



The Review of Stem Cell Therapy in Nigeria: The Way Forward

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Authors' contributions

All author contributed substantially to the manuscript and approved the final submission.

Article Information

DOI: 10.9734/JOCAMR/2021/v14i330245

Editor(s):

(1) Dr. Sahdeo Prasad, Texas Tech University Health Sciences Center, USA.

Reviewers:

(1) Mahmood S. Choudhery, King Edward Medical University, Pakistan.

(2) Dario Siniscalco, University of Campania, Italy.

(3) Reinhold Medina, Queen's University Belfast, United Kingdom.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/68516>

Review Article

Received 02 April 2021

Accepted 07 June 2021

Published 12 June 2021

ABSTRACT

Stem cells are unspecialized biological cells associated with self-renewal and proliferation abilities. Stem cell therapy involves the use of stem cells to deliver safe, effective, viable and consistent therapeutic interventions for debilitating health conditions. Many global researchers are striving to overcome the challenges associated with this therapy and Nigerians are not exempted from this struggle. As the country's health sector have suffered rigorous torments because of poor medical care and mismanagement of health facilities. However, it is expected that Nigeria should at least harbour one of the largest stem cell centres in Africa, to help cater for its citizens as well as non-citizens. Notwithstanding the ethical, financial, social, political, and religious challenges facing stem cell therapy in Nigeria, there is still hope for the nation's health sector to strive past these hurdles in the coming years but only if priority is placed on the well-being of citizens rather than in the search for profit. Future stem cell research in Nigeria should include the treatment of communicable and non-communicable diseases and will be of great importance if the government could harness stem cell therapy as a tool to boost its economy. Hence, this review paper focuses mainly on the present status of stem cell therapy in Nigeria and the way forward.

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Keywords: Stem cells; stem cell therapy; challenges; ethics; way forward.

1. INTRODUCTION

Over the years, the expansive research on stem cell therapy has revealed amazing treatment options for regenerative diseases, injuries, and other malfunctions of the body systems. The recent advances in medical and biological technologies paved way for the increasing success of stem cell therapy. The peculiar attributes of stem cells to self-proliferation, migration and differentiation into specialized cell aroused great curiosity amongst bioengineers, medical practitioners, and the general public for therapeutic purpose [1,2].

Stem cells are regenerative, or repair networks found mostly in multicellular organisms such as human beings. They are simply defined as unspecialized biological cells which have the unique feature of unlimited or prolonged self-renewal and differentiation into any cell of an organism [3]. The attribute of "stemness" in stem cells is greatly influenced by its niche or microenvironment which constitutes the signalling molecules, interaction between neighbouring extracellular matrix and intercellular communication [4]. Stem cells are classified based on their potency into totipotent, multipotent, unipotent and oligopotent stem cells [5].

Unlike the previous classification of stem cells based on potency, two main types of stem cells exist in mammals: Embryonic stem cells (ESCs) and Adult or Somatic stem cells (ASCs) [6]. Embryonic stem cells (ESCs) are pluripotent cells got from the inner cell mass of the blastocyst formed during successive mitotic divisions of the zygote, a totipotent cell that results from the fertilization of an oocyte by a spermatozoon. Examples of matured cell types that originate from ESCs include adipocytes, muscle cells, chondrocytes, hepatocytes, enterocytes and neurons.

Embryonic stem cells are immortal in culture and survive a long period of time though, genetic abnormalities such as karyotype abnormalities may arise during in vitro expansion of stem cells in culture, cell reprogramming and genome editing [7]. The ability to harness ESCs in vitro to generate specialized cells used for therapy is as a result of their pluripotency and unlimited expansive nature. The spontaneous differentiation trend of embryonic stem cells if not

controlled or checked as a safety criterion may give rise to undesirable teratoma formation during therapy. Therefore, to control differentiation process in ESCs, growth factors are introduced, or undifferentiated cells are separated from culture as only the desirable differentiated cell types are administered to patients [8]. Stem cells from amniotic fluid, cord blood, neonatal tissues and adult tissues are termed adult stem cells and could be unipotent, multipotent and oligo potent [9].

As a result of the uniqueness of pluripotent stem cells and their potentials as therapeutic tool for treatment of diseases, and with the ethical challenges of the embryonic stem cell and its immune incompatibility, the Induced pluripotent stem cells (iPSC) were engineered. Pluripotency of a cell is dependent on a complex system of signalling molecules and gene network specific for pluripotent cells. *Oct4*, *Sox2*, and *Nanog* genes are required to maintain pluripotency of the iPSCs. Induced pluripotent stem cells are obtained by reprogramming differentiated cells through the introduction of genes that maintains its pluripotency [10].

Stem cell therapy is the use of stem cells to treat or prevent a disease or condition and for interventions for debilitating health conditions such as Parkinson's disease, Alzheimer's disease, neurological disorders, congenital anomalies, cancers, diabetes, cardiovascular diseases, vision impairment, sexual dysfunction, multiple sclerosis, macular degeneration, burns, lost or damaged cells, tissues, and organs [4].

Stem cell therapy procedures are in four stages [6]. The processes include: extraction of cells from adipose tissues, bone marrow or umbilical cord through liposuction; concentration of harvested adult stem cells by centrifugation; activation of stem cells with a small dose of platelet rich plasma, which allows stem cells to grow in the new environment without any form of alterations in their biological structure; and then transplantation of activated stem cells into affected areas in patients using techniques such as X-rays and ultrasounds for maximum precision [11]. Stem cell therapy being naturally regenerative [12] with no surgical complications, is quicker, safer and requires lesser recovery time (about few weeks interval) unlike the conventional invasive approaches such as surgery.

Progressively, Nigeria in line with several other African countries have stem cell research centres but are lagging in clinical trials related to stem cell therapy. Therefore, this article is an attempt to elucidate the status of stem cell therapy in Nigeria and the way forward.

2. STEM CELL APPLICATION FOR TREATMENT OF SOME DISEASES

Haematopoietic stem cell transplantation (HSCT) is said to be the only established curative treatment for sickle cell anaemia currently accepted [13]. Clinical trials are still ongoing on the use of Mesenchymal stem cells for the treatment of liver and inflammatory bowel diseases. The MSc can be gotten from medical waste, can be easily expanded, show low immunogenicity and possess multiple functions which suggests their application for the treatment of different diseases [14].

Stem cell therapy is an alternative solution in situations where organ and tissue transplant become challenging as stem cells can be induced to become the specific cell needed for the repair of destroyed or damaged tissue. Diseases conditions such as osteoarthritis, diabetes, macular degenerations, strokes and neurodegenerative diseases can benefit from stem cell therapy. The possibility of generating heart muscle cells which will be transplanted to patients with heart diseases increases using stem cell technique [15]. There has been a successful delivery of healthy and fertile pups for the treatment of infertility in mice whereby sperm and functional egg was formed from iPSCs [15].

Stem cell therapy has been used for the treatment of Epidermolysis bullosa which is a disease condition that arises as a mutation in genes encoding collagens and laminins. Using genetically engineering autologous tissue-specific stem cells obtained from a biopsy specimen from unaffected skin that expresses the normal laminin protein has been used to generate 80% of the skin [16].

Basically, the identification of the molecular activities and debates that involves stem cells has propelled the foremost scientific research focus on stem cell application for treatment of diseases. Moreover, stem cell therapy has been evaluated in various neurodegenerative diseases, cancer, autoimmune, respiratory and blood diseases which includes but not limited to the following.

3. ALZHEIMER'S DISEASE (AD)

Alzheimer's disease (AD) also referred to as senile dementia is an irreversible, progressive neurodegenerative disease that destroys memory and other important mental functions [17]. Memory loss and confusion are the main symptoms for AD while the cause of the disease is still unknown though it is assumed to be a combination of genetic, lifestyle and environmental factors. It accounts for between 60% to 80% of dementia cases worldwide [18]. By the year 2018, 15,183 deaths were recorded [19] while 318,000 prevalence was recorded in 2015 [20]. Stem cell therapy promises to be a unique approach to treating Alzheimer's disease. For instance, there was significant progress in behavioural disorder and memory with no sign of tumour as neural precursor cells derived from embryonic stem cells were injected in mice [18]. In 2010, it was reported that apoptosis, markers of glial activity and oxidative stress were reduced in mouse brain as mesenchymal stem cells derived from human umbilical cord were injected into Alzheimer's mice. Likewise, cognitive abilities and learning memory in mice were returned [21].

4. LEUKEMIA

Leukaemia also known as blood cancer is a cancer of blood-forming tissues, hindering the body's ability to fight infection. Types include chronic lymphocytic leukaemia, acute lymphoblastic leukaemia and acute myeloid leukaemia. Leukaemia and lymphoma, both mostly resulting from the uncontrolled proliferation of white blood cells, were the first to be clinically treated using hematopoietic stem cells [22]. In the year 2020, 3378 new cases were reported with 7023 five years prevalence in Nigeria [23].

Treatment: radiotherapy or chemotherapy are employed to destroy the cancerous hematopoietic cells that were further replaced by the transplantation of either bone marrow or hematopoietic stem cells collected from the peripheral circulation of a matched donor, such as a patient's sibling, with similar human leukocyte antigens on the surface of their cells [22]. Allogeneic RIST (Reduced-intensity stem-cell transplantation) has been introduced as an important procedure to achieve complete remission in patients with leukaemia, especially if a human leukocyte antigen-compatible donor is used [24]. Any transplantation that uses a

conditioning regimen less than myeloablative is called reduced intensity stem cell transplantation (RIST). RIST (Reduced-intensity stem-cell transplantation) seems to be promising for a variety of hematologic diseases especially if disease activity is controlled prior to transplant [25]. Nevertheless, most physicians believe that RIST is not sufficient enough in regulating advanced hematologic malignancies and that intensification of preparative regimens is essential so as to improve their prediction. Small pilot studies revealed that RIST had been unsuccessful for advanced hematologic malignancies [26,27].

5. PARKINSON'S DISEASE (PD)

Parkinson's disease (PD) is a disorder of the central nervous system that affects movement often including tremors. [28]. Currently, there is no cure for Parkinson's disease but treatment purposes to improve symptoms [29]. One thousand four hundred and eight-five (1485) deaths were recorded in Nigeria in the year 2018 [30] with a prevalence of 67/100,000 as of May 2016 [31]. Typically, the original treatment is with the medication levodopa (L-DOPA) followed by dopamine receptor agonists whenever L-DOPA becomes less effective [32]. Although the pharmacological treatment is effective for some symptoms, there seems to be restrictions based on its decreased efficiency over time and side effects sets in [33]. In 2008, it was reported that the transplantation of foetal neural stem cells to mouse model of Parkinson's disease led to significant cellular and functional improvement with no record of any tumour type [34]. Use of mature multipotent stem cells in mouse model of Parkinson's improved apomorphine-induced rotational behaviour thereby regulating step and paw reaching test [35].

6. SPINAL CORD INJURY (SCI)

Spinal cord injury is a damage to any part of the spinal cord or nerves at the end of the spinal canal. It may happen due to a sudden blow or cut to the spine. Nigeria reports fewer than 100,000 cases per year. Restoration maybe achieved through replacement of stem or progenitor cells [36]. Preclinical studies performed on rats with a spinal cord injury revealed that transplanted mesenchymal stem cells in the injured spinal cord survived, migrated into the host tissue and led to axonal regeneration and motor function recovery [37].

7. DIABETES

Diabetes which is also called *Diabetes mellitus* is a group of diseases that result in too much sugar in the blood (high blood glucose), a metabolic disorder of chronic hyperglycemia characterized by disturbances to proteins, carbohydrates and fat metabolism as a result of relative or absolute insulin deficiency with dysfunction in organ systems [38]. Current prevalence in Nigeria among adults aged 20 – 69 years is reported to be 1.7% [39]. The International Diabetes Federation reported 2.7 million cases in Nigeria as of 2019 [40]. However, stem cell therapy has been used for its treatment where it was reported that several laboratory and clinical studies revealed mesenchymal cells to possess immunomodulation ability through regulation of the activity of B-lymphocytes, T-lymphocytes, Natural Killer cells and cytokines [41]. It was observed that these cells could potentially differentiate to insulin producing cells in special cultures [41].

However, among the above listed diseases, stem cell therapy against Alzheimer's disease, Parkinson's disease, Spinal cord injury and Diabetes are under investigation except leukemia which has been clinically proven and accepted.

Other common debilitating diseases in Nigeria that have been reportedly improved via stem cell therapy in animal models include: Stroke [42,43], Inflammatory bowel disease (IBD) [44,45], Chronic Kidney Disease (CKD) [46] and Breast cancer (BC) [47].

8. ETHICS AND CHALLENGES OF STEM CELL

An embryo is the rudimentary stage of development after fertilization of many celled organisms that has the potential of becoming an adult organism [49]. Embryos were believed to have the potential of becoming human beings if implanted into a woman's uterus at conducive conditions and at appropriate hormonal phase. These embryos could divide, develop into a foetus, and become a live-born child. Thus, Stem-cell research has generated a lot of ethical and political controversies over the years bringing into focus two ethical viewpoints or positions. One argues from a normative ethical position which agrees that the embryo as a human being, possesses rights that are inviolable and since stem-cell research involves the destruction of embryos, the process is

Table 1. Prevalence rate of some diseases in Nigeria

Diseases	Prevalence rate for the past 5 years	References
ALZHEIMER'S DISEASE (AD)	318,000	[20]
LEUKEMIA	7023	[23]
DIABETES	2.7 million	[40]
Hypertension	20.8 million	[48]
Breast Cancer	60296	[23]

unethical [50]. From this perspective, taking a blastocyst and removing the inner cell mass to derive an embryonic stem cell line is tantamount to murder [51].

The other viewpoint argues that it would be unethical not to pursue it given that this research may lead to cures for some serious diseases and alleviate suffering [52]. This was supported with an analogy, that every oak tree was an acorn, and it is completely senseless to conclude that every acorn is an oak tree. Therefore, the loss of an acorn cannot be assumed to be the loss of an oak tree [53]. Thus, the mere fact that embryos can have the potential to become a developed human being does not make them one by default. Again, embryo becomes a person only at the later stages of development rather than after fertilization [53]. Some opine that the embryo or blastocyst is just a clump of cells that can be used for research without restriction [51].

8.1 Immunological Rejection

This has over the years posed a serious challenge to successful stem cell transplants. Most times, a patient's immune system recognizes the transplanted stem cells as 'foreign' and attacks them. In this case, immunosuppressive drugs are given to recipients of the transplant to reduce the chances of rejection; this leaves the patient vulnerable to infection by any other viruses or microbes in the environment [54].

8.2 Ability to Introduce Tumor or Cancerous Cells

Stem cells transplant can introduce tumour and cancerous cells [55]. Cancer and tumor are consequences that occur when cells divide abnormally. The challenge for scientists is to find a balance between directing cell growth into specialized tissues that can replace damaged ones and ensuring that cells do not excessively grow and become cancer cells [55].

8.3 Identification of Stem Cells in Adult Tissues

Another major challenge that continues to overwhelm scientists and researchers is the identification of stem cells in adult tissues [55]. Adult tissues contain different types of cells, and this makes it difficult to locate stem cells in tissues that could contain thousands of different cells. The research involved is complex and even after cells are isolated, the process to successfully trigger differentiation into the desired cell type is another challenge for researchers. This requires an understanding of stem cell control and regulation that has yet to be fully gained [55].

9. STEM CELL IN NIGERIA

Undoubtedly, Nigerians have suffered rigorous torments in the health sector over the years due to poor medical care and mismanagement of health facilities by authorities. This instigated the absence of stem cell therapy in the country few years back, even when other nations of the world were trending in this technology. However, a remarkable breakthrough was recorded in 2011 when the first stem cell transplant on a 7-year-old sickle cell anaemia patient proved successful at University of Benin Teaching Hospital (UBTH) [56]. Six successful stem cell transplantation for sickle cell disease was reported and by July 2019 the first stem cell transplant on a 62-year-old patient with multiple myeloma was performed using Spectra Optia Apheresis system [57]. These heart-warming achievements heightened the interest of the Nigerian Government in the construction of several stem cell transplantation centres across the country. The establishment of Bone Marrow Registry, Nigeria (BMRN) in 2012 was a giant stride approach led by a leukaemia survivor, Seun Adebisi and his team with the aim of increasing global recovery statistics of Africans with blood disorders [58]. To expand the horizon of genetically diverse stem cell donors from Nigeria, BMRN plans to start the first umbilical cord blood bank in Africa thereby supporting

Haematopoietic Stem Cell Transplantation (HSCT) [58].

10. CHALLENGES OF STEM CELL THERAPY IN NIGERIA

In addition to global challenges to Stem cell therapy, Nigeria faces some peculiar challenges as follows:

10.1 Awareness

In a study done on the awareness of BMT for the treatment of sickle cell anaemia in tertiary health centres across some states in Nigeria, 64.5% of the respondent were aware that BMT can be used this however is low when compared to reports gotten from developed countries [59]. Due to low awareness, getting donors is a great challenge.

10.2 Beliefs

Religious and traditional beliefs are great hindrance for stem cell application in Nigeria. The human body is associated with some level of sacredness. This affects the advancement of therapeutic research that involves the human parts, for instance, the umbilical cord is seen as disposable biological by-product. However, these cords could be harvested during delivery and kept in the cord blood bank for research and treatment purposes [60].

10.3 Inconsistent Power Supply

One of the major challenges facing companies, organizations and the health sector in Nigeria is the unreliable and erratic power supply. Stem cell research and banking requires constant electricity supply to maintain and preserve cells in the bank. For effective utilization of a SCT machines, there must be an uninterrupted power supply to ensure apheresis and cryopreservation activities. In a situation where there is no constant power supply it is impossible to store stem cells in the bank. As a result of the fluctuations of electricity, electrical devices that are used are being damaged. Private organizations could decide to use either gas or fuel to power their electricity generating sets, thus incurring more expenses [61].

10.4 Shortage of Trained Medical Personnel and Poor Funding

SCT is a novel therapy which up till now, is not readily available in Nigeria with very limited

trained personnel. In Nigeria, the number of medical personnel such as the Medical Laboratory scientists, doctors, nurses, and other medical related professionals trained in stem cells technology are insignificant when compared to the country's population. Also, the statistics of health care growth in Nigeria is poor despite various commitment being made to fund the health sector. The advancement of Medical research in Nigeria is slow due to poor funding in this area. This inadequate trained professional could be as a result of no funding for the training as they are unable to fund their training in this area of medicine [62].

10.5 Inadequate Facilities and Building

The purchasing and maintenance of facilities needed for stem cell technology are expensive and are affected by poor funding. In most hospitals and laboratories in Nigeria, poor maintenance culture affects the machines used. Stem cell research centres in Nigeria are in Lagos and Abuja [63]. The insufficient number of stem cell centres make assessment of stem cells almost impossible as individuals will have to spend extra cost transporting to any of these two states.

Aside purchasing standard equipment, it is important to have backups for the equipment needed for SCT. It is also important to ensure that the diagnostic unit of the centre is standard particularly the Laboratory and Radio imaging technique.

10.6 Cost of Stem Cell Therapy

Accessibility is a major challenge for stem cell transplant in Nigeria, which is a result of lack of insurance coverage from government or private funds [64]. In 2011, commendable efforts were made in pioneering Bone Marrow Transplant (BMT) at the University of Benin Teaching Hospital (UBTH), Nigeria. However, this procedure could not be sustained at the UBTH because of lack of political will power from the Nigerian government. Presently, the cost of BMT which is done in only one private Hospital in Nigeria is approximately Ten million naira (10 million naira which is about 26000 USD) [61]. Drugs for SCT are very expensive to acquire in developing countries like Nigeria and the process of importing drugs from abroad has proven difficult throughout the years.

11. PROSPECTS AND WAY FORWARD

Notwithstanding the ethical, financial, social, political, and religious challenges facing stem cell therapy in Nigeria, there is still hope for the nation's health sector to strive past these hurdles in the coming years but only if priority is placed on the well-being of citizens rather than in the search for profit. Future stem cell research in Nigeria should include the treatment of communicable and non-communicable diseases and it will be of great importance if the Nigerian Government could harness stem cell research as a tool to boost its economy. More stem cell research centres should be set up across the country and expertise brought in from developed countries, with the target of harbouring one of the largest stem cell centres that can cater for both Nigerian citizens and non-citizens.

As most Africans are known for having lots of children especially in Nigeria where it is fashionable and symbolises ones status. In the Eastern part of Nigeria, most families have up to 8-10 children [65]. About 5 million children are born yearly in Nigeria [62] It is important to invest in cord blood banking as the stem cells isolated from them can serve as immune modulatory cells in allogeneic transplantation, used for bone regeneration and posses hematopoietic abilities. A Donor registry and Cord blood banking will open a revenue for improving the Nigerian economy.

Awareness will help in eradicating the hitch that traditional beliefs are imposing on stem cell technology in Nigeria. This can be achieved by enlightening everyone especially those in the rural areas and highly populated places like offices, markets, hospitals and schools on stem cell and its technology. Nigerian healthcare givers should be properly equipped with first-hand information on the biology of stem cells, relating ethical issues, research design, treatment procedures, benefits and the full implications of the therapy so as to rightfully guide patients, cell donors and the general public in making informed decisions and voluntary contributions respectively, based on their varying life principles [66].

Additionally, it is expected that Nigerian government should step up in the integral fight towards reducing mortality and morbidity rates across the nation through restructuring and strategizing of health policies and regulations in favour of stem cell treatment. This will expectedly

attract a wide range of international and local collaborators in the nearest future to aid in the funding and subsidization of medical fees for poor and vulnerable patients. The government should ensure adequate regular power supply for activities involved in apheresis and molecular biology. Furthermore, the federal government should strive to upgrade the public power supply to be as efficient as possible but, in the interim, provide an alternative automatic switch generating plant to provide regular alternative power supply.

"Skilled labour migration" is a major setback highlighted in stem cell therapy in Africa as Nigerian health workers readily relocate to developed countries due to more attractive conditions for their services. It is therefore pertinent for the government, agencies, non-governmental organizations (NGO's) and private institutions to treat Nigerian health workers with extensive care via providing alluring salaries and allowances to them [63]. The government should also sponsor medical professionals for on-the-job trainings and provide a conducive environment for their work; readily supporting hospitals involved in stem cell transplant to enable them to import the necessary drugs directly.

12. CONCLUSION

In conclusion, the gradual progress of stem cell research and therapy in the country, offers this technology as an anticipated acceptable remedy for non-communicable diseases by 2030. With all recommendations above put in place, stem cell research/technology will grow in leaps in the country with consequent reduction in morbidity and mortality caused by the diseases that currently seem to have no medical treatment.

DECLARATION

Code availability

Software application.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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