Biomarkers of Inflammation in the LSAH: A Derived Systematic Review

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Background

- Inflammation in humans are associated with a wide variety of pathologies. Acute inflammation is associated with a diversity of diseases from acute infection to gout.
- Chronic inflammation, or a low-grade inflammatory state lasting longer than six months, has been demonstrated to cause similar DNA damage to radiation exposure (causing double stranded breaks with failed corrections), predisposing subjects to cancer [10].
- The Lifetime Surveillance of Astronaut Health (LSAH) contains a wide variety of laboratory values on the astronaut corps and their earth-based analogs.
- This review sought to identify inflammatory biomarkers and to correlate them with those systematically collected at NASA.

Aim & Objectives

- The question prompting this derived systematic review and a future subsequent query of LSAH was the following: are astronauts more predisposed to inflammation than their non-astronaut counterparts? If so, to what degree are they experiencing inflammatory related health conditions?
- **Aim:** To identify biomarkers of acute & chronic inflammation, and their associated diseases
- Conduct a derived systematic review to identify biomarkers of inflammation
- Establish the normal ranges for those biomarkers available in the LSAH.

Methods

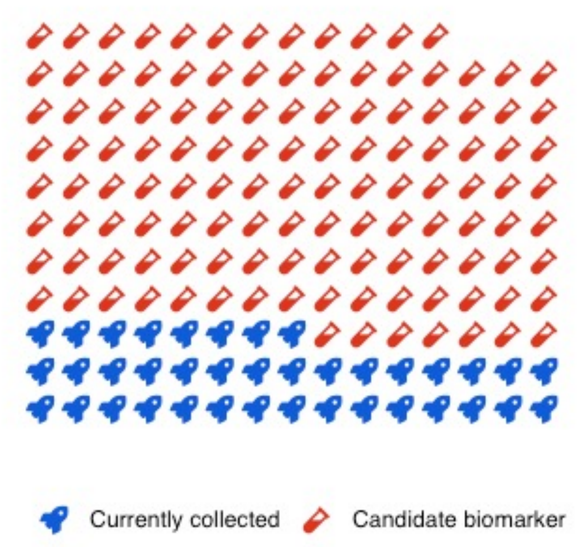
- A derived systematic review of the literature was conducted using PubMed. To further limit results, the PubMed filter "review" was added
- **Query (n=715):** ("diagnostic testing" or "lab testing" or "biomarker") AND ("chronic inflammatory disease" or "chronic inflammatory disease")
  - Terms must appear in title/abstract
  - 144 articles identified after adding "Review" filter
- **Inclusion:** Biomarker must be discussed in the context of human disease (in vivo)
- **Exclusion:** Genomics & transcriptomics were not considered to be biomarkers at the level of validation required for this search
- Limited biomarkers were found in the initial search, the search was expanded to a query using the keywords: "chronic inflammation biomarkers review", yielding 6 additional articles for review (Supplemental Figure 1).

Results

- **144 articles** identified
  - 33 full text reviews
  - 6 additional articles
- **145 diseases** assessed
- **162 biomarkers** identified
  - 1 in 4 currently collected

Figure 1

Number of biomarkers identified



Biomarkers identified in derived systematic review

The top 10 most frequently cited biomarkers, stratified by current collection at NASA

Systematically collected by NASA		Candidate biomarkers	
Biomarker	**Diseases**	**Biomarker**	**Diseases**
CRP (n=17)	↑: General Inflammation [2,4,5,11,16,23,33], DM/MetS [2,16,18,19,22], CVD [2,16,18,19], Cancer [2,10], AMD [18], COPD [3], Dementia [18], Depression [7], Other [21]	**IL-6** (n=18)	↑: DM/MetS [2,16,18,19,22,26], General Inflammation [2,5,23,33], Cancer [2,4,28], COPD [3], CVD [2], Depression [7], Other [21], TBI [31]
TNF-α (n=16)	↑: DM/MetS [18,19,22,26], General Inflammation [2,4,5,33], Cancer [20,28], COPD [3], CVD [19], Dementia [27], IBD [1], Infection [26], Kidney disease [23], Other [21], TBI [31]	**ICAM-1** (n=7)	↑: General Inflammation [2,5,33], Cancer [2,4], DM/MetS [2,22], CVD [2], Other [21]
CCL2 (n=10)	↑: General Inflammation [5,33], AMD [22], Bipolar [24], Cancer [4], COPD [14], Depression [24], DM/MetS [26], IBD [30], Kidney disease [23], Other [21]	**Fibrinogen** (n=6)	↑: General Inflammation [2,5,23], CVD [2,19], DM/MetS [2,19], Cancer [2], COPD [3] ↓: General Inflammation [26]
IL-1β (n=8)	↑: General Inflammation [4,5,33], AMD [22], COPD [3], Dementia [27], Other [21], TBI [31]	**IL-10** (n=6)	↑: AMD [22], Cancer [4], Dementia [27], TBI [31]
IL-1α (n=4)	↑: AMD [22], Dementia [27], General Inflammation [23]	**VCAM-1** (n=4)	↑: General Inflammation [2,5,33], DM/MetS [2,22], Cancer [2], CVD [2]
CCL5 (n=4)	↑: COPD [14], General Inflammation [5] ↓: Cancer [4]	**Adiponectin** (n=4)	↑: DM/MetS [26], General Inflammation [5] ↓: DM/MetS [2,19], Cancer [2], CVD [2]
IL-17 (n=3)	↑: AMD [22], Cancer [28]	**IL-8** (n=4)	↑: General Inflammation [4,5,33], CVD [31], TBI [31]
IL-4 (n=3)	↑: AMD [22], Cancer [4], Dementia [27] ↓: Dementia [27]	**IL-18** (n=3)	↑: DM/MetS [2,19], General Inflammation [2,23], Cancer [2], CVD [2]
NLR (n=3)	↑: Cancer [10], Other [8] ↓: MS [11]	**MMP-9** (n=3)	↑: AMD [22], CVD [33], Kidney disease [23], Other [22]
CCL3 (n=3)	↑: COPD [14], Depression [24], General Inflammation [5]	**TGF-β** (n=3)	↑: AMD [22], Cancer [28], General Inflammation [4]

"↑" and "↓" indicate the biomarker is increased or decreased in that condition, respectively. The list of sources cited in the table above is on the next slide of the poster.

Abbreviations: **DM/MetS** = Diabetes &/or metabolic syndrome; **CVD** = Cardiovascular diseases; **AMD** = Age-related macular degeneration; **TBI** = Traumatic brain injury; **NLR** = Neutrophil to lymphocyte ratio; **MS** = Multiple sclerosis.

Current Gaps

- Many interleukins are not currently being systematically collected at NASA, including the most frequently cited biomarker in this review (IL-6).
- As spaceflight moves into deep space exploration, it is important to consider novel biomarkers that are more stable (i.e. can be frozen for years).
- This review also identified novel biomarkers that could be ideal candidates for assessing inflammation during long duration exploratory spaceflight. Examples include:
  - **GlycA** - an inflammatory signal on NMR associated with many acute and chronic inflammatory markers
  - **CD138** - a plasma cell marker with similar disease associations
- Both GlycA and CD138 could be advantageous due to their:
  - **Stability** – Both can be frozen for extended periods of time
  - **Generalizability** – Both are elevated in several diseases
- TNF-α, on the other hand, is not elevated in serum for extended periods of time (compared to CD138), making it less ideal for evaluation on long duration missions.

Conclusions & Future Work

- The next step for this project is to query LSAH in order to determine the levels of inflammatory biomarkers within the astronaut corps, and to compare these against non-astronaut controls.
- In conclusion, while NASA collects many of the most relevant biomarkers established in this review, there are nonetheless quite a few that remain uncollected.
- The collection of these biomarkers represent as a surrogate of inflammation, but it is important to bear in mind that a more accurate measure of inflammation can only be given by comprehensive evaluation of a multitude of biomarkers at different molecular and cellular levels.
  - These systems level measures require cutting edge analytical technologies and bioinformatics and should be considered to provide more valuable indices of inflammation than what biomarkers in isolation can reflect.
- For the time being, and given the resources in existence, as we discover more about inflammation and its role in disease, there is the possibility that new biomarkers may be retroactively identified. In this sense, this derived systematic review has allowed assessment of the current inflammation related data available in the LSAH.

Supplemental materials

A list of citations, all 162 biomarkers identified in review, and the normal values for select inflammatory biomarkers currently available in the LSAH is available upon request from Dr. Susana Zanello.

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Disclosures

The authors declare no conflict of interest.

Citations

#	First Author	Citation
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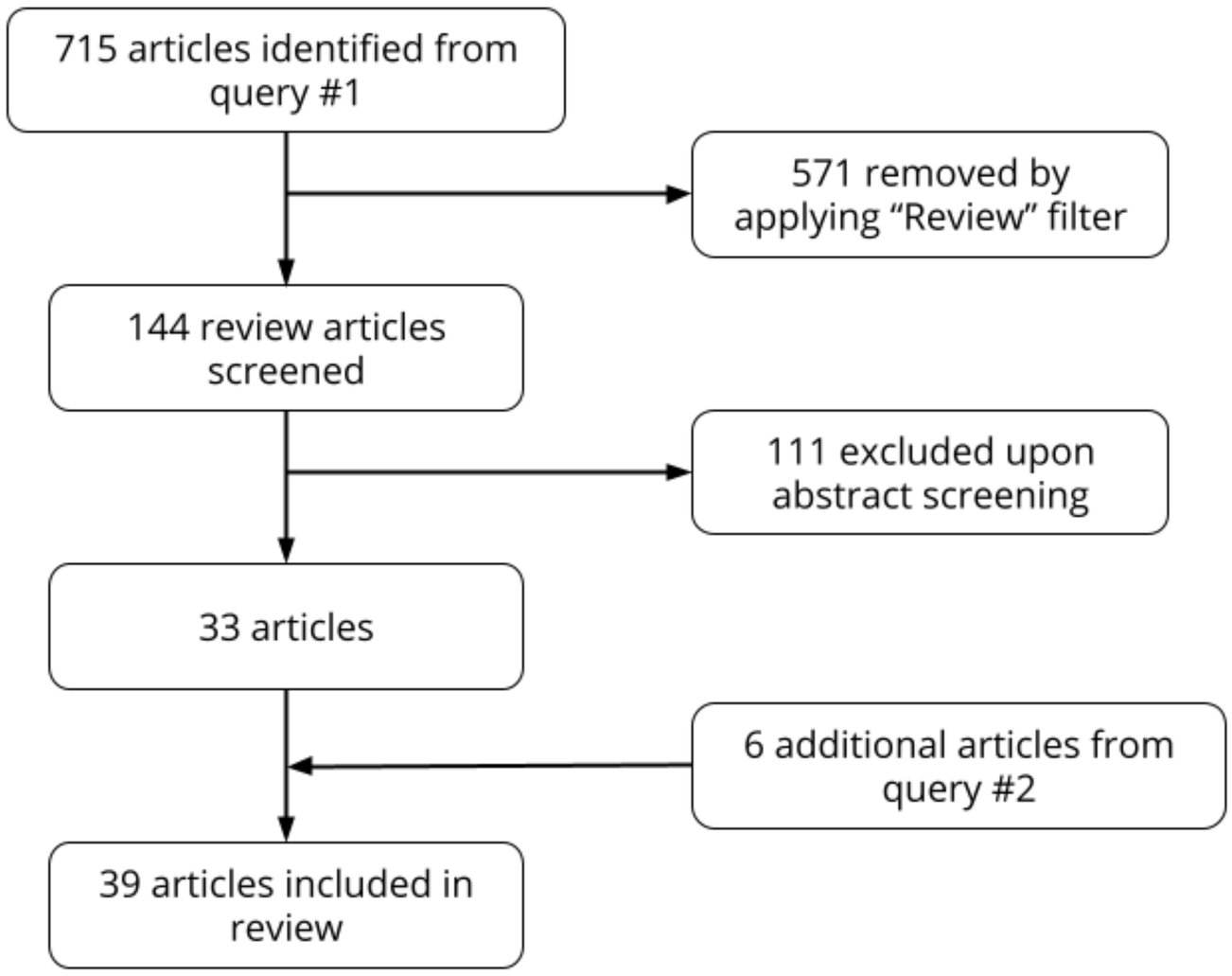
Supplemental Figure 1:
Study flow diagram



Query 1: ("diagnostic testing”[TIAB] or “lab testing”[TIAB] or “biomarker”[TIAB]) AND (“chronic inflammatory disease” [TIAB] or “chronic inflammatory disease”[TIAB])

Query 2: Keywords: “chronic inflammation biomarkers review”