Narrative Review

Immune dysfunction in spaceflight and diabetes mellitus – translating space observations to terrestrial disease

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Abstract

Introduction: Spaceflight alters normal physiology of cells and tissues seen on Earth. Immune cells and signaling molecules appear to be particularly affected, resulting in changes in leukocyte populations, such as signaling molecule responses to immune challenge, and effector function. Akin to spaceflight, diabetes mellitus produces significant immune system dysfunction. Applying observations and interventions from spaceflight to conditions such as diabetes mellitus may help to identify new approaches that combat their high clinical and financial burden.

Discussion: A literature review was conducted using PubMed, MEDLINE, and Google Scholar. Studies on immune cell function conducted in space and on diabetes mellitus-related immune dysfunction were included. Broad themes of immunosuppression were seen in both spaceflight and diabetes mellitus. Effects on lymphocytes, neutrophils, eosinophils, monocytes, fibroblasts, growth factors, and inflammatory factors are presented.

Conclusions: Immune responses to spaceflight and DM are inconsistent. The innate immune system responds similarly to spaceflight and DM. In contrast, the adaptive immune system responds differently to spaceflight than to DM. This difference may be the result of a glucocorticoid dominant response linked to innate immune suppression and an adaptive Th2 lymphocyte shift.

Relevance: Diabetes mellitus causes major morbidity and mortality. Further research is needed to elucidate mechanisms behind these differences and develop countermeasures for immunosuppression in space with application towards diabetic therapy on earth. Furthermore, commercial spaceflight makes it all the more necessary to elucidate these mechanisms as civilian participants with diabetes mellitus or other immune-altering conditions may soon be able to travel into space.

Tags: Cellular; diabetes mellitus; humoral; immune dysfunction; immune system; innate; microgravity; spaceflight

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Introduction

The prevalence of diabetes mellitus (DM) is projected to increase by 165% in the US by 2050 with tremendous economic costs (1). Besides hyperglycemia, complications of Diabetes Mellitus include hypertension, dyslipidemia, stroke, and cardiovascular disease (2). Prolonged hyperglycemia causes immune system dysfunction from reduced cell-mediated and humoral immune capacity alongside diminished leukocyte function (3).

These immune system alterations are similar to those generated by short-duration (e.g. missions of less than 1 week aboard the International Space Station) and extended-duration spaceflight. Systemically, spaceflight-induced immunosuppression causes decreased lymphoid cell reactivity, virus reactivation, increased infection rates, and impaired wound healing (4–6). On a cellular level, decreased immune cell function, gene expression, signal transduction pathways, and cytokine secretion are observed. The combined effects of microgravity, radiation exposure, and stress have been implicated as causing these effects (5).

Since space exploration began in 1961, voyages have increased in duration, subjecting astronauts to more sustained physiological changes. The massive cost of launching resources and personnel (estimated at $10,000 per pound) has inherently limited the number of human spaceflight subjects and space infrastructure available to conduct direct human research in space (7). Therefore, terrestrial analogs, (ex. Antarctica isolation missions, head down tilt, and clinostat models) are used to study spaceflight-induced physiological phenomena (8). Recent research on immune system dysfunction has shifted to terrestrial conditions manifesting in space, such as rashes/hypersensitivities and latent viral reactivations (5,6). However, a study assessing specific immune system derangements in space and comparing them to a disease with well-characterized immunoregulatory changes like DM is warranted to better understand the effects of spaceflight on the human being.

In this review, the effects of both spaceflight and DM on specific immune cells and signaling molecules are compared. While examining the unique conditions of spaceflight as a theoretical model for understanding immune dysfunction, we consider the putative crossover application to the study of immune alterations for DM populations.

Methods

This review was conducted using PubMed, MEDLINE, and Google Scholar for studies on immune function in spaceflight and DM. Search terms used for spaceflight studies include: ‘spaceflight’ / ‘microgravity’ / ‘weightlessness’ and ‘wound’ / ‘immune’ / ‘complement’ / ‘cytokine’ / ‘advanced glycation end product’ / ‘neutrophil’ / ‘monocyte’ / ‘lymphocyte’ / ‘eosinophil’ / ‘fibroblast’ / ‘macrophage’ / ‘platelet’ / ‘inflammation’. Additional terms resulted in duplicates.

Only studies of immune function carried out during spaceflight were included. 284 papers were surveyed. Papers not addressing the effects of spaceflight on the immune system and vasculature were excluded. Studies in simulated microgravity rather than real microgravity were also excluded. 37 papers were included for review.

Search terms used for DM studies were: ‘diabetes’ and ‘wound’ / ‘immune’ / ‘complement’ / ‘cytokine’ / ‘advanced glycation end product’ / ‘neutrophil’ / ‘monocyte’ / ‘lymphocyte’ / ‘eosinophil’ / ‘fibroblast’ / ‘macrophage’ / ‘platelet’ / ‘inflammation’ / ‘diabetic ketoacidosis’. Additional terms resulted in duplicates. 310 papers were surveyed. Only papers describing the effects of diabetes, hyperglycemia, and diabetic emergencies on the immune system and vasculature were included. 43 papers were included for review.

Results

Overall results are categorized in Tables 1 and 2, separated into spaceflight and DM immune changes, respectively, with further results presented.

Lymphocytes

Lymphocytes consist of T lymphocytes, B lymphocytes, and natural killer (NK) cells. T and B lymphocytes are a part of the adaptive immune system while NK cells are part of the innate immune system (9).

International Space Station (ISS) experiments demonstrate increased human lymphocyte apoptosis caused by DNA fragmentation and elevated mRNA levels of apoptotic hallmarks like p53 and calpain (10,11). Fitzgerald et al. posit that spaceflight hinders early lymphocyte activation by illustrating the effects of timing of polyclonal activation by pokeweed mitogen (PWM) on ex vivo lymphocyte immunoglobulin (Ig) and cytokine production and metabolism (12). Pre-flight PWM exposure induces an

increased metabolic rate in space-exposed lymphocytes up to control levels, whereas lymphocyte exposure to PWM during spaceflight does not.

Additionally, lymphocytes in spaceflight exposed to PWM do not increase Ig production whereas pre-flight activation with PWM increases Ig production (albeit slightly lower than pre-activated controls that have not experienced spaceflight). Lastly, lymphocytes activated with PWM during spaceflight do not increase cytokine production whereas pre-flight activation with PWM increases production to l levels seen in controls activated and cultured on the ground.

Lymphocyte alterations in DM are discussed in the following lymphocyte subsections.

T Cells

T lymphocytes are effectors of the cell-mediated immune response. CD4+ T-helper (Th) cells stimulate proliferation of plasma cells and CD8+ T cells. Regulatory T cells modulate T lymphocyte response. Upon stimulation, T lymphocytes undergo clonal selection forming memory cells for secondary exposure to antigens (13).

In spaceflight, there is decreased T cell activation and activity, decreased type IV hypersensitivity response, and a Th2 shift (4,14,15). Human peripheral blood lymphocytes studied aboard SLS-1 and IML-2 (Shuttle Spacelab Missions) using a T cell activator (concanavalin A) indicate a 56% depression of Interleukin-2 (IL-2) and IL-2 receptor secretion (14). This depression of the IL-2 receptor is thought to account for the decreased T cell activity observed in microgravity. (14)

Conversely, Crucian et al. found an increase in T cell function during short-term space missions (i.e., shuttle flights) and a decrease in T cell function in long-term missions (i.e., ISS missions) (16). Also observed was a Th2 cytokine shift towards humoral immunity over cell-mediated immunity, suggesting increased susceptibility to autoimmune disease, hypersensitivity reactions, and infectious processes (16). Another study of 15 astronauts revealed that 14 out of the 15 astronauts experienced a decreased delayed hypersensitivity response after exposure to a commercially-available hypersensitivity test (4).

Zhen et al. show that while there is an increase in the number of circulating T-regulatory cells in DM, their function is depressed (17). The hyperglycemic environment also affects a subset of T cells known as γδ-T cells. γδ-T cells normally reside in epithelium and function in barrier defense and post-injury wound healing (18). Another study using murine epithelial γδ-T cells showed chronically elevated tumor necrosis factor-α (TNF-α) in hyperglycemia leads to γδ-T cell dysfunction (18).

B Cells

Adaptive immunity is comprised of B lymphocytes, which form plasma cells producing Ig after stimulation by cytokines and interleukins. B cells, like T cells, are capable of forming memory cells providing accelerated response to secondary antigen exposure (19).

Studies on human B lymphocyte levels have indicated insignificant changes in space (20,21). However, an experiment by Boxio et al. using adult ribbed newt indicates a shift in Ig plasma concentrations. After being flown five months aboard Mir space station, their spleens were analyzed ten days after landing. IgY, the homolog to human IgA, was found to be elevated (22).

In DM, hyperglycemia lead to decreased release of IgM and ATP. When challenged with S. aureus, B cells exhibit a 55% decrease in P2X7 receptor-dependent secretion of IgM compared to controls. This may result in under-stimulation and differentiation of B cells in DM (23).

Natural Killer Cells

NK cells are lymphocyte-origin cells which exhibit innate immune system functions. NK cells target tumor cells, viruses, and some normal cells in the bone marrow and thymus (24).

NK cells in spaceflight show diminished counts and function. Fushs et al. demonstrated a reduction in NK cell cytotoxicity in humans and rats during both short-duration (defined as 3 months) and long-duration (up to 11 months) spaceflight, which was more prominent in the extended flight population (25). Similarly, a study of 72 astronauts showed reduced capacity of NK cells to recognize and kill target pathogens for up to 1-week post-flight after 3-11 months of spaceflight. Spaceflight-induced alterations in the ultrastructure of NK cell secretory and locomotor machinery are implicated (26). Furthermore, Tipton et al. and Crucian et al. report elevated neutrophil levels while NK cells are decreased in short-duration and long-duration crewmembers (16,27). Alternatively, Mehta et al. report 10 astronauts with unchanged NK cell numbers during preflight, within three hours post-flight, and

three days post-flight (28). However, cytotoxicity and lytic activity were decreased to approximately 40% of preflight values possibly due to stress response during spaceflight; post-flight urinary cortisol levels were also increased (28).

Type 2 diabetics have profound decreases in both NKG2D-positive NK cells and NKp46-positive cells compared to control subjects (29). Reduced expression of these receptors on NK cells is associated with impaired function (ex. reduced degranulation) when challenged with tumor cell lines (29). Furthermore, decreased NK cytotoxicity and lytic activity has been attributed to reduced expression of cell surface markers NKp30/p46 (30). These results are compatible with that of Lorini et al. who found lowered number and cytotoxic activity of CD16+ NK cells in type I diabetics compared with controls (31).

Monocytes

Monocytes of the innate immune system give rise to cells in tissues that can influence the adaptive immune system through antigen presentation, cytokine production, and receptor expression (32). Mature monocytes include macrophages and dendritic cells that function in phagocytosis, migration, antigen presentation, and cytokine production.

A study of monocytes in 25 astronauts and nine healthy control subjects across four missions of 5-11-day duration was performed by Kaur et al. Except for a surge immediately post-flight, monocyte counts three days post-flight and ten days pre-flight were comparable. Phagocytic ability was significantly reduced immediately post-flight and three days post-flight. Oxidative burst and degranulation ability were constant pre- and post-flight; however, this was significantly lower than that of healthy controls. The authors also found decreased expression of CD32 and CD64, monocytic surface markers for complement activation. Overall, the results showed decreased phagocytic ability (33).

Monocytes of astronauts show upregulation of toll-like receptor 4, which recognizes lipopolysaccharide (LPS) in gram-negative bacteria (34). When challenged with LPS, astronauts' monocytes show decreased production of IL-6 and IL1-β, increased expression of IL-8 (a granulocyte chemoattractant posited to contribute to granulocyte demargination upon landing), and increased expression of IL-1ra (IL-1 receptor antagonist). The astronauts' monocytes also expressed increased levels of LPS-binding protein. These irregular values returned to normal levels after five months except for IL-1ra, which remained elevated five-fold compared to controls even at six to twelve months after landing. This illustrates diminished response of spaceflight-exposed monocytes to gram-negative bacterial challenge (34).

DM results in decreased monocytic chemotaxis, phagocytosis, and altered response to LPS(35). Geerlings et al. and Peleg et al. demonstrated monocytes isolated from patients with DM express lower levels of cytokines including IL-1 and IL-6 compared to normal patients (35,36). Conversely, the prolonged inflammatory response to injury in DM patients leads to an increase in monocyte numbers and overproduction of inflammatory cytokines (37).

Growth Factors

Growth factors regulate cellular proliferation. Hematopoietic growth factors are important cells for the growth, survival and differentiation of blood cells and include colony stimulating factor (CSF) for the induction of lymphocyte hematopoiesis and transformative growth factor-β (TGF-β) for the inflammation/fever response (38). An inhibitor of cell division, TGF-β antagonizes growth factors that promote anabolism, such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) (39).

Davidson et al. studied the effects of spaceflight on the intrinsic capacity of rats to form granulation tissue in a simulated wound after injection of FGF and PDGF (40). Results showed blunted response of granulation tissue formation to PDGF and FGF in flight animals compared to ground controls, which exhibited increased granulation tissue production. The flight group showed decreased cellularity and decreased collagen concentration of granulation tissue (40).

Mirza et al. identified that macrophage TGF-β and IGF-1 production is decreased in wound sites in diabetic mice (41). Lerman et al. report that VEGF, another essential protein in wound healing, is under-produced in diabetic murine fibroblasts (42).

Neutrophils

Neutrophils undergo granulopoiesis in the bone marrow, and secrete defensins, myeloperoxidase, and lysozyme to disrupt bacterial cell walls as part of oxidative burst (43).

Short-duration spaceflights (2-11 days) result in increased leukocytes predominantly due to elevations in neutrophils (27). Similarly, study of blood hematopoietic cells in ribbed newts in spaceflight revealed an increase in the relative proportion of new neutrophils (44).

Stowe et al. investigated the effects of 8-15 days of spaceflight on circulating subpopulations of leukocytes, stress-induced hormones, Ig levels, and neutrophil function (45). Results indicated a 1.5-fold increase in neutrophils and a statistically significant slight decrease (<10%) in lymphocytes upon landing compared to pre-flight measurements (45). Urinary epinephrine, norepinephrine, and cortisol were significantly increased after landing. The increase in band neutrophils (9/16 astronauts) was implicated by with the increase in cortisol. Similarly, elevated epinephrine was posited to contribute to the increase in plasma neutrophils and reduced marginated pool, which refers to the neutrophils adhered to blood vessel walls. Neutrophils are known to demarginate in response to stress hormones such as cortisol and epinephrine. Neutrophils exhibited different adhesion molecule expression, with increased L-selectin and decreased MAC-1 from spaceflight (45).

Kaur et al. analyzed neutrophil phagocytosis, oxidative burst, and degranulation ability in twenty five astronauts during four shuttle missions (5-11 days) compared to nine control subjects (46). Results illustrated neutrophils were increased in number by 85% at landing compared to preflight values. Escherichia coli phagocytosis and oxidative burst abilities were not significantly altered in astronauts landing after five-day missions. However, these two metrics were significantly lower than those in controls for the 9- to 11-day missions. Surface marker expression and degranulation changes were not observed before or after missions (46).

Neutrophils exhibit decreased adherence, chemotaxis, phagocytosis, and oxidative burst capability in type 1 and type 2 DM(47). Furthermore, L-selectin, a marker of neutrophil activation, is increasingly shed and results in increased adhesion to the endothelium (48).

Eosinophils

Eosinophils kill helminths, modulate inflammation, and account for 2% of leukocytes (49).

Aboard biosatellite Cosmos-2229, ribbed newts were investigated for changes in blood hematopoietic cells. After a twelve day spaceflight, the animals showed a several-fold decrease in the number of lymphocytes and eosinophils (44).

Diabetic ketoacidosis (DKA) is an emergency of DM. In DKA, eosinophil counts are greatly reduced compared to non-DKA diabetic patients and non-DM controls. Non-DKA diabetics and normal controls have median normal eosinophil counts of 6595/mm3 and 6008/mm3, respectively, while DKA diabetics median eosinophil count is 28/mm3 (50).

Fibroblasts

Fibroblasts produce extracellular matrix and collagen, providing the structural framework for animal tissues playing a key role in wound healing (51).

Experiments aboard Cosmos-2229 by Tairbekov et al. demonstrated morphologic changes in nucleus size and shape of fibroblasts as well as delayed cell growth and division rate compared to control conditions (52). From 1995-1997, a series of studies of individual fibroblasts and cell associations were performed under various gravity conditions (0.00001-5g) using clinostats, centrifuges, and real microgravity in space. The results showed cultured fibroblasts in space exhibit decreased growth rate, inhibited cell division, and inhibited migration compared to controls (53). In another study, human fibroblasts underwent gene expression changes after spaceflight, relegating them to premature replicative senescence or apoptosis (54). Further experiments show a decrease in fibroblast progenitor cells in the bone marrow of rats after 14 days of spaceflight on the Cosmos-2044 biosatellite (55). Moreover, fibroblasts in space produced 146% increased collagen in vitro relative to controls (56).

Fibroblasts undergo similar modifications in DM. Brem et al. cultured fibroblasts from diabetic foot ulcers showing reduced migration and proliferation capability in relation to controls(57). Loots et al. similarly cultured fibroblasts from diabetic ulcers and found irregular intracellular morphologies such as dilated endoplasmic reticulum and lack of microtubular structures. Additionally, fibroblasts showed decreased proliferative capability compared to controls from non-diabetics (58).

Diabetic mouse fibroblasts in vitro demonstrated abnormal response to hypoxic challenge compared with controls. DM fibroblasts were not stimulated and

did not increase VEGF production unlike controls (increased VEGF three-fold) (42). Additional studies in diabetic rats showed 50% decrease in collagen production, but without decrease in other proteins (59).

Inflammatory Markers

IL-1 is a major proinflammatory cytokine that potentiates immunocompetent cells(60). In humans, IL-10 is produced in greatest quantities by regulatory T cells and is anti-inflammatory. IL-15 mediates T cell proliferation (61). TNF-α is a pro-inflammatory cytokine (62). IFN-γ activates monocytes, which increases inflammatory signaling contributing to chronic inflammation (63).

Cell and molecular-based studies in spaceflight by Semov et al. identified changes in TNF-α and IL-related gene expression in space-flown human fibroblasts. TNF-α converting enzyme (TACE), a molecule that cleaves TNF-α into functional form, is induced in fibroblasts during spaceflight (64). This leads to elevated TNF-α levels without any change in TNF-α mRNA levels. Additionally, Semov et al. found downregulation of IL-15 receptor α chain (IL-15ra). The ligand of IL-15ra is IL-15, which is a regulator of macrophage pro-inflammatory cytokines. There is also upregulation of IL-1rn, a receptor antagonist of IL-1α and IL-1β which neutralizes their function. The authors hypothesize that the changes in IL-15ra and IL-1rn are attempts to regulate pro-inflammatory states and bone resorption (64).

Crucian et al. show that in short and longer-duration spaceflight there is a decrease in IFN-γ:IL10 ratio, favoring a switch to the Th2 subset of CD4+ T cells(16). Alternatively, Irina et al. found that IFN-γ exhibited both increased and decreased levels in different astronauts during 3-11 month spaceflight (26).

Inflammatory factors are elevated in DM patients. CD4+CD28null T-lymphocytes, which are not found at high levels in non-diabetic patients, are increased in DM. This T-cell population secretes high levels of inflammatory cytokines, including IFN-γ (65). Multiple studies have shown that in diabetic wounds, a pro-inflammatory state is promoted via increased levels of IL-1β and TNF-α along with decreased levels of IL-10, TGF-β, and IGF-1 (37,41). Additionally, Taylor et al. found TNF-α to be chronically elevated in hyperglycemic mice (18).

Discussion

The literature surveyed illustrates broad themes of immunosuppression and effector cell dysfunction in both spaceflight and DM. It is important to note that the body of research in DM is significantly larger than that in spaceflight. Thus, the diabetes literature offers specific insights that may not yet be elucidated in spaceflight research.

With few exceptions, spaceflight and DM exert similar effects on the innate component of the immune system (i.e. neutrophils, eosinophils, NK cells, monocytes, adhesion molecules, and fibroblasts) and different effects on the adaptive component (i.e. B cells and T cells). For instance, neutrophils increase L-selectin expression and decrease killing ability in both spaceflight and DM. Conversely, spaceflight does not seem to impact B cell function while DM depresses B cell function. Effects on other cells and molecules studied, such as endothelium and immunoglobulins, are still unclear.

Glucocorticoids such as cortisol have been shown to suppress inflammation, a process initiated by the innate immune system (66). During spaceflight, cortisol levels appear to be elevated. Studies demonstrated that, compared to pre-flight values, cortisol levels were significantly elevated during day 1 of Space Launch System-1 (SLS-1), the majority of the 15-day SLS-2 mission, and days 1-4 of Space Transportation System-95 (67–69). Cortisol levels measured during missions longer than 80 days, such as Skylab, Salyut and Mir, were mostly elevated compared to pre-flight values with a few exceptions (70–72). The variability in cortisol levels in longer term missions may be due to mission specific stressors (73). Nevertheless, the marked increase in glucocorticoids in astronauts during spaceflight may significantly suppress innate immunity.

The difference in effects of DM and spaceflight on the adaptive immune system may be explained by the Th2 shift observed in astronauts (16). A similar lymphocyte shift towards the Th2 subset has been described during stress responses (74), and may counteract any decrease in humoral immunity that would otherwise be observed in spaceflight (74). This may explain the unchanged humoral immune function in astronauts. Type I DM patients have been shown to have Th1 dominant cytokines and a deficiency in Th2 activity (74). The absence of observed Th2 shift in DM may account for differing adaptive immune response between the conditions.

One particularly striking difference between DM and spaceflight is the response of fibroblasts. Fibroblasts increase collagen synthesis in space and decrease collagen synthesis in DM (56,75). The increased fibroblast activity in spaceflight is an exception to the observed pattern of innate immune suppression. It is important to note, however, that the increased fibroblastic activity in space was observed in vitro while the decreased fibroblastic activity in diabetic mice was observed in vivo (56,75). Specific in vivo experiments on human fibroblast collagen synthesis in space were not found. The increase in collagen synthesis in vitro may be a fibroblastic response to mechanical unloading resulting from microgravity.

The present study has several limitations, primarily due to the nature of spaceflight experiments. In the spaceflight literature, there exists variability in organismal model, mission duration, and various confounding factors. For instance, studies utilizing ribbed newts indicate a shift towards increased immunoglobulin secretion whereas human studies have shown constant levels of immunoglobulin (20,22). Launch and landing times as well as post-mission dissection time for animal models also affect study results. Other confounding factors include concurrent effects of microgravity, radiation, psychological stress, and altered circadian rhythms on astronauts. Additionally, the variation between populations in DM studies (eg. Type I vs Type II DM, adult vs. pediatric, level of glycemic control) limits our ability to more precisely define effects of DM on the immune system.

Conclusion

Ultimately, spaceflight and diabetes mellitus both result in immune dysfunction, with notably similar deleterious effects on the innate arm of the immune system. Given the ubiquitous and damaging nature of DM on patients and health systems worldwide, continued research and development of novel diagnostic and therapeutic modalities is imperative. Due to the similarity of innate immune effects presented between DM and spaceflight, the unique conditions of spaceflight may serve as a theoretical model for understanding immune dysfunction with crossover application to such study in DM. Such interdisciplinary research may lend itself to basic science discoveries and advances in prevention and therapeutics in both domains. As spaceflight scientific research in general is still a nascent field, it is reasonable to follow continued work in this area to help inform a more complete picture of the immune effects for comparison with terrestrial diseases.

Further comparative investigation focusing on specific elements of cellular and molecular dysfunction may identify possible countermeasure development with beneficial applications both for spaceflight and crossover application against diabetic immunosuppression across the globe. Further, the unique environment of spaceflight provides a valuable platform to observe and apply interventions for altered physiology that will likely yield interventions for other terrestrial health issues. Future space exploration will only lead to longer missions and the elucidation of new physiologic alterations; application of such findings in a space-to-ground pathway can yield translational clinical benefit to multiple disease states, such as visual impairment, autoimmunity, hypersensitivity, viral infection, and latent reactivation.

Supplementary Content

Table 1: Summary of the effects of spaceflight on the immune system.
Table 2: Summary of the effects of diabetes mellitus on the immune system.

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Table 1. Summary of the effects of spaceflight on the immune system
Ig = immunoglobulin; NK = natural killer; IFN = interferon; ISS = International Space Station; mRNA = messenger ribonucleic acid; IL1rn = interleukin-1 receptor antagonist; HUVEC = human umbilical vein endothelial cell; SLS-1 = Space Launch System-1; IML-2 = International Microgravity Library-2

Ref #	Year	Study Type	Objective	Population Investigated	Flight Duration	Findings
B Cells						
20	1993	Review article	Review of countering immune dysfunction in spaceflight	Humans in spaceflight	Not reported	Brief, reversible postflight increase of IgA/IgG concentration but otherwise resistance of the humoral immune system to influence of spaceflight
21	2013	Cohort observational studies	Review of the qualitative and quantitative changes in the innate and adaptive immune systems of humans in spaceflight	Humans following spaceflight	8 to 195 days	Levels of IgA, IgM, IgG did not change significantly in the post flight blood serum of cosmonauts in 8-11-day missions and 128-195-day missions.
21	2013	Cohort observational study	Review of the qualitative and quantitative changes in the innate and adaptive immune systems of humans in spaceflight	Human peripheral blood cells following spaceflight	169 to 438 days	IgA, IgM, IgG synthesis by B-cells from cosmonauts was significantly suppressed following stimulation by *Staphylococcus aureus* on the first day following 169- and 438-day spaceflights
22	2005	Parallel group experimental study	Adult animals immunized in-spaceflight and spleens analyzed for presence of immunoglobulin post-spaceflight and compared to animals living on Earth	*Pleurodeles waltl* aboard Mir space station	5 months	IgY immunoglobulins in spaceflight animals were three-fold elevated over animals living on Earth
25	1991	Cohort observational study	Examination of mononuclear cells before, during, and after spaceflight	72 cosmonauts in spaceflight	3 to 11 months	Reduced capacity of NK cells to recognize and kill target pathogens for up to a week post-spaceflight. Spaceflight-induced alterations in the ultrastructure of the NK cell secretory and locomotor machinery may explain this occurrence
Eosinophils						
43	1996	Parallel group experimental study	Analysis of blood and hematopoetic cells	Ribbed newts in spaceflight	12 days	Several-fold decrease in number of eosinophils
Fibroblasts						
50	1994	Parallel group experimental study	Comparison on time-related changes in spaceflight-exposed cell morphology compared to ground controls	Mouse embryo connective tissue cells in spaceflight		Morphologic changes in nucleus size and delayed cell growth and division rate compared to 1g control conditions
51	2000	Parallel group experimental study	Comparison of cells cultured in space to ground controls and simulated microgravity	Fibroblasts and osteoblasts cultured in spaceflight		Fibroblasts cultured on solid substrate in space exhibit decreased growth rate, inhibited cell division, and inhibited migration compared to ground controls
52	2008	Parallel group experimental study	Evaluation gene expression in comparison to ground controls	Human fibroblasts in 5 days of spaceflight	5 days	Changes in gene expression following spaceflight predispose fibroblasts to premature replicative senescence or apoptosis
53	1991	Parallel group experimental study	Bone marrow compared to ground controls	Rats exposed to spaceflight	14 days	Decrease in number of fibroblast progenitor cells was observed.
54	1995	Parallel group experimental study	Analysis of collagen synthesis in comparison to ground controls	Human fibroblasts grown in spaceflight for 4-20 hours	4-20 hours	Fibroblasts in spaceflight produced 146% increased collagen in vitro relative to ground controls.

Ref #	Year	Study Type	Objective	Population Investigated	Flight Duration	Findings
Growth Factors						
39	1999	Parallel group experimental study	Analysis of wound healing in the presence of growth factors	Fisher-344 rats in spaceflight	10 days	Blunted response of granulation tissue formation in response to growth factors in spaceflight rats compared to ground controls including decreased cellularity and decreased collagen concentration
Inflammatory Factors						
52	2008	Parallel group experimental study	Post-spaceflight comprehensive immune assessment including peripheral leukocyte subset analysis, early T cell activation potential, and intracellular/secreted cytokine profiles	17 Space Shuttle crewmembers and 8 ISS crewmembers	Not reported	Increased IFN-gamma:IL10 ration decreased in short- and long-duration spaceflight, favoring a switch to the Th2 subset of CD4+ T cells.
25	1991	Cohort observational study	Examination of mononuclear cells before, during, and after spaceflight	72 cosmonauts in spaceflight	3 to 11 months	IFN-gamma exhibited both increased and decreased levels in different astronauts during spaceflight.
62	2002	Parallel group experimental study	Microarray analysis of mRNA expression	Human fibroblasts exposed to spaceflight	Not reported	TNF-alpha converting enzyme was induced in fibroblasts during spaceflight, leading to increases in TNF-alpha levels without increases in TNF-alpha mRNA levels. Additionally, IL-15 receptor alpha chain, whose ligand is a regulator of macrophage pro-inflammatory cytokines, was found to be downregulated. IL1rn was found to be upregulated.
Lymphocytes						
12	2009	Parallel group experimental study	In-flight and pre-flight polyclonal activation of cells by pokeweed mitogen	Human lymphoid cells in spaceflight aboard ISS	12 days	Spaceflight hinders early lymphocyte activation events as evidenced by the absence of increased metabolic and Ig production rates and failure to increase cytokine production upon exposure to mitogens
44	1999	Cohort observational study	Analysis of peripheral blood and neutrophil-endothelial cell adhesion assays	16 astronauts in spaceflight	8-15 days	Slight decrease in lymphocyte count post-spaceflight
10,11	2012, 2016	Parallel group experimental study	Cells activated aboard ISS compared to cells activated on Earth	Human peripheral blood mononuclear cells in spaceflight	48 hrs	Spaceflight triggers human lymphocyte apoptosis as evaluated by DNA fragmentation and accumulation of p53
Monocytes						
32	2005	Parallel group experimental study	Analysis of blood samples collected 10 days pre-spaceflight and 3 hours and 3 days post-spaceflight	25 astronauts in spaceflight	5 to 11 days	Except for a brief surge immediately post-spaceflight, monocyte counts 3 days post-spaceflight and 10 days pre-spaceflight were comparable. Phagocytic ability was significantly reduced and expression of monocytic surface markers CD32 and CD64 was decreased in astronauts post-spaceflight

Ref #	Year	Study Type	Objective	Population Investigated	Flight Duration	Findings
33	2008	Parallel group experimental study	Analysis of blood samples collected 10 days pre-spaceflight and 3 hours, 3 days, and 15 days post-spaceflight	20 astronauts in spaceflight	10 to 13 days	Post-spaceflight upregulation of toll-like receptor 4 (TLR4) and downregulation of CD14. This was accompanied by a diminished response of the monocytes to gram-negative bacterial challenge as measured by a decrease in production of IL-6 and IL1-beta, and an increase of the IL-1 receptor antagonist and IL-8 in comparison to controls. IL-8 upregulation is posited as a contributing factor to granulocyte demargination.
Neutrophils						
26	1996	Cohort observational studies	Review of short- and long-term immune suppression in humans in spaceflight	Humans in spaceflight	2-57 days	Increase in neutrophils post-spaceflight
44	1999	Cohort observational study	Analysis of peripheral blood and neutrophil-endothelial cell adhesion assays	16 astronauts in spaceflight	8-15 days	1.5-fold increase in neutrophils post-spaceflight, reduced marginated pool, and increased post-spaceflight band cell counts in 9 of 16 astronauts possibly related to elevated levels of urinary epinephrine, norepinephrine, and cortisol
43	1996	Parallel group experimental study	Analysis of blood and hematopoetic cells	Ribbed newts in spaceflight	12 days	Increase in the relative proportion of new neutrophils
45	2004	Parallel group experimental study	Analysis of blood samples taken 10 days pre-spaceflight, immediately upon landing, and 10 days post-spaceflight compared to 9 control subjects	25 astronauts in spaceflight	5-11 days	85% increase in neutrophil counts immediately post-spaceflight compared to 10 days pre-spaceflight. No significant difference in *Escherichia coli* phagocytosis or oxidative burst ability was observed in astronauts landing from 5 days of spaceflight, but these two metrics were significantly lower than controls following 9-11 days of spaceflight.
NK Cells						
27	2008	Parallel group experimental study	Post-spaceflight comprehensive immune assessment including peripheral leukocyte subset analysis, early T cell activation potential, and intracellular/secreted cytokine profiles	17 Space Shuttle crewmembers and 8 ISS crewmembers	Not reported	Statistically significant decrease in NK counts post-spaceflight
20	1993	Review article	Review of countering immune dysfunction in spaceflight	Humans in spaceflight	Not reported	Reduction in NK cell cytotoxicity in humans and animals was observed during short-and long-duration spaceflight, sometimes in concurrence with a reduced production of interferons
26	1996	Cohort observational studies	Review of short- and long-term immune suppression in humans in spaceflight	Humans in spaceflight	7-366 days	Decreased in NK cell count post-spaceflight
5	2001	Cohort observational study	Analysis of blood samples collected 10 days pre-spaceflight and 3 hours and 3 days post-spaceflight	10 astronauts in spaceflight	9 to 10 days	No statistically significant change in NK cell counts during or after spaceflight. Decrease in cytotoxicity and lytic activity by approximately 40% post-spaceflight possibly in association with increased cortisol levels

Ref #	Year	Study Type	Objective	Population Investigated	Flight Duration	Findings
Surface Adhesion Molecules						
44	1999	Cohort observational study	Analysis of peripheral blood and neutrophil-endothelial cell adhesion assays	16 astronauts in spaceflight	8-15 days	Increased L-selectin, decreased membrane attack complexes, and increased adhesion of granulocytes to TNF-alpha stimulated HUVEC
T Cells						
4	1993	Cohort observational study	Human skin hypersensitivity test	15 astronauts on US space shuttle missions and orbital Mir station	4 to 177 days	Delayed skin hypersensitivity response in astronauts, T-lymphocyte responsiveness to mitogens depressed by average of 56% during and after spaceflight
27	2008	Parallel group experimental study	Post-spaceflight comprehensive immune assessment including peripheral leukocyte subset analysis, early T cell activation potential, and intracellular/secreted cytokine profiles	17 Space Shuttle crewmembers and 8 ISS crewmembers	Not reported	Increase in T-cell function during short term spaceflight and decrease in T cell function during long term missions. Th2 cytokine shift was observed, indicating a shift towards humoral immunity over cell-mediated immunity
14	1996	Cohort observational study	T cell activation using concanavalin A mitogen	Human peripheral blood lymphocytes on SLS-1 and IML-2 spaceflights	2 to 366 days	Spaceflight depresses IL-2 and IL-2 receptor secretion in response to Con A mitogen

Table 2. Summary of the effects of diabetes mellitus on the immune system.
Ig = immunoglobulin; ATP = adenosine triphosphate; DKA = diabetic ketoacidosis; VEGF = vascular endothelial growth factor; IGF-1 = insulin-like growth factor-1, TGF = transforming growth factor; IL = interleukin; mRNA = messenger ribonucleic acid; ELISA = enzyme linked immunosorbent assay; LPS = lipopolysaccharide; NKG2D = Natural Killer Group 2D; NK = Natural Killer; STZ = Streptozotocin; Tregs = regulatory T cells

Ref #	Year	Study Type	Objective	Population Investigated	Findings
B Cells					
23	2013	Parallel group experimental study	Stimulation of B cells with S. aureus and flow cytometry analysis	Human peripheral B cells	55% reduction of IgM secretion by B cells and 50% reduction in ATP secretion in environment of elevated glucose
Eosinophils					
48	2013	Cross-sectional observational study	Quantification of leukocytes	50 patients with diabetic ketoacidosis, 50 patients with diabetic ketosis, 50 diabetic patients with stable glycemic control, 50 controls	Non-DKA diabetics and normal controls have median normal eosinophil counts of 6595/mm^3 and 6008/mm^3, respectively, while DKA diabetics median eosinophil count is 28/mm^3
Fibroblasts					
41	2003	Parallel group experimental study	Cell culture and immunoassay of mice fibroblasts	Diabetic mice	Murine fibroblasts grown in vitro showed a 75% decrease in migration compared to controls and were not stimulated by hypoxic conditions in contrast to control fibroblasts which demonstrated a two-fold upregulation in activity. Additionally, diabetic fibroblasts did not increase VEGF production in response to hypoxic challenge while the normal controls upregulation VEGF production three-fold
55	2007	Review article	Review of wound healing in diabetes	Diabetic foot ulcers using diabetic mice	Fibroblasts isolated from the non-healing edge of diabetic foot ulcers show reduced migration and proliferation.
56	1999	Cross-sectional observational study	Evaluation of fibroblast cultures using microscopy	Fibroblasts isolated from ulcers of 4 Type II diabetic patients	Fibroblasts isolated from ulcers of Type II diabetics demonstrated significantly reduced proliferation compared to controls and exhibited a deranged morphology marked by multiple lamellar and vesicular bodies, absence of microtubular structures, and a dilated endoplasmic reticulum
57	1988	Parallel group experimental study	Quantification of cartilage and bone collagen production	Diabetic rats	Collagen production in articular cartilage and bone of diabetic mice was 51% and 52%, respectively, of collagen production in non-diabetic controls. Non-collagen protein production in these tissues was not found to be significantly reduced.
Growth Factors					
40	2013	Parallel group experimental study	Immunoassay of proinflammatory molecules	Macrophages isolated from chronic wounds of 5 type 2 diabetic patients & diabetic mice	In Type 2 diabetic patients, the authors noted decreased levels of healing-associated markers CD206, IGF-1, TGF-beta, and IL-10. Furthermore, in diabetic mice, macrophage release of IGF-1 and TGF-beta was maintained at significantly lower levels than control mice at post injury day 10

Ref #	Year	Study Type	Objective	Population Investigated	Findings
41	2003	Parallel group experimental study	Cell culture and immunoassay of mice fibroblasts	Diabetic mice	Fibroblasts isolated from diabetic mice demonstrated a sevenfold reduction in production of vascular endothelial growth factor compared to controls
Inflammatory Factors					
18	2010	Parallel group experimental study	Microarray and flow cytometry analysis	Mouse skin epithelium	Elevated gene expression of TNF-alpha was observed in mouse skin epithelium
36	2000	Parallel group experimental study	Evaluation of wound healing	Diabetic mice	Diabetic mice showed elevated IL-1beta and TNF-alpha mRNA levels into the late phase of repair, suggesting a prolonged inflammatory response
40	2013	Parallel group experimental study	Immunoassay of proinflammatory molecules	Macrophages isolated from chronic wounds of 5 type 2 diabetic patients & diabetic mice	In Type 2 diabetic patients, the authors noted decreased levels of healing-associated markers CD206, IGF-1, TFG-beta, and IL-10. Furthermore, in diabetic mice, macrophage release of IGF-1 and TGF-beta was maintained at significantly lower levels than control mice at post injury day 10
Monocytes					
34	1999	Review article	Review of immune dysfunction in diabetic patients	Humans with diabetes	Decreased chemotaxis is seen in polymorphonuclear leukocytes of patients with diabetes
35	2007	Review article	Review of the pathogenesis and management of infections in diabetic patients	Humans with diabetes	Reduced chemotaxis in diabetic patients when compared to controls
36	2000	Parallel group experimental study	Evaluation of wound healing	Diabetic mice	Diabetic mice showed elevated IL-1beta and TNF-alpha mRNA levels into the late phase of repair, suggesting a prolonged inflammatory response
Neutrophils					
34	1999	Review article	Review of immune dysfunction in diabetic patients	Humans with diabetes	Monocytes of diabetic patients demonstrate decreased chemotaxis, phagocytosis. Furthermore, monocytes of Type I diabetics have shown lower production of IL-1 and IL-6 after stimulation by LPS in comparison to the monocytes of Type II diabetics and controls.
46	2003	Cross-sectional observational study	Measurement of serum L-selectin using ELISA	51 Type 2 diabetic patients	Higher serum levels of L-selectin have been associated with the increased leukocyte-endothelial cell adhesion
NK Cells					
28	2013	Cross-sectional observational study	Analysis of NK cell subsets	51 Type II diabetic patients and 54 age matched controls	Decrease in NKG2D positive NK cells from 55.5% in controls to 44% in diabetic patients and NKp46 positive cells from 50% to 23%, resulting in deducing degranulation capacity of the NK cells when challenged with tumor cell lines

Ref #	Year	Study Type	Objective	Population Investigated	Findings
29	2007	Cross-sectional observational study	Analysis of peripheral blood using flow cytometry	197 Type I diabetic patients	Decrease in NKG2D receptor expression and decreased NKp30/p46 expression associated with reduced NK cell activation in diabetic patients
30	1994	Cross-sectional observational study	Immunofluorescence analysis	25 Type I diabetic patients and 9 age-matched controls	Lowered CD16+ NK cells numbers and cytotoxic activity in diabetic patients
Surface Adhesion Molecules					
46	2003	Cross-sectional observational study	Measurement of serum sL-selectin using ELISA	51 Type 2 diabetic patients	sL-selectin levels were significantly elevated in Type 2 diabetic patients when compared with controls.
T Cells					
17	2012	Parallel group experimental study	Analysis of Tregs	STZ-induced diabetic mice	Inducing diabetes in mice increases the number of circulating CD4+CD25+ T regulatory cells but these cells showed defective immunosuppressive function
18	2010	Parallel group experimental study	Microarray and flow cytometry analysis	Mouse skin epithelium	Hyperglycemia reduces gamma delta T cell populations to half of that in the normoglycemic state and those that remain are impaired in their function by TNF-alpha
63	2002	Cross-sectional observational study	Analysis of T cells in stable and unstable angina	Peripheral blood mononuclear cells from patients with angina	CD4+CD28null T cells produce IFN-gamma