



MESENCHYMAL STEM CELLS RESEARCH IN CARTILAGE REPAIR: WHERE IS MALAYSIA TODAY?

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ABSTRACT

Advances in Mesenchymal Stem Cells (MSC) research has initiated the development of new therapeutic strategies that brings promise to patients suffering from damaged cartilage. It has been generally accepted that research conducted in developed countries are more advanced than those of developing nations although, the need for the utilization of such technologies are more pronounced in the latter. Despite its importance, it is unclear as whether the research progress of developing countries is comparable to that of developed nations. To determine this, Malaysia being a typical developing country was selected as a comparative model. A review on research related to MSC in cartilage repair or fundamental studies using MSCs for the past 10 years (from 2001 till 2011) was performed using online research databases which included PubMed, Scopus and ISI Web of Knowledge. RESULTS: Of the 42 countries, Malaysia ranked 22nd in number of publications, while amongst the Asia-Pacific countries Malaysia is number 6 of 9. Developed and developing countries contributed 80.1% and 19.9% of the published articles in this field respectively. Despite being a developing country, China ranks second in the world. There were significant differences ($p < 0.01$) in the publication numbers, total budget for research and %GDP for research between the developed and developing nations. The amount of GDP, %GDP for research and total budget for research demonstrate significant correlations ($p < 0.01$). Although Malaysia ranks low in terms of total publication worldwide, it has the highest number of publications comparable to larger and more affluent countries such as Israel, Turkey and Norway. CONCLUSION: There appears to be a strong relationship between GDP and research publication in MSC for cartilage repair. Despite being a developing country with relatively lower GDP, Malaysia is progressing significantly in this area of research but remains remarkably behind China and other advanced countries.

1.0 Introduction

Articular cartilage disease is one of the major causes of morbidity worldwide, having a substantial influence on health and quality of life in the adult population. Although not life-threatening, disease of this tissue can pose a huge financial burden on any individual or existing health system¹. Disease of the joint accounts for approximately half of all chronic conditions reported for people above the age of 65 years². It has been estimated that these conditions have increased to as much as 25 percent over the past decade globally³. According

to the results of a nationwide survey, musculoskeletal diseases are one of four chronic diseases commonly presented in urban-dwelling older people in Malaysia. Among the possible diseases of the joint, it appears that injury to the articular cartilage of the knee is considered as one of the more serious conditions, as it is commonly progresses into a degenerative state. These conditions alone contribute to 80% of cases seen with regards to all knee problems⁴.

Regardless of the type of injury, it has been demonstrated that intrinsically, articular cartilage has poor regenerative ability.

While the non-surgical options have been considered to be largely ineffective, the use of surgical intervention has been somewhat promising⁵. Among the many techniques advocated, reparative marrow-stimulating techniques have been previously described. Others included autologous chondrocyte implantation (ACI) and osteochondral grafting^{6,7}. These techniques however, did not produce mid to long term results. Despite these limitations, many studies have promoted the use of cell therapy i.e. ACI over other surgical modalities. In a systematic review performed recently, all but one study demonstrated that the benefit of ACI over other treatment modality is more favourable^{8,9}. However, it has been postulated that the use of ACI in this case did not produce the desired long-term effects owing to the limitations in the proliferative ability of the transplanted chondrocytes. It has now been suggested that cells with higher proliferative and differentiation potential will produce better repair outcomes, i.e. mesenchymal stem cells¹⁰. These cells may be generated in cartilage or in the tissues adjacent to it and migrate into the cartilage without the need of prior activation, hence resulting in improved tissue remodeling¹¹.

Mesenchymal stem cells (MSC) may participate in tissue regeneration in several ways. It has been suggested that MSC directly differentiate into tissue-specific cells and thus will substitute the damaged or lost cells. Alternatively MSC may indirectly influence tissue regeneration by secreting a range of soluble factors; promoting tissue vascularization, cell proliferation and, differentiation within the tissue and whilst modulating the inflammatory processes¹². Several studies showed that implantation of MSCs either alone or in a scaffold into degenerated human peripheral joints have shown some positive outcome in articular joint repair outcomes^{13,14}. Its use has been viewed as a viable and promising alternative, especially when considering that conventional therapies have failed to produce good long term outcomes. Hence, it comes to no surprise that cartilage treatment using MSC has been actively researched with the aim to harness its regenerative potential. Until recently, the use of cultured mesenchymal stem cells to regenerate cartilage has been primarily in studies using animal models. Recent reports however, indicate that these technologies are now being translated into patients¹⁵.

Traditionally, developed countries are the leaders in this field of research. However, with the need for this treatment in many developing countries, related research conducted in countries such as Malaysia have become increasingly important. More so when we consider that the majority of the world population is located in these countries. It is also more likely that the use of these and other related technologies will more widely be utilized in this part of the world. Despite the importance of performing research in these related technologies in many developing countries, the progress of these research programs does not appear to be evident. The

reasons may be many folds. It may be a misconception that developed nations, being more affluent, have a higher advantage than that of the developing countries. This might be due to the lack of publicity of the research conducted in these countries which have led to the lack of visibility in their research undertakings. Regardless of the circumstances, determining the true progress of research in this area is important since this fact has not been previously evaluated. In order to determine this, a systematic review of all published materials related to “mesenchymal stem cells” and “repair of the articular cartilage” that has been indexed in several databases were examined and compared. Comparative analyses were conducted to establish the state of progress in many countries and more importantly, to the relative progress of developing nations as compared to the more affluent developed nations. The focus will also be on Malaysia as the main reference point, taking into consideration that Malaysia is a typical developing nation of high potential.

2.0 Materials and Methods

2.1 Search strategy

Online databases including PubMed, Scopus and ISI web of knowledge search was performed. The term ‘cartilage’, ‘cartilage repair’ and ‘stem cells’ was used without restriction to language. The results were searched for cartilage repair for each country and reviewed systematically to obtain the studies that were deemed suitable (Fig.1).

2.2 Study selection

All publications about Mesenchymal stem cells and cartilage repair from January 2001 up to 31st December 2011 were selected. Studies that were also included, presented relevant key words such as chondrogenesis and scaffolds. Other studies which did not match the search criteria included but was not limited to osteogenesis, bone and wound healing, and documents which were patents, notices and announcements were excluded from further review. Duplicates were removed from the pool of reviewed articles.

2.3 Statistical Analysis

Non-parametric analyses were employed in this study. Mann-Whitney U and Spearman Rho tests were used to determine the significant differences between the median value and any correlations in the respective analyses. P value was determined to be significant as less than 0.05.

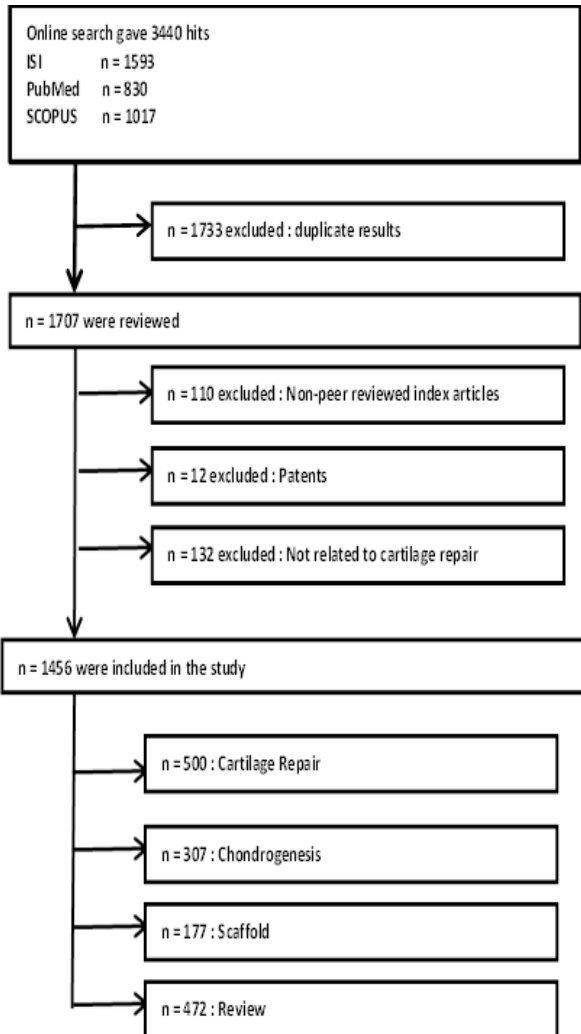


Fig.1 Inclusion and Exclusion criteria flow chart

3.0 Results

3.1 Study characteristics

The on-line literature search using PubMed, Scopus and ISI web of knowledge produced 3,440 hits. After excluding duplicates, 1,863 were reviewed for suitability. Studies that were included were those published between and including, 2001 to 2010. Different types of treatment methods including MSC alone for cartilage repair ($n = 503$), *in vitro* differentiated MSC (Chondrogenesis) ($n = 307$), MSC on a scaffold ($n = 182$) and reviews on cartilage repair ($n = 471$) were stratified. Data were further stratified according to the different countries, which numbered 42 in total. Publications with affiliations to more than one country was divided equally in terms of merits e.g. publication with 2 nations, each gets half a publication.

3.2 Clinical Outcome

World Scenario

From 2001-2011, 42 countries contributed to publications for this type of research. There were 3 countries that dominated the scene: The USA, China and Germany. There were in total 748 (40.1%) articles from these 3 countries alone. There were 405 publications from the United States, making this country the highest contributor of research in this area in the world. Of these articles, it was found that 206 studies were studies using MSCs for repairing cartilage, 50 were on scaffold related studies together with MSCs and 149 were review articles. Next in line is China, with a total of 212 publications; of which 47 were reviews, 90 were on cartilage repair and 42 with different types of scaffolds. Germany is in third place, having a total of 131 published papers in cartilage repair (Table 1).

The number of publications from developed countries ($n=27$) are higher than those of developing ($n=15$) countries (1167 vs. 92). The 10 highest numbers of publications are generally of the developed nations. Of these, 4 are from Asian countries while the remainder is from Western countries. Although China is in the developing status, it ranks second in terms of publications and is one of the only developing countries listed among the top 10 producer of publications in this field. Malaysia ranks 22nd after Israel.

The scene in Asia Pacific region

In this region, there were only 9 countries listed. China leads the rest of these countries with a total of 212 publications of which 47 were reviews, 90 were on cartilage repair and 42 were on the use of different types of scaffolds. Next is Japan which has published 122 articles. Malaysia on the other hand, only published a total of 8 papers within four years (2008-2011). Although this number is low, in comparison to most other developing countries in this region, Malaysia remains ahead of India and Thailand, as shown in Fig2. Emphasis on the different research areas within this topic varies between different countries and is summarized in Fig 3.

3.3 Analysis of GDP, GERD and number of published materials

There were significantly more developed countries than developing countries included in the study list ($p<0.01$). In addition, developed countries produced significantly more publications in this area than that of developing countries ($p<0.01$: 1167 vs. 289).

A summary of the GDP (per capita) against the number of publications in this research area is summarized in Table 2. Although China has the 3rd lowest GDP per capita in this list,

it produces the second highest number of publications. It is also apparent that certain developing countries such as Malaysia have more publications in this area of research than several advanced countries such as Finland and Denmark.

Despite several disparities being observed, in general there was a correlation between the general amount of allocated research fund, gross domestic product per capita (GDP), gross

expenditure for research and development (GERD) and the number of publications in this area. Significant correlations were observed between GERD and number of publications ($p < 0.01$), GDP and number of publications ($p < 0.01$) and, %GDP for research and number of publications ($p < 0.01$). There was a strong correlation observed between the ranking among the publications number and the GDP status ($p = 0.016$).

Table 1 World scenario: Number of published papers from the year 2001-2011

COUNTRIES	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	TOTAL	GR/YR	GDP*	%GDP**	GERD
DEVELOPED COUNTRIES																
AUSTRALIA	-	-	2	0	0	4	2	7	9	6	4	34	3.78	40836	2.25	918.81
AUSTRIA	-	-	-	1	0	0	1	2	0	0	1	5	0.63	41805	2.75	1149.6
BELGIUM	4	0	2	2	0	3	1	1	0	0	1	14	1.27	37677	2	753.54
CANADA	1	0	0	0	1	1	4	3	2	4	9	25	2.27	40457	1.95	788.91
CROATIA	-	-	-	-	-	-	-	-	1	1	0	2	0.67	18338	-	-
CZECH REPUBLIC	-	-	-	-	-	-	4	1	0	1	0	6	1.20	25933	1.55	401.96
DENMARK	-	-	-	-	1	0	0	0	0	1	1	3	0.43	37741	3.05	1151.1
FINLAND	2	1	0	0	0	0	0	1	0	1	0	5	0.45	36723	3.83	1406.5
FRANCE	2	1	0	2	3	3	2	5	7	7	9	41	3.73	35048	2.21	774.56
GERMANY	2	2	7	6	8	14	13	16	21	22	20	131	11.91	37935	2.85	1081.1
GREECE	-	-	-	-	1	0	0	0	1	0	0	2	0.29	27624	0.55	151.93
IRELAND	-	1	0	1	1	0	1	2	2	9	4	21	2.10	39507	1.75	691.37
ISRAEL	1	0	0	1	1	0	2	0	0	4	0	9	0.82	31004	4.2	1302.2
ITALY	-	-	1	1	2	6	5	3	9	6	7	40	4.44	30165	1.3	392.15
JAPAN	1	4	6	9	11	10	18	16	9	17	21	122	11.09	34362	3.47	1192.4
NETHERLANDS	-	3	0	0	0	3	4	1	5	7	3	26	2.60	42330	1.87	791.57
NORWAY	-	-	-	-	-	-	-	3	3	0	2	8	2.00	53376	1.85	987.46
POLAND	-	-	1	0	0	1	0	0	0	0	1	3	0.33	20136	0.72	144.98
PORTUGAL	-	-	-	-	-	1	2	1	4	2	3	13	2.17	23204	1.65	382.87
SINGAPORE	-	-	-	4	1	5	4	1	1	11	7	34	4.25	59936	2.6	1558.3
SLOVAKIA	-	-	-	-	-	-	-	-	-	1	1	2	1.00	23384	-	-
SOUTH KOREA	1	0	0	2	1	5	5	4	12	8	15	53	4.82	31753	3.4	1079.6
SPAIN	-	1	0	1	0	2	1	2	4	11	5	27	2.70	30622	1.4	428.71
SWEDEN	-	-	2	1	2	3	3	1	2	0	1	15	1.67	40613	3.62	1470.2
SWITZERLAND	1	1	1	0	2	1	5	8	6	6	3	34	3.09	43508	3	1305.2
UNITED KINGDOM	-	1	1	6	3	5	17	13	6	18	16	86	8.60	35974	1.81	651.13
USA/US	20	20	28	24	27	26	34	43	45	71	68	406	36.91	48147	2.81	1352.9
DEVELOPING COUNTRIES																
BRAZIL	-	-	-	-	-	1	0	1	0	3	1	6	1.00	11845	1.2	142.14
BULGARIA	-	-	-	-	-	-	-	-	1	0	0	1	0.33	13562	-	-
CHILE	-	-	-	-	-	-	-	-	-	2	0	2	1.00	16171	-	-
CHINA	4	4	4	8	10	17	23	34	27	29	52	212	19.27	8394	1.55	130.11
EGYPT	-	-	-	-	1	0	0	0	0	1	3	5	0.71	6504	-	-
HUNGARY	-	-	-	-	1	0	0	0	2	0	0	3	0.43	19647	1.2	235.76
INDIA	-	-	-	-	-	1	0	0	1	2	1	5	0.83	3703	0.85	31.476
IRAN	-	-	-	-	-	-	-	1	2	1	3	7	1.75	12258	-	-
LITHUANIA	-	-	-	-	-	-	1	0	0	0	0	1	0.20	18769	-	-
MALAYSIA	-	-	-	-	-	-	-	2	1	0	5	8	2.00	15578	0.7	109.05
MEXICO	-	-	-	-	-	-	1	1	0	0	0	2	0.40	15121	0.38	57.46
SOUTH AFRICA	-	-	-	-	-	-	-	1	0	0	0	1	0.25	10977	0.95	104.28
TAIWAN	-	-	1	1	2	1	1	5	7	8	4	30	3.33	37931	2.35	891.38
THAILAND	-	-	-	-	-	-	-	-	-	-	1	1	1.00	9693	-	-
TURKEY	-	-	-	-	-	-	1	1	1	0	2	5	1.00	14615	0.9	131.54
TOTAL	39	39	56	70	79	113	155	180	191	260	274	1456				
* World Economic Outlook Database-September 2011, International Monetary Fund.																
** Battelle, R&D Magazine, International Monetary Fund, World Bank, CIA World Factbook																
GR/YR - Growth Rate/Year, GDP - Gross domestic product, GERD - Gross domestic expenditure on R&D, PUB - Publication																

Comparison between the developed and developing countries demonstrated significant differences ($p < 0.01$) between the total GDP of developed countries (968,138 Billion USD) as compared to the developed countries (214,768 Billion USD). There were also significant differences ($p < 0.01$) between the amounts of GERD of developed countries (22,309.15 Billion USD) as compared to the developed countries (1,833.18 Billion USD).

4.0 Discussion

In the analyses, the disparity in the GDP, GERD and number of publications between the developed and developing countries is apparent. This was reflected in the low number of published materials from developing countries than those of developed nations. It is also clear that from this study, that the work done in this area of research is strongly related to the amount of funding and the GDP of any given country. However, China does not appear to follow this observation. Despite having a low GDP, the publications (which reflect the amount of research works) are high, being second to only the United States.

Table 2 Summary of GDP Ranking and publication ranking (42 countries)

DEVELOPED COUNTRIES				
COUNTRIES	GDP	RANK	PUBLICATIONS	RANK
SINGAPORE	59936	1	34	8
NORWAY	53376	2	8	17
USA/US	48147	3	406	1
SWITZERLAND	43508	4	34	8
NETHERLANDS	42330	5	26	12
AUSTRIA	41805	6	5	19
AUSTRALIA	40836	7	34	8
SWEDEN	40613	8	15	13
CANADA	40457	9	25	11
IRELAND	39507	10	21	12
GERMANY	37935	11	131	2
DENMARK	37741	12	3	20
BELGIUM	37677	13	14	14
FINLAND	36723	14	5	19
UNITED KINGDOM	35974	15	86	4
FRANCE	35048	16	41	6
JAPAN	34362	17	122	3
SOUTH KOREA	31753	18	53	5
ISRAEL	31004	19	9	16
SPAIN	30622	20	27	9
ITALY	30165	21	40	7
GREECE	27624	22	2	21
CZECH REPUBLIC	25933	23	6	18
SLOVAKIA	23384	24	2	21
PORTUGAL	23204	25	13	15
POLAND	20136	26	3	20
CROATIA	18338	27	2	21
DEVELOPING COUNTRIES				
TAIWAN	37931	1	30	2
HUNGARY	19647	2	3	7
LITHUANIA	18769	3	1	9
CHILE	16171	4	2	8
MALAYSIA	15578	5	8	3
MEXICO	15121	6	2	8
TURKEY	14615	7	5	6
BULGARIA	13562	8	1	9
IRAN	12258	9	7	4
BRAZIL	11845	10	6	5
SOUTH AFRICA	10977	11	1	9
THAILAND	9693	12	1	9
CHINA	8394	13	212	1
EGYPT	6504	14	5	6
INDIA	3703	15	5	6

The reason may be multiple: Firstly, with a thriving economy and focusing development on selected regions of its country, China can afford to focus on various areas of high expenditure projects, such as those of mesenchymal stem cells¹⁶. In 2011, China's commitment to research has been tremendous and it produces one of the highest numbers of publications in the world despite having a research budget of only 1.55% of its GDP¹⁷. Secondly, the substantial growth in this area of research may result from China's focus in moving towards this field of study, whilst other developed countries such as Norway, may not find this research an area of priority. In our comparative analyses, it appears that China is the only developing country which falls in the top 10 countries producing publications related to MSC and cartilage repair. Amongst the Asian countries, China leads in the number of publications followed by Japan, South Korea, Singapore and Taiwan.

Where does Malaysia fair in this field of research? Malaysia falls 22nd in the world ranking in terms publications but ranks 6th amongst the Asian countries. In this review analysis, Malaysia had published in total 8 articles on cartilage repair related to the development of MSC applications. Despite being significantly challenged in budget, population size and GDP, Malaysia produces publication numbers which is at par with many developed and larger countries like Israel, Iran, Turkey and India. It can be concluded from this analyses that Malaysia remains focused in this area of research considering that the budget constraints. With the present view that Malaysia needs to keep ahead in its development of the present research and that with a vision for a 2020 Malaysia i.e. to be a developed nation, research into the area of MSC for cartilage repair will remain one of its top priority. The future for research in this area looks bright for this country but yet its success remains to be seen. With global competitors like China, who at the moment despite having a low GDP has outranked many developed nations and is growing at a very fast pace, it might be difficult for countries like Malaysia to compete in the near future.

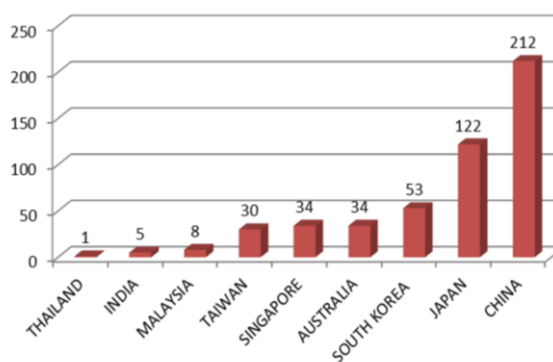


Fig. 2 A bar graph demonstrating the total number of papers published in Asia Pacific Countries from 2001-2011.

While trying to determine the direction of research and the trend over the past decade, it was clear to the authors of this paper that the use of cultured mesenchymal stem cells to regenerate cartilage has primarily been limited to applications involving animal models. Many of these studies used rabbits, goats and pigs as representative models which may or may not be a good translational model. This trend has however appear to have changed in recent years. Several studies involving humans have been reported but have been of mainly case reports and case series. From our extensive search, apart from the two published case reports¹⁵, there have been one clinical trial¹⁸ published thus far. All of which demonstrated successful regeneration of the articular and meniscus cartilage in human knees when applied. Interestingly, these studies were conducted in Asian countries. This reflects the research direction, which certain countries have decided to take, i.e. to make translational studies as a priority, to which the west appears to be slower to respond. This may be due to the stringent regulations imposed in developed nations however, this notion remains speculative.

Despite the strong correlation demonstrated between the financial strength of a country and its productivity in research, it is still unclear if the measure used is completely relevant or reflective of the actual ability of the country to perform in this field. Priorities of research vary from country to country, with the amount of funding to this particular field. For example, countries such as Norway may be affluent but remains out of this area of research as it has not been the country's priority to do so. One can also argue that the limitations of the present analyses to denote that research into this area is indicated by the number of peer-reviewed published materials may not be appropriate. However, to determine the actual number of research activity specific for the topic in hand may be difficult and impractical to conduct. These are the recognized limitations of the present review and needs to be considered when making any further conclusion from the data analyzed.

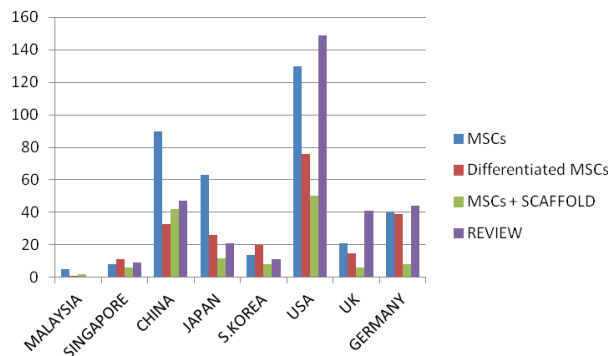


Fig. 3 Comparison between the number of articles published based on the different types of experiments and types of publication.

5.0 Conclusion

There is a strong correlation between the wealth of a country and the publication output in the areas of research involving MSC in cartilage repair although; it can be argued that the relationship may be multi-factorial. In trying to determine where Malaysia is in this research area, as compared to the rest of the world, it is apparent that the progress made is significant but remains substantially lagging when compared to several developed nations. However, it is growing and for the amount of funding made available, it appears that Malaysia is comparable or even ahead to its contemporaries.

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