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REVIEW ARTICLE

Comparison of Osteogenic and Chondrogenic Differentiation Potential between Wharton's Jelly and Adipose Tissue Mesenchymal Stem Cells as the Alternatives of Bone Marrow Mesenchymal Stem Cells: A Systematic Review

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Abstract

Introduction Currently, Bone Marrow is the most common source of Mesenchymal Stem Cell (MSC). The limitation of the source and pain post harvesting procedure make the next alternative of BM-MSC is needed. Wharton Jelly, offer a low cost and pain free collection method. Adipose tissue provides abundant amount stem cell and has a interestingly compatible osteogenic and chondrogenic activity. The objective of this study is to search alternative Bone Tissue Engineering (BTE) source other than BM-MSC.Materials and Method Literature search was conducted using several search engines. This review used all In vitro experimental comparison of Adipose Tissue Mesenchymal Stem Cells (AT-MSC) and Wharton's jelly stem cell (WJ-MSC). We compared osteogenic and chondrogenic differentiation potential between these MSCs. The group of comparison is divided into two sub groups, animal MSCs and human MSCs.Result and Discussion The first study that compared osteogenic and chondrogenic differentiation from animal AT-MSC and WJ-MSC consists of 7 trials. Most of the result shows that AT-MSC has greater osteogenic differentiation potential compared to WJ-MSC and controversial result for chondrogenic differentiation between them. The second studies consist of 3 trials. In these studies, the results were more homogenous and concluded that AT-MSC has higher osteogenic differentiation potential than WJ-MSC but the chondrogenic differentiation were not significantly different. Conclusion AT-MSC may be more appropriate than WJ-MSC for ontogenesis and bone repair usage.

Keywords: *Oestrogenic differentiation, Chondrogenic differentiation, Wharton's jellies Mesenchymal Stem Cells, Adipose Tissue Mesenchymal Stem Cells.*

Introduction

Many condition of bone defects required bone regeneration to be satisfactorily treated. One of the research field that focus on the bone regeneration is the using of many stem cells types to establish the most effective treatment of the defects. MSCs are useful pluripotent cells that can be found in many tissues. In general, bone marrow, umbilical cord, and adipose tissue have been identified as the main resources of MSC that applied to human[1]. The most common of MSC that usually been used is isolated from adults bone marrow through aspiration process[2]. BM-MSC is still considered to be the gold standard for stem cells application to achieve bone regeneration[3]. The limited resource and pain that emerge during aspiration procedure of BM-MSC has encouraged many researchers to seek another resource for BTE. Particularly, the osteogenesis and chondrogenesis potential of MSC to repair bone defects has been studied by many researcher. In addition to bone marrow, other tissue can be useful as the resource of MSC. AT-MSC and WJ-MSC may become alternative sources of MSC to treat bone defects, and non-unions[4]. These MSC are multipotent which has potential of differentiating into various cell types such as osteoblasts and chondroblast [5,6]. Both cell

types offer a perfectly natural and controversy free source of stem cells. They also might be the most abundant source of stem cells, bearing in mind that the global birth rate per year is extremely high and the fact that adipose tissue is a residual product of liposuction procedure[7,8] Wharton's jelly is a clear and mucoid tissue that insulates and protects the arteries and vein of umbilical. It contains my fibroblast like stromal cells, collagen fibers, and proteoglycans. Wharton's jelly is the postnatal source of fetal stem cells[9]. One of the facts that the capability of MSC is decreased by the donor age is not implied in Wharton's jelly. WJ-MSC possesses an early embryonic state that retains telomere at highest length so that protects them from premature loss of viability. Among all of the advantages of MSCs, they possess several disadvantages including inhibitory property of Osteogenic and chondrogenic differentiation, endochondral bone formation, and regulation of mineral deposition in extracellular matrix by Non-Steroidal Anti Inflammatory Drugs (NSAID) [10,12] However, these disadvantages are not applied to WJ-MSC.AT-MSC has the potential to differentiate into a several type of cells that includes osteoblast, chondrocytes, and adipocytes[13]. Like Wharton's jelly, AT-MSC could also easily obtain from the donor. A single liposuction procedure can provide a lot of tissues and cells compared to bone marrow aspiration. The procedure is also causing less pain and less invasive. Moreover, the isolation of stem cells from bone marrow is less effective and cells often contaminated[14,16]. Both of Wharton's jelly MSC and Adipose tissue MSC have the ability to differentiate to osteogenic and chondrogenic cells. These types of MSCs also provide many advantages compared to bone marrow MSC. The objective of this systematic review is to provide the comparison of adipose tissue derived mesenchymal stem cells and Wharton's jelly derived mesenchymal stem cells osteogenic differentiation potential.

Materials and Method

A literature searching was conducted using several search engines on September 2017; those were PubMed, EBSCO, Scopus, Cochrane and Google Scholar. The keywords used were (Wharton's jelly or adipose MSC or Mesenchymal stem cells) AND ("osteogenesis" or "chondrogenesis" or "osteogenic" or "chondrogenic"). This searching was limited by date of publication and English language articles to be included. Citation alert was also applied in this searching process. Our PICO and searching strategy were mentioned in Table 1.

Table 1: PICO

population	**Animal and Human**
Index Tests	Mesenchymal Stem Cells
Comparisons	Adipose Tissue and Wharton's Jelly
Outcome	Osteogenic and Chondrogenic differentiation

We searched the literature using Me SH Term as follows:

Mesenchymal Stem Cells: "Adipose mesenchymal stem cells", "Wharton's jelly mesenchymal stem cells", "derived stem cells"

Osteogenic: "Osteogenic potential", "Osteogenic differentiation"

Chondrogenic: "Chondrogenic potential", "Chondrogenic differentiation"

Markers and Methods: "Alkaline phosphatase", "Calcium deposition",

"Osteocalcin", "Osteoprotegerin", "Alizarin red S", "Alcian blue"

Inclusion Criteria

- Studies/reviews describing mesechymal stem cells osteogenic differentiation or chondrogenic differentiation
- Studies/reviews describing the advantages of adipose tissue and Wharton's jelly mesenchymal stem cells
- Studies/reviews describing factors associated with alternative mesenchymal stem cells in bone tissue repair
- Studies/reviews describing regenerative medicine and new developments in osteogenic and chondrogenic differentiation potential of mesenchymal stem cells
- English language2002-2017
- Older studies were included if referenced by recent studies and deemed to be relevant

Exclusion Criteria

- Studies/reviews that did not describe one of above
- Language other than English
- Published prior to 2002 unless referenced by recent study and deemed to be relevant
- The article does not include a full text review

Criteria for Studies

Types of Studies

We reviewe in vitro studies of animal and human adipose derived mesenchymal stem cells versus Wharton's jelly mesenchymal stem cells respectively. Only full-text studies which were collected from the search engine aforemention were used. Unpublished articles and abstract only were not included in this study.

Types of Population

The population of studies in this review were divided into 2 groups. First group consists of animal MSCs. The second group of comprises human MSCs.

Types of Index Tests

The Index tests were mesenchymal stem cells from Adipose Tissue derived compared to Wharton's jelly. All animal AT-MSC were compared to animal WJ-MSC, and all human AT-MSC were compared to human WJ-MSC.

Types of Outcome Measures

The outcome of intervention was the osteogenic and chondrogenic differentiation potential in each group based on in vitro experiment.

Study Selection and Data Extraction

All studies were screened for duplication manually. This entire duplication-free article underwent title and abstract examination using inclusion and exclusion criteria. Studies fulfilled inclusion and exclusion criteria underwent full text review. Osteogenic and Chondrogenic differentiation of Adipose and Wharton's jelly MSC from every eligible full text was extracted and analysed.

Results and Discussion

Wharton's jelly and adipose tissue have a potential to be the alternative of mesenchymal stem cells in the treatment of bone and cartilage problems. Their osteogenic capability is proven by the differentiation of these mesenchymal stem cells into osteogenic and chondrogenic cells like osteoblast and chondroblast. The osteoblast produce bone matrix during the regeneration of bone. On the other side, bone formation and repair by osteoblast are the basic of skeletal healing when there is a bone defect. The process of fracture healing exhibits similarity with the process of natural endochondral ossification[17]. The capability of MSC to differentiate into osteogenic, adipogenic, and chondrogenic mesodermal lineages is an important feature that verify the multi potentiality of MSC.[18] Although both MSC have similar advantages the ability to differentiate into osteogenic and chondrogenic differentiation, the determinant question relies: which MSC has the higher osteogenic and chondrogenic potential between AT-MSC and WJ-MSC? The MSC that has a higher osteogenic and chondrogenic potential then has greater chance to be the alternative of BM-MSC in the using of MSC to treat bone defect and OA.

In Vitro Ontogenesis and Chondrogenesis Potential of Animal AT-MSC and WJ-MSC Compared to BM-MSC

In vitro comparison of adipose derived MSC and Wharton's jelly derived MSC that focus on the capability of osteogenic and chondrogenic differentiation has been done by many researchers. Barberini et al[19] was first describing the results of their research that compared the differentiation potential of adipose tissue and umbilical cord derived from canine MSC. The adipose derived MSC was extracted from adipose tissue and the UC MSC can be isolated from umbilical cord tissue, Wharton's jelly, or from umbilical cord blood[20,21]. The in vitro differentiation potential was observe red on the 15th days from UC group and on the 8th day on the Adipose MSC. On these days, all the MSC have been reached the passage three (P3), it means the cells reached homogeneous culture at this point[22]. The osteogenic differentiation was confirmed by calcium matrix staining using Alizarin Red S dye. The chondrogenic differentiation occurred after the 21st days and was confirmed by deposition of hyaline matrix that stained with Alcian blue. Seven trials that compare the MSC capability in bone regeneration

potential with in vitro experimental design study are included in this systematic review. All of the experiment was done by using animal mesenchymal stem cells that come from animal. The trials then divided into two groups, first group is comparing the osteogenic differentiation potential of the MSC, and the second group is comparing the chondrogenic differentiation potential of the MSC. From the study that has been done by Barberini D. et al[19]. It was observed that the UC derived MSC do not multiply as rapidly as AT derived MSC, similar to the study that has been done by Lovati AB et al. The period of time that required to differentiate also longer in UC derived MSC than AT MSC[23]. Despite the difference in time required for differentiation, there were no differences in differentiation potential of AT-MSC and UC derived MSC[19]. This result are different compared to the study that has been done by Janina Burk et al[24]. and Toupadakis et al[25]. That said the osteogenic differentiation were higher in AT-MSC and lower in UC derived MSC significantly. On the study that has been done by Byung-Jae Kang et al[26]. It was found that osteogenic differentiation was most intense in AT-MSC that revealed by the degree of Alizarin Red S staining. On contrary, chondrogenic differentiation was found higher in UC derived MSC and lower in BM-MSC significantly. Berg et al[27]. and Lovati et al[23]. On their study also found that UC derived MSC has the most prominent ability of Chondrogenic differentiation. In other Study, Giovanni et al[28]. Found that intense chondrogenic differentiation was the same in AT-MSC and UC derived MSC. All of these conflicting results emphasize that culture media is also affected the differentiation potential of MSC.

Table 2: In Vitro Osteogenic and Chondrogenic differentiation potential between animal AT-MSC and WJ-MSC

Ref	Staining Method	Osteogenic Differentiation	Chondrogenic Differentiation
Barberini et al.	Alizarin red S Alcian blue	AT-MSC = WJ-MSC	WJ-MSC>AT-MSC
Janina Burk et al.	Alizarin red S	AT-MSC >WJ-MSC	
Toupadakis et al.	Alizarin red S	AT-MSC >WJ-MSC	
Berg et al.	Alcian blue		WJ-MSC>AT-MSC
Byung-Jae Kang et al.	Alcian blue		AT-MSC>WJ-MSC
Lovati et al.	Alcian blue		WJ-MSC>AT-MSC
Giovanni et al.	Alcian blue		AT-MSC = WJ-MSC

In Vitro Osteogenic and Chondrogenic Potential of Human AT-MSC and WJ-MSC Compared to BM-MSC

There were three studies that compare the osteogenic and chondrogenic differentiation potential of human AT-MSC with WJ-MSC. All of the study use different parameter with same in vitro experimental study design. On the study that has been done by Alicja Zajdel et al[29]. The comparison of the osteogenic potential between AT-MSC and WJ-MSC was assessed with osteogenic differentiation markers such as mineralization capability, alkaline phosphates (ALP) activity, Osteoprotegerin (OPG), and Osteocalcin (OC). With measurement of these markers, the most suitable MSC that can be applicable for bone regeneration can be chosen. Both MSC were cultured in MSC growth medium. All the MSC were harvested in the third passage after 21 days, and then the osteogenic marker analyses were performed. The calcium deposition of AT-MSC was measured 1.3 times more than the calcium deposition in WJ-MSC, this result was statistically significant (p=0.00002). The ALP activity also measured at the 21st day and the analyses result showed that the ALP activity of AT_MSC was 4 times higher than WJ-MSC, this result also give a significant result statistically (p=0.00002). Another marker that has been measured was OPG secretion. This marker was the sign for the beginning process of osteogenic differentiation. It was found that WJ-MSC has 1.5 times higher OPG compared to AT-MSC (p=0.0002). The last maskers were OC secretion. This marker was the sign for advance stage of osteogenic differentiation process. It was found that WJ-MSC has 2.4 times higher OC compared to AT-MSC (p=0.002). Higher concentration of ALP and calcium deposition but lower OC that was secreted by AT-MSC were suspected caused by overproduced matrix that caused down regulation on OC secretion.[30,31] Aron S et al[32]. In their study compare the osteogenic and chondrogenic differentiation of AT-MSC and WJ-MSC through standard induction protocols. The bone forming ability of MSC followed by RT-qPCR to analyze RUNX2 and ALP mRNA expression RUNX2

is the master transcription factor of osteogenic development. ALP is an early marker of osteoblastic differentiation. And very important for extracellular matrix maturation From their experiment, it was found that all the RUNX2 gene expression are the same within two groups, but AT-MSC shows higher level of ALP gene expression than WJ-MSC and after 14 days, the alizarin red staining result showed high calcium accumulation in AT-MSC and lower calcium accumulation in WJ-MSC. High RUNX2 and low ALP in WJ-MSC group indicates that there was an osteogenic differentiation potential but low capability of underwent calcification process. These result was in agreement with the result of Yu et al[33]. That found the similarity of RUNX2 expression with different osteogenic potential between two groups. For chondrogenic differentiation potential comparison of AT-MSC and WJ-MSC, it was found that all of the MSC have the same potential to differentiate.

Paola Romina et al[34]. Study shows similar results. It was found that AT-MSC ang WJ-MSC have the capability to differentiate into osteogenic and chondrogenic cell phenotypes, but judging by alizarin red s staining, AT-MSC revealed higher calcium deposition compared to WJ-MSC. The chondrogenic differentiation potential was tested by toluidine blue solution, and the result of glycosamingly can that formed in both groups was not significantly different.

Table 3: In Vitro Osteogenic and Chondrogenic differentiation potential between human AT-MSC and WJ-MSC

Ref	Experimental Parameter	Osteogenic Differentiation	Chondrogenic Differentiation
Alicja Zajdel et al	Expression of ALP, OPG, OC, and mineralization capability	AT-MSC> WJ-MSC	
Aron S. et al.	RUNX2 and ALP mRNA gene expression	AT-MSC>WJ-MSC	AT-MSC=WJ-MSC
Paola Romina et al.	Calcium deposition and Glycosaminglycan formation	AT-MSC>WJ-MSC	AT-MSC=WJ-MSC

Conclusion

Overall, in vitro comparison between AT-MSC and WJ-MSC show a higher osteogenic potential in AT-MSC to WJ-MSC, but the chondrogenic differentiation potential is still inconclusive. It might be concluded that AT-MSC has been more appropriate than WJ-MSC for osteogenesis and bone repair usage. Hence more study to evaluate the healing effect of these MSCs in cartilage is needed.

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