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Review Article

Quadriceps Muscle Mechanics and Knee Osteoarthritis - A 2022 Update

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Abstract

Background: Knee joint osteoarthritis is a highly disabling disease with no distinct cause that persists unabated despite decades of research. Among the various possible causes and factors that influence the progression of the disease other than age and trauma may be various forms of muscle dysfunction, especially among the key knee extensor muscle group known as the quadriceps femoris.

Aim: This narrative review strove to examine some pertinent past and recent 2022 research highlights in this respect and to offer possible research recommendations in this regard.

Methods: To achieve the review aims, the PUBMED data base and others housing reports aligned with this topic was searched using the key words knee osteoarthritis and quadriceps/knee extensor muscles. Pertinent 2022 and related data were carefully examined and the study researchers' approaches, conclusions, and recommendations were duly recorded.

Results: Many diverse studies within the desired topical theme prevail, rendering it challenging to discern or extract any meaningful trend or conceptuality sound deterministic theory of causation or pathogenic osteoarthritis insights. Even in the realm where multiple publications are available on a single theme, conclusions and design approaches remain inconsistent and of possible moderate quality at best.

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Conclusion: Efforts to examine and intervene to avert one or more manifestations of quadriceps muscle dysfunction may prove to be highly important in the realm of favorably influencing or minimizing excess osteoarthritis knee joint dysfunction, regardless of whether knee extensor muscle dysfunction is a reactive, rather than a causative factor, but requires a more profound evidence base.

Keywords

Articular Cartilage; Knee Joint; Osteoarthritis; Quadriceps Muscle; Pathology

Introduction

Osteoarthritis, a widespread chronic degenerative disorder of one or more joints such as the knee produces a high degree of disability among immense numbers of adults, especially those in the higher age ranges [1]. A disease with no specific clearly defined cause, and very few successful methods for treating this, including medications, injections, physical therapy, and on occasion surgical interventions, novel findings pointing to possible mechanisms that may be harnessed towards preventing the disease, rather than accepting the disease is inevitable are highly sought. In this regard, a major advancement has been the acceptance that osteoarthritis is a disease of the whole joint, wherein muscle and its viability and physiology may play a highly salient mediating or moderating role in controlling those spatial and temporal joint loading factors that influence the quality of articular joint cartilage biochemistry, structure and its functional properties and that can possibly be intervened upon favorably and non-pharmacologically, where indicated, to a high degree [2].

Indeed, there is a reasonably sound and emerging evidence base in support of the idea that muscles can be detrimentally impacted by osteoarthritis, along with the possibility that pathology of the neuromotor system leading to muscle dysfunction may promote joint dysfunction in its own right, and may hence be an important osteoarthritis treatment target for clinicians that cannot be overlooked [3-6]. As such, and unsurprisingly, Mohajer, et al., concluded that knee osteoarthritis does appear to be associated with longitudinal objectively measured decreases in the cross-sectional area dimensions of the quadriceps muscles, as well as increases in its intramuscular adipose tissue constituents [6]. These two potentially modifiable risk factors, while not the only possible muscle abnormalities that may be injurious to the knee joint, are noteworthy because they tend to point to changes in the properties of the quadriceps muscle as being predictive of downstream knee osteoarthritis symptom worsening and knee replacement. Recent work by Toth, et al., while failing to detail the subject's pre surgical clinical muscle status among their knee joint surgical candidates found the effects of total knee arthroplasty on skeletal muscle at the cellular and subcellular levels to cause skeletal

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muscle fiber atrophy and contractile dysfunction in older adults, as well as molecular mechanisms underlying impaired contractility [7]. These results revealed the presence of multiple profound effects of knee joint replacement surgery on muscle fiber size and intrinsic contractility early after surgery that may contribute to functional disability, however, it is possible these muscle abnormalities were present prior to surgery. This would be consistent with knowledge that the presence of various forms of muscle abnormalities may impact cartilage integrity, for example if muscle weakness or poorly coordinated muscle functions allow abnormal and persistent physical stresses to be placed on a joint [8,9]. As well, excessive muscular forces or muscle contractile dysfunction due to nerve damage or intrinsic changes in the muscle property such as muscle fiber degeneration might be expected to hasten the development or progression of the disease as suggested by Fink, et al., [10].

The ability of muscle to contract effectively, is also implicated in the synthetic and degradative processes of normal articular cartilage, as well as joint shock absorption during loading, hence abnormalities in this respect, such as static loading or no loading situations or alterations in the quadriceps femoris tendon along with quadriceps weakness may be worthy of future study [1,11,12]. Other data imply various degrees of joint impact resulting in joint tissue injuries in the face of a failure of timely muscle protective mechanisms may produce disturbances of cartilage metabolism that leads to chondrocyte death, cartilage loss and an eventual loss of joint function even in a physiologically normal joint [13].

Moreover, Van den Noort, et al., recently showed there may be a high percentage of non-contractile muscle tissue in the vastus medialis muscle (an important quadriceps muscle component) as measured using a standard imaging approach and that the presence of this structural alteration is associated with muscle weakness [14]. That is, the extent of the prevailing percentage of non-contractile muscle tissue categorized as being high or low seemed to be an important compositional property of the vastus medialis muscle driving the degree of quadriceps muscle strength measured isokinetically and longer sit to stand times. Mansfield, et al., who conducted a scoping review of central nervous system measures during selected motor tasks supports the plausibility of an important role for muscle in individuals with knee osteoarthritis [15]. Common motor deficits highlighted were those associated with decreases in neural activation, the presence of central nervous system sensitization, decreased quadriceps muscle spindle responsiveness, and increased triceps surae muscle activity, among other attributes of muscle function and structure.

In view of these possibilities, it thus seems plausible to suggest that in addition to static factors, abnormal dynamic forces imparted by muscle, as well as muscle weakness, or poor coordination may contribute towards the onset or progression of articular cartilage damage that leads to cartilage loss. That is, a failure to generate those specific forces needed to protect a joint, as well as muscle contractions that are poorly coordinated or suboptimal may be expected

to predictably produce or exacerbate articular cartilage degenerative processes as opposed to a universal progressive ‘wear and tear’ theory of osteoarthritis pathology [16,17].

Whether this effect is indeed causative or even if not, this idea seems worthy of study, given the enormous burden of the disease and the fact age is often not a factor in explaining either the presence of the disease or why the disease manifests on one side and not the other or at one set of joints and not others [1]. At the knee for example, many cases of osteoarthritis occur unilaterally, not bilaterally, as one would expect if age alone was the causative factor. As well, age cannot explain how degeneration is often confined solely to one area of a joint surface and why osteoarthritic cartilage is not the same as aging cartilage. Finally, since joint surgery which reduces pain and provides a sound mechanical surface does not always improve an osteoarthritis individual’s mobility, nor their strength capacity or ability to contract their muscles in a timely way and is often followed by a re-occurrence of symptoms or surgical failure exploring what factors that might be contributory to the osteoarthritic disease process and possibly to its initiation and progression, remains a high priority [18].

Because of the strong possibility that muscular disturbances in general, and specifically those that may be localized to the quadriceps muscle, the key knee stabilizer, may be implicated in the risk of incurring knee joint osteoarthritis, and/or a more severe detrimental outcome than is often evidenced via radiological examination, this brief was designed to explore current research observations and conclusions in this respect.

Specific Aim

This work was specifically aimed toward examining the most current research documenting any knee osteoarthritis-knee extensor muscle associations, and whether pursuing this topic appears to be a topic of merit. Gaps in the literature were sought, along with sources of evidence that might inform or solidify various current clinical practices and prevention efforts.

Methods

Using the PubMed data base, the world’s largest research repository and the key terms knee osteoarthritis and quadriceps or knee extensor muscles or muscle dysfunction, all 2022 articles related to this topic were scanned and examined for relevance. This year was specifically selected for study in light of possible changes to the nature of research approaches and patient presentations in the post COVID realm. Previous data are included as indicated in this report to provide context for this ensuing discussion, and readers are directly to past reviews that can be examined separately to highlight the level of interest, scope, and findings that undergird this realm of inquiry [19-24]. Excluded were balance studies, ligament and meniscus studies,

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exercise or physical intervention studies, post-surgical studies, lab studies, and mixed studies that did not focus solely on the knee extensors in the context of knee osteoarthritis. No quantitative analyses were conducted and all research designs were considered acceptable. It was taken for granted that PubMed peer reviewed current journals would provide some insights into what is needed and why in the future, regardless of any research flaws, and housed most of the articles located in PubMed Central and Google Scholar that represent the overall current scope and field of endeavour.

Results

Key Findings

When applying the PubMed data base to search for articles published in 2022 on knee osteoarthritis and its possible link to the status of the quadriceps femoris muscles, a topic that dates back to 1946, a total of 1,101 potential references were observed as of November 24, 2022, with 731 of these focusing primarily on the topic of knee extensor muscle strength and its observed association with knee osteoarthritis. However, these alone were clearly found to be non-uniform and some, for example studied the topic of isometric muscle strength with a sophisticated device, others with a hand held device. The mode of muscle measures applied is also inconsistent across studies, for example static versus dynamic quadriceps strength tests that may well address differing functional attributes may explain the presence of inconsistent findings in this body of current literature. Moreover, the full spectrum of how muscle may impact or be impacted by the presence of knee osteoarthritis is challenging to discern given that several listed studies only examined post-operative muscle status at the knee in selected ways, but not their pre-operative status, while differences in concentric versus eccentric forms of quadriceps muscle contraction also appeared to yield inconsistent strength associated findings. As such, even if only considering the topic of knee extensor strength alone, believed to impact knee osteoarthritis progression, what was observed could not be duly aggregated in our view with any meaningful result. As well, temporal features of quadriceps muscle attributes cannot be readily discerned in our view on the basis of either current or past research as well as in consideration of parallel studies embedded in the data base that do not examine strength, but examine multiple alternate aspects of quadriceps muscle structure and function among quite varied knee osteoarthritis samples. Additionally, some studies refer to findings of patella femoral osteoarthritis and not tibia femoral located knee osteoarthritis, and to manifestations of one quadrant of the quadriceps muscle and not the three others.

At the same time, housed in the same data base are multiple studies comparing various modes of treating osteoarthritis muscle, even though very few studies located focused on the actual question of what role muscle does play in knee osteoarthritis, and if this is purely a reactive one or not. Additionally, very few carefully examined muscle structural and reflexive control

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features that may be highly pertinent in elaborating upon the pathogenesis and treatment of knee osteoarthritis, and that would further the many gaps in the literature others have noted in the past. Indeed, it can be said that in 2022 most emergent topics that have undergone peer review and have received possible funding, have not provided any clear insight into the rationale for their study focus, given the fact this area of thought is emergent rather than established. None appeared to be reflective of possible COVID-19 implications as far as older adults with definitive knee osteoarthritis could be affected negatively in terms of pain and muscle function. For example, while a substantive number of postings discussed various forms of intervention designed to foster muscle function and relieve pain, or compared one aspect of muscle function to another, most failed to clearly provide any clear mechanistic rationale for their chosen research approach and those variable[s] that were examined, and took it for granted that therapy conducted in the community would be comparable in post COVID situations to those that prevailed in per COVID periods.

Consequently, in addition to the lack of depth in this material, and even after Google Scholar and PubMed Central were explored for cross references with little additional materials being found, it is our view any attempt to synthesize currently posted findings would prove marginal at best in light of its diversity, lack of a sound theoretical framework, the use of secondary data sets, mathematical, and multiple cross sectional or retrospective studies, rather than controlled studies or prospective studies designed to rule out confounders [25,26].

In short, the PubMed data base and its analogues currently appear to house multiple articles related to knee extensor muscle strength, while also housing a variety of studies that have recently examined other quadriceps muscle attributes such as: 1) muscle rate of force development, 2) the separate forces of each quadriceps head under low load conditions, 3) quadriceps strength asymmetry, 4) knee joint osteoarthritis peri-articular muscle strategies, 5) stationary seated isokinetic quadriceps torque measures at varying velocities and 6) muscle stiffness among widely varied samples with non-uniform research designs and sampling procedures, and strength tests and others conducted in anatomic positions that vary from non-weight bearing to weight bearing and that may or may not represent those used in daily functions in any detail when trying to establish their relevance in the realm of knee osteoarthritis. In addition, confusion is increased when considering the inclusion of studies that have measured diverse movement patterns, stair versus level walking attributes, plus those conducted at varying contractile speeds or via the use of skeletal muscle inflammatory markers [22,27]. The extent of quadriceps muscle fat infiltration aspects of quadriceps muscle inhibition and its possible sources muscle volume and cross sectional areas among varied samples and disease stages and presentation pose additional complexity in efforts to uncover any distinctive clinical attribute worthy of targeted study [17,28-31]. At the same time, only limited attempts currently pertain to collecting data as regards important actual knee osteoarthritis indicators such as knee joint effusion, muscle pathology, muscle perturbation responses, aging and knee muscle spindle correlates and any long COVID-19 muscle or pain impacts that might prove

highly salient. Indeed, and unsurprisingly, despite the obvious and laudable dedicated efforts of many researchers, almost all current clinical publications emerging in 2022 revealed the authors had concluded their results were modest at best and would thus require further exploration to establish their clinical relevance as discussed by Sequiera, et al., [32]. In addition, even though muscle may indeed not be the most beneficial target to address in the context of knee osteoarthritis in the future, especially if this is imprecisely measured, it was assumed by most authors that the knee extensors are a highly valid target to examine or intervene upon in the realm of knee osteoarthritis, regardless of what aspect is addressed specifically.

For example, on the basis of indirect evidence implicating muscle in influencing peak external knee adduction moment during gait and hence the progression of knee osteoarthritis and the possible fact other factors account for any progressive knee damage, Lee, et al., who conducted a study comprising 35 patients with unilateral medial osteoarthritis and varus deformity who were candidates for open wedge osteotomy found that the most salient predictor of this force indicator was the muscle endurance data recorded from the knee extensor muscles [33,34]. However, multiple linear regression analysis showed that quadriceps endurance score assessed a total work variable that emerged at a test speed of 180 °/sec was the only factor independently associated with the adduction moment measures. Also noteworthy was that although the adduction moment of the assessed knees correlated with the endurance measures, they did not correlate with the quadriceps strength muscle measures, a frequently assumed fact underpinning the importance given clinically to knee extensor strengthening exercises, albeit not necessarily always with robust results or gender based similarities [25,26].

In this regard, and unsurprisingly Metcalfe, et al., found cases diagnosed with knee osteoarthritis do experience abnormal loads of their major weight bearing joints bilaterally, and these abnormalities persist despite treatment of the affected limb [35]. These findings tended to suggest that the presence of either pre-existing muscle pathology and /or an alteration in afferent input to the central nervous system and long term adaptations may preside and if untreated may prove detrimental to articular cartilage in vulnerable joints such as the knee, and hence precision of any intervention is essential. This idea is not simplistic and will involve careful analysis if the goal is to avert possible knee extensor muscle weaknesses from increasing the risk of developing or perpetuating knee osteoarthritis in both men and women [36-39]. Why this weakness tends to be asymmetrical from side to side in unilateral cases, and the specific influence of proprioception changes, stability deficits, joint range of motion factors, intra-articular sensory neurons, pain and associated muscle compensatory responses, and joint biomechanics, along with muscle cross sectional area ratio measures and their independent or collective presence appear to impact on the severity of osteoarthritis-related morphological changes at the knee should also not be overlooked [31,40-43]. Indeed, careful analyses have revealed that quadriceps muscle weakness is found to be consistently associated with the measure of patella alta and bone marrow lesions in patella femoral knee osteoarthritis cases

[44]. However, even here, Amin and colleagues found greater quadriceps strength was only protective against cartilage loss at the lateral compartment of the patellofemoral joint, but not at other joint sites, again suggesting a need for very careful pre-treatment assessments and program planning efforts and outcome expectations thereof [45].

In this context, Ling, et al., who found changes in motor unit physiology associated with early knee osteoarthritis was the variable that correlated with the degree of radiographically assessed osteoarthritis severity, also reported muscle strengthening may not always protect an individual from osteoarthritis, if the more complex association of muscle function and joint physiology are not carefully weighed and considered [46]. Given its role as both an afferent and efferent structure that not only produces movement, but relays proprioceptive information that promotes function, joint stability, and shock absorption, this argument does seem like one that merits further exploration.

Alternately, and in support of this viewpoint, early work by Messier, et al., implied that the presence of any uneven declines in quadriceps strength surrounding a knee joint could sensitize an individual to the detrimental effects of high impulse loads more highly than if the muscles were well balanced and coordinated temporally and in magnitude since the quadriceps muscles are highly important shock absorbers [47]. In time, if unrelieved, the exposure of the knee joint cartilage to excess loading impacts can be expected to induce cartilage damage that in consequence produces reactive effects in the knee joint muscle structure and function that perpetuates the magnitude and extent of the condition including changes in the properties of muscle afferent neurones that might influence the peripheral drive of spinal excitability and plasticity adversely [48,49]. According to Hurley, the presence of joint damage, might in turn foster a situation of further abnormal articular afferent inputs that thereby reduces voluntary quadriceps femoris activation, and that may prevent the threshold for stimulation of muscle hypertrophy from being reached, which impedes rehabilitation [50]. Moreover, abnormal articular afferent information may also decrease gamma-motoneurone excitability causing proprioceptive deficits that reduce the ability of the quadriceps to protect the knee joint.

Hence, even though animal models studied closely by Herzog and Longino revealed muscle weakness alone can independently increase the risk for joint degeneration processes that lead to osteoarthritis, and Yousef, et al., noted quadriceps muscle weakness did cause a state of increased degeneration of the retro-patellar cartilage of arthritic rabbits, this group implied future work is needed here to delineate whether muscle weakness directly affects joint degeneration, or if changes in function and movement execution associated with muscle weakness are responsible for the increased rate of the onset and progression of osteoarthritis [51,52]. Egloff, et al., noted that while muscle weakness can induce osteoarthritis, that may impact walking ability, it is also possible that it is the strength imbalance between the knee flexors and extensors of an affected leg in the later stages of the disease rather than knee extensor strength alone that can promote further wear of an already disrupted knee joint surface

[53-55]. Hence it is suggested that measures of both strength, and muscle co-activity assessed in parallel can probably provide additional information related to knee osteoarthritis and how to mitigate its progression and severity than failing to do this [56]. Other research shows that there should probably be more attention paid to the role of intra muscular fat in the knee musculature as this found to be positively associated with an increased risk of radiographic knee osteoarthritis [57]. Moreover, having a proportionally lower lean body (muscle) mass to lower joint-protective ability may yet lead to knee osteoarthritis changes due to the lower joint protection ability of the muscle, rather than be caused by the condition [58]. In other work, Conroy, et al., found muscle quality (specific torque) defined as strength per unit of muscle area for both the entire thigh and quadriceps to be a significant predictor of radiographic knee osteoarthritis, regardless of pain levels [59].

In addition, a variety of abnormalities of muscle composition, and other related aspects of muscle structure may accompany osteoarthritic joint damage and/or independently or collectively foster the development of the disease and its magnitude and severity [60-62]. This may implicate more than strength of the quadriceps, including a role for deficits in the flexibility of the quadriceps muscle, its stiffness profile, as well as how specific individual forces of the individual quadriceps muscles impact cartilage viability, vastus medialis fat infiltration and an associated reduced annual loss of medial tibial and patella cartilage volumes, various patterns of muscle fatigue and possible clinically relevant alterations in quadriceps tendon stiffness [63-66].

Additional Findings

As well as some of the aforementioned observations, a recent report by Chun, et al., who studied patients with early knee osteoarthritis did show the presence of decreased muscle strength was associated with an increase in activity limitations in the patient group [39]. However, the researchers concluded, that further well-designed experimental studies are indicated in this regard before any clinical implications about the causal role of muscle in osteoarthritis dysfunction can be validated. Muscle steadiness, expressed as the coefficient of variance [%] and peak power frequency [Hz] elicited during maximal voluntary knee extensor torque generating tests, which seems to be a distinctive muscle attribute related to its strength and self-reported function in cases with knee osteoarthritis, may yet be worth examining further in the future even if findings here are presently unconvincing [68].

According to Alnahdi, et al., subjects with knee osteoarthritis do have significant muscle impairments that affect physical function and that should be targeted in therapy [69]. However, they too affirmed further research is needed to explore the relationship between quadriceps strength and knee osteoarthritis initiation and progression and to determine the optimal exercise prescriptions that may be able to augment outcomes in this patient population.

Metcalfe, et al., concluded that patients with knee osteoarthritis do experience abnormal loads of their major weight bearing joints bilaterally and abnormalities persist despite treatment of the affected limb, hence further treatment may be required if we are to protect the other major joints following joint knee joint replacement surgery [35]. Callahan, et al., propose that more attention be directed towards variations in whole muscle contractile kinetics in adults with advanced-stage knee osteoarthritis, where even the size and function of single muscle fibers may be worthwhile to investigate [70].

Murray, et al., on the other hand observed quadriceps power measures tended to explain more variance in knee flexion angle and knee adduction moment during gait in knee osteoarthritis than quadriceps strength, especially in terms of the effect of multiple loads on knee joint mechanics and should therefore not be neglected, and should be assessed relative to a variety of loads, an idea also observed by Reid, et al., [71,72].

Hodges, et al., support the hypothesis that it is the presence of an augmented medial knee muscle co-contraction that underpins the faster progression of medial knee osteoarthritis, while the increased duration of lateral muscle co-contraction tended to protect against medial cartilage loss [73]. Another study implied it is eccentric quadriceps muscle torque deficits in women that may influence early knee osteoarthritis presentation, while how strength was assessed determined the association between multiple daily activity measures and in the case of knee osteoarthritis among the general population of Lahore, Pakistan quadriceps strength was found to not be a noteworthy or interactive disease correlate [74-76]. Thus in the absence of sound carefully controlled studies, the application of knee extensor exercises to slow down the disease progression may prove to be ineffective, or spuriously effective, rather than not [74].

Indeed, as recently outlined by Oiestad, et al., in an updated systematic review, while there are studies that have examined the interaction between the knee extensors and the degree of knee osteoarthritis, these tend to be of low rather than of high quality, and a role for other factors cannot be discounted with any degree of certainty. This was also the conclusion for patella femoral osteoarthritis as explained by Carvalho, et al., [77]. Other data, for example that by Rutherford, et al., imply a key role for muscle fatigue rather than muscle strength in this regard, but a role for altered muscle activation mechanisms and inflammation may likewise play a key role in this regard [78,79]. Yet again, alternate evidence implies muscle ‘thickness’ may be the salient variable that influences knee joint osteoarthritis according to Tanagushi, et al., and Yoon, et al., [80,81].

To further complicate the data outcomes and inferences highlighted to date, research by Gong, et al., show gender variations in quadriceps strength and its association with structural abnormalities at the knee that imply more gender based sub group studies are indicated [82]. In addition, the effects of knee extensor muscle weakness may impact knee cartilage sites differentially according to Xu, et al., thus a failure to examine all potential vulnerable cartilage

sites that could be affected by osteoarthritis, and only studying selected joint sites may surely lead to erroneous conclusions [83].

Indeed, it seems current and past results do imply osteoarthritis quadriceps femoris associated forms of dysfunction do prevail quite consistently in general, but what is reported and what emerges from the various research offerings reflect what muscle attribute is assessed, as well as what disease indicator is studied, or how much muscle fat mass prevails, rather than any overriding ‘law’ or unified framework of influence [84]. As well, emergent results may depend on the magnitude as well as the type of knee osteoarthritis studied, as well as how and what measurement instruments and analyses are applied or conducted, and their temporal sequence [82]. Tung, et al., further imply that it is measures of muscle capacity utilization, while not found to be associated with pain during walking among a sample of adults with knee osteoarthritis, that is a potentially unreported or unexplored realm of possible relevance that should yet be explored further in the future because current tests failed to employ one or more challenging activities of daily living in their mobility test paradigm that might reveal considerable and novel insights [85].

Alternately, Takahashi, et al., propose that in case of medial knee osteoarthritis, it is compensatory overstrain of the rectus femoris muscle that leads to its hypertrophy and possible flattening of the central aponeurosis curvature that could cause overstrain and abnormal stress loading of the knee cartilage when the limb is used [86]. Thus assessing the thickness and central aponeurotic curvature of the muscle may yet provide a useful and simple test for evaluating overstrain caused by rectus femoris compensation that could engender multiple changes in cartilage structure and function.

Discussion and Implications

Knee osteoarthritis is a painful highly disabling disease that not only poses an enormous burden on many adults in all parts of the world, but years of study have not produced returns commensurate with the immense investment in efforts to understand the disease etiology. Moreover, even though considerable effort has been spent to address the role of muscle in this regard, as outlined in this report the current body of salient studies, while premised on some tentative support for a possible clinically important knee extensor muscle influence in knee osteoarthritis, clearly fail to prove or point to any definitive findings that could impact clinical practices significantly and favorably. Hence the case for more timely and precise preventive steps against knee osteoarthritis, while a laudable goal, remains an elusive quest, at best, and in our view cannot be undertaken currently in 2022 with any degree of certainty because most researchers concluded much more work is needed to unravel the largely observational associations among limited samples, and a sentiment expressed by many almost 10 years ago or more [12].

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Indeed as observed in prior reports, almost all current researchers whose published results are located in the PubMed 2022 data base found more uncertainty in their observations than they had possibly anticipated. Unsurprisingly, most researchers tended to strongly advocate for continuing careful research to examine the importance of muscle in the context of both the onset as well as the progression of osteoarthritis of the knee joint in the future. However, which approach best ‘maps’ with the actual nature of the disease must be better clarified, since few well designed comparison studies exist, and those that employed multiple measures may unwittingly have elicited muscle fatigue or pain reactions that would not occur in more carefully construed isolated test conditions. As well, even though the parameters of muscle reactivity, fatigue and rate of force development, along with muscle spindle and joint sensory mechanism deficits may have a strong bearing both on muscle as well the joint tissues, these attributes are seldom examined when compared to measures of strength alone.

At the same time, muscle weakness, the most frequent observable osteoarthritis associated muscle deficit, is not considered by all to be as strongly implicated as other factors, such as muscle volume [12,42]. Others show the negative effects of ipsilateral and contralateral muscle asymmetry, both structural and functional, and the potential importance of the ability of muscle to contract in a coordinated and timely fashion. Others show cases identified as having poor vastus medialis muscle quality or the presence of excess knee extensor intramuscular fat deposits tend to show a higher degree of osteoarthritis disease severity at an early disease stage [80,87]. Others show knee muscle coordination rather than knee muscle strength may be the more salient pathogenic factor [88]. To better characterize any related quadriceps muscle impact on osteoarthritis incidence and progression at the knee the use of appropriate ultrasonic, biomechanical and neurological analyses at the outset of the disease, as well as before surgery has consequently been suggested [88].

At present, while evidence that treating muscle does appear to improve function in some instances, efforts to clarify the mechanisms underpinning this effect might prove enlightening and should probably be explored. Similarly, why this does not occur in all cases should be examined, especially since excess exercise could worsen the state of joint effusion and inflammation plus muscle inhibition that worsen the ability to protect the joint from impact. As was concluded in 2017 [21], the current literature base, while expanding and promising, remains too diverse and non-compelling to definitively drive clear evidence based guidance in our view.

What it does imply is that early careful assessments that examine the degree to which muscle strength, endurance, fat mass, cross-sectional area, and reactivity are compromised using agreed upon measures, may not only greatly advance the idea of precision medicine in this respect, but it may prevent or allay the condition and/or the extent of any ensuing additional joint involvement and deterioration. In addition, surgical outcomes may be improved. In addition, the more recent finding of differences in the organization of the motor cortex in adults

with and without osteoarthritis suggests that the motor pathways themselves, including the understudied gamma motor neuron pathway may be strongly implicated in motor disturbances associated with some forms of knee osteoarthritis [89]. As such, we propose that unless this body of data is acknowledged, it may be difficult to improve muscle function either non-operatively or via corrective joint surgery in all cases. Other muscle attributes requiring more study are those associated with muscle fat mass, muscle inhibition, muscle spasm, muscle rate of force development, muscle inflammation, muscle contractures, muscle size, muscle endurance, and their association with mobility, pain, clinical presentation, and mobility limitations across a wide spectrum of the knee osteoarthritis population.

However, despite the laudable insights provided by multiple teams of researchers over the last few years in particular, the multiple viewpoints studied, plus the oftentimes divergent findings, render it challenging to establish whether quadriceps muscle pathology is of key import in the knee osteoarthritis disease cycle and if so, in what respect. Indeed, while it seems one can prove the muscles surrounding an osteoarthritis knee do not present or function in the same way as those of a healthy knee, regardless of age, what specifically is the key variable of major clinical relevance to address that could yield functional long term benefits remains unclear at best.

Even if publication bias is not a concern in the current realm, some data sources that clearly highlight the role of one factor and not others, do not always yield like results. Moreover, some are intuitively confusing and may reflect challenges in comparing data based on subjective measures, lengthy time periods, secondary data sets, and mathematical models that may not be generalizable. At the same time, the data measures are consistently variable rather than standardized even when the same muscle attribute is being assessed. It also seems the varied measures employed are largely assumed reliable and valid, but many are potentially untested in this regard. As well, the degree to which samples represent the spectrum of disabling knee osteoarthritis that may now be exacerbated by COVID-19 associated outcomes and restrictions is dubious at best. Since only funded studies and well supported research groups are likely able to conduct studies in this realm, more support for clinical studies that employ agreed upon valid classification of the disease criteria, protocols that include imaging and molecular measures and that are designed to carefully assess any muscle abnormalities across the spectrum of early as well as late stage disease in a uniform manner appear warranted.

In the interim, one can safely conclude what is needed therapeutically, if anything, and why, and for what duration and purpose, and at what disease stage, remains uncertain at best. It may also be thought that until we are better informed respecting the nature of osteoarthritis that the opportunity for effective remediation for this disease will remain poor as was recently demonstrated for pre-surgical physical therapy efforts, which were not maintained after surgery did not relieve pain or disability unless the exercises produced increases in muscle strength greater than 30 percent or which left exercising patients worse off post-surgery than anticipated or showed muscle pathology to emerge post-surgery [7,90-93].

Alternately, having a better understanding of all the mechanisms that might contribute to the disease, especially those that underlie the motor abnormalities found in osteoarthritis may provide hope for minimizing the immense burden of this prevalent disorder, as well as for improving outcomes, which currently remain suboptimal as far as pain and disability are concerned. In particular, the ability to both intervene as early as possible and to apply well-reasoned evidence-based data to prevent the emergence and persistence of quadriceps muscle coordination deficits and others may prove highly satisfactory for many [94].

Since different components of the quadriceps muscles may undergo differing rates or mechanisms of pre-or post-arthritic change, uncovering those most relevant in this regard, and applying target specific treatment approaches accordingly may prove especially helpful for maximizing life quality, the status of the knee muscles in the event surgery is required, plus possibly averting the spread of the disease to other knee and/or distant joint sites. The routine assessment of muscle circumference, muscle fat and tissue content, coupled with an exam of basic reflexive neurological status, measures of gait and lower limb loading using a force plate, plus quadriceps power and endurance in early as well as moderate cases of knee osteoarthritis and that may be especially helpful in securing more precise insights into ant prevailing quadriceps pathology and its optimal rehabilitation where indicated has been discussed [95-99].

Encouraging those at risk for the disease or its worsening to be vigilant about adhering ro their exercise recommendations, as well as being more mindful to avert any harm that could occur consequent to excessive exercise or incorrect joint usage is also indicated. Those in the higher age ranges, those with multiple chronic health conditions, those in pain, those suffering from long-COVID and excess body weight might be selectively targeted in this regard.

With increasing evidence that multiple pharmacologic approaches do not yield long term benefits, and that joint injections, and surgery are not without risk and high costs, we are hopeful researchers will pursue this line of endeavor and refer to the key past and current reviews noted in this limited report. We propose this is a fruitful topic to pursue, notwithstanding the obvious limitations of this review, including its narrative focus, its selective discourse, the use of only certain key words and data bases, and that this discourse may serve as a guide for future improvements that can yield more systematic topic clarity. Current research limitations that include, but are not limited to small diverse samples, limited or no follow up periods, varied sample exclusion and inclusion criteria, unknown measurement properties, chronic disease and external confounders that were not accounted for, and the possible impact of multiple measures on muscle attributes, along with variable cut off points render all current data less than robust in the interim, regardless of approach are all areas where advancements are highly recommended.

On the other hand, it is probable that this field of endeavor, while highly promising, will continue to suffer from many design deficits and inconclusive or discrepant findings including

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those related to inter-laboratory differences that currently obstruct valid comparisons of gait datasets and others from a diverse population of adults with varying degrees of knee osteoarthritis. One step that has recently been advocated in this regard and that could be extended in multiple ways to promote harmonization of various study protocols are the desire and willingness to develop collaborative efforts that can enable valid comparisons between labs. As well, multicenter trials that employ multidisciplinary and sustained international efforts involving all major stakeholders appear essential in this regard [3,100].

Conclusion

In light of the limited progress made in understanding how the key knee extensor musculature at the knee joint is implicated in knee osteoarthritis, it is concluded:

1. Osteoarthritis of the knee joint, a currently burgeoning incurable and disabling condition will continue to induce immense adverse impacts at the individual and societal levels that will not be readily ameliorated in the near future without concerted and well-designed multi center collaborative research efforts that carefully examine the structural and functional properties and adaptations of the knee extensor muscles that appear to be important correlates of the disease across various disease stages using agreed upon validated and reliable measures and perspectives.

2. To overcome deficits in the current data base, it is concluded that more empirically derived study questions, more comprehensive neuromuscular assessment among subgroups that are conducted at different disease stages using carefully conceived imaging and biomechanical examinations of the knee joint functional and muscular systems, at well-conceived time intervals, and with the assurance of their intra and inter rater high reliability, will prove highly relevant and insightful in advancing this field of inquiry in all likelihood.

Conversely, not only will standard interventions prove suboptimal at best unless concerted well designed substantive research efforts are made, but if an individual with knee osteoarthritis is not responding to conservative treatment after several weeks of intensive intervention or is showing declining function, rather than any improvements at any time, even after knee replacement surgery, the presence of irreversible damage within the confines of the neuromotor system should be carefully sought.

Conflict of Interest

All the author declare no conflict of interest regarding any aspect of the manuscript.

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