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Menstrual Blood Derived Stem Cells and their Scope in Regenerative Medicine: A Review Article

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Abstract:- The menstrual fluid that is produced due to the endometrial shedding during the menstrual cycle in a women contains the blood cells that plays a major role in cell restoration and repair, these cells constitute the mesenchymal stem cells. The Men SC shave a wide range of attractive properties such as easy and frequent availability without involving any invasive and ethical complications. These cells posses all the properties of Stem cells and even have a better rate of cell proliferation and differentiation compared to the other stem cell sources. These factors have caused increased significance of these cells among the researchers. Hence they could be a source for research and clinical application.The main focus in this review include their effects in various disease like Liver Disease, Diabetes Mellitus, Stroke, Duchenne muscular dystrophy, Ovarian related disorder, Myocardial Infarction, Asherman Syndrome, Alzheimer's disease, Cutaneous Wound and provide an update on the cells in their novel form. These cells should be further investigated for their immunological properties along with various other demographic factors. Although, at present less data is available regarding the long term clinical approach, these cells could be a potential option for regenerative therapy, cartilage engineering and chondro protective differentiation.

Keywords:- *Menstrual cells, restoration, proliferation, Chondroprotective, differentiation.*

I. INTRODUCTION

During the course of the entire reproductive phase of a women, the human endometrium which is the innermost lining of the uterus go through numerous cycles of shedding, differentiation and regeneration. The endometrial stem cells(Endo SCs),composed of epithelial stromal, endothelial cells promote the cyclical regeneration of the endometrium(1). These continual remodelling process take place almost around 400 times in the reproductive phase of a woman until menopausal age is attained (2). The menstrual blood is composed of mesenchymal stem cells(MSCs). These cells are highly proliferative in nature, and makes them more favourable to be employed in clinical practice. The MSCs have so far been isolated and studied from other body sources like bone marrow, dental pulp, adipose tissue, synovial membrane and umbilical cord (3). The MSC was isolated from menstrual blood cells MSCs by Meng and colleagues in 2007 (4). During the study these cells exhibited properties such as multiple differentiation. While on the contrary, the rate of proliferation and differentiation capacity of these cells were much greater than the bone marrow derived MSCs(BMMSCs). This is further suggestive that Menstrual stem cells can be beneficial in clinical applications. In addition, the collection of MenSCs are not associated with any complications as it does not require ethical policies or any invasive surgical procedures. This can also provide an added option of collecting the sample multiple times from the same donor(5).Despite the fact that, the bone marrow derived MSCs have been attributable preferential attention to multiple therapeutic applications, it is also characterised by certain limitations, as it is an invasive procedure, and most often involves ethical issues from the donors perspective. (6),(7). Thus, they can be employed as a beneficial source of MSCs, that could be used free from the limitations of the former. The characteristics of MenSCs like increased ability to proliferate, doubling time that is short in nature, chromosome karyotyping that is sustained upto 68 generations, manifests further that MenSCs are the perfect source of cell regeneration system that can be comprehensively used in therapeutic applications like transplantation systems, cancer treatment, disorders of the neurological system (8),(9). They can hence be considered and explored as the best source of MSCs. This novel source from menstrual fluid was discovered years back by Meng et al. and Cui et al., which was further termed as menstrual blood derived stem cells(MenSCs).(10)(11)

II. BASIC CHARACTERISTIC OF MENSCS

The proliferating ability of MenSCs is found to be twice the ability of BM-MSCs. The studies that were performed by Meng et al. And team recorded that MenSCs from a healthy woman increases by two-fold when the required culture conditions are supplied, at every 20h.(12)(13). This causes the high rate of expression in the embryonic trophic factor and extracellular matrix(ECM). However, they exhibit the same phenotypic properties as the BM-MSCs including the surface marker expression, spindles(14). In addition, they differentiated into cells like neurosphere(15). Factors such as stable genetic properties, high rate of proliferation could be suggestive that they could exhibit potential therapeutic properties. Using the most appropriate techniques of differentiation, they can be made into different parts like neurocytic, pancreatic, hepatic and adipocytic(16)(17)(18). Moreover, research is being conducted on the immunomodulative properties of MenSCs(19). Further studies conducted by Hida et al. Showed that in a scaffold culture system these cells elucidated cardiogenic differentiation(20).

In fact, the therapeutic application of MenSCs are nowadays been gauged for the management of certain diseases. This could be a beneficial advantage in the areas of regenerative medicine. This is found to be so because of

they can efficiently migrate and differentiate into the site of injury, provide good mediation of immune response. Nowadays, the clinical trials conducted uphold the therapeutic benefits due to the transplantation of MenSCs.http://www.clinicaltrials.gov/

The purpose of this review article is to impart data in the recent advancements in the field of regenerative medicine and replenish the available information about the characteristics, nature and application of MenSCs and an elucidation on its therapeutic application in the management of certain diseases.

III. THERAPEUTIC POTENTIAL

A. Diabetes Mellitus

Diabetes Mellitus(DM), specifically type-I(DM), is a disease that is caused due to the deficiency of the ß-cells of the pancreas to secrete insulin. This causes alteration in the normal metabolism that can cause decreased level of insulin and further leads to elevated glucose level(21). From the studies conducted, it was found that the MenSCs could enhance the regeneration of ß-cells further increasing the number of insulin producing cells. This is done due to the differentiation of endogenous progenitor cells by the increased expression of neurogenin 3, nkx6.1, pax. From the above studies, it was concluded that in the recent times, the most effective management of diabetes is the transplantation of the islet cells, but it has limitations such as very less number of ready pancreatic donors. This has reduced the clinical application of these methodology(22). There has been a relation that shows the relation between the venous systemic blood and the menstrual blood. In a prospective, cohort study conducted it was concluded that the menstrual blood served as a potent and reliable marker for determining the levels of HbA1C, especially among women with DM during their reproductive age. This method has further advantages such as non-invasive, cost-effective and authentic(23).

B. Duchenne Muscular Dystrophy

Duchenne muscular dystrophy(DMD) is a genetic defect that causes increased inflammatory response. It is caused due to the degeneration of the x-linked chromosome that causes muscle weakness(24).There is a muscular dystrophy glycoprotein complex(DGC-DMD), that plays a role in the stabilisation of the sarcolemma. In the myocardial ECM, this complex showed increased protein expression in the DMD model of mice and was concluded by Umezva and team. This helps in restoring the muscle degeneration and repair the abnormalities of the skeletal muscles(25). In a study performed by Mori et al.2005, jt was found that the MenSCs have a higher rate of replication compared to the stem cells, and the growth rate was higher in the experimental conditions provided. As of now, there is no specific therapeutic approach for the management. In vitro and In vivo trans differentiation of the muscular dystrophic cells intoanti-atropic cells was observed, the human menstrual cells could be a potential factor(26).

C. Asherman Syndrome

This is caused dominantly in woman. The condition is caused when there are adhesions in the uterine cavity. This is presented with infertility, menstrual abnormalities like amenorrhea, dysmenorrhea and less menstruation(27). In a 3 year clinical study, consisting of 7 women with Asherman syndrome, the autologous transplantationof MenSCs caused better endometrial thickness(28).Evidences show that such transplantation of MenSCs increased the rate of angiogenesis, the endometrium thickness improved and the pregnancy was improved(29).Therefore they could be a potential option for the management of this condition.

D. Cutaneous Wound

Cutaneous regeneration aids in repairing the damaged part of the skin without the formation of scars. A chain of biological repair mechanisms plays a role in the restoration of the wounded tissue and heals the cutaneous wound. The primary objective of cutaneous regeneration is to improve the damaged skin without the formation of scars. In a mouse model experiment performed by Cuenca et al. Concluded that these cells improved wound healing and elevated the formation of new blood vessels. This better rate of proliferation was because MenSCs secreted cytokines, PDGF, MMP3, MMP10 which actively participate in wound repair(31). For the analysis of wound healing, the area of wound was captured(Canon Inc. Tokyo. Japan) and level of healing was calculated with the equation,

Wound Closure%=1-open wound area/Initial wound area*100

But, the potential long term side effects of this therapy should be taken into consideration(32). It is also to be noted that when the MenSCs interact with the inflammatory environment of the wound, the beneficial properties of the cells increased(33).

E. Ischemic Stroke

Ischemic stroke is the most commonly seen type of stroke that could cause serious nerve damage and can also lead to serious nerve damage and can also lead to life long mental and physical alterations(34). At present, stem cell therapy is used to better the nerve damage caused due to the stroke. Borlongan et al. Performed an in vitro experiment in a rat model and determined that MenSCs reset the oxygen glucose deprivation(OGD) in patients presented with ischaemic stroke(35). Menstrual blood combine the characteristics that are beneficial in therapeutic practice and improve the treatment outcome of stroke patients and prevent long term complications(36).

F. Hepato-Repair Potential

The differential ability of the hepatic cells was studied In vitro by Khanjani et al.,2015 and this approach was practiced in the management of liver conditions. When experiments was performed on a with mice acute liver it showed good rate of differentiation and improved the survival rate of the mice. It was also found that when MenSCs were transplanted in liver, they localized within 2 hours and provided good response. The response showed that it improved the liver histology and the architecture of the liver parenchyma within short duration of the

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injection(37). However, they reduced the level of serum liver enzymes and metabolites(AST,ALT,urea and total bilirubin in the mice. Fathi Kazoroomi et al. Proved the hepato-protective and repair role of MenSCs in the mice with acute liver damage. They found that the degeneration of hepatocytes was reduced and increased the level of collagen fibre deposition and a good improvement in the glycogen storage in the liver(38). Chen et al. Demonstrated that the differentiation and proliferation occurred when the transplanted MenSCs migrated into the fibrotic area of the liver, and acted on the collagen, thereby improving the function of liver. Nonetheless, it cannot be as effective in case of severe hepatic damage like end-stage liver fibrosis with only some healthy parenchymal liver cells because of the poor environment of the hepatic cells. This can be a area of research to determine the utility of these cells in case of severe damage to the liver. Therefore, further data and research is needed to provide evidences regarding the regeneration of hepatocytes in this context(39).

G. Pelvic Organ Prolapse

The wide therapeutic potential of MenSCs has enabled its application in the management of women's gynaecological disorder called pelvic organ prolapse. Different approaches have been performed for the investigation of this application. One such approach by Ulrich et al and team comprised of using a non-degradable mesh and degradable nanofiber mesh that was examined on rodents and animal models. The results from this study showed that they exhibited paracrine effects. To further enhance the credibility of the approach, Emmerson et al and team drafted an approach in which paramagnetic nanoparticles was invasively administered into ovine to facilitate vaginal repair. On administration, 10-20% of the MenSCs stayed for 30 days from the day of administration. Several conclusions were drawn at the end of this study like the method of usage of large animal models and the steps involved in the delivery of MenSCs and the mesh. Certain alterations were included in the protocol that helped in minimizing the rate of adverse events and also this study lead to the FDA banning of polypropylene vaginal mesh. This led to postulating the importance of these approaches in clinical study(41).

H. Critical Limb Ischaemia

Limb damage that occurs in the pathological and physiological alterations due chronic blood loss leading to limb pain is termed as Critical Limb Ischaemia(CLI)(42). The clinical trial data that is available nowadays support the MenSCs undergoing angiogenesis and stimulating the growth of cells. But, data is still not sufficient regarding the application of MenSCs needed for this method. To explain this, a series of experiments was performed by Murphy et al. And colleagues using a mouse model. They administered MenSCs in CLI and concluded that these cells improved the condition in this model. The probable factors that lead to these included three,1. These cells produced large numbers of growth factors, IL-4, HIF-1alpha, MMP3 and MMP10 that exhibited paracrine roles. 2. They blocked the pro-inflammatory signalling pathway and further leading to no inflammatory response. 3. The cells facilitated large cell differentiation because they produced large number of endothelial progenitor cells. Therefore, from all these theoretical approach, it can be stated that it could be a beneficial method for the treatment of CLI in contrast to the conventional therapeutic approach(44).

I. Myocardial Infarction

The ischaemic condition of the heart leading to the death of cardiac cells is termed as Myocardial Infarction(MI), it is a type of coronary artery disease(CAD)(48). The damage to the cells and extreme alteration in the hemodynamic mechanisms and in certain cases even death. This is backed by the study performed by Hida et al. And team who found that when MenSCs were transplanted into the cardiac cells, they significantly restored the damage that was caused to the cells(46). Furthermore, studies performed by Jiang et al. And team concluded that these MenSCs had a major effect on apoptosis, increased rate of cell proliferation and increased secretion of C-kit cells in the mouse model of MI(47). Wang and team determined that the administered MenSCs could suppress the p38 signalling pathway, thereby extracellular signal-regulated kinases 1 and 2(ERK1/2) and STAT3 was blocked. It was also further noted that there was an inhibition of endothelial cells which caused decrease in the number of mesenchymal cells and regression of tissue fibrosis(48). In vitro studies concluded that these cells have enhanced cytoprotective and paracrinic effects caused due to the secretions of miR-21(micro RNA). Hence, it can be concluded that the use of MenSCs have a beneficial role in the restoration of cardiac function due to their paracrinic activity and the micro RNAs released from exosomes.

J. Alzheimer's Disease

It is a neurological disorder that is caused due to amyloid-beta production, it is characterised by continuous and progressive loss of memory function and also cognitive impairment. These neurological features are caused by hyper phosphorylation of tau proteins comprised of extracellular neurofibrillary tangles(NTFs) and amyloid plaque deposits(50). Studies performed indicated that when MenSCs was transplanted into the brain of mouse model APP/PSI, it drastically improved the spatial characteristics and showed improved memory in AD(51). It was also found that they reduce the plaque amyloid formation and tau hyper phosphorylation. Furthermore, the expression of Amyloid degrading enzymes was decreased and significantly reduced the rate of inflammation. These can be conclusive that MenSCs improve Alzheimer’s disease by the degradation of Amyloid cells and anti inflammatory effect.

K. Therapeutic Applications And Other Concerns

There are wide range of studies that are currently being performed with respect to MenSCs. Already the application of BM-MSCs are being extensively researched(52). There are many sources of mesenchymal stem cells that are present in our body capable of proliferation. In recent times, the most commonly used is BM-MSCs, the other sources include, amniotic membrane, placenta and menstrual blood. These sources should also be widely studied. Different diseases in human could be treated with the available sources of stem cells in the body. Special characteristics of MenSCs include their immunomodulatory properties, and also their non-invasive properties. They could be a

beneficial approach in the treatment of various concerns. They have excellent proliferative and regenerative ability. Hence, they could be a safe and favourable option(53)(54). Studies suggest that there are no large scale complication associated with the therapy in case of nude model mice under study(55). In patients, presented with multiple sclerosis there were improvements observed and laboratory investigation was found to be normal(56). Nevertheless, the survival rate of these cells in foreign bodies is not yet well defined. It is to be still understood how these cells act on different bodies and their survival rate. Data should be still be made available regarding the safety concerns and the markers to efficiently manage these cells in In vivo conditions(57)(58)

IV. CONCLUSION

Menstrual blood cells are nowadays widely under clinical study owing their properties. It is been found that these cells have beneficial effects in the management of different condition like Alzheimer's disease, Duchenne muscular dystrophy, ovarian syndrome, Diabetes Mellitus, Ischaemic Stroke, Acute lung injury, Cutaneous Wound. These cells have a large spectrum of potential benefits due to their ability to restore the body tissues. In order to attain the ultimate target, the sample collection should provide high quality and a consistent nature of these cells.

This review article was done with the objective to highlight the various therapeutic approaches in the management of diseases owing to the properties of Menstrual cells. There are different areas where it could be a good option.

However, in spite of the therapeutic effect, their complications and associated complications such their effect on a foreign body should be gauged into along with their long-term safety. In addition, certain factors should be clinically addressed such as heterogenesity of MenSCs in clinical settings. Hence, even though more data is required. They also can be used in various therapeutic approach that are still in clinical study. This could lead in advantageous contributions in the area of regenerative medicine and different clinical approaches. It can be concluded that these cells provide significant changes in the end therapeutic outcomes. Since, this approach is still under different stages of clinical study, they could become a realistic and more reachable approach compared to tgr conventional methods of treatment.

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