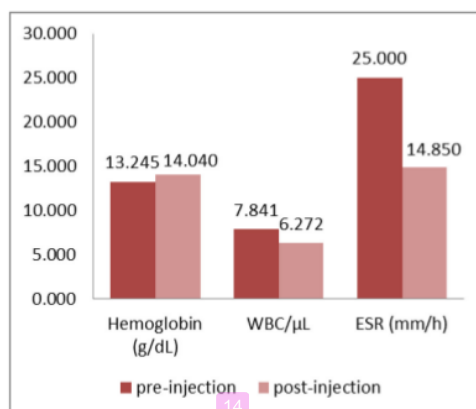

Figure 1. Hematology test result of pre-injection and post-injection of MSCs

Table 2. Hematology of pre-injection and post-injection of MSCs analysis using T-test

Paired Samples Test									
		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Hb_post Hb_pre	.79500	.97088	.21710	.34061	1.24939	3.662	19	**.002**
Pair 2	WBC_post WBC_pre	-1.56900	2.62567	.58712	-2.79785	-.34015	-2.672	19	**.015**
Pair 3	ESR_post ESR_pre	-10.15000	19.51861	4.36449	-19.28499	-1.01501	-2.326	19	**.031**

In the urinalysis examination, protein and blood levels in urine of patients with autoimmune diseases after MSCs injection are negative. This is different from the initial condition before MSCs injection, where there were 1 patient with positive protein level and 5 patients with positive blood level in their urine, although there is no statistically significant different found between pre-injection and post-injection ($p > 0.05$). Blood protein and blood levels in the patient's urine are presented in Figures 2 and Table 3.
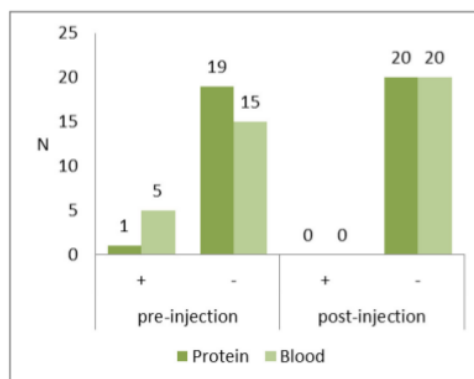

Figure 2. Urinalysis test result of pre and post injection of MSCs

Table 3. Hematology of pre and post injection of MSCs analysis using Chi-Square test

Chi-Square Tests					
	pre-injection		post-injection		Exact Sig. (2-sided)
	+	-	+	-	
Protein	1	19	0	20	**1.000[a]**
Blood	5	15	0	20	**.125[a]**

a. Binomial distribution used

In the inflammatory examination, the average of hsCRP of the patients decreased after stem cell injection with $p \leq 0.001$ where statistically was a significant different between pre-injection and post-injection of MSCs ($p < 0.05$). Meanwhile, the average of C3 complement and C4 complement of the patients increased after stem cell injection with $p \leq 0.001$. This also indicates a statistically significant different between pre-injection and post-injection of MSCs ($p < 0.05$) as shown in Figures 3 and Table 4.
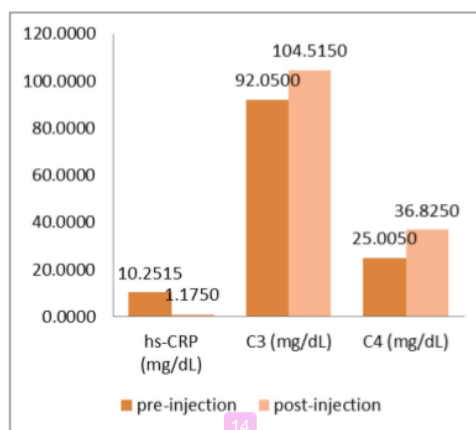
Figure 3. Inflammatory test result of pre-injection and post-injection of MSCs

Table 4. Inflammatory of pre-injection and post-injection of MSCs analysis using T-test

		Paired Samples Test							
		Paired Differences							
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
					Lower	Upper			
Pair 1	hsCRP_post hsCRP_pre	-9.07650	6.89284	1.54129	-12.30245	-5.85055	-5.889	19	**.000**
Pair 2	C3_post C3_Pre	12.46500	12.68631	2.83674	6.52763	18.40237	4.394	19	**.000**
Pair 3	C4_post C4_pre	11.82000	8.21850	1.83771	7.97362	15.66638	6.432	19	**.000**

In the immunology examination, ANA and anti-dsDNA of patients with autoimmune diseases after MSCs injection are negative. This is different from the initial condition before MSCs injection, where there were 17 patients from 20 patients total with positive ANA. It also found a statistically significant different between pre-injection and post-injection with $p \leq 0.001$ ($p > 0.05$), although there is no statistically significant different found in anti-dsDNA pre-injection and post-injection. ANA and anti-dsDNA levels in the patients are presented in Figures 4 and Table 5.
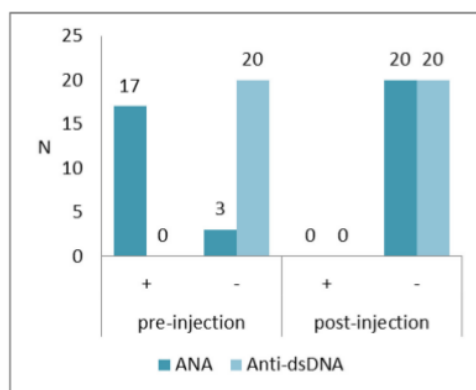

Figure 4. Immunology test result of pre-injection and post-injection of MSCs

Table 5. Immunology of pre and post injection of MSCs analysis using Chi-Square test

Chi-Square Tests				
	pre-injection		post-injection	
	+	-	+	-	Exact Sig. (2-sided)
ANA	17	3	0	20	.000[a]
Anti-dsDNA	0	20	0	20	.[a]

a. Binomial distribution used

Discussion

Autoimmune diseases (ADs) are condition arising from an abnormal immune response to a normal body part. ADs divided into systemic and organ-specific autoimmune disorders, depending on principal clinico-pathologic features of each disease. Systemic autoimmune may affect joints, skin, kidneys, heart, lungs and red blood cells. Systemic autoimmune include SLE, Sjogren's syndrome, scleroderma, rheumatoid arthritis, and dermatomyositis. Meanwhile, organ-specific diseases primarily target one specific organ, include IDDM, Hashimoto's thyroiditis, and Graves' disease. The criteria for ADs may be include direct evidence from transfer of pathogenic antibodies or pathogenic T-cells, indirect evidence based on reproduction of autoimmune disease in experimental animals, and circumstantial evidence from clinical clues [1,2].

Recently, many in vitro studies have reported that mesenchymal stem cells (MSCs) have immunomodulatory properties and immunosuppressive effects on MHC-mismatched lymphocytes proliferation by inhibiting naïve, memory and activated T-cells, B-cells, NK-cells and dendritic cells. Adipose-derived mesenchymal stem cells are becoming an alternative source of MSCs because of abundant, easily accessible and obtainable with little patient discomfort, also large amounts can be easily found [10]. In the first clinical trial, autologous adipose-derived mesenchymal stem cells were used for treatment of widespread traumatic calvarial bone defects [16]. Recent study conducted clinical trial adipose-derived mesenchymal stem cells for treatment tertiary failure diabetes mellitus type 2. The study obtained levels of blood glucose at fasting and 2-hour postprandial also insulin were significantly decreased after adipose-MSCs implantation and the result was better than insulin treatment only [14].

In this study, twenty patients with autoimmune diseases, include RE, SLE, Spondyloarthropathy, and Behcet's Diseases were treated with autologous adipose-derived mesenchymal stem cells implantation through catheterization. The laboratory analysis result of patients before and after MSCs application were measured to be compared, include hematology (haemoglobin, white blood cell, and erythrocyte sedimentation rate), urinalysis (protein and blood levels), inflammatory (high sensitivity c-reactive protein, C3 complement, and C4 complement), also immunology (anti-nuclear antibodies and anti-double stranded DNA).

Haemoglobin (Hb) plays an important role in maintaining the red blood cells. Autoimmune disease may lead antibodies directed against the person's own red blood cells (RBCs) cause them to burst (lyse), leading to an insufficient number of oxygen-carrying red blood cells in the circulation [17]. From the study result, patients after treated with MSCs had statistically significant increase in Hb (p=0.002) than before MSCs injected. This indicates that MSCs are able to improve the performance of hemoglobin in the body.

Leukocytes, the white blood cells (WBCs) are an important part of the immune system. It is frequently a sign of an inflammatory response, most commonly the result of infection. While the erythrocyte sedimentation rate (ESR) is the rate at which red blood cells (RBCs) sediment in a period of one hour. It is a common hematology test and a non-specific measure of inflammation associated with conditions such as infections, cancers, and autoimmune diseases [18,19]. From the study results, patients after treated with MSCs had statistically significant decrease in the number of leukocytes (p=0.015) and ESR (p=0.031) than before MSCs injected. This indicates that MSCs are

able to improve the performance of leukocytes and erythrocyte sedimentation rate to reduce the inflammatory in the body.

The urinalysis is commonly used to assess renal injury (glomerulonephritis, interstitial nephritis) and will show proteinuria, hematuria or active sediment (erytrocytes or leukocytes casts). Many other illnesses such as diabetic nephropathy, poorly controlled hypertension, or infections will test similarly but when autoimmune disease is suspect, the common laboratory evaluation will serve as an initial red flag to pursue further testing [20]. From the test result, urinalysis of patients reveals proteinuria, dysmorphic RBCs, WBCs, and RBC cellular and granular casts before conducted with MSCs injection. The presences of protein and blood in patient's urine after conducted with MSCs significant decreased even no found statistically. This indicates that adipose-derived MSCs can repair the renal function.

High sensitivity C-reactive protein (hsCRP) was named for its reactivity to the C polysaccharide in the cell wall of S. pneumoniae. CRP is an innate immune protein. It helps opsonize pathogens for phagocytosis and activates the complement system. CRP production is under the control of IL-1, IL-6, and TNF-α. Changes in serum CRP concentration change more quickly than ESR and makes CRP may be a better reflection of current inflammation. Unlike the ESR, CRP is fairly stable serum protein whose measurement is not time-sensitive and not affected by other serum components. The magnitude of inflammation directly relates to the concentration of CRP. Levels <0.2 mg/dl are considered normal, while >1.0 mg/dL are suggestive off inflammation and/or infection [21,22]. From the test result, hsCRP in patients showed decrease after MSCs injection. It it also statistically significant different between pre-injection and post-injection with $p \leq 0.001$ ($p < 0.05$). This indicates that adipose-derived MSCs are able to improve the performance of immune protein in the body.

The complement cascade is a complex, tightly regulated series of proteolytic enzymes, regulatory proteins and cell surface receptors that mediate and augment both complement, humoral and cellular immune response. Individual components, such as C3, C4 and factor B, are measured by nephelometry and ELISA. Serum levels of complement components can serve as markers of disease activity. In immune complex deposition disease, serum complement proteins are consumed and serum levels decrease. Decreased C3 and C4 indicate increased consumption and indicate disease activity. Deficiencies of early complement components (C1 to C4) may increase the risk for development of immune-complex diseases [21,22,23]. From the test result, the average of C3 complement and C4 complement of the patients increased after stem cell injection and statistically significant different between pre-injection and post-injection of MSCs with $p \leq 0.001$ ($p < 0.05$). This indicates that adipose-derived MSCs are able to augment the immune response of the body.

Anti-nuclear antibody (ANA) is a diverse group of antibodies that react against nuclear, nucleolar, or perinuclear antigens. These antigens represent cellular components such as nucleic acid, histone, chromatin, nuclear and ribonuclear proteins. ANA is common to most autoimmune diseases and the presence of low titer ANA occurs more frequently in elderly populations must be caution. Methods used for detection utilize immunofluorescence testing of the patient's serum using cell substrate. Screening patient's serum for the detection of ANA with ELISA provides high sensitivity but lacks specificity. Historically, a human laryngeal epithelioma cancer cell line (HEp2 cells) have been used as the cell substrate because the result offers the advantage of detecting a nuclear fluorescent pattern. However, because of the time and expense for testing with HEp2 cells, the assay procedures are largely done by ELISA methods [21,22]. From the test result found a statistically significant different in ANA between pre-injection and post-injection with $p \leq 0.001$ ($p > 0.05$). This indicates that stem cell therapy may give a good response to heal the autoimmune diseases.

Anti-double stranded DNA (anti-dsDNA) are an important marker used in the diagnosis and monitoring of ADs. Antibodies to dsDNA are highly specific for SLE. However, some patients with other rheumatic diseases or chronic active hepatitis may have mildly or moderately elevated serum titers. Anti-dsDNA was typically measured using radioimmunoassay. The more common current tests employ an immunofluorescence assay (IFA) or ELISA. The IFA utilizes a target antigen

Crithidia luciliae, a flagellated protozoa containing a dsDNA-containing small organelle called a kinetoplast. The antibodies to dsDNA are detected semiquantitatively by demonstrating IgG bound to the kinetoplast. In contrast, with ELISA testing, the dsDNA is bound to the solid phase of the microwell plate. The serum is incubated and then the bound IgG is detected [20,21]. From the test result found no statistically significant different in anti-dsDNA pre-injection and post-injection.

Conclusion

Adipose tissue is one of the most potent and concentrated source of mesenchymal stem cells as an anti-inflammatory and tissue protecting agent which is promote healing and minimal invasive. In this study, 20 patients with autoimmune diseases treated with autologous adipose-derived mesenchymal stem cells implantation showed a good response. MSCs are able to improve the performance of hemoglobin as shown in Hb which statistically significant increased ($p=0.002$). MSCs are able to reduce the inflammatory as shown in the number of leukocytes ($p=0.015$) and ESR ($p=0.031$) which statistically significant decreased. MSCs can repair the renal function as shown in no presences of protein and blood in patient's urine. MSCs are also able to augment the immune response of the body as shown in hsCRP which statistically significant decreased ($p \leq 0.001$), while C3 and C4 complements statistically significant increased ($p \leq 0.001$). ANA and anti-dsDNA showed a negative result which means MSCs therapy may give a good response to heal the autoimmune diseases.

Competing Interests

The authors declare that they have no competing interests.

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