Post-traumatic knee osteoarthritis: epidemiology, cost-burden and rationale for b...

Introduction:

Osteoarthritis (OA) represents a chronic burden to the American healthcare system, and treatments aimed at reducing symptoms and preventing OA progression have long been a focus of medical research. Although many potential therapies have been explored in animal models, current efforts to translate basic science findings to clinical patient care have had limited success. While OA is typically a progressive disease, a subset of patients develop secondary OA as a direct result of a traumatic injury to the joint. This form of OA is termed post-traumatic OA (PTOA) and occurs in certain cases after structural damage to the joint, such as fracture, acute ligamentous sprain, or chronic instability[1]. Patients with progressive PTOA eventually require major stabilizing surgery for treatment of severe disease, with total joint replacement most common. There is a large and unmet need in delaying progression of PTOA, resulting in a significant cost burden on our overall healthcare system and quality of life.

The first estimates of PTOA incidence, prevalence, and burden of disease was published more than a decade prior in 2006[2]. This study, in the absence of any national population data, extrapolated institutional experience with PTOA to a population wide estimate. Their estimates corresponded to approximately 5. 6 million individuals with OA of any joint attributable to prior trauma with an aggregate financial burden of $3. 06 billion in direct costs, approximately 0. 15% of the total US heal care direct cost outlay at the time.

With increasing population sizes and prolonged lifespans since 2006, this review represents a summary of the current literature published since that initial study and focusses on knee specific PTOA, outlining its cost burden on the US healthcare system and outlines possible non-operative, regenerative strategies that could potentially reduce the overall disease and cost burden of knee PTOA.

Prevalence of osteoarthritis

Osteoarthritis is a highly prevalent health condition – a 2015 CDC study found that approximately 54. 4 million persons or 12% of the population in the U. S. report having a diagnosis of OA in any joint[3]. This crude prevalence is matched by an age-standardized prevalence of 4% in the U. S., exceeding the global average of 3. 8%[4]. In a 2012 CDC National Health Survey, OA accounted for nearly 20% of all healthcare visits in the U. S.[5], and while a national Dutch population sample showed that OA of the hand is the most prevalent form of OA[6], a follow-up study from the Fallon Community Health Plan in Massachusetts (USA) showed that OA of the knee is the most prevalent symptomatic OA[7].

Prevalence of knee osteoarthritis

Knee OA is more common in women, affected 1. 5-4 females for every one male[8]. While population studies in the US show that nearly 13. 8% of U. S. citizens over the age of 26 years[9]to 50% of those 75 years and older have radiographic evidence of knee OA[10], the prevalence of symptomatic knee OA is significantly lower, with values ranging from 12. 1% in the NHANES III study to 16. 3% of participants aged 55-64 in the Johnston County

Osteoarthritis Project (JCOP)[11]. The JCOP also showed that the lifetime risk of symptomatic knee OA was 45%[12], and data from the Fallon Community Health Plan showed an age- and sex-standardized incidence of knee OA of adults aged 20-89 to be 240/100, 000-person years[13]. Roughly 7. 1 million individuals live in the United States with knee OA[14].

Prevalence of post-traumatic osteoarthritis

Generally, claims data is a reliable source of disease prevalence, but PTOA was not featured as a code in the ICD-9; consequently, there are no estimates from health care claims data before 2016 and retrospective numbers must be used as estimates of disease prevalence. In the U. S., about 12% of the vast number of patients with symptomatic OA of the hip, knee, or ankle can be classified as PTOA, and a retroactive chart review examining knees specifically found that approximately 10% of patients diagnosed with knee OA should be reclassified as having knee PTOA[15]. Using population data from 2011-2012, roughly 360, 000 females and 250, 000 males would fall under the classification of knee PTOA[16]. This represents roughly 0. 32% of the U. S. population over 25 years of age[17].

A 2011 meta-analysis of 24 observational studies found that patients with a history of knee injury have a pooled odds ratio of 4. 2 (95% CI, 3. 11-5. 66) to develop OA compared to patients with no prior history of knee injury[18]. That same meta-analysis showed that specified knee injuries to cartilage and ligaments or fractures of the femur, knee, and tibia conferred an even higher odds ratio of 5. 95 (95% CI, 4. 57 – 7. 75) for eventual development of OA of the knee[19]. A separate cohort study of 1, 566 combat injured warriors

showed that 100% of individuals with traumatic knee injuries resulted in knee PTOA, although the higher predictive value may be attributed to the greater degree of trauma soldiers would develop compared to civilians[20]. The rates of PTOA are notably high in current military and veteran populations and in patients with particular comorbidities, including heart disease, diabetes, and obesity[21].

I/O of Disability from PTOA:

The burden of disability from PTOA involves physical, psychological, and socioeconomic factors[22]. Given the multifactorial nature of these effects, both direct and indirect costs are effected. Direct costs represent five types of consumption of healthcare resources: ambulatory visits, prescription medications, home health care visits, hospital discharges, and “ residual” costs, representing other types of direct care [23] . Indirect costs represent lost wages and their associated burden[23].

Cognitive disability

PTOA represents an often-constant source of pain, and constant pain greatly affects baseline functioning and leads to decreased quality of life[24]. OA in general remains one of the worst health-related quality of life profiles compared with other chronic conditions[25]. A 2016 systematic review found that on mental health surveys that patients with OA score roughly the same as breast cancer patients[26], and this decreased perceived quality of life can have an effect on indirect costs of PTOA.

Socioeconomic Impact

Two forms of indirect cost can be described: absenteeism refers to the total amount of work and subsequent wages that are missed as a result of PTOA, and presenteeism refers to the loss of productivity while working attributable to PTOA[27]. A systematic review showed a wide range of days absent from work due to OA symptoms, from 3. 3 days[28]to 40. 6 days[29](assuming normal wages, an absence of these lengths result in $566 to $3, 616 missed wages, respectively). Four studies that reported indirect losses due to both absenteeism and presenteeism using the Work Productivity and Activity Impairment (WPAI) questionnaire showed that annual indirect costs of OA vary from $7, 622 for workers with mild OA to $29, 935 for workers with severe OA [26] . Extrapolating prevalence data of PTOA, this represents a minimum of $5. 4 billion in indirect costs.

Quality of Life

One metric utilized to measure years of optimal health lost because of poor health or disability is the disability-adjusted life years (DALYs)[30]. This metric, developed by the World Bank to allow comparison of health across countries, quantifies the gap between healthy and diseased patients[31]. In their model, one DALY would represent the loss of one year of full health for one individual. With roughly 700, 000 patients falling under the classification of knee PTOA, it alone would then be responsible for over 100, 000 disability-adjusted life years (DALYs) in North America, a sizable effect that demonstrates the debilitating nature of the disease[32]. This amount is roughly equivalent to the total number of DALYs of hepatitis B and C combined, both rightly seen as public health priorities[33]. This metric refers

only to the disability caused by osteoarthritis itself and neglects many other side effects of PTOA on patients, including mental health and productivity.

While OA is possible in any diarthrodial joint in the body, OA of the knee consistently has much higher rates of pain and disability than other joint OAs[34]. OA has a profound effect on quality of life, and in the U. S. specifically, OA is being defined by an increasingly negative impact as the prevalence of arthritis-attributable activity limitation has increased from 35. 9% in 2002 to 42. 8% in 2015[35].

In the presence of such disability, many patients seek both non-surgical and surgical solutions for OA management. A 2015 US study sought to quantify both the direct and indirect costs of managing knee OA for both insured and uninsured patients[36]. Lifetime direct medical costs attributable to knee OA were estimated at $12, 400 ($19, 600 undiscounted) with current TKA eligibility criteria, approximately 10% of total direct medical costs. The overwhelming majority of costs were attributable to total knee arthroplasty (TKA), followed by non-surgical regimens consisting of “ NSAIDs, annual physician, visits, physical therapy, assistive devices, acetaminophen, and gastro-protective agents”. Another study found that direct and indirect costs were contingent on the age of the patient when they underwent TKA, showing that on average, TKA increased lifetime direct costs by $20, 635, but that it resulted in societal savings in lower indirect costs from improved functional status[37]. Direct medical costs from TKA exceeded societal savings as patients grew older and therefore accrued less indirect benefit. A meta-analysis of OA costs that used non-OA as a comparator showed total annual direct costs for the OA group as 2-4 times as high as the costs of the

non-OA group[38]. Annual medication costs were consistently estimated over $1000, translating to over $7. 1 million for PTOA patients. Total direct costs varied from $1442 – $21, 335 annually, representing at least $1 billion in annual costs to treat PTOA.

Surgical Treatments

Patients who develop OA as a direct result of acute injury often develop OA faster than patients with no past injuries to the joint and the disease tends to progress more quickly and manifest more severely than matched cohorts[39]. Once OA becomes severely symptomatic, the only definitive treatment is TKA, a major surgery that is often associated with post-surgical pain and disability. Global studies have shown that 85% of the direct costs of OA treatment are due to the costs of joint replacement surgery[40].

In a large OA cohort, lifetime likelihood for OA patients of undergoing TKA was 39. 9%[41]. Another study found that with patients diagnosed with symptomatic OA, 52. 2% of males and 50. 6% of females will eventually undergo TKA at some point in their lives, and of those patients, 14. 9% of males and 17. 4% of females will undergo subsequent revision[42]. Applying these values to the most recent U. S. population data from 2011-2012, approximately 312, 000 patients with a current diagnosis of PTOA will one day undergo TKA with a total cost burden of $4. 9bn on the American healthcare system.

Importantly for the subject of TKA in PTOA patients, a retrospective chart review of the entire Medicare database examined patient characteristics, TKA outcomes, and long-term complications in patients undergoing TKA for

both primary OA and PTOA[43]. This study, examining a combined 257, 611 patients with primary OA and 3, 509 patients with PTOA, showed several conclusions pertinent to the treatment of PTOA. Although pre-surgical characteristics were similar, PTOA patients had higher incidence of periprosthetic infection (OR 1. 72, p <0. 001), cellulitis or seroma (OR 1. 19, p <0. 001), knee wound complications (OR 1. 80, p <0. 001), TKA revision (OR 1. 23, p= 0. 01), and arthrotomy/incision and drainage (OR 1. 55, p <0. 001). A similar but smaller study corroborated the previous study, showing that TKA undertaken for PTOA patients had a higher rate of complication, although patient-reported outcomes and satisfaction was comparable[44]. Studies have also shown that up to a third of patients who underwent TKA go on to experience chronic pain post-operatively that must be treated [41]).

Surgical Revisions

This fails to consider the cost of TKA revision surgeries – TKA patients with PTOA experience higher rates of post-operation complications than other TKA patients, and even with conservative estimates more than 50, 000 revision surgeries will result from initial TKA attempts to treat PTOA at a cost of over $750 million[45]. This represents a compounding burden on top of existing treatments – not only are patients and the larger system burdened with the initial costs of treating traumatic knee injuries, but failing to prevent the progressing degeneration leads to a substantial burden on total healthcare costs in the U. S .

A cost analysis of two large cohorts with knee OA found that improvements in quality of life with TKA were smaller than previously shown, and in

patients with less severe disease, performance of TKA was economically unjustifiable [41] . Although TKA did improve OA specific measures of quality of life, such as WOMAC and KOOS, Ferket et al. counseled that referring patients with less severe disease to non-surgical treatment in the hopes of halting progression of the disease would be more economically viable than TKA surgery. This economic viability becomes even more pronounced when findings from a retroactive study are considered, showing that patients with PTOA undergoing TKA are more likely to experience post-operative complication than patients with normal OA undergoing TKA[46] , [47]. More post-operative complications translate to an even greater financial burden on the healthcare system and on individual patients. This presents an opportunity for focused treatments that would ultimately decrease the economic burden of TKAs while simultaneously improving patient outcomes and highlights the need for novel, cost effective treatment strategies for PTOA that may help reduce the financial and physical burdens of PTOA.

There may be evidence that TKA should be more strongly considered for patients with specific subsets of traumatic injury. One study found that the largest improvements in pain and functional scores were in patients with isolated articular deformities[48], and there has long been a need for identifying the correlation between patient characteristics and ultimate outcome. While studies are ongoing, treatment should be focused on decreasing overall progression.

Potential Treatment

Importantly, multiple studies have shown that treatment has the potential to postpone TKA in PTOA patients. One study showed that distal femoral varus osteotomy combined with fresh osteochondral allograft significantly delayed progression to TKA over time; 10-years post-surgery, only 11% of patients had underwent TKA[49]. This represents an invasive approach to delaying disease progression but also emphasizes the potential role non-invasive regenerative strategies can play in PTOA treatment. Non-invasive strategies could potentially allow for more natural and stable healing, and, by avoiding surgery, many surgical complications and costs can be avoided. Other non-surgical interventions have been shown to be cost-effective for OA of the knee, and in total, subsequent OA of the knee may be prevented with prophylactic measures initiated after traumatic damage to the knee, reducing the overall burden of the disease on the patient and the US healthcare system.

Opportunity for Orthobiologics in PTOA

Platelet rich plasma (PRP) is derived from autologous blood and contains a platelet concentration that is higher than baseline. It is hypothesized that growth factors released from platelets participate in tissue healing [50] . Because many musculoskeletal tissues exist in hypoxic and nutrient-poor environments, PRP has been explored to augment repair in tissues with low healing ability[50]. With a myriad of functions, platelets are beneficial in all three phases of wound healing: inflammation, proliferation, and remodeling [50] . Briefly, during the initial stages of wound repairs, platelets are directly involved in hemostasis, and, through formation of a fibrin matrix, activated

platelets signal inflammatory cells to migrate into the tissue. Embedded in the fibrin matrix, activated platelets release a steady stream of numerous growth factors including platelet-derived growth factor (PDGF), transforming growth factor (TGF-β), vascular endothelial growth factor (VEGF), and many others[51]. It can also alter the aberrant imbalance between catabolic and anabolic processes in cartilage[52]. Clinical use of PRP originated in the 1980s mostly in cardiac, dental, and maxillofacial surgery departments. Recent experiments have begun to look at the therapeutic roles of PRP for a variety of musculoskeletal injuries, including tendinosis, temporomandibular joint dysfunctions, plantar fasciitis, and, relevant to our discussion, osteoarthritis. While there exists an established safety profile for PRP applications, methods of PRP preparation as well as its composition vary widely between studies; this makes direct comparisons between studies difficult and has long been a hindrance in wider PRP application[53].

Typical protocols for PRP preparation involve removing a patient’s whole blood through routine venipuncture and subsequently centrifuging the blood either once or twice. Centrifugation causes separation of the whole blood into three distinct layers: a bottom layer composed mainly of red blood cells, a middle interphase layer containing a high number of leukocytes, and a top layer containing a supraphysiologic concentration of platelets. The top layer is isolated either with or without the middle leukocyte layer – the product is then known as either leukocyte-rich PRP or pure PRP, respectively. This PRP is then injected into areas of musculoskeletal injury.

Unfortunately, there is a limited number of studies examining the use of PRP in alleviating the symptoms specifically of PTOA, as most studies have

examined its potential role in treating the broader class of OA in several joints. Pertinent to this review, PRP has been specifically examined in the treatment of mild to moderate knee OA. A metanalysis of six separate studies was performed evaluating the efficacy of intra-articular injections of PRP in knee OA[54]. All studies showed treatment with PRP resulted in significant improvement in clinical outcomes, including pain, stiffness, and overall physical function. Although there have been calls for trials evaluating hyaluronic acid in preventing PTOA[55], a comparison between PRP, hyaluronic acid (HA), and placebo showed that PRP resulted in greater improvements in both pain and function. Post-treatment WOMAC scores were significantly lower for patients treated with PRP than patients treated with HA at 3-, 6-, and 12-month timepoints.

The preceding metanalysis did not compare the efficacy of corticosteroids to PRP or HA, as corticosteroids have been shown to decrease pain and have been hypothesized to break the positive-feedback cycle of inflammation and degeneration in OA[56]. Evidence is casting doubt on that hypothesis, with emerging studies indicating both that corticosteroids do not seem to halt the progression of OA and have in part can accelerate disease progression[57]. A recent prospective randomized trial examined both short-term and long-term effects of PRP, HA, and corticosteroid treatments on functional outcomes in knee OA.[58]There was a significant effect on the WOMAC score with all treatments at 3, 6, 9, and 12 months. While the clinical effect of intra-articular PRP injections was similar to the other two treatments at 3 months, PRP injections showed significantly lower WOMAC scores 6, 9, and 12 months after treatment. An additional metanalysis examined 19 different non-

surgical treatments for mild to moderate OA and found that PRP had the greatest point estimate of the treatment effect[59]. This shows that PRP is a valid treatment option for those with symptomatic knee OA, and could decrease the cost burden of progressive OA and subsequent TKA.

Considering the proposed mechanisms of PRP, PTOA represents an ideal injury model where PRP could have a large impact on long-term structural and functional outcomes. If PRP was able to slow the progression, possible reverse establish disease and thereby remove the need for TKA surgery in just 5% of patients with PTOA, over $2. 5 million dollars would be saved at a national level, a sum not including savings from avoided post-operative complications and revision surgeries.

There are approximately 700, 000 US adults with knee PTOA, and annual treatment of PTOA costs at least $5. 4 billion in indirect costs and $1 billion in direct healthcare costs. Assuming existing surgical rates, lifetime TKA costs for the estimated 700, 000 US adults with PTOA will cost more than $5. 6 billion and result in relatively increased rates of post-operative complications and TKA revisions when compared with primary OA cohorts. Surgical intervention is often not effective in improving clinical outcomes which leads to a higher financial burden on the US healthcare system.

Conclusion

Regenerative interventions may play a potential role in delaying post-traumatic osteoarthritis progression, possibly decreasing the need for eventual knee replacement and thereby reducing the sizable economic burden TKA secondary to PTOA has on the US healthcare system. Because of

its acute initial presentation, trauma to the knee represents an appropriate scenario to evaluate prophylactic IA administration of PRP to reduce potential OA progression. (Placeholder1)

https://www. boneandjointburden. org/fourth-edition/viiia0/definitions

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[1]Carbone, A., & Rodeo, S. (2016). Review of current understanding of post-traumatic osteoarthritis resulting from sports injuries. *Journal of Orthopaedic Research, 35* (3), 397-405. doi: 10. 1002/jor. 23341

[2]Brown TD, Johnston RC, Saltzman CL, Marsh JL, Buckwalter JA. Posttraumatic osteoarthritis: A first estimate of incidence, prevalence, and burden of disease. *J Orthop Trauma* . 2006; 20(10): 739-744. doi: 10. 1097/01. bot. 0000246468. 80635. ef [doi].

[3]Barbour KE, Helmick CG, Boring MA, Brady TJ. Vital signs: prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation — United States, 2013—2015. *Morb Mortal Wkly Rep* . 2017; 66: 246–253. DOI: http://dx. doi. org/10. 15585/mmwr. mm6609e1

[4]Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: Estimates from the global burden of disease 2010 study. *Ann Rheum Dis* . 2014; 73(7): 1323-1330. doi: 10. 1136/annrheumdis-2013-204763 [doi].

[5]National health interview survey. https://www. cdc. gov/nchs/nhis/index. htm.

[6]van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. comparison of radiological osteoarthritis in a dutch population with that in 10 other populations. *Ann Rheum Dis* . 1989; 48(4): 271-280.

[7]Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. *Br Med Bull* . 2013; 105: 185-99.

[8]Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. *Br Med Bull* . 2013; 105: 185-99.

[9]Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the united states: Arthritis data from the third national health and nutrition examination survey 1991-94. *J Rheumatol* . 2006; 33(11): 2271-2279.

[10]x

[11]Jordan JM, Helmick CG, Renner JB, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in african americans and caucasians: The johnston county osteoarthritis project. *J Rheumatol* . 2007; 34(1): 172-180. doi: 0315162X-34-172 [pii].

[12]Jordan JM, Helmick CG, Renner JB, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in african americans and caucasians: The johnston county osteoarthritis project. *J Rheumatol* . 2007; 34(1): 172-180. doi: 0315162X-34-172 [pii].

[13]Oliveria, S. A., Felson, D. T., Reed, J. I., Cirillo, P. A. and Walker, A. M. (1995), Incidence of symptomatic hand, hip, and knee osteoarthritis among

patients in a health maintenance organization. Arthritis & Rheumatism, 38: 1134-1141. doi: 10. 1002/art. 1780380817

[14]Barbour KE, Helmick CG, Boring M, Brady TJ. Vital Signs: Prevalence of Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation – United States, 2013-2015. *MMWR Morb Mortal Wkly Rep* . 2017; 66(9): 246-253. Published 2017 Mar 10. doi: 10. 15585/mmwr. mm6609e1

[15]Barbour KE, Helmick CG, Boring M, Brady TJ. Vital Signs: Prevalence of Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation – United States, 2013-2015. *MMWR Morb Mortal Wkly Rep* . 2017; 66(9): 246-253. Published 2017 Mar 10. doi: 10. 15585/mmwr. mm6609e1

[16]Deshpande BR, Katz JN, Solomon DH, et al. Number of Persons With Symptomatic Knee Osteoarthritis in the US: Impact of Race and Ethnicity, Age, Sex, and Obesity. *Arthritis Care Res (Hoboken)* . 2016; 68(12): 1743-1750.

[17]https://factfinder. census. gov/faces/tableservices/jsf/pages/productview. xhtml? src= CF

[18]Muthuri SG, McWilliams DF, Doherty M, Zhang W. History of knee injuries and knee osteoarthritis: A meta-analysis of observational studies. *Osteoarthritis and Cartilage* . 2011; 19(11): 1286-1293. doi: https://doi. org/10. 1016/j. joca. 2011. 07. 015.

[19]Muthuri SG, McWilliams DF, Doherty M, Zhang W. History of knee injuries and knee osteoarthritis: A meta-analysis of observational studies.

Osteoarthritis and Cartilage . 2011; 19(11): 1286-1293. doi: https://doi. org/10. 1016/j. joca. 2011. 07. 015.

[20]Rivera JC, Wenke JC, Buckwalter JA, Ficke JR, Johnson AE. Posttraumatic osteoarthritis caused by battlefield injuries: the primary source of disability in warriors. *J Am Acad Orthop Surg* . 2012; 20 Suppl 1(0 1): S64-9.

[21]Barbour KE, Helmick CG, Boring M, Brady TJ. Vital Signs: Prevalence of Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation – United States, 2013-2015. *MMWR Morb Mortal Wkly Rep* . 2017; 66(9): 246-253. Published 2017 Mar 10. doi: 10. 15585/mmwr. mm6609e1

[22]Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. *Br Med Bull* . 2013; 105: 185-99.

[23]https://www. boneandjointburden. org/fourth-edition/viiia0/definitions

[24]Xie F, Kovic B, Jin X, He X, Wang M, Silvestre C. Economic and humanistic burden of osteoarthritis: A systematic review of large sample studies. *Pharmacoeconomics* . 2016; 34(11): 1087-1100. doi: 10. 1007/s40273-016-0424-x [doi].

[25]Hopman WM, Harrison MB, Coo H, Friedberg E, Buchanan M, VanDenKerkhof EG. Associations between chronic disease, age and physical and mental health status. *Chronic Dis Can* . 2009; 29(3): 108-116.

[26]Xie F, Kovic B, Jin X, He X, Wang M, Silvestre C. Economic and humanistic burden of osteoarthritis: A systematic review of large sample studies.

Pharmacoeconomics . 2016; 34(11): 1087-1100. doi: 10. 1007/s40273-016-0424-x [doi].

[27]Bushmakin AG, Cappelleri JC, Taylor-Stokes G, et al. Relationship between patient-reported disease severity and other clinical outcomes in osteoarthritis: A european perspective. *J Med Econ* . 2011; 14(4): 381-389. doi: 10. 3111/13696998. 2011. 583703 [doi].

[28]Kleinman https://www. ncbi. nlm. nih. gov/pubmed/19952796? dopt= Abstract

[29]Berger A, Hartrick C, Edelsberg J, Sadosky A, Oster G. Direct and indirect economic costs among private-sector employees with osteoarthritis. *J Occup Environ Med* . 2011; 53(11): 1228-1235. doi: 10. 1097/JOM. 0b013e3182337620 [doi].

[30]Murray CJL, Salomon JA, Mathers CD, Lopez AD (eds.) (2002). Summary measures of population health: concepts, ethics, measurement and applications. WHO, Geneva

[31]Devleesschauwer B, Maertens de Noordhout C, Smit GS, et al. Quantifying burden of disease to support public health policy in Belgium: opportunities and constraints. *BMC Public Health* . 2014; 14: 1196. Published 2014 Nov 21. doi: 10. 1186/1471-2458-14-1196

[32]https://www. who. int/healthinfo/global_burden_disease/estimates_country/en/

[33]https://www. who. int/healthinfo/global_burden_disease/estimates_country/en/

[34]van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. comparison of radiological osteoarthritis in a dutch population with that in 10 other populations. *Ann Rheum Dis* . 1989; 48(4): 271-280.

[35]Boring MA, Hootman JM, Liu Y, et al. Prevalence of Arthritis and Arthritis-Attributable Activity Limitation by Urban-Rural County Classification – United States, 2015. *MMWR Morb Mortal Wkly Rep* . 2017; 66(20): 527-532. Published 2017 May 26. doi: 10. 15585/mmwr. mm6620a2

[36]Losina E, Paltiel AD, Weinstein AM, et al. Lifetime medical costs of knee osteoarthritis management in the United States: impact of extending indications for total knee arthroplasty. *Arthritis Care Res (Hoboken)* . 2015; 67(2): 203-15.

[37]Ruiz D, Jr, Koenig L, Dall TM, et al. The direct and indirect costs to society of treatment for end-stage knee osteoarthritis. *J Bone Joint Surg Am* . 2013; 95(16): 1473-1480. doi: 10. 2106/JBJS. L. 01488 [doi].

[38]Xie F, Kovic B, Jin X, He X, Wang M, Silvestre C. Economic and humanistic burden of osteoarthritis: A systematic review of large sample studies. *Pharmacoeconomics* . 2016; 34(11): 1087-1100. doi: 10. 1007/s40273-016-0424-x [doi].

[39]Rivera JC, Wenke JC, Buckwalter JA, Ficke JR, Johnson AE. Posttraumatic osteoarthritis caused by battlefield injuries: the primary source of disability in warriors. *J Am Acad Orthop Surg* . 2012; 20 Suppl 1(0 1): S64-9.

[40]A. Chen, C. Gupte, K. Akhtar, P. Smith, and J. Cobb, " The Global Economic Cost of Osteoarthritis: How the UK Compares," Arthritis, vol. 2012, Article ID 698709, 6 pages, 2012. https://doi. org/10. 1155/2012/698709.

[41]Ferket, B. S., Feldman, Z., Zhou, J., Oei, E. H., Bierma-Zeinstra, S. M., & Mazumdar, M. (2017). Impact of total knee replacement practice: Cost effectiveness analysis of data from the Osteoarthritis Initiative. *Bmj* . doi: 10. 1136/bmj. j1131

[42]Weinstein, A. M., Rome, B. N., Reichmann, W. M., Collins, J. E., Burbine, S. A., Thornhill, T. S., . . . Losina, E. (2013). Estimating the Burden of Total Knee Replacement in the United States. *The Journal of Bone and Joint Surgery-American Volume, 95* (5), 385-392. doi: 10. 2106/jbjs. l. 00206

[43]Bala A, Penrose CT, Seyler TM, Mather RC, 3rd, Wellman SS, Bolognesi MP. Outcomes after total knee arthroplasty for post-traumatic arthritis. *Knee* . 2015; 22(6): 630-639. doi: 10. 1016/j. knee. 2015. 10. 004 [doi].

[44]Scott CE, Davidson E, MacDonald DJ, White TO, Keating JF. Total knee arthroplasty following tibial plateau fracture: A matched cohort study. *Bone Joint J* . 2015; 97-B(4): 532-538. doi: 10. 1302/0301-620X. 97B4. 34789 [doi].

[45]Robinson JC, Pozen A, Tseng S, Bozic KJ. Variability in costs associated with total hip and knee replacement implants. *J Bone Joint Surg Am* . 2012; 94(18): 1693-1698. doi: 1262702 [pii].

[46]Bala A, Penrose CT, Seyler TM, Mather RC, 3rd, Wellman SS, Bolognesi MP. Outcomes after total knee arthroplasty for post-traumatic arthritis. *Knee* . 2015; 22(6): 630-639. doi: 10. 1016/j. knee. 2015. 10. 004 [doi].

[47]Scott CE, Davidson E, MacDonald DJ, White TO, Keating JF. Total knee arthroplasty following tibial plateau fracture: A matched cohort study. *Bone Joint J* . 2015; 97-B(4): 532-538. doi: 10. 1302/0301-620X. 97B4. 34789 [doi].

[48]Shearer DW, Chow V, Bozic KJ, Liu J, Ries MD. The predictors of outcome in total knee arthroplasty for post-traumatic arthritis. *Knee* . 2013; 20(6): 432-436. doi: 10. 1016/j. knee. 2012. 12. 010 [doi].

[49]Drexler, M., Gross, A., Dwyer, T. et al. Knee Surg Sports Traumatol Arthrosc (2015) 23: 1317. https://doi. org/10. 1007/s00167-013-2828-x

[50]Wu PI, Diaz R, Borg-Stein J. Platelet-rich plasma. *Physical Medicine and Rehabilitation Clinics of North America* . 2016; 27(4): 825-853. doi: https://doi. org/10. 1016/j. pmr. 2016. 06. 002“.

[51]Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA. Platelet-rich plasma: A milieu of bioactive factors. *Arthroscopy* . 2012; 28(3): 429-439. doi: 10. 1016/j. arthro. 2011. 10. 018 [doi].

[52]Andia I, Maffulli N. Platelet-rich plasma for managing pain and inflammation in osteoarthritis. *Nat Rev Rheumatol* . 2013; 9(12): 721-730. doi: 10. 1038/nrrheum. 2013. 141 [doi].

[53]Cianca JC, Jayaram P. Musculoskeletal injuries and regenerative medicine in the elderly patient. *Phys Med Rehabil Clin N Am* . 2017; 28(4): 777-794. doi: S1047-9651(17)30057-8 [pii].

[54]Meheux CJ, McCulloch PC, Lintner DM, Varner KE, Harris JD. Efficacy of intra-articular platelet-rich plasma injections in knee osteoarthritis: A systematic review. *Arthroscopy: The Journal of Arthroscopic & Related Surgery* . 2016; 32(3): 495-505. doi: https://doi. org/10. 1016/j. arthro. 2015. 08. 005.

[55]Laith M. Jazrawi & Jeff Rosen (2011) Intra-articular Hyaluronic Acid: Potential Treatment of Younger Patients with Knee Injury and/or Post-Traumatic Arthritis, The Physician and Sportsmedicine, 39: 2, 107-113, DOI: 10. 3810/psm. 2011. 05. 1900

[56]Takagi, S., & Blaha, J. (2018). The suitable use of intra-articular corticosteroid injection in knee osteoarthritis. *Osteoarthritis and Cartilage, 26* . doi: 10. 1016/j. joca. 2018. 02. 585

[57]Jayaram P, Ikpeama U, Rothenberg JB, Malanga GA. Bone marrow-derived and adipose-derived mesenchymal stem cell therapy in primary knee osteoarthritis: A narrative review. *PM R* . 2019; 11(2): 177-191. doi: 10. 1016/j. pmrj. 2018. 06. 019 [doi].

[58]Huang, Y., Liu, X., Xu, X. et al. Orthopäde (2019). https://doi. org/10. 1007/s00132-018-03659-5

[59]Vannabouathong C, Bhandari M, Bedi A, et al. Nonoperative treatments for knee osteoarthritis: An evaluation of treatment characteristics and the

intra-articular placebo effect: A systematic review. *JBJS Rev* . 2018; 6(7): e5. doi: 10. 2106/JBJS. RVW. 17. 00167 [doi].