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Integrated Review Article

Obesity and its Muscle Based Manifestations and Osteoarthritis

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Abstract

Childhood and adult obesity rates continue to increase, along with those reported for osteoarthritis. Some studies reveal a detrimental impact of excess body fat on joint status that may commence in early life. Here we examine some recent literature that point out why it may not be justified to adopt a fat acceptance stance for those at risk for osteoarthritis due to behavioral risk factors. This mini review specifically examines whether excess fatty tissue has an immediate and possible lasting impact on muscle, a key structure involved in joint functions. The data are quite compelling in support of muscle as both a protective organ and one with a secretion role that may yet impact joint tissues adversely in the presence of obesity.

Background

Osteoarthritis, the leading cause of pain and disability worldwide, disproportionally affects individuals deemed to be obese. However, even though obesity is considered an important risk factor for osteoarthritis initiation and progression it remains unclear as to precisely how obesity may directly affect those key joints most affected by osteoarthritis.

Although mechanical mechanisms are commonly cited in this regard, the actual causes and associations are being found to be increasingly complex and extend beyond a sole role for mechanical explanations. This is partially due to the combination of obesity associated metabolic, biomechanical, and inflammatory factors found to accompany increased adiposity and where cell-signaling from the fat cell can influence cellular effects on different cells, rather than simply affecting body weight. In particular, adipose or fat cells, appear to be strong mediators of muscle influence [1,2], including sarcopenia or muscle mass losses [3], body composition [4] and joint degeneration in their own right [5,6].

Muscle is also key to being able to move smoothly and plays a critical role in body temperature, as well as for purposes of joint protection and posture, and regulation of skeletal muscle mass [7]. Older adults who experience muscle wasting more readily than younger adults may thus be susceptible to multiple health challenges, especially in the presence of an encroachment of fat to replace muscle tissue or alter its composition and structure in those deemed obese. This may lead to delays in muscle responsiveness, abnormalities in muscle contractile functions and structure, alterations in lipid metabolism, as well as muscle inflammation and the production of pain provoking inflammatory products [8,9] such as adipokines derived from adipocytes [2,10]. Muscle may further influence joint as well as bodily functions and bone metabolism since it is the source of hundreds of peptide containing organelles that also serve endocrine functions and are collectively termed "myokines" [7,9-12], and that can collectively help to regulate muscle mass and function, as well as trigger diverse metabolic effects [13]. As such, it is proposed muscles do more than move the limbs, and rather than muscle mass alone, muscle constituents such as myokines that are stored in muscle and released in response to muscle contraction may determine the quality of joint reaction protection mechanisms, as well as effectively communicating with other organs such as adipose tissue, bones, and brain tissues to mediate multiple physiological effects [10,12,14,15], but which may foster obesity if functioning abnormally [16]. In addition, several of these cytokines and peptides collectively termed 'myokines' may exert their effects within the muscle itself and since many proteins produced by skeletal muscle are dependent upon sufficient levels of muscle contraction, their beneficial influence in response to muscle contraction or training may wane in face of sedentary behaviors and fat muscle accumulation and can thus possibly mediate osteoarthritis risk as well as the risk of other health conditions [11]. While this idea has been disputed by several emergent interest groups and others [17-19], the health implications of being obese may arguably foster the risk of osteoarthritis damage and its severity, even if those espousing 'fat activism' who aim to palliate biases that may inflict the obese person as well as discredit related evidence may want to ignore the now established fact that adipose tissue, along with skeletal muscle, and heart tissues are network linked endocrine organs that secrete several molecules in both normal and pathological conditions [19]. Even if we discount the overwhelming number of studies linking obesity and osteoarthritis and possible mechanisms of action, we know that the numerous diverse muscle based proteins and their molecular targets and effects do appear to constitute part of a closed network of interactive physiological circuits and mechanisms. Hence can this fact be readily ignored without unwanted repercussions, especially if these network effects are found to play a crucial role in obesity extent and persistence and above all in cardiac diseases associated with obesity that may explain high rates of osteoarthritis cardiovascular manifestations [12] as well as inflammatory and oxidative damage features characterized by obesity as well as osteoarthritis.

In this regard, and based on this idea, it appears that even if being obese does not raise the risk for mortality [20], the presence of unmitigated obesity can help to foster the progression of joint damage both directly through its weight associated effects, as well as indirectly through its diverse peptide activation and secretion effects that markedly influence the onset and perpetuation of various degrees of chronic inflammation. As such, obesity can be expected to induce a potentially more rapid joint degenerative process as well as a set of painful movement challenges compared to a joint surrounded by healthy fat free muscle tissue or lean muscle mass. As such it may impact cardiac health status, the degree of sedentary lifestyle adoption, the increasing need for narcotic medications, functional and social disability, as well as a greater need for early surgery and possible heightened post surgical infection risk [21].

Yet, although intervention to reduce muscle fat and promote the presence of a lean and functionally adequate muscle mass may be helpful in this respect [22], contemporary trends towards 'fat acceptance' and efforts to counter medically oriented obesity messages and directives for political or other reasons may jeopardize the willingness and motivation of an obese adult with osteoarthritis to either consider as well as to comply with life affirming recommendations to lose weight, and increase muscle strength, even though obesity and low muscle mass is found significantly associated with the presence of end stage knee osteoarthritis [23].

Moreover, the increasing controversies in this realm and a strong anti-fat discourse following [18] and move to accept fatness as a normal feature of many in the population may fail to address the health risks of such a blanket one sided approach at a time when the population is aging and osteoarthritis is among the leading cause of disability in this group. To examine this issue, this mini review elected to explore if indeed a case can be made for efforts to achieve and maintain a healthy weight across the lifespan-as this applies to an urgent imperative to reduce the immense prevailing and anticipated future social and economic as well as individual osteoarthritis burden. Since muscle is an organ in its own right and that can be both sensitive to excess fat and induce inflammatory products that mar good health if ignored, it examines if this knowledge should be made more mainstream. Alternately, it explores if withholding the correct information or skewing the impact of obesity for young as well as older adults will possibly harm some children in their formative years, as well as later on life, rather than helping them to prevent a life of immense pain.

The theoretical basis for this is that bone and skeletal muscle, both implicated in osteoarthritis, are integrated organs and their coupling can be moderated by both joint movement as well as in a non-mechanical fashion, i.e., through the endocrine associated activity of muscle, which secretes a panel of cytokines and proteins named myokines, and that are synthesized and secreted by myocytes in response to muscle contraction. Myokines in turn, are able to regulate muscle metabolism as well as serving an endocrine regulatory function on distant organs and tissues, such as bone, adipose tissue, brain and liver.

Other related data show the prevalence of obesity in combination with sarcopenia a term that that denotes the well established observation of an age-related muscle mass, strength or physical function loss in a high number of adults ages 65 years and older is indeed considered a high-risk geriatric syndrome that stems from both muscle and the presence of excess body fat [24]. This current narrative review discusses how obesity can possibly impact muscle cellular mechanisms and pathways that lead to its impairment, as well as having possible direct impacts on vulnerable joints and overall health.

Aims

In line with the above discourse, the specific purpose of this current mini-review was to carefully examine the research findings documented over the past five years, along with the overall science-based knowledge on the obesity impacts on skeletal muscle and their possible relevance to osteoarthritis disability to discern if this health issue should be addressed by clinicians and others even though a strong case for 'fat' as an exaggerated health determinant prevails.

Methods

To achieve the goals of this report, the present search strategy employed the terms, inflammation, muscle, myokines, obesity, and osteoarthritis collectively and independently. First all available articles on the topic were screened, and then for those published between the time period Jan 1, 2013-May 31, 2023 in the PUBMED, and Google Scholar data bases were scanned as a previous article on this theme was published in 2012. To provide some clarity as to whether there is clinical evidence that obesity can either heighten joint vulnerability or add pressure to a joint, as well as a risk of functional limitations, articles that addressed these issues were examined and downloaded if deemed relevant. In addition to stand alone full length research reports, systematic reviews were deemed acceptable. No abstracts or foreign non-English articles were analyzed, however, and all forms of studies were deemed acceptable.

After completing a comprehensive scan of the relevant literature, only a narrative review was deemed suitable. Although it was not possible to include all possible publications, which extend into the tens of thousands of reports, by aiming to include the most up to date findings on this topic, plus an overview of relevant prior work, a broad picture of the state of the art regarding the themes of this review was anticipated.

To this end, relevant articles that were downloaded were scrutinized and the discussion below first outlines some general findings, followed by some specific clinically relevant observations. An attempt was made to categorize findings as either supportive of a possible obesity muscle structure impact, versus any non supportive or contrary viewpoint, bearing in mind negative studies are less likely to be published than positive studies.

For consistency the term osteoarthritis was adopted to describe the various forms of this disease as opposed to any specific type or joint, and it was decided try to focus on cellular muscle changes that could impact joint safety and physiology rather than neuromuscular features of this disease. For a summary of prior studies readers are referred to the 2012 review by Pedersen and Febbraio [9].

Results

General Observations

It is well established that osteoarthritis, the most common form of arthritis, is a highly prevalent disease particularly in subjects over 65 years of age no matter where they reside. While in the past it was considered a mere consequence of age-related cartilage tissue degradation lining one or more freely moving joints such

as the knee, where it has been universally associated with progressive observable degrees of anatomical and functional joint impairment, in recent decades, a more extensive dynamic view, implicating the synovial tissue lining the joints, as well as the underlying bony tissue and a host of inflammatory destructive mediators of cartilage degradation prevails. Other factors such as those derived from the muscles surrounding the joint, along with obesity have also been receiving more attention than not [25].

As research in this respect has demonstrated, it is not aging per se that is the sole osteoarthritis mediator, but it appears obesity, which is not inevitable in many cases, has been cited to be the most important risk factor explaining the high incidence and extent of progression of osteoarthritis. This is explained partially on the basis of possible overloading the joints due to excess weight which in turn leads to the destruction of articular cartilage, as well as other factors such as excess adipose deposition, insulin resistance impacts, and possible improper coordination of innate and adaptive immune responses [26].

In particular, emerging data reveal sarcopenia, broadly defined as the age-related decline in skeletal muscle mass, quality, and function, and one associated with chronic low-grade inflammation and an increased likelihood of adverse health outcomes is more common than not. In addition, this situation can be further degraded by the encroachment of fat to replace muscle mass that can further impair the delicate balance between muscle protein synthesis and degradation. At the same time, emergent data reveals muscle secretes many important physiological vital organelles and strongly influences important communication channels between muscle tissues and other organs.

In turn, some of these factors have been implicated in regulation of skeletal muscle mass, function, and pathologies and may be considerably perturbed in the presence of excessive adiposity. Moreover, age-related sarcopenia has been reported to be more prevalent in the presence of obesity; as well as in response to its effects on comorbidities and physical activity levels.

In this review, the aim was to specifically examine evidence pointing to the fact that adiposity may exacerbate age-related sarcopenia, as well as adipose-skeletal muscle communication processes including the secretion and processing of novel myo- and adipokines, plus the role of extracellular vesicles in mediating inter-tissue cross talk in the context of osteoarthritis. It has been argued that a better understanding of the physiological significance of these factors, and their potential as therapeutic targets in combating muscle wasting [27] and possible features of osteoarthritis risk and pathology may prove insightful and clinically relevant.

Another body of research shows both physical inactivity and abdominal adiposity, reflecting accumulation of visceral fat mass-a source of systemic inflammation, are associated with the occurrence of multiple chronic diseases, such as osteoarthritis, insulin resistance, atherosclerosis, neurodegeneration and tumor growth. Other evidence suggests a protective effect of exercise may to some extent be ascribed to its anti-inflammatory effect, which can be mediated via a reduction in visceral fat mass and/or by induction of an anti-inflammatory environment with each exercise bout. The finding that muscles produce and release various muscle based cellular mediators known as myokines is put forth as the mechanism whereby exercise influences metabolism, inflammation, and specific endocrine effects on visceral fat cells. Others work locally within the muscle, and their effects can influence signaling pathways involved in fat oxidation [8].

In terms of osteoarthritis relevance, Pedroso *et al*. [28] have concluded current literature to show that the thigh muscles of people with knee osteoarthritis can have an increased degree of fat infiltration, both between and within the muscles (inter- and intramuscular fat). At the same time, the presence of fat mass in the thigh muscles appears associated with the prevailing degree of systemic inflammation, poor physical function, and muscle impairment and may lead to metabolic impairments as well as muscle dysfunction.

Raynauld *et al.* [29] demonstrated, for the first time, that the extent of fat infiltration of the vastus medialis knee muscle is a strong predictor of cartilage volume loss and the occurrence and progression of bone marrow lesions found in osteoarthritis. Importantly, the combined data of muscle area, percent fat, and body mass index identified patients at higher risk for knee osteoarthritis progression.

Yet despite the above observations and others [30] along with their immense clinical relevance for reducing suffering, the emergence of multiple fat advocacy and acceptance groups and tactics that largely focus on the social aspects of fatness and proclaim health at any size as a mantra may not concur with either medical obesity interpretations or their proven behavioral remedies as far as preservation of joint status and disabling osteoarthritis [31].

Specific Research Observations

The finding that muscle can serve as a key endocrine organ involved in multiple vital body functions and energy balance, along with evidence that adipose tissue is active and can release mediators that modulate muscle and bone metabolism is being highlighted in increasing numbers and modes of inquiry [10]. Indeed, several exercise studies now show related favorable impacts on selected muscle myokines and that appear to reduce the extent of prevailing fat tissue both locally, as well as centrally. On the other hand, reductions in physical activity and increases in energy intake, both linked with aging, consistently lead to the multiplication of fat cells, along with the recruitment of immunological cells known as macrophages. These cells release pro-inflammatory degrading signaling molecules termed adipokines produced by adipose tissue and found in osteoarthritis that may foster a state of reluctance to exercise due to pain and limited cardiovascular capacity as well as reduced muscle strength and functional impairment [30-36].

According to Hong *et al*. [37] and Kalinkovich *et al*. [38] fat accumulation in muscle tissue that provokes the secretion of pro inflammatory myokines can be shown to promote a cascade of impacts, including adverse oxidative stress influences that lead to mitochondrial dysfunction, impaired insulin signaling, and muscle atrophy. To compound the problem, the presence of a decreased muscle mass can aggravate insulin resistance, as well as aggravating sarcopenic obesity, while disturbing relative shear and compressive joint forces that underpin function and joint force generation, plus joint kinematics [5,39] and that may contribute to accelerated joint damage in those with obesity. In turn, these myokines may exacerbate adipose tissue inflammation and may foster a state of chronic low grade systemic inflammation, that results in an adverse and vicious circle that perpetuates the presence of adipose tissue and skeletal muscle inflammation, thus triggering and supporting a state of sarcopenic obesity.

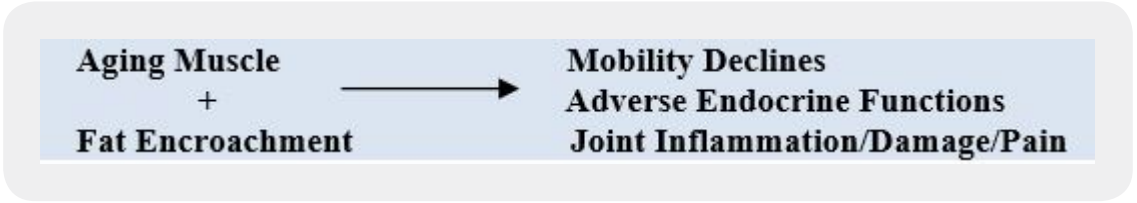
As such, obesity and ageing place a tremendous strain on the global healthcare system, even if osteoarthritis is not evident. However, osteoarthritis and its progression clearly parallel both the age-related findings of sarcopenia characterized by decreased muscular strength, as well as decreases in muscle quantity, quality, and functional performance. Sarcopenic obesity, in particular, where muscle mass losses and obesity are combined clearly has a substantial influence on the older adults' health in general, as well as their joint status that can be explained by the presence of an altered or impaired muscle related myokine response [9]. Muscle myokines released during muscle contraction also play an important role in controlling muscle growth, muscle function, and metabolic balance, as well as possible joint synovial fluid status [40] and can predictably induce or aggravate a state of obesity, plus a dual state of sarcopenia and obesity [16,21,41]. However, even though physical exercise and nutrition can indeed be shown to slow the progression of sarcopenia and particularly that of sarcopenic obesity and its inflammatory impacts that may raise the osteoarthritis disease and disability risk [9,16], none of these proven behavioral approaches are likely to be implemented if one adopts a stance that 'fat acceptance', 'healing from sizeism', and the 'right to be fat' must take precedence over being assisted to overcome any health implications. Unfortunately it appears that a sole focus on the obese person as having a valid or perceived marginalized identity and that medical science is biased is however paramount and thus a social injustice lens must preside over any clinically relevant implications of the adipose condition, at all costs, even in the face of actual joint damage or its risk [42,43]. In addition, some authors, such as Katz *et al*. [44] specifically fail to mention either obesity or muscle inflammation in the context of osteoarthritis even though they advocate for exercise.

Moreover, even though exercise induced muscle myokine secretion appears to foster an anti inflammatory effect [14], exercise as well as other recommended strategies may not prove successful if the sarcopenic obesity linkage is not duly acknowledged and intervened upon accordingly.

In the meantime, Pedroso *et al*. [28] found people with knee osteoarthritis to exhibit a higher intramuscular fat fraction than healthy controls, thus they may experience excess disability. In addition, Karlsson *et al*. [29] note women and men with idiopathic knee osteoarthritis may have a specific body type wherein a higher body mass induces a greater joint load, and a proportionally lower muscle mass degrades the efficiency of any joint-protective ability, and thus this group might be specifically targeted to avert joint damage as well as any chronic and sustained inflammatory impact on the host, systemically, or locally, as well as impaired muscle integrity, and possible metabolic dysfunction [32,33]. Furthermore, certain cytokines, released by both skeletal muscle and adipose tissue and that exhibit a bioactive effect; and that are called adipo-myokines may modulate some, if not all, the molecular events that prevail in osteoarthritis.

It appears therefore, that the weight of the evidence implies that among the impacts of obesity on health, systemic excess adipose tissue, as well as subcutaneous adipose tissue is significantly and negatively associated with muscle mass and its force generating and protective features, and could be related to the presence and progression of osteoarthritis of one or more freely moving joints such as the knee [45]. Visceral adipose tissue is also associated with a tendency towards an increased degree of cartilage loss and the production of pro inflammatory cytokines. Intra-muscular adipose tissue associated with osteoarthritic can also communicate bi directionally and negatively with various other tissues and life affirming physiological pathways. In addition, the underlying mechanisms for the roles of the systemic and local fat on osteoarthritis damaged

tissues could induce a potent combination of noxious biomechanical, metabolic, inflammatory and fat fibrosis factors [45]. It is also apparent that skeletal muscle implicated in osteoarthritis is part of an endocrine system that can produce hundreds of myokines with the power to influence local as well as distant cellular signals and functioning, including, but not limited to brain tissue, vascular tissue, bone and adipose tissue as well as intra- and inter-muscular cells and pathways of influence [46] as depicted below.



Discussion

Osteoarthritis, a chronic degenerative joint disorder that leads to immense disability and affects more than 500 million population worldwide, and once believed to be caused by the wearing and tearing of articular cartilage over time, is now more commonly referred to as a chronic whole-joint disorder that is initiated with biochemical and cellular alterations in the synovial joint tissues, which leads to the histological and structural changes of the joint and ends up with the whole tissue dysfunction [47]. While no cure for osteoarthritis prevails, its burden may yet be due in part to a lack of any comprehensive understanding of the pathological mechanism underpinning its initiation and progression. It has thus become evident that a better understanding of all the possible pathological signaling pathways and key molecules involved in osteoarthritis is crucial for improving upon or validating therapeutic targets and intervention design.

More recently, in addition to a focus on muscle as pathogenic factor, a host of muscle-derived cytokines and chemokines known as myokines have been shown to have far-reaching impacts on multiple body processes and non muscle organs through their specific signal networks. This set of understandings that indicates myokines in skeletal muscle communicate with other organs, and can influence their physiological functions as well as whole-body energy metabolism is taken to explain the connection between exercise, and the possible development of diseases such as osteoarthritis, especially in the case of the older adult with low muscle mass and excess muscle fat mass [48]. It also explains the inflammatory impact of sarcopenic obesity [8], even though a role for sarcopenic obesity in osteoarthritis is unproven [3].

In this regard, and while the higher incidence of osteoarthritis in cases deemed obese is related to several factors, including excess weight that can impose heavier loads on joints as one explanation, another factor strengthening the case for vigilance and control of body fat rather than blanket acceptance, may be the established finding of an active synthesis by fat cells or adipocytes of pro inflammatory mediators that can adversely affect joint tissues locally as well as tissues in other locations. Moreover, emergent data on myokines and muscles showing muscle is not only a key factor in joint function and protection, but it is also a powerful secretion organ that can surely be implicated conceptually to explain the association between obesity and osteoarthritis and the benefits of exercise, versus the negative outcomes of exercise non adherence cannot be ignored. Unfortunately, many older adults with osteoarthritis, with or without metabolic syndrome, are

at increased risk for a sedentary lifestyle, and lower than desirable participation in daily physical activity practices and a subsequent inability to maintain a healthy weight and overall health status.

Since osteoarthritis imposes a severe burden on society, as well as families and the affected person, and is not inevitable in all cases, it appears the emergent pleas for 'fat acceptance' at any body size and the movement's lack of focus on preventable obesity associated health associated ramifications can yet prove more disabling than not for many. Moreover, even if surgery is eventually indicated, or medications expedite enormous weight losses, efforts to maximize chances of a high life quality may yet depend on acknowledging the importance of weight normalization as well as muscle building activities as essential [49].

Research that goes beyond the physical and examines if aging older adults and youth who are excessively overweight can benefit more from accepting they are at risk for adverse health, and intervening accordingly, will be a greater advantage than those who focus solely on being accepted socially and without bias. Advocates who strongly favor fat acceptance and offer negative perspectives on the provision of health and imply therapy is a potential form of bullying, should make every effort to justify their claims among fat activists to contradict prevalent positions and findings of contemporary medical research [50].

Even though not all data that prevail have been examined, and no consensus exists to date as to obesity impacts on an aging joint, or how to best measure this attribute, osteoarthritis researchers can however be confident that if they look closely at muscle and how its multiple attributes may place a joint at risk for degeneration and how this may be averted or mitigated in a safe low cost manner in the case of aging and sarcopenic obesity will likely find highly insightful clinically meaningful and applicable results.

Conclusion

Regardless of limitations, a fairly detailed overview of the issue of whether obesity is a threat to aging well being has shown:

- Aging adults and children who are overweight should receive advice about their health risks.
- Viewing muscle as an endocrine organ as well as a means of motion could improve the ability to comprehend the development of some forms of osteoarthritis.
- Excess muscle fat mass may heighten joint degeneration risk and magnitude if ignored.
- Limiting muscle fat and maximizing muscle mass could protect the joint as well as susceptibility of youth and aging adults to other chronic conditions.
- Simply accepting fat status as a social construct requiring acceptance and failing to acknowledge its health risks could lead to much excess suffering and enormous public health and social costs.
- Dieting alone or other forms of weight loss that may simultaneously induce muscle mass losses in their own right should be avoided.

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