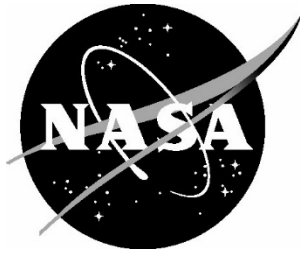


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Concern of Intervertebral Disc Damage Upon and Immediately After Re-exposure to Gravity (Inactive)

Jean D. Sibonga, Ph.D.
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March 2025

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Concern of Intervertebral Disc Damage upon and Immediately After Re-exposure to Gravity (inactive)

Human Research Program

Human Health Countermeasures Element

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TABLE OF CONTENTS

Section	Page
I. PRD RISK TITLE: CONCERN OF INTERVERTEBRAL DISC DAMAGE UPON AND IMMEDIATELY AFTER RE-EXPOSURE TO GRAVITY (INACTIVE).....	1
II. STATUS.....	1
III. EXECUTIVE SUMMARY.....	1
IV. INTRODUCTION.....	3
V. EVIDENCE.....	4
A. Spaceflight Evidence.....	4
1. Astronaut Case Report.....	4
2. Astronaut Chart Review.....	4
3. Spaceflight Data Updates- 2017 Evidence Report.....	4
4. Flight Studies with Rodents.....	6
B. Ground-based Evidence (ground analogs and general terrestrial research).....	7
1. Bed rest Analog for Spaceflight Effects.....	7
2. Animal Models.....	8
C. Computer-based Models and Simulation.....	8
VI. RISK IN CONTEXT OF EXPLORATION MISSION OPERATIONAL SCENARIOS.....	8
A. Premise for the IVD Concern.....	8
B. Premise for Separating Back Pain from IVD Injury.....	8
VII. DAG review AND INTEGRATION WITH OTHER RISKS.....	9
VIII. KNOWLEDGE BASE.....	9
IX. CONCLUSION.....	9
X. REFERENCES.....	10
XI. TEAM.....	14
XII. LIST OF ACRONYMS.....	14

LIST OF TABLES

Section	Page
Table 1. Relative comparison of the elapsed time in 1 G	8

LIST OF FIGURES

Section	Page
None	

I. PRD RISK TITLE: CONCERN OF INTERVERTEBRAL DISC DAMAGE UPON AND IMMEDIATELY AFTER RE-EXPOSURE TO GRAVITY (INACTIVE)

Description of Concern: Given the morphological and possible biochemical changes in the IVD (intervertebral disc) during mechanical unloading in space, there is the possibility of IVD damage upon and immediately after re-exposure to gravity (1/6, 3/8 or 1G). Evidence has suggested that astronauts have a higher incidence of intervertebral disc (IVD) damage than the general population. However, on-going postflight surveillance of the astronaut cohort has not substantiated an increased incidence of IVD damage in astronauts that is directly related to spaceflight exposure. Further studies have attempted to characterize the effects of spaceflight on the vertebral unit (vertebral bodies/IVD/musculature) but the data have not further informed the concern for IVD injury to elevate to a risk and suggest that postflight herniation may be more associated with preflight risk factors.

II. STATUS

Inactive There is no Work/research currently being done towards this risk

III. EXECUTIVE SUMMARY

There is an increased incidence of back pain expressed by crewmembers in space. Additionally, herniated Intervertebral Discs (IVD) have been diagnosed in returning Skylab and Shuttle astronauts on landing day, and after varying periods of time in the postflight period. Such injuries in astronauts, however, may be related to their careers as aviators (either high performance jet pilots and/or helicopter pilots). However, the evidence of IVD injuries raises the concern that astronauts are at increased risk during loading scenarios experienced during or after exploration missions (for example, re-entry to a gravitational field, activities on planetary surfaces).

To date, flight data related to potential back injuries have focused upon spine elongation and the well-established effects of mechanical unloading on intervertebral discs (IVDs). IVDs are the articulating connective tissue between vertebral bodies of the spinal column where the IVD acts as a shock absorber to the mechanical loads experienced in the axial direction. The connective tissue of joints is devoid of vasculature so exchanges between nutrients and waste products are accomplished by the influx and efflux of fluid. In general, the diurnal fluctuations in IVD volume of the spine are induced as the individual transitions between sleep (supine) and ambulation (upright), although the spine is subjected to a variety of mechanical forces with daily activities in 1 G. However, during prolonged bed rest or spaceflight, the absence of axial and muscular loading to the spine causes the IVDs to swell with increased fluid intake. Consequently, the changes in IVD volume were considered major factors for the elongation of the spine, the increase in height and the loss of lordotic curvature. IVD changes may also account for the occurrence of back pain, although the exact cause for the latter is not well defined. Tissue analyses of animals, mechanically unloaded in space and ground-based models, reveal changes

in IVD biochemical composition. Spaceflight-induced changes to IVDs may predispose the IVD to injury during reloading. No flight studies have investigated whether a specific exercise regimen, performed during real or simulated weightlessness, can effectively impart axial loads to the human spine to mimic the diurnal changes in IVD volume experienced on Earth. Restoration of IVD volume, after spaceflight and bed rest, has been observed with return to upright position in a 1-G environment, but the recovery time course has not been systematically assessed. Likewise, IVD biochemical and biomechanical properties, before and after spaceflight, have not been investigated.

In brief, extended exposures to microgravity are associated with increased reports of back pain during flight and may be related to the occurrence of IVD herniations in astronauts after flight. The etiology for these observations may be multi-factorial given the number of documented physiological risk factors induced in space, which include muscle atrophy, tissue degeneration, bone fracture and accelerated bone loss. Thus, further investigations are needed to generate more evidence to better define the risk.

IV. INTRODUCTION

In a questionnaire survey of astronauts who had flown in space, sixty-eight percent of the population reported generalized back pain, with some astronauts rating the pain between severe to moderate (Wing *et. al.*, 1991). This discomfort is considered most painful early during the spaceflight but is attenuated as flight duration progresses. At face value, the cause of back pain in space may be associated to the elongation of the vertebral column by IVD expansion or to other causes. Lower back pain in humans, for example, is also associated with trunk muscle weakness (Dvir and Keating, 2003; Ho., 2005) suggesting that the reduced biomechanical forces from space-induced atrophy of lower back muscles may be a contributing factor. Alternatively, pain caused by IVD changes may be related to increased strain of proximal facet joint capsules (Moneta *et. al.*, 1994), fractured innervated vertebral end-plates (Boos *et. al.*, 1995; Hicks, *et. al.*, 2002), disc degeneration (Straus, 2002), or herniation of annulus fibrosis (Collacott *et. al.*, 2000).

Irrespective of the exact cause of back pain, there may be an increased risk for IVD injury or damage when the swollen IVDs of crewmembers (under the weightlessness of transit) are subjected to excessive forces or torques, e.g., while subsequently performing work on planetary surfaces. Exploration missions on planetary surfaces may introduce habitability issues that could induce excessive torsional stress, an established risk factor for herniation of annulus fibrosus (Farfan and Cosette, 1970). For instance, excessive axial rotation could occur while carrying large masses in the partial G environment by a crewmember with de-conditioned back muscles and may consequently subject IVDs to lateral shear forces. Regardless, there are minimal data (medical evaluations or research) that characterizes the biomechanical and biochemical changes in IVDs in crewmembers during or after flight to assess how such changes predisposes the IVDs to injury under re-loading.

However, herniated nucleus pulposus *is* known to occur in aviators exposed to high G environments (Mason *et. al.*, 1996) and has occurred in astronauts after a mission. There were three separate occurrences of IVD injury on the day of landing as determined by chart reviews and personal communication with crewmembers and flight surgeons (medical chart reviews, personal communication). The relative risk rate of IVD injury in the astronaut population has only recently been evaluated (Johnston *et. al.*, 2010). There is no evidence, however, connecting the origin of an IVD injury with changes in IVDs because of spaceflight – that is, no morphological and/or biochemical changes in IVD composition.

Nevertheless, the results of this retrospective characterization of IVD injury in the astronaut population raises the concern that spaceflight-induced changes to IVDs require further analyses. Additional evidence would describe the spaceflight-induced changes and elucidate how these morphological and biochemical changes predispose the nucleus pulposus to herniation during compressive loading. Based upon the IVD tissue analyses of animals, biochemical changes to the nucleus pulposus during spaceflight or disuse will affect the ability of the osmotic pressure and elasticity of the nucleus pulposus to resist compressive loading (Pedrini-Mille *et. al.*, 1992; Morey-Holton and Globus, 2002; Hutton *et. al.*, 2002). Biochemical changes in the IVDs of crewmembers after flight have not been identified. However, there is *in vitro* research with bovine cartilage explants to use magnetic resonance technology to correlate changes in IVD proteoglycan content with the $T_{1\rho}$ relaxation rates of protons (Wheaton *et. al.*, 2005). This biomarker will enable non-invasive monitoring of proteoglycan content as a method

of assessing the biochemical impact of weightlessness.

V. EVIDENCE

A. Spaceflight Evidence

1. Astronaut Case Report

The quantification of spine elongation during weightlessness had been performed in a single astronaut during the 84-day Skylab 4 mission (Thornton *et. al.*, 1987). Changes in height were monitored during weightlessness (to the 1/16 in.) which described an asymptotic increase in height during flight that appeared to plateau 29 days into the flight. The absolute height change was 1.5 inches at the end of the mission. The increase in spine elongation is presumed associated with the expansion of IVDs during axial unloading. There was also a reported case of spine pain on landing day which was associated with herniated IVD (personal medical communication).

2. Astronaut Chart Review

The reports of several astronauts developing cervical or lumbar herniated nucleus pulposus (HNP) in the immediate period following landing on earth prompted a retrospective review by NASA flight surgeons to evaluate the incidence of IVD damage in the astronaut population (Johnston *et. al.*, 2010). The review sought to clarify whether spaceflight increased the risk for IVD damage because of (a) the exposure to both low- and high G environments during a mission; (b) the extended periods in an abnormal posture; and/or (c) the changes to IVD structure due to its expansion in the absence of axial loading in space. Specifically, this retrospective study compared the incidence of herniated nucleus pulposus (IVD damage) in astronauts to an age-matched control population of persons who have not flown in space. Although the postflight incidence of IVD damage in astronauts is apparent, it is unclear whether and how the spaceflight-induced changes predispose the IVDs to injury. Evidence indicates that many of the injured astronauts had previous and multiple exposures to excessive G (between 6-20 G) as high-performance jet pilots or excessive vibration as helicopter pilots.

Notably, the pathophysiology of IVD injury after spaceflight has not been clearly identified. The documented expansion of disc volume after spaceflight, together with the IVD injuries after reloading in Earth's gravity, suggests that the adaptive changes of the IVD in weightlessness disrupts the balance between osmotic pressure of the nucleus pulposus and the resistive collagen structure of the annuli fibrosus, thereby reducing the ability of the IVD structure to withstand re-exposure to G forces. Repeated, previous exposures to excessive G forces in high performance jets, however, may have also weakened IVD structures, particularly in the cervical vertebrae, increasing the susceptibility of these IVDs to damage. Thus, the risk of spaceflight induced IVD injury in astronauts needs to be discriminated by comparing the absolute risks of the astronaut population with that of a terrestrial control cohort with similar pilot flight history.

3. Spaceflight Data Updates

Report: Bailey JF, Miller SL, Khieu K et al.. From the international space station to the clinic: how prolonged unloading may disrupt lumbar spine stability. Spine J 2018 January 18(1):7-14 doi:10.1016/j.spine.2017.08.261.

Study Summary: Characterization of spine adaptation to spaceflight was performed to understand the etiology for low back pain and the risk for postflight herniation observed in astronauts.

Pre- to postflight changes in lumbar spine anatomy, health and biomechanics data were determined in ISS astronauts (n=6) after typical mission spaceflight durations of 6 months. Measured outcomes were acquired for multifidus and erector spinae at L3-L4. Data were acquired by MRI (3T) and dynamic fluoroscopy conducted 30 days preflight and 1-day after return. In contrast to the perception that intervertebral disc swelling during spaceflight increases the risk for back stiffness and injury, this study observed that the loss of curvature in the lumbar spine was primarily due to multifidus atrophy--which has been similarly observed with terrestrial populations. There was no evidence of wedging for either the lumbar discs or vertebrae in the astronauts. There appeared to be association between preflight vertebral endplate insufficiency and postflight back pain and disc herniation.

HRP Relevance: Albeit a study of only six astronauts, the results suggest that IVD swelling is not the major contributor to postflight back pain and injury observed in astronauts. **The data suggest that postflight risks may be more associated with preflight pathologies that may have been exacerbated during spaceflight.** Although the study results appeared to negate the hypothesized etiology for backpain/injury, the characterization by this study increased the understanding of the etiology and suggested an alternative causality and recommended an effective management approach to reducing this postflight risk -- which may involve the identification of astronauts preflight who may require greater protection during specific design reference missions (DRMs).

Report: Chang DG, Healey RM, Snyder AJ, et. al., Lumbar spine paraspinal muscle and intervertebral disc height changes in astronauts after long-duration spaceflight on the International Space Station. Spine. 2016 15:41(24):1917-1924.

Study Summary: Characterization of changes to the intervertebral disc (IVD) unit during spaceflight was described as well as per Bailey et. al., 2018. Functional cross-sectional area (FCSA) measured in paraspinal muscle (PSM) of 6 ISS astronauts was the quantified outcome. Declines of total FCSA detected after the mission with partial recovery of loss by 6 weeks. Changes in IVD heights was not detected at any timepoint.

HRP Relevance: **Study results indicate that changes to the IVD height or volume during spaceflight is not the primary risk factor contributing to in-flight back pain or the occurrence of postflight back injury (i.e., herniated disc pulposus) in astronauts.** Study suggests that the prevention of atrophy in paraspinal musculature may be the approach for an in-flight mitigation strategy.

Report: Laws CJ, Berg-Johansen B, Hargens AR et. al., The effect of simulated microgravity on lumbar spine biomechanics: an in vitro study. Eur Spine J201625(9):2889-97.

Study Summary: A model, using ex vivo human lumbar segments was used to artificially induce disc swelling and to simulate forward bending. The model could increase the understanding of how biomechanical changes during spaceflight could induce back pain during and/or injury observed after return from spaceflight

HRP Relevance: This model demonstrated the effects of simulated disc swelling to reduce flexibility, and the effects of increased annular strain and nuclear pressure induced with forward bending. **Together with loss of lordosis, these risk factors could likely account for herniated discs observed back on Earth after typical 6-month missions highlighting targets for mitigating interventions (e.g., forward bending).** The concern for injury on Martian surface after a 6-month sojourn is unknown but could be a risk.

Report: Mateus J, Hargens AR. Bone hemodynamic responses to changes in external pressure. Bone 52(2013):605-610.

Mateus J, Hargens AR. Photoplethysmography for non-invasive in-vivo measurement of bone hemodynamics. *Physiol Meas* 201233(6):1027-1042.

Study Summary: These studies 1) quantified bone hemodynamic responses to changes in external pressure and 2) identified key regulatory mechanism for these hemodynamic responses. Inadequate blood perfusion may be associated with reduced bone mineral density.

HRP Relevance: Photoplethysmography is used to measure bone and skin perfusion in response to changes in external pressure. Bone perfusion is decreased at all negative pressures; perfusion is increased with positive pressure with the myogenic response (i.e., in arteries and arterioles to keep a constant blood flow) being the key regulatory mechanism over all pressures. Study provides an interesting and valid characterization although the maturity as a contributing risk factor for spaceflight-induced bone loss and for back pain may be low for the HRP.

Report: Sayson JV, Lotz J, Parazynski S, Hargens AR. Back pain in space and post-flight spine injury: Mechanisms and countermeasure development. *Acta Astronautica* 2013 86:24-38.

Study Summary: An early report suggests causalities to back pain experienced during spaceflight and back injury manifested postflight. The contributing risk factors to back pain were initially thought to be related to increased swelling of the IVD, and back compression (fetal positioning) was suggested as an in-flight countermeasure.

HRP Relevance: Subsequent to the increased incidence of postflight herniated discs first reported in LD astronauts, **this current report provided a comprehensive characterization of changes to the IVD unit, which included bone and muscle measurements. This seminal study substantiated a role of spaceflight to exacerbate spinal pathophysiology(ies) that were present in astronauts before spaceflight.** While the risk manifests in the postflight period, the incidence and the characterizations in astronauts suggest that the risk could be increased during exploration class missions to Mars following long sojourns in microgravity.

Reports: Garcia KM, Harrison MF, Sargsyan ER et al. (2018) Real-time ultrasound assessment of astronaut spinal anatomy and disorders on the International Space Station. *J Ultrasound Med* 37(4):987-999. Doi:10.1002/jum.14438. Epub 2017

Harrison MF, Garcia KM, Sargsyan AE et al. (2018) Preflight, In-flight and postflight imaging of the cervical and lumbar spine in astronauts. *Aerosp Med Hum Perform*. 89(1):32-40. Doi:10.3357/AMHP.4878.2018.

Study Summaries: The self-reported back pain in astronauts during spaceflight has been attributed to the anatomical changes to the back and morphological changes to the IVD unit(s). Ultrasound (B mode typically used for non-bone tissue) is currently the only in-flight modality that is available on the ISS to characterize serial changes to the back during spaceflight. Reports verify and describe a method for using the B-mode ultrasound to describe qualitative changes to the IVD. The use of ultrasound by long duration astronauts with no previous expertise in sonography demonstrated the ability of crewmembers, with no previous proficiency in ultrasound use, to generate diagnostic quality under remote conditions of the ISS.

HRP Relevance: The aim is to demonstrate the utility of B-mode ultrasound for real-time monitoring of changes to the IVD unit which may be inducing back-pain during spaceflight (Aim: to drive real-time clinical response) and for describing back changes that increase the risk for observed postflight IVD injuries (Aim: to inform development or implementation of in-flight countermeasures).

4. Flight Studies with Rodents

Flight experiments with rodents allow *ex vivo* tissue biopsy and assessment of molecular, morphological/histological, and biomechanical status of the IVD – outcomes meant to complement and further understand the IVD findings in astronauts. Results generally corroborate and further increase the understanding of the molecular and mechanical response of the IVD.

Past studies range from 5 to 30 days of spaceflight and all studies-to-date include live animal return to Earth. Early findings in rats from COSMOS 2044 (14 days of spaceflight) show spaceflight reduces the annuli mass, increases the collagen to proteoglycan ratio (with the former elevating and the latter decreasing), increases leaching of proteoglycans after water immersion in lumbar IVD compared to the ground-based controls, all implicating negative biomechanical changes from spaceflight and return to Earth (Pedrini-Mille *et. al.*, 1992; Maynard, 1994). The COSMOS 1887 experiment with rats (12.5 days of spaceflight) used microscopic and histological assessment of cell morphology across lumbar IVD regions, showing accumulation and expansion of the notochordal cells in the nucleus pulposus, hypertrophy in the cartilage endplate, and altered arrangements of collagen, proteoglycan, and glycoaminoglycans dependent on position in the annulus fibrosus suggesting a looser vertebral column following spaceflight and return to Earth (Földes *et. al.*, 1996). More recent studies of caudal IVDs from mice flown on the Space Shuttle (13-15 days of spaceflight) show decreased disc height and biomechanical properties compared to controls (Bailey, *et. al.*, 2012; Bailey, *et. al.*, 2014) and characterized the lack of recovery of these parameters within 1 week once Earthbound (Bailey *et. al.*, 2012). Lumbar discs appeared less sensitive to spaceflight (Bailey *et. al.*, 2014). A 30-day mission with mice on Bion M-1 shows spaceflight reduces bending strength and alters the *ex vivo* failure location/mechanism of caudal spinal segments compared to controls (Berg-Johansen *et. al.*, 2016). Taken together, these studies bolster the mechanistic understanding of the physiology and biomechanics of the risk of disk herniation and can be extrapolated, while considering their limitations, to astronauts.

B. Ground-based Evidence (ground analogs and general terrestrial research)

1. Bed rest Analog for Spaceflight Effects

IVD volume changes were quantified by magnetic resonance imaging in response to varying scenarios of axial unloading (LeBlanc *et. al.*, 1994). The cross-sectional areas and the transverse proton relaxation constants (T2) of IVDs were indices used to monitor adaptive changes of the IVDs to overnight bed rest (over 5 weeks and 17 weeks) and after 8 days of spaceflight. The averaged expansion of IVDs with bed rest appeared to reach an equilibrium anywhere between 9 hours and 4 days of unloading with the expansion ranging between 10-40% of baseline, pre-bed rest values (mean=22%). There were mild increases in T2 relaxation times relative to increases in disc area. Restoration of IVD volumes after unloading was not evaluated systematically but the Table (below) provides a relative comparison of the elapsed time in 1 G at which time the measured IVD volumes were no different from baseline measurements; the relative periods of recovery appear to lengthen as the period of IVD adaptation to unloading increases.

Table 1. Relative comparison of the elapsed time in 1 G

Period of Unloading	Relative Time before Recovery
8 days spaceflight	< 24 hours
5 weeks bed rest	days
17 weeks bed rest	> 6 weeks

2. Animal Models

Ground-based models of spaceflight allow further study of IVD physiology and mechanics, modeling particular or integrated environmental hazards of spaceflight (e.g., altered gravity, space radiation.). The hindlimb-unloading model for rodents has been used to study musculoskeletal disuse and shown to mimic some responses of spaceflight. In brief, IVD changes (Hargens and Mahmood, 1999; Holguin and Judex, 2010; Holguin *et. al.*, 2011; Holguin *et. al.*, 2013) associate with molecular indices indicative of matrix remodeling events (Yasuoka *et. al.*, 2007) and inflammation (Li *et. al.*, 2019).

C. Computer-based Models and Simulation

The literature reports the application of Finite Element Modeling (FEM) to IVDs under the lower osmotic pressure of the space environment. Under this scenario, FEM shows that the appearance of a crack in the IVD experiencing lower osmotic pressure will increase the IVD risk for injury (Wognum *et. al.*, 2006). Likewise, FEM was used to demonstrate that static loading alone will not promote fluid extrusion from IVDs swollen during bed rest or weightlessness. Fluid expulsion will increase with the increased frequency of loading (Cheung and Zhang, 2003). Future work in this simulation capability could be pursued.

VI. RISK IN CONTEXT OF EXPLORATION MISSION OPERATIONAL SCENARIOS

A. Premise for the IVD Concern

Although evidence to define the etiology of back and IVD injury *remains an open issue*, the following assumptions and presumptions were considered when the risk was first evaluated in the context of exploration missions.

1. The absence of axial loading and of forces due to atrophy of back muscles may predispose crewmembers to IVD injury.
2. The risk of detrimental changes to back and to IVD structure and biochemistry will increase with increasing unloaded periods in weightlessness.
3. The risk for back injury and for IVD damage will be greater with the larger G forces experienced during re-entry, landing and surface activities.

B. Premise for Separating Back Pain from IVD Injury

In 2014, an informational presentation to the JSC Human System Risk Board undergirded the board decision to separate IVD injuries postflight in astronauts from the inflight astronaut back pain (Risk of Spaceflight Adaptation Back Pain - SABP). Observations of SABP accumulated over 1961-2019 suggesting the following (quantified data not shown):

1. The risk for SABP in ISS crewmembers is 100% and has been/can be routinely treated by flight surgeons after crewmembers arrive to ISS.
2. Short-term treatment used on-orbit may range from body positioning to medication to modification of activity levels.

3. Symptoms are identified as mild or moderate, targeted to the lumbar region, and more frequent during sleep period.
4. Current countermeasures and standards for SABP are considered adequate and effective.

Hence the concern for SABP is considered Accepted and has been transferred to Medical Conditions Risk. Because the incidence of SABP is high amongst crewmembers, a Watch and Monitoring disposition has been implemented for management of the concern.

VII. DAG REVIEW AND INTEGRATION WITH OTHER RISKS

DAG Review: Because there is no evidence to support elevating IVD injury from a Concern to a Risk no DAG has been generated at this time.

Integration with other risks: The etiology for these observations may be multi-factorial given the number of documented physiological risk factors induced in space, which include muscle atrophy, tissue degeneration, bone fracture and accelerated bone loss.

VIII. KNOWLEDGE BASE

Gaps in knowledge: The underlying mechanisms for postflight IVD injury in astronauts are unknown, though extrapolations can be made from animal studies.

State of Knowledge/Future work: Further characterization of spaceflight effects to back/IVD injury could be explored (clinical and bench research data) in order to establish contributions from or influence to: paraspinal muscle atrophy, bone mass loss and skeletal and IVD degeneration per spaceflight DRMs. This characterization would help inform which mitigating approaches are operationally preferred, e.g., screening for pre-existing spinal pathologies, preflight exercise strengthening, mitigation during transit, or post-flight surveillance and rehabilitation. Moreover, knowledge regarding the various loading activities during exploration missions (e.g., resistive exercise, IVA, and EVA activities) and after return to Earth are needed to help mitigate injury by engineering-out the excessive loading. As with the risk for bone fracture, computer modeling would identify and quantify loads/ torques for the probabilistic assessment of back and/or IVD injuries and mitigating countermeasure or strategies would employ engineering-out the injury hazards. Hence, the concern for IVD injury has been transferred to the Risk of Injury from Dynamic Loads (formerly referred to as *Occupant Protection*).

IX. CONCLUSION

In sum, reports in the literature had suggested that adaptation to the space environment can directly or indirectly induce back pain and may increase the risk for injury when crewmembers are re-subjected to gravity-enhanced mechanical forces and torques. Back pain is commonly reported by crewmembers during spaceflight studies and observations suggest that it may be resolved inflight by body positioning (e.g., forward bending). The elongation of

the spinal column is in part associated with space adaptation syndrome (to weightlessness) and not to increased IVD heights and volumes. A chart review of 321 astronauts, previously suggesting that there may be an increased risk for IVD injury in astronauts, is currently supplemented by flight data suggesting that the postflight risk for back and/or IVD injury is more related to existing preflight conditions. Given the association of mechanical unloading with distortions in IVD morphology, alterations in biochemistry (proteoglycan and collagen content) and in reduced forces of attached muscles it is not unreasonable to suspect that spaceflight exposures could exacerbate any pre-existing conditions in astronauts.

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XII. LIST OF ACRONYMS

EVA	Extravehicular activity
FEM	Finite element modeling
GAG	Glycoaminoglycan
HNP	Herniated nucleus pulposus
IVD	Intervertebral discs
LSAH	Longitudinal Study of Astronaut Health
mRNA	Messenger Ribonucleic Acid
NASA-JSC	National Aeronautics Space Administration- Johnson Space Center
PRD	Program Requirements Document