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SPONDYLOARTHRITIS (M KHAN, SECTION EDITOR)

Spondyloarthritis on the Move: Biomechanical Benefits or Harm

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Abstract

Purpose of Review Physical activity is beneficial in several diseases including spondyloarthritis despite mechanical stress being suggested as a trigger of disease onset or activity. Moreover, there is no clear answer as to where physiological loading of the joints ends and pathological overloading begins. The aim of this review is to provide an overview of what is known about exercise and biomechanical loading in spondyloarthritis.

Recent Findings Recent studies focused on the impact of mechanical loading in healthy individuals and spondyloarthritis patients, demonstrating an overlap between the groups and pointing out possible beneficial and detrimental activities. The discovery that several animal models of inflammatory arthritis are dependent on mechanical stress helps unraveling the involved molecular pathways.

Summary There is a knowledge gap between the beneficial effect of exercise reported in clinical trials and the harm seen in observational studies and animal models. Imaging studies provide a first step in joining these two opposites by highlighting a wide-ranging spectrum between healthy and diseased joints. Future research is warranted on specific interventions in well-defined patient populations and in animal models in order to understand the pathogenesis. Targeted exercise therapy and prevention should be considered specific goals.

Keywords Spondyloarthritis · Physical activity · Exercise · Mechanical loading

Introduction

Physical activity is associated with health benefits and can be an outstanding preventive strategy or a curative treatment in a wide range of diseases. Exercise can reduce rates of all-cause mortality, cardiovascular disease, depression, and many more [1]. In chronic inflammatory musculoskeletal disorders, the bones, joints, muscle, and tendons, the structures that allow us to move and exercise, are directly affected. Consequently, the ability to move in patients suffering from this group of diseases is highly affected by the illness, but also the opposite holds true: the disease course could be influenced by mechanical stress caused by movement and exercise [2].

The link between mechanical loading and joint disease has been of particular interest in spondyloarthritis (SpA), a group of chronic inflammatory diseases with predominant axial, as in ankylosing spondylitis (AS) or predominant peripheral manifestations, as in most forms of psoriatic arthritis (PsA). Enthesitis is a primary disease feature, with inflammation occurring at the insertion sites of the tendons and ligaments into the bone [3]. These tissue transition zones are anatomic sites exposed to important biomechanical stress. Trauma has long been recognized as a potential trigger of enthesitis and subsequently arthritis in PsA [4]. Further data suggest that this mechanistic concept can be applied to the whole spectrum of SpA diseases and may also extend into understanding other forms of inflammatory joint disease [2]. Yet, exercise strategies have traditionally been regarded as an important part of the treatment of SpA and feature prominently in therapy guidelines and recommendations [5]. Up until now, there is no clear answer towards the question as to where physiological loading of the joints ends and pathological biomechanical stress begins.

The aim of this review is to provide an overview of what is known about the impact of mechanical loading in SpA patient and models, with a specific focus on studies published in the last 2 years.

This article is part of the Topical Collection on *Spondyloarthritis*

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Current Exercise Recommendations for SpA Patients

Exercise has been a part of the treatment of AS for many decades, following observations in the first half of the twentieth century that immobilization preserved only posture but not function of those affected [5]. In the most recent ASAS-EULAR management recommendations for axial spondyloarthritis (AxSpA), regular exercise is encouraged, and physicians are advised that the benefit of physical therapy should be considered in every patient, taking into account the feasibility and costs [6]. This recommendation is evidence based on a 2008 Cochrane review demonstrating that an individual home-based or supervised exercise program is better than no intervention and that supervised group physiotherapy is superior to home exercises with regard to spinal mobility, physical function, and patient global assessment [7]. Also, a systematic literature review that summarizes nine studies reports a beneficial but small effect of regular exercise on disease activity, pain, function, and spinal mobility [8]. In the ACR guidelines, physical therapy is recommended for AxSpA patients, favoring land-over water-based exercise, yet mentioning that the evidence base for these recommendations is limited with regard to efficacy and supported by the decreased feasibility of aquatic therapy. Furthermore, ACR guidelines recommend strongly against spinal manipulation in patients with spinal fusion or advanced spinal osteoporosis to avoid the risk of causing severe harm as described in numerous case reports [9, 10]. The ACR guidelines for psoriatic arthritis (PsA) recommend some form of exercise or physical therapy but again warn that the recommendation is supported only by low to very low-quality evidence. Indeed, data were extrapolated from studies of patients with rheumatoid arthritis and osteoarthritis, due to a complete lack of specific studies in PsA patients [11].

While there appears to be a clear consensus that physical activity is beneficial, evidence for more specific recommendations regarding the type, the intensity and the duration of interventions, the patient profiles, and the disease status is lacking. Therefore, the 2018 EULAR guidelines for physical activity in people with inflammatory arthritis and osteoarthritis highlight an extensive research agenda that can be understood as priorities, while simultaneously emphasizing that the public health recommendations for physical activity in the four domains of cardiorespiratory exercise, muscle strength, flexibility, and neuromotor exercise, are effective and safe for these patients [12].

The Benefits of Exercise in SpA Patients

In an SpA patient, exercise capacity and disease course can mutually influence each other. In 45 AxSpA patients, physical activity was recorded for 1 week with an accelerometer. Walking time and number of steps taken per day were associated with better Bath AS functional index (BASFI), AS quality of life (ASQOL), and 6-min walk test (6MWT) outcomes, and longer walking events were associated with a better Bath AS metrology index (BASMI), BASFI, and 6MWT reports [13]. Because of the cross-sectional nature of the study, causality cannot be determined, but multiple recent studies confirm the beneficial effect of general physical activity in SpA patients, in particular on disease activity and measurements of physical functioning. A meta-analysis of randomized controlled trials (RCTs) of exercise programs in AS showed a beneficial effect of exercise on disease activity as measured with the Bath AS disease activity index (BASDAI) and the physical function as measured by the BASFI. However, the heterogeneity of the studies included was considered too extensive to draw more specific conclusions [14]. In another meta-analysis on data from AxSpA patients, aerobic exercise by itself improved the BASDAI score, but not more than routine physiotherapy, and there was no effect on the BASFI score or inflammatory parameters [15]. In an RCT of high-intensity aerobic exercise and strength training for 3 months in 100 patients with AxSpA, the investigators recorded an improvement of disease symptoms (pain, fatigue, and stiffness), ankylosing spondylitis disease activity score (ASDAS), BASDAI, inflammatory markers, function, and cardiovascular health. Important to note in this trial is that patients with moderate to high disease activity that did not perform regular exercise were selected, thereby likely reflecting a specific population from daily practice [16]. Secondary analysis showed that the 3-month exercise program had beneficial long-term effects on leisure time physical activity, but nevertheless the difference in ASDAS had disappeared by 12 months [17]. In 54 patients with longstanding AS, exercise during leisure time was negatively associated with the development of spinal immobility [18].

Together, these results suggest that any kind of exercise is better than none, even in patients with active disease, but that the effect might only last for the duration of the intervention. Besides this, one should take into account that SpA patients show specific alterations in movement. In a small cross-sectional study, gait deviations were detected in 18 AS patients when compared with healthy controls. More specifically the authors report differences in joint angles and movement of the hip, trunk, knees, and feet, as well as lower gait velocity, shorter step length, and shorter stride length in AS patients [19]. Similarly, 9 AS patients had altered intersegmental coordination of the spine during lifting [20]. This leads to the question whether specific types of exercise could be of extra benefit in SpA. In one study in AS patients, inspiratory muscle training was added to conventional exercises. This led as expected to increased inspiratory muscle strength but also to increased functional exercise capacity and decreased disease activity [21]. In PsA patients, high-intensity interval training for 11 weeks did not change the disease activity as measured by DAS44 [22], and resistance training for 12 weeks did not influence the DAS28 but did decrease disease activity as measured by BASDAI and increased functional capacity and

quality of life, however, without a measurable difference in muscle strength [23]. The patient characteristics in the last 2 trials were largely similar except for a longer disease duration in the trial with resistance training (11 years as compared with 5 years), and the BASDAI score is more susceptible to confounding factors than the DAS44 and DAS28, but nevertheless these results warrant further research looking into the possible extra benefit of muscle strength over cardiorespiratory exercise in PsA.

Exercise can and should likely also be used in a preventive setting: longitudinal data from the HUNT study in psoriasis patients showed that high levels of physical activity reduce the risk of subsequent development of PsA, independent of BMI [24].

The Potential Harm of Mechanical Loading in SpA Patients

None of the RCTs report detrimental effects of physical activity in SpA patients, but the specific interventions studied were carefully designed in order not to be harmful. For better information on the question whether mechanical loading could harm SpA patients, observational studies are necessary.

Occupational activities include a variety of mechanical strains often wielded for years and are therefore of great interest. In a cohort analysis of 307 PsA patients, occupations that involve repetitive hand motions and require finger dexterity were associated with increased peripheral joint damage. Interestingly, none of the occupational exposures, including those consisting of twisting, bending, or whole body vibration, were associated with radiographic axial damage although 43% of the patients had radiographic signs of sacroiliitis according to the modified New York criteria [25••]. These results therefore differ from a similar study in AS patients from 2008, where a detrimental impact on inflammation and structural damage of occupational activities involving bending, twisting, stretching, and whole body vibration were shown [26].

Pregnancy results in prolonged and increased biomechanical loading of spine and sacroiliac joints. Two studies in pregnant SpA patients, one in 103 PsA patients and one in 166 AxSpA patients, showed overall stable disease, but further analysis revealed some interesting observations [27, 28]. In AxSpA there was a small peak in BASDAI during the second trimester as compared with 6 weeks postpartum, confirming earlier studies. The authors mention that this can be partly due to restarting of medication after delivery, but this may not explain why the peak is seen in the second and not in the third trimester when biomechanical stress is presumed to be the highest [28]. During pregnancy there are several other factors that have an impact on the sacroiliac joint, including the increased production of relaxin, a hormone providing ligament laxity in the sacroiliac joints that peaks at the end of the first and during the second trimester [29]. In PsA patients, there was a small peak in DAS28-CRP, BASDAI, MHAQ, and self-reported pain scores at 6 months postpartum as compared with 6 weeks postpartum, despite restarting of medication in the postpartum and again confirming earlier studies. In the PsA study, only 12% of patients had axial involvement, and the difference between the studies might reflect the difference between peripheral and axial loading: while in PsA increased axial load during pregnancy did not seem to affect disease activity, the increased manual labor postpartum while taking care of a baby puts extra strain on the peripheral joints.

Traumas as a potential trigger in PsA and the concept of a deep Koebner phenomenon have been long debated [4]. A matched cohort study demonstrated that patients with psoriasis exposed to trauma ($n = 15{,}416$) are at increased risk of developing PsA in comparison with matched unexposed patients ($n = 55{,}230$). Interestingly, this was only observed for bone and joint trauma (i.e., fractures and sprains, respectively) and not for skin or nerve trauma [30•].

Alternatively, also avoidance of activity can be studied. Within PsA patients, avoiding physical activity was associated with less entheseal inflammation as measured by ultrasound. Surprisingly, no association was found between entheseal inflammation and BMI or regular exercise. As possible explanations for these seemingly contradicting results, the authors suggest insufficient power of the study and the method used for recording avoidance but also add that this might point to the hypothesis that the tendons and entheses respond to a change in physical activity rather than to physical activity itself [31]. Longitudinal studies are needed to investigate whether the response of entheses to physical activity is indeed altered in PsA.

A Need for Objective Measurements that Reflect Exposure to Mechanical Stress

A major limitation in the conducted clinical trials is the lack of specific markers of response or non-response to physical activity [12]. In the last 2 years, two papers were published searching for possible links between serum markers that are increased in SpA patients and mechanical load. One trial in AxSpA patients measured after 6 months of twice weekly group supervised physiotherapy sessions, the change in C-reactive protein, matrix metalloproteinase degraded collagen type II, and citrullinated vimentin, three markers known to be increased in the serum of AxSpA patients. Despite small but favorable changes in patient-reported outcomes after the intervention, no changes were detected in the biomarkers [32].

El Jamal et al. demonstrated in vitro that gene expression levels of sphingosine 1-phosphate (S1P), a bone anabolic molecule elevated in the serum of SpA patients, were increased in mouse primary chondrocytes exposed to cyclic stretch. In addition, the presence of TNFα or IL17 leads to a synergistic

effect, and inhibition of this pathway could reduce the osteogenic differentiation potential of the cells. They hypothesize that the presence of S1P in entheseal chondrocytes could locally favor abnormal ossification under influence of mechanical stress and cytokines [33]. Yet, further evidence for this hypothesis in clinical samples of SpA patients is missing.

The Spectrum of MRI Findings between Healthy and Diseased—Impact of Mechanical Stress

While the use of MRI of the sacroiliac joints in the assessment of AxSpA has led to earlier diagnosis, it also contributes to potential false positives as the specificity of characteristic features may be lower than initially anticipated, in particular in the setting of exercise or increased load [34]. Nevertheless, insights into overlapping imaging features between healthy and diseased individuals and their context can give us new views on the pathology. Indeed, over the last decade, multiple studies demonstrated the presence of low-grade bone marrow edema (BME) in the sacroiliac joint in a fairly high proportion of healthy individuals and patients with nonspecific low back pain [35]. In the past 2 years, similar studies have been performed but with a strong focus on asymptomatic healthy individuals exposed to increased mechanical strain.

Prolonged mechanical stress as seen during pregnancy and after delivery can induce BME around the sacroiliac joints with features similar to the BME seen in AxSpA patients. In a prospective age-matched case-control study, MRI scans of AxSpA patients were compared with healthy women in the first week after delivery. A positive MRI according to the ASAS criteria was seen in 63.3% (19/30) of healthy women compared with 86.7% (26/30) of patients. Even more, if BME was present in postpartum women, they found it to be indistinguishable from inflammatory sacroiliitis based on extent and distribution of changes. Structural changes like fatty bone marrow or erosions were rarely present in postpartum women. Interestingly, BME did not correlate with the presence of lower back pain or with delivery mode [36].

Similar to pregnancies, increased mechanical axial strain can be caused by sport activities. In a study in 20 recreational runners and 22 elite ice hockey players, MRI scans were explored for the frequency and anatomic distribution of sacroiliac joint lesions. The proportions of runners and hockey players fulfilling the ASAS definition of active sacroiliitis were 30–35% and 41%, respectively. Fat metaplasia occurred less commonly and was without topographic correlation, and almost no erosions were seen. Most of the MRI signals were noted in the posterior lower ileum and anterior upper sacrum. The authors point out that these signals could be reflective of mechanical stress injury, degenerative joint disease, vascular signals, or anatomic variants [37]. In a subsequent study, they showed that a number of false positives can be avoided by assessment in two perpendicular planes, taking into account four easy recognizable constitutional sacroiliac joint features associated with non-specific BME: vascular partial volume effect, deep iliac ligament insertion, fluid-filled bone cysts, and lumbosacral transitional anomaly. The first two were the most frequently reported features and were mostly located in the posterior lower ilium [38•]. Nevertheless, these data suggest that biomechanical stress is a likely trigger of sacroiliac inflammation but does not by default lead to chronic disease.

A pilot study in 22 military recruits aimed to investigate the effect of intense physical training on the sacroiliac joints. MRI at baseline already showed a SpA Research Consortium of Canada (SPARCC score) ≥ 1 in 40.9% of the participants, fulfilling the ASAS criteria in 22.7%, with a slight but statistically not significant increase after 6 weeks of training. In contrary to the studies in pregnant women and athletes, in this study, 27.3% of subjects presented with structural lesions already at baseline, but not enough demographic details about the type of activities prior to the study are available to draw any further conclusions. The authors emphasize that this was an already physically active population before the start of the study and that a similar study in untrained individuals might lead to different results and that a median SPARCC score of 3 still is low compared with the SPARCC scores of ≥ 5 seen in AxSpA cohorts and RCTs [39].

The latter observation was also made in an MRI study directly comparing inflammatory lesions between AxSpA patients ($n = 47$), healthy individuals ($n = 47$), and patients with chronic back pain ($n = 47$). In AxSpA, lesions were more extensive with SPARCC scores ≥ 5 and deep lesions with an increase in signal extending ≥ 1 cm from the articular surface. SPARCC scores between healthy individuals and chronic back pain were similar. This study also included a small group of women with postpartum back pain ($n = 7$), showing a slightly increased SPARCC score as compared with healthy individuals, and a group of frequent runners ($n = 24$) showing no more lesions than the healthy individuals, although little lifestyle data were collected, meaning that within the healthy individuals group, running activity was not excluded. Furthermore, BME lesions in healthy participants were preferably located in the posterior lower iliac bone [40].

In summary, these studies further confirm that pregnancy and extensive physical activity are possible non-SpA-related causes of low-grade sacroiliac joint BME, as was earlier observed for obesity and age-related degeneration [41]. This low-grade BME was shown to have a different progression compared with extensive BME in a study including 604 unselected low back pain patients including an unknown proportion of SpA patients. In this group, low-grade BME was prevalent but mostly transient and only rarely developing into extensive BME or structural lesions. In contrast, extensive BME strongly predicted the development of new structural lesions in the same region [41].

Importance of Mechanical Loading in Animal Models of Arthritis

To elucidate the mechanisms by which physical activity can influence joint homeostasis and disease, animal models remain an important tool. This certainly applies to SpA as biopsies of affected tissues such as entheses and sacroiliac joints from patients are rarely possible. In recent years, several well-known animal models of arthritis were demonstrated to be at least partly dependent on biomechanical loading. However, rodent models come with several limitations, the strongest among these likely the quadrupedal gait of mice and rats as compared with bipedal humans, a feature that will impact biomechanical stress in specific joints.

The first arthritis model shown to be dependent on mechanical stress is the spontaneous arthritis in DBA/1 mice, who suffer from a short course of inflammation in the hind paws followed by entheseal ankylosis [42]. In these mice, increasing the biomechanical strain to the level necessary for disease onset was done by adjusting environmental factors like grouped caging of male mice from different litters and limiting the amount of bedding material.

In 2014 unloading of the hind paws by tail suspension provided clear proof of principle that biomechanical stress is contributing to inflammation [43]. When applying tail suspension to the frequently used TNFΔARE, collagen-induced arthritis (CIA) or collagen-antibody-induced arthritis (CAIA) models, onset of arthritis in the hind paws can largely be prevented, while disease remains unaltered in the front paws [44••]. In the CAIA model in DBA/1 mice, this approach could not only prevent inflammation but also subsequent new bone formation [43]. On the contrary, increasing the loading by voluntary running leads to increased severity of arthritis in the same models [44••]. This mechanical stress-dependent arthritis develops irrespective of adaptive immunity as was demonstrated in RAG2-deficient mice. In the antibody-driven models, CIA and CAIA, the difference in biomechanical loading does not affect the production or activity of auto-antibodies neither influences systemic inflammation as measured by the serum levels of several cytokines and chemokines [44••, 45]. Several underlying mechanisms were identified: increased signaling through the Erk1/2 MAPK signaling pathway in the TNFΔARE mice, recruitment of classical monocytes orchestrated by the chemokine CCL2 in the TNFΔARE and CAIA models, and complement activation in the CAIA model. Furthermore, by in-depth anatomy and micro-CT studies, the calcaneus-cuboid-metatarsal V and the cuneiform I-metatarsal I joint regions in the hind paws where multiple tendons attach were identified as the mechanosensitive sites most prone to erosions, mimicking the distribution of erosions in rheumatoid arthritis and of erosions and enthesophytes in SpA patients [44••].

Of note, all these models show a link between mechanical loading and peripheral arthritis, but up until now, no animal model with axial involvement has been shown to depend on biomechanical stress. Also the possible beneficial effects of biomechanical loading on the joints have not been addressed in animal models of inflammatory arthritis despite being extensively studied in the field of osteoarthritis, where physical activity can have beneficial effects on the cartilage depending

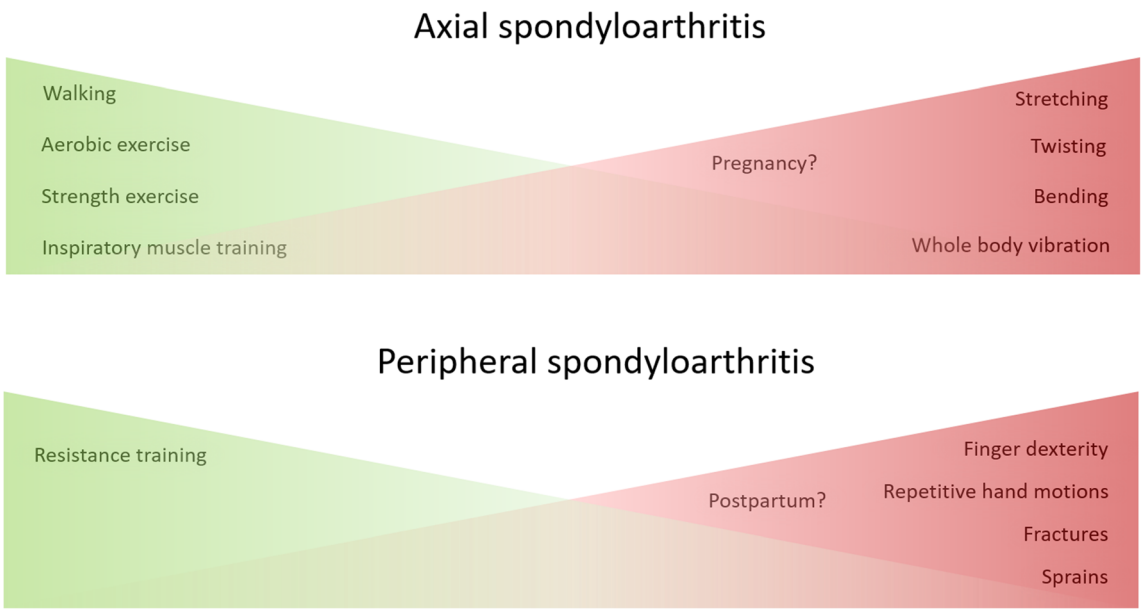

Fig. 1 Potential beneficial (green) or detrimental (red) effect of different types of biomechanical loading reported in clinical trials

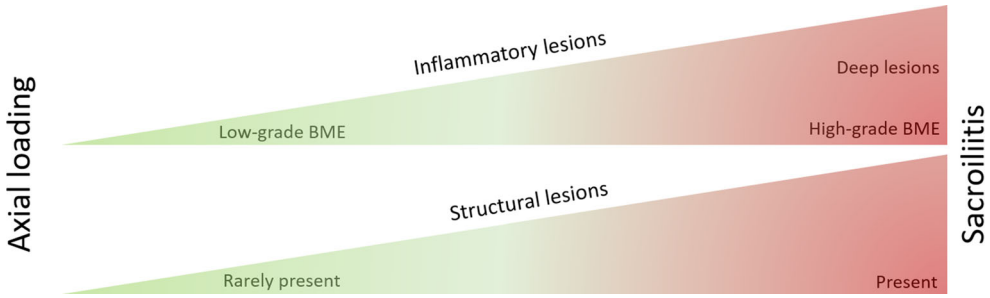

Fig. 2 MRI features in the sacroiliac joint associated with axial loading or sacroiliitis. (BME bone marrow edema)

on the duration and intensity, as well as the health status of the joint before the experiment [46].

Conclusion

The relationship between mechanical loading and SpA is complex. The overall beneficial effect of physical activity in clinical trials is mild, and most outcome measurements available are potentially influenced by general well-being, but there were no harmful effects observed in SpA patients. In recent years, there were no studies confirming the harm of insufficient mobilization, yet, at least a certain baseline of physical activity is necessary to maintain joint stability [47]. Conversely, multiple observational studies demonstrate excessive mechanical strain to be a likely trigger for disease activity and indicate potential differences between peripheral and axial loading (Fig. 1). MRI studies are able to partly bridge the knowledge gaps, by demonstrating a spectrum of sacroiliac joint abnormalities in both healthy and diseased individuals across a wide range (Fig. 2), hinting towards a role for mechanical loading in triggering disease in the genetically susceptible individual. Several molecular pathways were shown to be involved in the mechanosensing of joints in animal models of inflammatory arthritis.

Further research is warranted and could focus on the type, intensity, and duration of specific types of physical activity in well-defined patient populations. Ideally this should include direct comparison between different interventions. Also investigating the involved molecular pathways in beneficial exercise in animal models would be of great interest. Bridging the gap between the beneficial effects seen in clinical trials and the harm in observational studies and animal models would lead to an important benefit for patients, because physical activity is a low cost and widely accessible treatment, with a potential in both curative and preventive strategies, in comparison with the current standard of care in SpA.

Compliance with Ethical Standards

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- • Of importance
- •• Of major importance

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