

## **ADIPOSE-DERIVED STEM CELL THERAPY ON NON-COMMUNICABLE DISEASE: A SYSTEMATIC REVIEW**

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### **ABSTRACT**

The increasing number of non-communicable diseases demands practical therapy innovations, including adipose-derived stem cell application. This study aimed to analyze the effectiveness of adipose stem cell therapy on non-communicable disease patients. The method used in this study was a systematic review according to PRISMA 2020 guidelines. The database search was done on PubMed, Google Scholar, Proquest, and the EBSCO host database between 2016 and 2021. ROBINS-I tool and RoB-2 were used to assess the risk of bias in the clinical trial study. The first literature search identified a total of 2615 articles. After exclusion for some reason, 6 articles were included in this systematic review study. A total of five studies were included in this study. Based on the risk of bias assessment of the included studies, it was found that all studies had a low risk of bias in all domains. This study showed that the efficacy of adipose-derived stem cell therapy was inconsistent; however, the results were promising. In addition, the results showed that adipose-

derived stem cell therapy was safe without significant side effects. Further study was needed to identify therapeutic strategies based on Evidence-based Medicine (EBM).

**Keyword : Stem Cell; adipose; non-communicable disease; treatment;systematic review**

## INTRODUCTION

Recently, the scientific world has been growing, especially medical sciences. The advancement of medical science has caused a shift in disease patterns, where non-communicable diseases replaced the transmissible disease that was previously dominant. Even though there is a shift towards non-communicable diseases, some countries still face the double challenge of communicable and non-communicable diseases (Habib and Saha, 2010). The shifting pattern of the diseases was significantly influenced by the environmental changes, community behaviors, demographic transitions, technologies, economics, and socio-cultural changes (Barouki et al., 2012). The increase in the non-communicable disease burden is in line with the elevation of its risk factors, such as obesity, high blood pressure, unhealthy eating patterns, diabetes mellitus, lack of physical activity, alcohol consumption, and smoking (Barouki et al., 2012; Habib and Saha, 2010; Nethan et al., 2017).

Non-communicable diseases (NCDs) are chronic diseases not transmitted from one patient to another in the environment. Generally, NCDs develop slowly over a long period (Habib and Saha, 2010). NCD causes two-thirds of mortality globally, which is equal to 38 million lives annually [4]. The ultimate causes of death are

diabetes mellitus, cardiovascular diseases, certain types of cancers, and COPD (chronic obstructive pulmonary disease) (Kontis et al., 2014). During the last decade, the mortality rate that was caused by NCD was elevated by 15%, with the most significant increase found in Africa, the Mediterranean, and Southeast Asia (Dans et al., 2011; Siegel et al., 2014).

The significant burden of morbidity and mortality due to NCD made it the primary concern in the development of the medical sciences. Currently, the management of NCD relies on drugs that are consumed routinely almost throughout life (Low et al., 2015). Therefore, medical science developments focused on more specific and effective treatment. And one of the prospective therapy in the future is the application of adipose-derived stem cells (AD-MSCs) (Mizuno et al., 2012; Patricia A Zuk, 2010).

Stem cells are undifferentiated cells that able to renewal, and are able to differentiate into various types of cells (Ullah et al., 2015) In addition, they have immunomodulating properties and paracrine effects in response to tissue injuries; therefore, they might be used to treat injury and diseases to replace damaged or missing cells (Mora and Rojas, 2013) Therefore,

they are regarded as one of the solutions for NCDs therapy (Savitz et al., 2011).

Adipose tissue is a particularly enticing source for adult stem cells because the human body has large reserves that can be obtained in substantial quantities by minimally invasive methods (Mazini et al., 2019). AD-MSCs are mesenchymal cells that can be obtained from the abundant adipose tissue, and adhered to plastic culture vessels, and have the ability to proliferate and differentiate into multiple cell lineages in vitro (Mazini et al., 2019; Si et al., 2019).

## METHODS

The selection process of articles was done according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guideline 2020 (Page et al., 2021). Article searches were done using combination of keywords: “adipose-derived stem cells” AND “non-communicable diseases” OR “diabetic” OR “cancer” OR “stroke” OR “chronic obstructive pulmonary disease” OR “degenerative disease” in the PubMed, Google Scholar, Proquest, and EBSCO host database. Only articles that were published between 2016 - 2021 were used. This systematic review had been registered in PROSPERO with registered number [CRD42022342179].

### Study selection process

The article selection process was performed by analyzing and consolidating based on exclusion and inclusion criteria. The inclusion criteria for article selection were original

The substantial resources of AD-MSCs, their properties, and the possibility to be applied in regenerative medicine and cell therapy have made them the main focus of an investigation by many researchers. However, there are no specific guidelines regarding using AD-MSCs for NCD treatments. Currently, this therapy is limited only to animal research and clinical trials. Based on the description mentioned above, this systematic review aims to analyze the existing literature about the effectiveness of AD-MSCs in NCD patients' treatments.

experimental studies, randomized and non-randomized controlled trials, and studies identifying the effects of AD-MSCs therapy on NCD. Exclusion criteria were non-English language articles, no full-text available, articles in non-scientific journals and single group studies.

### Data extraction

The article searching was performed from June 1, 2022, to June 30, 2022. The outcomes that we seek for this systematic review were the first's author name and year of publication, subjects, the country in which the study was conducted, the design of the study, the use of AD-MSCs for NCD, and potential adverse effects. Two researchers reviewed the articles. Below is the diagram of the performed research process. The primary outcome assessed was the effectiveness of stem cells in inducing symptomatic and clinical improvements in NCD. Another result that was also measured was the safety of the stem cell application.

## Study quality and risk of bias

We used the Risk of Bias in Non-Randomized Intervention Studies tool (ROBINS-I) to assess the quality of prospective studies and the potential risk of bias of the included experimental non randomized studies (Thomson et al., 2018). The tool can be divided into the following areas: (i) entanglement bias, (ii) study participant selection bias, (iii) exposure measurement bias, (iv) exposure misclassification bias during follow-up, (v) missing data bias (vi) bias for outcome measurement, and (vii) bias in the selection of reported results. Risk of bias was assessed as 0 –

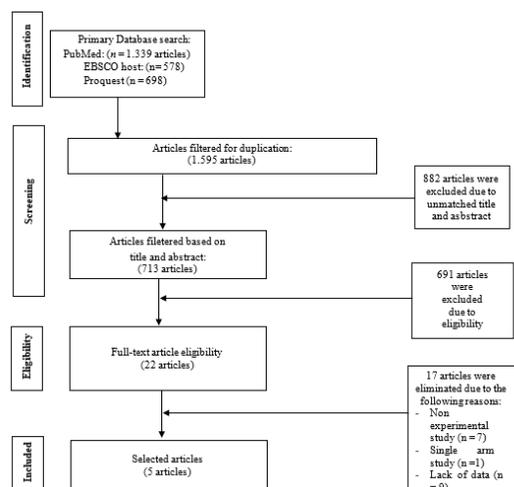
no response. 1-low risk; 2-moderate risk; 3-severe risk; and 4-critical risk.

Randomized studies will use the RoB-2 tool. Five domains were assessed: i) randomization process; ii) the deviation from intended intervention; iii) missing outcome data; iv) outcome measures; and v) selection from reported outcomes (Minozzi et al., 2020).

Two reviewers (KT and CO) independently assessed bias risk and assessed the strength of evidence in all relevant studies. Any disagreements/different evaluation between the two researchers are resolved by consensus or consultation with a third researcher (RJ).

## RESULTS

The results of the search process can be seen in **Figure 1**. The first literature searching identified total of 2615 articles. Initial full-text eligibility identified 22 articles. After exclusion for some reasons, a total of 6 articles included for this systematic review study.



**Figure 1.** Flow Diagram (PRISMA)

## Study characteristics

**Table 1** summarizes the characteristics of the chosen studies. There were 5 studies involving humans as research subjects. There were 3 non-randomized clinical trials and 2 randomized clinical trials included. The list of diseases studied included were ischemic stroke, diabetic ulcer, ovarian failure, obesity and erectile dysfunction.

All studies were published between 2016-2021. The highest number of research subjects included in the study were research conducted by Moon KC et al (Moon et al., 2019) (n=30). The majorities of the human research subjects were adults. Only one study by Shree et al (Shree et al., 2019) used animal subjects for AD-MSCs research. List of countries that conducted research on AD-MSCs were Spain,

South Korea, Iran, India and Greece.

**Table 1.** Article characteristics of the included studies

### Outcome Measurements and Adverse effects

Study found that AD-MSCs could be potential in NCD, but study by Mashayekhi M et al (Mashayekhi et al., 2021) and de Celis-Ruiz E et al (de Celis-Ruiz et al., 2022) found that AD-MSCs didn't have statistically significant benefit. Most of the studies found that AD-MSCs didn't have serious side effects after being administered in human and animal subjects.

### Assessment Risk of Bias

Based on the risk of bias assessment of the included studies, it was found that all studies had low risk of bias in all domains. No moderate or high risk was found in the included studies.

## DISCUSSION

Of the five articles, four of the studies were performed on human subjects, and one study was conducted on mice. The studies on NCDs addressed ischemic stroke, diabetic ulcer, ovarian failure, obesity and ED.

The results showed that AD-MSCs implantation improved both of neurological status and motor function after stroke. Motor function recovery levels depends on the type of stroke and the number of transplanted cells (Schulz et al., 1995) Vu et al. showed that the

**Table 2.** Risk of bias of the non-randomized studies according to the Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) tool.

Author Profile, year (Ref)	1 <sup>st</sup> Domain	2 <sup>nd</sup> Domain	3 <sup>rd</sup> Domain	4 <sup>th</sup> Domain	5 <sup>th</sup> Domain	6 <sup>th</sup> Domain	7 <sup>th</sup> Domain	Overall Domain
Mashayekhi M et al. (2021)(Mashayekhi et al., 2021)	+	+	+	+	+	+	+	Low risk of bias
Shree et al. (2019)(Shree et al., 2019)	+	+	+	+	+	+	+	Low risk of bias
Protogerou, et al.(2019)(Protogerou et al., 2019)	+	+	+	+	+	+	+	Low risk of bias

N/A. not applicable; 1st Domain: confounding; 2nd Domain: selection of participants; 3rd Domain: classification of intervention; 4th Domain: deviation from interventions; 5th Domain: missing outcome data; 6th Domain: measurement of outcomes; 7th Domain: selection of reported result; Overall. Risk of bias assessment: 0—No information; 1—Low; 2—Moderate; 3—Serious; 4—Critical.

effectiveness of MSCs in the stroke treatment was dose-dependent. Therefore, identifying/determining the optimal dose for the use of MSCs as stroke therapy is a difficult factor (Vu et al., 2014) In the safety aspect, adipose-derived stem cell therapy performed on ischemic stroke patients did not cause harmful side effects (de Celis-Ruiz et al., 2022).

A study on adipose-derived stem cell therapy in patients with ovarian failure aimed to determine the therapy safety and recovery of

menstruation, hormone levels (FSH), and anti-Müllerian hormone. There were no side effects or secondary complications found in this study. The resumption of menstruation was observed in the three groups of subjects at different doses. Additionally, there was a decrease in FSH levels, however, this finding was inconsistent (Mashayekhi et al., 2021). The mechanism of how adipose-derived stem cells affect follicular regeneration is still unclear, but another study found the occurrence of neo-oogenesis. The predominant risk factor, such as autoimmune diseases and genetic diseases, can play a role in ovarian failure and eventually lead to infertility. Various features of FOP have increased gonadotropin levels, decreased estrogen, and amenorrhea (Sheikhansari et al., 2018).

A significant success in the therapy of adipose-derived stem cells was achieved in the phase II study on diabetic ulcer patients. Those studies indicated that heterologous adipose stem cell panels might be effective and safe for the treatment of non-infectious non-ischemic diabetic foot ulcers (Moon et al., 2019) MSCs can localize specifically to the the targeted area by detecting the expression of human leukocyte antigen type I (HLA-1), a marker for assessing MSCs in vivo (Cao et al., 2017).

In terms of the effectiveness of the therapy, inconsistent results were found among studies. The low number of research subjects, treated diseases, and study design contribute to these

inconsistencies. These inconsistencies might be due to the adipose-derived stem cells, which were obtained from different anatomical areas that might show various characteristics, such as adipose-derived stem cells that were acquired from the superficial abdominal region would undergo more significant apoptosis than those from the upper arm, medial thigh, and trochanteric areas (Bunnell et al., 2008; Jeffrey M. Gimble et al., 2017). Adipose-derived stem cells that are isolated from various locations, in addition to cell types and species, as well as various harvesting procedures affect the quality, functionality, and plasticity of the stem cells.

Overall, the results of the reviewed studies claimed that adipose-derived stem cell therapy in humans was considered safe without significant side effects (Fraser et al., 2008). Furthermore, all studies about adipose-derived stem cell therapy showed an improvement in the patient's condition as expected. The abundance of adipose stem cells, their convenience in cell retrieval, their ability to differentiate into multiple lineages and release various cytokines, and their immunomodulatory effects suggest that adipose stem cells may have a significant role in regeneration (Ceccarelli et al., 2020; Zhang et al., 2020). Therefore, further studies in humans to develop a standardized method for cell isolation, culture conditions, proliferation, identification and characterization methodologies, as well as safety and efficacy guarantees are needed.

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