

Adipose-Derived Stem Cell Therapy for Streptozotocin Induced Diabetic Nephropathy in Adult Male Albino Rat

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ABSTRACT

Diabetes mellitus (DM) is a rapidly spreading epidemic that has a significant negative influence on both health care expenses and patient quality of life (Garg and Duggal 2022). Globally, diabetes affects about 463 million people. Recent estimates indicate that 382 million individuals have been diagnosed with the disease, and by 2030, that figure is predicted to rise to 592 million (Halsey 2023). Diabetic nephropathy (DN) is considered one of the most serious microvascular complications, which resulted from chronic elevated blood sugar levels and DN can eventually cause severe renal impairment that can reach to renal failure (Samsu 2021). "Diabetic nephropathy" (DN) refers to a well-defined kidney disease, directly associated with a long duration of diabetes and often confirmed by histological lesions (Syed, Moni et al. 2025). DN is a heterogeneous disease characterized by the presence of albuminuria and/or reduction of eGFR in people with diabetes (An, Wu et al. 2022).

Current treatments are known to have serious adverse effects. Due to the high rates of side effects and the overall ineffectiveness of existing medicines, new treatment approaches must be investigated. Stem cell therapy has become a promising area of treatment due to its high rate of proliferation, minimally invasive process, and lack of ethical concerns.

Keywords: diabetic nephropathy, streptozotocin, stem cells.

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Introduction

Diabetes is a highly prevalent chronic

metabolic disease, affecting more than 400 million individuals worldwide

(Lotfy, Adeghate, Kalasz, Singh, & Adeghate, 2017). It's a group of metabolic diseases (Hædersdal, Andersen, Knop, & Vilsbøll, 2023) which are caused by the development of hyperglycemia which resulted from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels (Madan et al., 2023). Diabetic kidney disease (DKD) is a serious microvascular complication that affects nearly 40% of individuals with diabetes (Naaman & Bakris, 2023). Presently, it's the leading cause of end-stage kidney disease (ESKD) worldwide (Priyadarshani, de Namor, & Silva, 2023). The classical presentation of nephritis is characterized by hyper filtration and albuminuria in the early phases which is then followed by a progressive renal function decline (Helal, Fick-Brosnahan, Reed-Gitomer, & Schrier, 2012). Stromal Vascular Fraction (SVF) is a heterogeneous collection of cells contained within adipose tissue that is traditionally isolated using enzymes such as collagenase (Nguyen et al., 2016). With the removal of adipose cells, connective tissue and blood from lipoaspirate, comes the SVF, a mix including mesenchymal stem cells, endothelial precursor cells, T regulatory cells, macrophages, smooth muscle cells, pericytes, and pre adipocytes (Naaman & Bakris, 2023).

Mesenchymal stem cells can be isolated from various sites, including bone marrow,

adipose tissue, and cord blood (Jin et al., 2013). Bone marrow derived mesenchymal cells (BMSCs) can facilitate tissue repair by producing growth factors, cytokines, and extracellular matrix (Bunnell, 2021) and promoting the migration of other cells (Yamakita et al., 2011). Adipose Mesenchymal-derived stem cells (AMSCs) are multipotent cells in adipose tissue with characteristic similar to those of BMSCs (Bajek et al., 2016). However, AMSCs are easy to harvest and there is minimal donor morbidity (Oedayrajsingh-Varma et al., 2006).

Hyperglycemia is known to be responsible for generation of advanced glycation end-products (AGEs), which can disturb the function and structure of the kidneys and initiate histological and morphological changes typical of DN (Wu, Ding et al. 2023) which leading to damage of the matrix, glomerular basement membrane, and other components in the glomerulus. Hyperglycemia also activates protein kinase C (PKC) pathway with production of endothelin-1 and vascular endothelial growth factor, determining glomerular damage and the direct oxidization of pivotal structures such as DNA, carbohydrates, lipids, and proteins. ROS can induce increased PKC activation, transforming growth factor - β (TGF- β) expression and angiotensin-II (Ang-II) levels (Jubaidi, Zainalabidin et al. 2022), promoting fibrotic processes in the interstitium of renal tubules and remodeling of the extracellular matrix in the mesangium . Moreover, Ang-II determines several effects on the kidneys, mediated by local and systemic activation of the Rennin Angiotensin Aldosterone System

(RAAS). Hyperactivation of Ang-II causes proteinuria, increases glomerular capillary pressure and permeability, and stimulates inflammation and macrophage infiltration, leading to the production of inflammatory and profibrotic cytokines and extracellular matrix (ECM) remodeling (Maranduca, Clim et al. 2023). Moreover, it promotes renal cell proliferation and hypertrophy. In the progression of renal disease, RAAS plays a main role. The RAAS can be distinguished into a systemic and intra-renal role RAAS and both of them are involved in the pathogenesis of DN lesions (Karimi, Maleki et al. 2024). Systemic RAAS is a group of molecules that starts from the secretion of renin from the juxtaglomerular cells in the kidney which cleaves angiotensinogen (AGN) producing angiotensin I (AGTI) which then converted into angiotensin II (AGTII) via the angiotensin converting enzyme (ACE). AGTII is the main effector of the RAAS and acts through angiotensin receptors AT1 and AT2 (Martyniak and Tomasik 2022). The paracrine role of AGTII has been proved with the discovery of high concentration of intratubular and interstitial AGTI and AGTII. It has recently been demonstrated that renin may act independently of the generation of AGTII, confirming the existence of an intrarenal RAAS. Several studies have also demonstrated a reduction in circulating AGTII levels in diabetic patients, suggesting that the effect of AGTII on the progression of kidney disease is mediated by paracrine mechanisms in the kidney. AT1 receptor is widely expressed across the kidney tubules, glomerular wall, and arterial vasculature. These receptors

have a well-known vasoconstrictive effect on systemic circulation and stimulate the secretion of aldosterone (Nagarajan 2023). Mesenchymal stem cells can be isolated from various sites, including bone marrow, adipose tissue, and cord blood (Jin et al., 2013). Bone marrow derived mesenchymal cells (BMSCs) can facilitate tissue repair by producing growth factors, cytokines, and extracellular matrix (Bunnell, 2021) and promoting the migration of other cells (Yamakita et al., 2011). Adipose Mesenchymal-derived stem cells (AMSCs) are multipotent cells in adipose tissue with characteristic similar to those of BMSCs (Bajek et al., 2016). However, AMSCs are easy to harvest and there is minimal donor morbidity (Oedayrajsingh-Varma et al., 2006).

Stem cell treatment is one promising field of medicine. Due to their fast rate of multiplication, absence of ethical difficulties, and less invasive method, mesenchymal stem cells (MSCs) have garnered interest (Golchin et al., 2020).

stem cells:

In addition to differentiating into other cell types, stem cells may self-renew and generate an infinite number of identical daughter cells (Shah and Khan, 2021).

Stem cells are a kind of immature cell that may be sourced from many tissues; they possess the ability to proliferate and regenerate over an extended period of time (Tkemaladze, 2023). These stem cells have the remarkable ability to develop into any kind of cell in the body, depending on their origin (Poliwoda et al., 2022).

Properties of stem cells

1. the ability to renew one's own cells—that is, to divide many times while maintaining their undifferentiated state (Chhabra and Booth, 2021).

2. Poliwoda et al. (2022) defined "potency" as "the capacity of a cell to differentiate into other cell types." Stem cells are classified into the following categories based on their potency:

a) Trans differentiation is possible between embryonic and extraembryonic cell types in totipotent stem cells. These cells are created when an egg and sperm fuse. The cells that are created during the first rounds of cell division in a fertilized egg are also considered totipotent (Cai et al., 2022).

b) Almost every kind of cell may be differentiated from pluripotent stem cells (Gordeev et al., 2021).

c) According to Rosner et al. (2023), multipotent stem cells have the ability to develop into many cell types that belong to a closely related family.

d) Myeloid and lymphoid stem cells are two of the few cell types that oligopotential stem cells may develop into (Poliwoda et al., 2022).

e) The number of cell types that can be differentiated from unipotent stem cells is one. What sets stem cells apart from other types of cells is their ability to replenish themselves (Laplane and medicine, 2022).

Types of stem cells

1-Embryonic stem cells

The inner cell mass of a blastocyst, an early stage preimplantation embryo, is the source of human embryonic stem cells, which are pluripotent (Park et al., 2024). In the first week after fertilization, embryonic cells are

extracted from the egg cells. All cell types may be differentiated from them (Moris, 2023). Nevertheless, an immunological response might develop as a side effect of embryonic stem cell treatment. Furthermore, their origins in developing embryos make their usage contentious (Habib et al., 2022)

2- Induced pluripotent stem cells (IPSCs)

An artificial method of producing IPSCs involves reprogramming adult somatic cells via the forced expression of certain genes (Kim et al., 2022). Mesodermal, endodermal, and ectodermal cells are all within their range of possible differentiation. Patients' own somatic cells may be used to create IPSCs, which eliminates immunogenic rejection and ethical concerns (Cerneckis et al., 2024).

3- Umbilical cord blood stem cells

One potential place to find mesenchymal stem cells is in the human umbilical cord. Human umbilical cord mesenchymal stem cells have quicker self-renewal capabilities and are collected painlessly, in contrast to bone marrow stem cells (Shi et al., 2022).

4- Adult stem cells (Somatic stem cells)

Adult stem cells are ubiquitous, unspecialized cells that may divide endlessly to repair injured tissues (Mannino et al., 2022). According to de Morree and Rando (2023), these cells have the remarkable ability to proliferate and produce every kind of cell in the organ from where they originated.

There are no moral issues with using them in research. Most research on them has been conducted on rats and mice, which are used as models for people (Gopalarethinam et al., 2023). Adult stem cells come in a wide variety, including:

a) Neural stem cells

They self-renew and are found in the central nervous system. Both in vivo and in vitro proliferation is within their capabilities. Human neural stem cells that have been transplanted travel to different parts of the brain and develop into neurons (Willis et al., 2022).

b)

mammary stem cells

According to Liu et al. (2022), stem cells found in the breast can self-renew in both living organisms and laboratory settings. In addition to producing new luminal and myoepithelial cells, they can also restore the mammary gland (Martignani et al., 2020).

c)

haematopoietic stem cells

Bone marrow and blood from the umbilical cord both include haematopoietic stem cells, which have the ability to develop into any kind of blood cell (Yamashita et al., 2020).

d)

mesenchymal stem cells (MSCs)

Isolating mesenchymal stem cells (MSCs) from many tissues such as the umbilical cord, adipose tissue, olfactory mucosa, lungs, bone marrow, and placenta is possible (Kouchakian et al., 2021).

Subcutaneous adipose tissue is a rich source of MSC, and it is readily accessible by liposuction and other minimally invasive surgical procedures. Because of their minimal donor site morbidity and ease of accessibility, ASCs are great choices for many cell-based therapies (Li et al., 2023).

Medical professionals are showing a growing interest in these cells because of their potential for in-situ or intravenous

transplantation, immunosuppressive effects that lessen graft failure, and capacity to differentiate into targeted cells in response to local conditions and culture conditions (Yang et al., 2020b; Miccelli et al., 2021).

Relevant sections

Morphology of mesenchymal stem cells

Mesenchymal stem cells are characterized by a tiny cell body and many long, thin processes. There is a huge, spherical nucleus in the middle of the cell body, and its nucleolus is quite visible. The nucleus seems transparent because it is encased in finely scattered chromatin particles. Golgi apparatus, rough endoplasmic reticulum, polyribosomes, and mitochondria are also present in modest quantities inside the cell body (Yim and Leong, 2017).

Application of stem cell therapy in management of diseases

1-

stem Cells for Diabetes:

When the pancreas stops making enough insulin, the result is diabetes, which is characterized by an imbalance in blood insulin levels. There have been several attempts to find a way to stop needing insulin shots by transplanting either the pancreas or the islet of Langerhans. Following implantation, the recipient often rejects the pancreas and islet cells (Shapiro et al., 2017).

Because stem cells do not cause rejection, they are a viable option (Hogrebe et al., 2023).

2-

stem cells for renal diseases:

One treatment option for chronic renal failure is stem cell therapy, which has the

potential to aid in cellular repair and remodeling of the kidneys (Almeida et al., 2022). Administered stem cells have the potential to enter the bloodstream and go to injured areas inside the kidneys when the patient is in acute renal failure. Therefore, they are able to respond to various local stimuli, such as hypoxia or ischemia, and subsequently secrete chemokines, growth factors, immunomodulatory cytokines, and vasoactive factors. Therefore, MSCs and other stem cells may aid in the full recovery of patients with acute renal failure. This information is sourced from Kanduri et al. (2021).

3-

tem cells for cardiovascular diseases:

Heart conditions, both old and new, may be safely and effectively treated with adult stem cell treatment. Potential pathways for stem cell-mediated cardiac disease recovery include myocardial cell regeneration, increased angiogenesis, and growth factor release (Chang et al., 2021).

4-

tem cells for liver diseases:

Cirrhosis of the liver due to alcoholic liver disease, hepatitis C and B, and end-stage liver disease have all been treated using stem cells (Zhang et al., 2020). Stem cell infusion was administered to patients with decompensated cirrhosis via a peripheral vein. According to Zheng et al. (2023), there are no reported negative effects in patients throughout the follow-up period.

5-

tem Cells for Treatment of Wounds:

Scar tissue often replaces the disordered collagen structure, hair follicle loss, and

abnormal vascular structure that develops in injured tissue. According to Riha et al. (2021), stem cells play a crucial role in facilitating the regeneration of injured tissues.

6-

tem cells for renal diseases:

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7- Stem cells for inflammatory bowel diseases

Animal and human studies have shown that MSC have more therapeutic promise than conventional drugs for treating UC in mouse models and in people (Jiang et al., 2024).

Due to their ability to decrease inflammation in the intestines, stimulate long-term repair of the intestinal mucosa, and substantially enhance patient quality of life, stem cells have emerged as a promising alternative therapy for inflammatory bowel diseases (Wang et al., 2021).

Discussion:

According to studies on stem cells, mesenchymal stem cells (MSCs) have the

ability to divide themselves and replenish themselves. They can house the injured area, reduce inflammation by secreting cytokines, promote healing by expressing growth factors, and release anti-apoptotic substances; these characteristics give them therapeutic effects in various inflammatory diseases, including ulcerative colitis.

Conclusion

Results from this meta-analysis support the use of stem cells in the treatment of diabetic nephropathy.

Future directions

Overall, it seems that the research approach was solid and appropriate. Stem cell therapy for ulcerative colitis was defined in a clear and concise review. The study's findings provide a streamlined and current synopsis of stem cell treatment for diabetic nephropathy.

Research should focus on enhancing stem cell effectiveness and delivery, developing new cell types and engineering strategies, and standardizing protocols for personalized treatment.

List of Abbreviations

DN: ulcerative colitis.

MSCs: Mesenchymal stem cells.

IPSCs: Induced pluripotent stem cells.

Conflict of interest

The writers have stated that they have no competing interests. The final version of the manuscript was reviewed and approved by all authors.

Authors Contribution

In this study, each author had an equal say.

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