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Hot Topic

Increasing Public Interest in Stem Cell Injections for Osteoarthritis of the Hip and Knee: A Google Trends Analysis



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ABSTRACT

Background: Stem cell injections are being offered to patients as a nonoperative treatment for osteoarthritis of the hip and knee. To our knowledge, no peer-reviewed data exist to document the usage frequency of these injections nor to quantify the public interest in these injections. We sought to use Google Trends to provide a quantitative analysis of interest in hip and knee stem cell injections at the population level.

Methods: Google Trends search parameters were set to obtain query data from January 2010 through December 2017. 'Arthritis,' 'osteoarthritis,' 'stem cell,' 'injection,' 'knee,' and 'hip' were entered in various combinations to obtain the highest yield search volume. Trend analyses were performed.

Results: Six linear models were generated to show trends in the volume of searches for the United States and the World. Model fit was good, and regression analysis showed significant trends over time for all searches. Use of search terms increased significantly over time (all models $P < .001$). Adjusted R-square values ranged from 54.4% to 78.1%. All trends showed an upward trajectory for the entirety of the study time period.

Conclusion: There has been a marked and statistically significant rise in search query volume related to stem cells and osteoarthritis of the hip and knee since 2010. Online interest in stem cell injections may suggest increased utilization of these procedures. Well-designed clinical studies are required to keep pace with the rising popularity and public interest in this intervention for hip and knee arthritis.

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Stem cell therapy is a commonly explored biologic adjuvant treatment for musculoskeletal injuries. Stem cells are theorized to be efficacious toward augmenting repair processes in structures such as cartilage and tendon which have inherently low healing potential. In areas of inflammation and acute injury, these cells serve as a biologic scaffold and promote repair [1,2]. Stem cells have proven to be effective in cases with bone loss secondary to trauma, nonunion, and femoral head osteonecrosis [3–5]. There is much interest in the ability of stem cells to stimulate the growth of hyaline cartilage as a treatment alternative for degenerative joint

disease [6]. The impact of degenerative arthritis on articular cartilage is disabling for many patients, and present therapies are targeted toward symptomatic relief. Regenerative medicine with stem cells is hypothesized to alleviate pain and prevent progression of this disease unlike the alternative nonoperative treatment methods to date.

Reports on elite athletes and celebrities experiencing beneficial effects from regenerative medicine have helped to popularize stem cell therapy over the past decade. Clinical centers have responded by offering stem cell therapy for osteoarthritis [7]. The stem cell market has expanded rapidly with investments of over 18 billion USD in stem cell companies from 2011 to 2016 [8]. While this would certainly suggest that the use of stem cell therapy for osteoarthritis has likely increased in use and popularity, little data exist to support this hypothesis. General public interest in stem therapy for degenerative joint disease in the knee and hip is not known and has not been previously quantified.

Internet search engines have become popular resources for health information for patients and physicians. Google Trends is an

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internet surveillance tool that computes how often a particular search-term is entered relative to the total search volume. Google Trends and its ability to analyze disease epidemiology continues to gain popularity in medical science after being pioneered by Ginsberg et al who published findings on influenza outbreaks in *Nature* [9–11]. Considering the successful employment of Google Trends in other health-related contexts, the present study was designed to explore the utility of this tool to track trends in public interest in information regarding stem cell procedures.

The aim of this study was to explore the utility of the Google Trends tool to track public interest in information regarding stem cell procedures for hip and knee arthritis. Our hypothesis was that searches related to stem cell treatment for hip and knee arthritis would have increased over the past several years.

Methods

Potential search terms were identified in a collaborative manner among members of the adult reconstruction team. Focused search engine language related to stem cell procedures about the knee and hip for degenerative joint disease was discussed. Combinations and permutations of ‘arthritis,’ ‘osteoarthritis,’ ‘stem cell,’ ‘injection,’ ‘knee,’ and ‘hip’ were surveyed.

When a search is performed in Google Trends, data and graph results are generated if the search terms meet a certain threshold of volume. We entered the unique search criteria above into Google Trends to generate a graph of the data. In Google Trends, the results are returned on a scale from 0 to 100. A value of 100 represents the highest proportion for the terms queried within a selected region and time frame, while lower numbers at other timepoints are calculated as fractions of that assigned maximum. Depictions of the data allow for evaluations in rates of change and comparisons among search terms.

Using the data generated by Google Trends, we created a database for the interest volume per term from January 2010 to December 2017. Minitab, version 17, was used to analyze the data. Linear, quadratic, and exponential growth models were generated, and the models were evaluated using standard measures of accuracy (mean absolute percentage error, mean absolute deviation, and mean squared deviation). Regression analysis was also completed for the volume per term to determine if there was a significant increase of usage over time [12].

Results

Figure 1 shows the data and linear trends for searches with the keyword ‘arthritis’ and ‘osteoarthritis’ and stem cell or stem cell

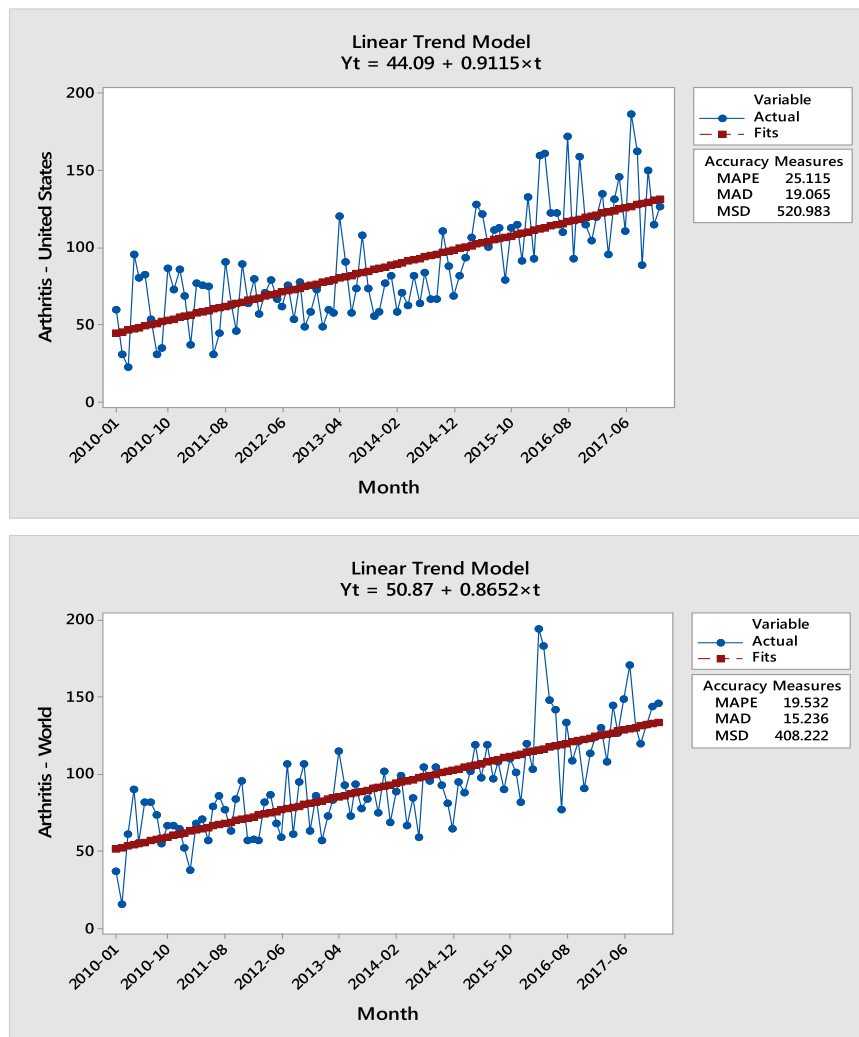


Fig. 1. Linear trend models for arthritis (United States and World). MAPE, mean absolute percentage error; MAD, mean absolute deviation; MSD, mean squared deviation.

injections for searches in the United States and available information for all countries. Search volume has increased >50% from 2010 to 2017. Figure 2 illustrates the data and linear trends for searches using various combinations of the keywords ‘hip stem cell’ and ‘hip injection’. Figure 3 presents the data and linear trends for permutations of the keywords ‘knee stem cell’ and ‘knee injection’. When comparing Figures 2 and 3, search volume related to the knee resulted in trend lines with much greater slope. Of note, when world data were obtained to examine interest between countries, the United States was the only country to record any volume of searches for ‘knee stem cell injections,’ ‘hip stem cell injection,’ and ‘osteoarthritis stem cell’ queries.

For all trend analyses, the linear model had the best measures of accuracy, with mean absolute percentage errors ranging from 19.5% to 43.9%. Use of terms increased significantly over time (all models $P < .001$). Adjusted R-square values ranged from 54.4% to 78.1%. All trends showed an upward trajectory for the entirety of the study time period.

Discussion

This is the first study to apply Google Trends to gauge the public interest in stem cell therapy for hip and knee osteoarthritis. The results of this study suggest a large increase in the number of “hits”

for each search term over the period of record, and based on the equations derived from the trend analyses and the results from regression analysis, we should anticipate a continued increase in internet searches for all of the terms in this study.

The prevalence of knee and hip degenerative joint disease continues to increase with the aging population and increasing prevalence of obesity. Kurtz et al have reported that patients aged less than 55 years comprise the most rapidly growing subset of patients undergoing total joint arthroplasty in the United States [13]. This is a global phenomenon; the Finnish Arthroplasty Registry demonstrated a more than 20-fold increase in total knee arthroplasty in the 50-59 age group over a 20-year period [14]. But, while hip and knee arthroplasty have become increasingly accepted procedures for severe arthritis even in young patients, limitations and concerns exist. Decreased patient satisfaction and increased lifetime risk of revision, reaching up to 1 in 3 in those patients aged 50-55 years, suggests a need for alternative therapies [15–17]. Stem cells, with their pluripotent properties and ability to generate new cells in existing healthy tissues and repair tissues in those structures that are injured or damaged, have been hypothesized as one novel treatment.

Mesenchymal stem cells (MSCs) have an ability to develop and proliferate into mesodermal tissue. They also have been shown to inhibit proteolytic enzymes responsible for cartilage degeneration

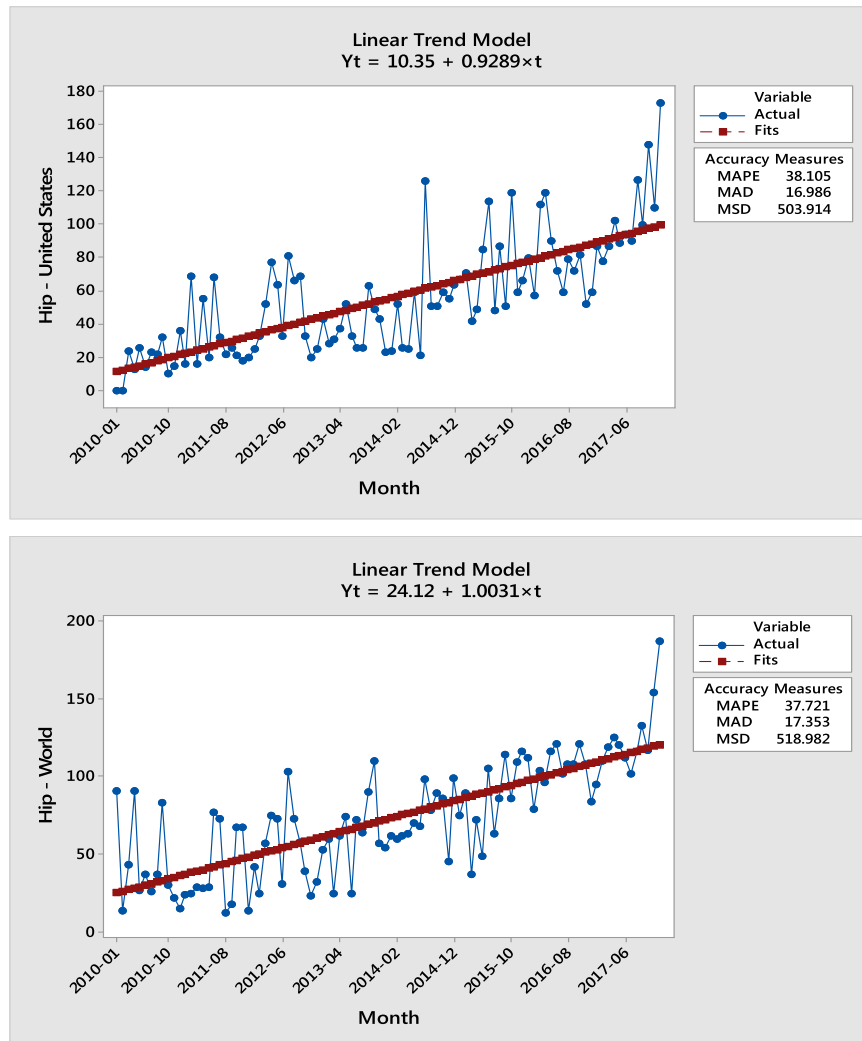


Fig. 2. Linear trend models for hip stem cell (United States and World).

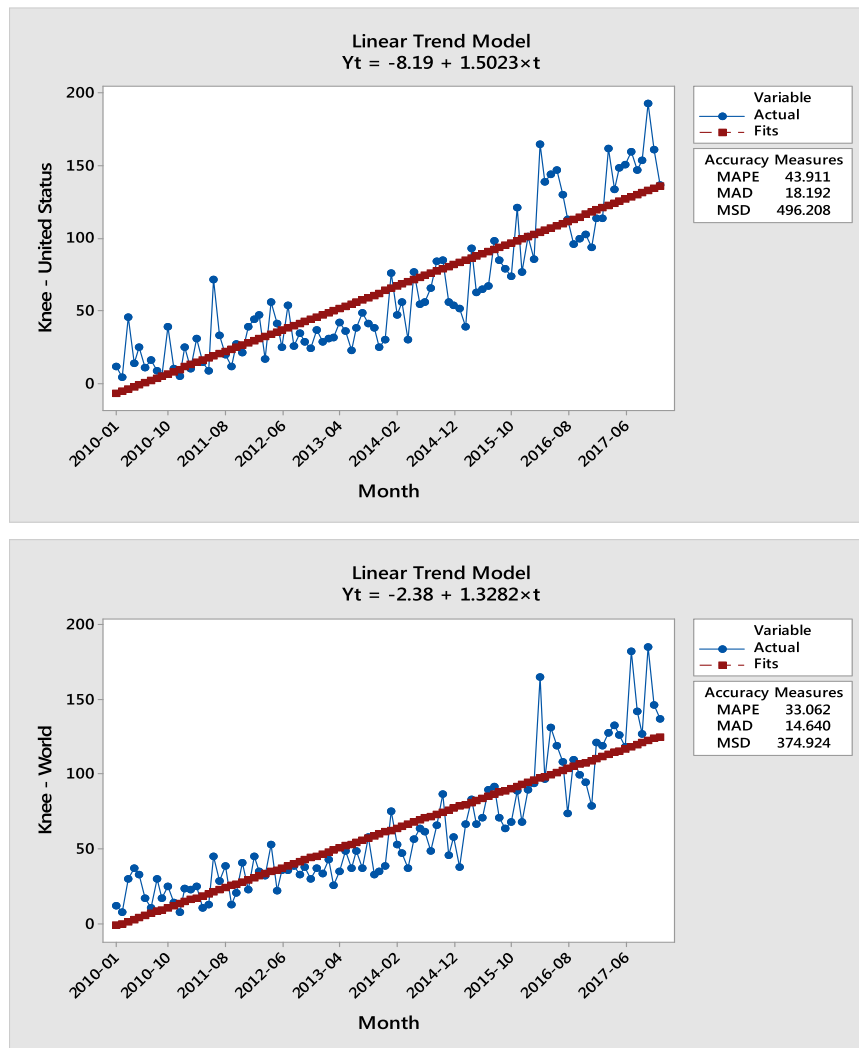


Fig. 3. Linear trend models for knee stem cell (United States and World).

[18]. There are numerous techniques described for stem cell preparation and implementation with a few animal models examining a pure intraarticular injection modality. Sato et al looked at commercially available human stem cells suspended in either hyaluronic acid or phosphate-buffered saline and the effects on arthritic knees in guinea pigs. Following direct injection, immunohistochemistry showed partial cartilage regeneration [19]. Murphy et al showed reduced degeneration of articular cartilage and subchondral sclerosis in goats after articular injection [20]. Lee et al utilized a porcine model where cartilage defects were surgically created. After injection with autologous MSCs harvested from the iliac crest suspended in hyaluronic acid, there was evidence of cartilage healing histologically [21]. There is one clinical case study designed to examine effects of percutaneous injection of MSCs in the setting of degenerative joint disease that has been published to date. Centeno et al harvested iliac crest marrow and prepared MSCs suspended in phosphate-buffered saline. The subject underwent repeat iliac crest marrow harvest and was subsequently injected with the MSCs and isolated nucleated cells. Follow-up MRI obtained at 6 months after procedure illustrated increased meniscus and cartilage volume compared with imaging preprocedure. A large reduction in modified VAS score was also recorded [22].

But, while animal models have suggested some theoretical benefit, there is a lack of rigorous clinical data to support the

efficacy of stem cell injections in routine clinical use for hip and knee arthritis. Systematic reviews of this topic have shown that only a small number of studies exist, most are not randomized and lack an adequate control group, contain very small numbers of patients, and are at risk of bias [23,24]. The results of randomized controlled trials have been mixed with some suggesting efficacy while others have shown no improvement compared with control [25]. While stem cell use appears to be largely safe and has potential use in the nonsurgical management of arthritis, further good quality research appears needed before routine use can be recommended [26]. This is particularly important given the high cost associated with these injections and the potential vulnerability of the patients seeking out these treatments [27]. Safety is also a concern with these injections; the Centers for Disease Control recently issued a report on 12 patients who developed infections after intraarticular stem cell injections [28]. The United States Food and Drug Administration has issued a public notice about the safety concerns with these unproven stem cell therapies [29] and sent warnings to multiple stem cell clinics for unsafe practices [30].

Quantifying the incidence of stem cell injections for osteoarthritis is difficult to do given the lack of standardization, oversight, and data collection. We are not aware of any large national databases or registries that would allow us to study this topic. Google Trends is a powerful tool that has been used to assess disease

outbreaks and developing health-care trends in medicine. Web-based behavior has been shown to predict public behavior, which in our case would suggest that the incidence of stem cell injections has been on the rise and may continue to increase in popularity. While the monitoring of online queries can provide insight into human behavior that would be difficult or impossible to explore otherwise, limitations to these big data studies obviously exist. Google data are deidentified and may result in sampling bias. The results may not fully consider areas with limited resources and internet utilization. There are other search engines available which Google Trends does not capture. It is also possible that queries entered on these topics are entered by a more select number of users repeating searches rather than unique individuals. The effects of this may be minimal given reports of Google handling at least 2 trillion searches per year. Finally, it should be emphasized that these data only represent interest and not whether there is an associated particular stance on stem cells and lower extremity osteoarthritis. We cannot correlate search activity with actual utilization of stem cell injections.

In conclusion, our study has shown a clear increase in search engine volume and public interest in stem cell injections for hip and knee arthritis since 2010. While some early *in vitro* data suggest MSCs have potential application in arthritis, there remains minimal evidence for the efficacy for stem cell therapy from properly controlled, randomized studies, and stem cells injections for arthritis remain investigational. Physicians treating patients with osteoarthritis should expect interest in these injections to continue to increase. The authors urge caution when counseling interested patients given the paucity of clinical data and substantial cost associated with these injections.

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