Systematic Reviews /Meta-analyses

A Systematic Review and Meta-Analysis of Silicon Nitride and Biomaterial Modulus as it Relates to Subsidence Risk in Spinal Fusion Surgery

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ABSTRACT

Introduction: For decades, researchers and surgeons have sought to determine the optimal biomaterial for spinal fusion implants. Successful fusion is associated with improved quality of life while failures are often associated with costly and complex revisions. One common failure is subsidence. Biomaterials with higher modulus are thought to be related to subsidence risk but this has not been thoroughly investigated. The aim of this systematic review and meta-analysis is to assess silicon nitride and biomaterial modulus as they relate to subsidence risk in spinal fusions.

Methods: A systematic review was conducted using the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines. Databases searched included PubMed-Medline, Google Scholar, Embase, EBSCO, and Cochrane Library. Study quality was assessed according to the Newcastle-Ottawa Scale. A network meta-analysis was chosen, allowing for direct and indirect comparisons for multiple treatments using a Bayesian hierarchical framework with Markov chain Monte Carlo methods. Outcomes were reported as odds ratios with 95% confidence intervals. Heterogeneity between studies was evaluated using the I² test. A pairwise meta-analysis was also produced to compare the results of network analysis for consistency. Publication bias was assessed using a funnel plot, Egger test, and Begg test. All analyses were conducted using R (Project for Statistical Computing, ver. 4.0.4).

Results: The initial search yielded a total of 821 articles. After removal of duplicates and screening based on inclusion and exclusion criteria, 64 articles were available for review and 13 were selected for meta-analysis. Biomaterial implant types in the final studies included: silicon nitride (Si₃N₄), polyetheretherketone (PEEK), titanium (Ti), and two composites, nano-hydroxyapatite/polyamide 66 (n-HA/PA66) and a carbon fiber reinforced polymer (CFRP). A total of 1,192 patients were included in this analysis – 419 with titanium implants, 460 with PEEK, 96 with Si₃N₄, 332 with n-HA/PA66, and 35 with CFRP. Titanium had the highest rate of subsidence compared to other biomaterials. Pairwise analysis was consistent with these results. Both the Egger test (p = 0.28) and Begg test (p = 0.37) were found to be non-significant for publication bias.

Conclusions: Spinal fusion implants derived from Si₃N₄, compared to PEEK and titanium, do not appear to be correlated with increased subsidence risk.

Introduction

For decades, researchers and surgeons have sought to determine the most optimal biomaterials for spinal fusion surgery. The rational is both sensible and economic. Improved healing and adequate fusion are associated with improved quality of life, faster return to work, less pain, less opiate use, and fewer repeat surgeries. [1] This is in stark contrast to failed fusions, often due to pseudoarthrosis or subsidence. Failures are associated with costly and often more complicated revisions as well as serious downstream consequences for patients. Many have posited that biomaterials with higher modulus of elasticity are directly related to subsidence and, therefore, failed fusion. [2] However, this belief has not been thoroughly investigated. To best facilitate fusion, it has been posited that biomaterials used within the disc space had to mimic the

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properties of native bone. Similarly, radiolucent biomaterials were preferred so that future radiographic interpretation was not hindered. This resulted in decades of widespread adoption of polyetheretherketone (PEEK). However, as implant biology and surface interfaces were more closely evaluated at the cellular level, new concerns arose over PEEK’s bioreactivity and healing.[3] The properties of both PEEK and titanium for interbody fusions were rigorously compared in the literature with little consensus after over two-hundred-and-fifty papers published on the topic.[4]

Many novel biomaterials have since been introduced, purporting various benefits with respect to fusion rates, healing, anti-bacterial properties, radiographic properties, surface interfaces, and more. Despite innumerable publications comparing some of the options, the ultimate choice in utilization has often been relegated to surgeon comfort or devices and options they used in training. Silicon nitride (Si$_3$N$_4$) is one particular biomaterial that the authors felt lacked organized clinical data and conclusions despite a plethora of strong basic science data. It also appeared to be a viable competitor to the increasingly popular advances in titanium technology, such as 3D printed and surface engineered options. The sparse data that does exist suggests that silicon nitride may afford earlier fusions and less infections from inherent bacteriostatic properties.[5–7] However, contradictory data also exists (i.e., SNAP trial[8]) that alludes to the fact that Si$_3$N$_4$ may not be superior or even comparable to PEEK, whereas another RCT by McEntire BJ et al.[9], demonstrated non-inferiority to PEEK.

To provide evidence-based practice recommendations, our objective was to conduct a systematic review to better understand the totality and quality of the data available. Secondarily, we sought to analyze subsidence risk as it relates to modulus of elasticity. The purpose of this study was to therefore conduct a meta-analysis based on a structured systematic literature review to assess silicon nitride and biomaterial modulus as they both relate to subsidence risk in spinal fusion surgery.

**Materials and Methods**

**Search Strategy**

A systematic review was first conducted using the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines.[10] Databases searched included PubMed-Medline, Google Scholar, Embase, EBSCO, and Cochrane Library. The literature search was conducted by authors JA and RS and was restricted to articles published in English from January 2000 to September 2021. It was performed using specific key words related to prospective or retrospective studies involving patients undergoing spinal fusion surgery using cage implants with an identified biomaterial, with assessment for subsidence.

Figure 1. PRISMA Flow Diagram

Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis Campbell Systematic Reviews, 18, e1230. https://doi.org/10.1002/str2.1230
Table 1
Summary of Studies

| Study                  | Quality of Evidence | Study Design | Country  | Surgery | Biomaterial          | Surgical Indication | Biomaterial by Levels |
|------------------------|---------------------|--------------|----------|---------|-----------------------|---------------------|-----------------------|
|                        |                     |              |          |         | Ti       | PEEK   | Si$_3$N$_4$ | n-HA/PA66 | Carbon Fiber |
| Arts et al. 2017       | Good                | RCT          | Netherlands | ACDF    | PEEK (Medicrea Manta) | -                   | C3-4 (1); C4-5 (6); C5-6 (30); C6-7 (19); C7-T1 (2) |
| Cabrera et al. 2012    | Good                | Retrospective | Germany  | ACDF    | Celspace Titan cage with Plasmapore coating (Aesculap) | -                   | C3-4 (1); C3-5 (7); C5-6 (23); C6-7 (13); C5-6 (20); C6-7 (6) |
| Chen et al. 2013       | Good                | RCT          | China    | ACDF    | SynCage-C (Synthes) | -                   | C3-6 (14); C4-7 (15) |
| McEntire et al. 2020   | Good                | RCT          | Netherlands | TLIF    | PEKK box cage (Depuy Spine) | -                   | L4-5 (7); L5-6 (1) |
| Nemoto et al. 2014     | Good                | Retrospective | Japan    | TLIF    | Capstone (Medtronic) | -                   | L4-5 (7); L5-5 (16); L5-5 (15) |
| Niu et al. 2010        | Good                | Prospective  | Taiwan   | ACDF    | VIGOR-r cage (Advanced Spine Technology) | -                   | C3-4 (6); C4-5 (10); C5-6 (17); C6-7 (4) |
| Wrangel et al. 2017    | Fair                | Retrospective | Germany  | PLIF    | NR       | -                   | L3-4 (5); L4-5 (6); L5-5 (11); L5-5 (18); L5-5 (7) |

(continued on next page)
Table 1 (continued)

| Study          | Quality of Evidence | Study Design | Country | Surgery | Biomaterial | n-HA/PA66 | Surgical Indication | Biomaterial by Levels |
|----------------|---------------------|--------------|---------|---------|-------------|-----------|---------------------|-----------------------|
| Deng et al. 2016 | Fair                | Retrospective | China   | TLIF    | -           | -         | Sichuan University and Department of Orthopedics, The First Affiliated Hospital of Chongqing Medical University | Degenerative or isthmus spondylolisthesis, degenerative disc disease, lumbar stenosis, lumbar disc herniation or recurrent lumbar disc herniation | -                    |
| Hu et al. 2019a | Good                | Retrospective | China   | ACCF    | -           | NR        | Cervical spondylosis | C4 (7); C5 (25); C6 (20) | C4 (9); C5 (29); C6 (17) |
| Hu et al. 2019b | Good                | Retrospective | China   | ACCF    | -           | NR        | Cervical spondylosis | C3-4 (5); C4-5 (10); C5-6 (18); G6-7 (14) | C3-4 (4); C4-5 (12); C5-6 (22); G6-7 (13) |
| Yang et al. 2013 | Good               | RCT          | China   | ACCF    | -           | Cage (Sichuan National Nano Technology Co.) | Cervical degenerative diseases | C3 (3); C4 (8); C5 (15); C6 (6) | C3 (3); C4 (11); C5 (13); C6 (8) |
| Yoo et al. 2014  | Good                | Retrospective | South Korea | ACCF    | -           | Carbon fiber composite frame cages (Co-Ligne AG) | Cervical degenerative diseases | C3-4 (1); C4-5 (4); C5-6 (16); G6-7 (2) | C3-4 (3); C4-5 (2); C5-6 (20); G6-7 (10) |
| Zhang et al. 2014 | Fair               | Retrospective | China   | ACCF    | -           | Cage (Sichuan National Nano Technology Co.) | Multilevel cervical spondylotic myelopathy | C4 (6); C5 (16); C6 (3); C4-5 (10); C5-6 (11) | C4 (7); C5 (36); C6 (9); C4-5 (11); C5-6 (8) |

*NR = not reported
Ti = titanium
PEEK = polyetheretherketone
Si3N4 = silicon nitride
n-HA/PA66 = nano-hydroxyapatite/polyamide66
Table 2
Patient Demographics by Included Study:

| Study          | Number of Patients (Female/Male) | Age (range or ±SD) | Smoking Status |
|----------------|----------------------------------|--------------------|----------------|
|                | Ti  | PEEK | Si$_3$N$_4$ | n-HA/PA66 | Carbon Fiber | Ti  | PEEK | Si$_3$N$_4$ | n-HA/PA66 | Carbon Fiber |
| Arts et al. 2017 | -   | 48 (23/25) | 52 (23/29) | - | - | - | 49.4 [28-67] | 39.6% (19/48) | - | - |
| Cabrera et al. 2012 | 44 (18/26) | 42 (14/28) | - | - | 51.1 ± 8.9 | 57.6 ± 11.1 | - | - | 61.4% (27/44) | - | - |
| Chen et al. 2013 | 29 (12/14) | 31 (15/16) | - | - | 45.7 ± 7.2 | 47.2 ± 6.8 | - | - | 24.1% (7/29) | - | - |
| McEntire et al. 2020 | - | 48 (33/15) | 44 (28/16) | - | - | - | 53.0 ± 9.5 | - | - | 35.4% (17/48) | - | - |
| Nemoto et al. 2014 | 23 (1/22) | 25 (2/23) | - | - | 40.7 ± 10.2 | 42.9 ± 10.4 | - | - | NR | NR | - |
| Niu et al. 2010 | 28 (13/15) | 25 (13/12) | - | - | 49.5 ± 11.5 | 52.2 ± 10.5 | - | - | NR | NR | - |
| Wrange et al. 2017 | 15 (5/10) | 25 (18/7) | - | - | 63 ± 12 | 69 ± 10 | - | - | NR | NR | - |
| Deng et al. 2016 | - | 142 (82/60) | 124 (63/61) | - | - | 53.65 ± 14.43 | 53.28 ± 12.51 | - | - | NR | NR | - |
| Hu et al. 2019a | 52 (24/28) | - | - | 54.9 ± 9.5 | - | - | 56.5 ± 10.4 | NR | - | NR | - |
| Hu et al. 2019b | - | 51 (23/28) | - | - | 47 (22/25) | 51.3 ± 9.5 | 52.5 ± 10.4 | - | 15.7% (8/51) | - | 21.3% | - |
| Yang et al. 2013 | 32 (12/20) | - | - | 46.8 ± 7.2 | - | - | 47.6 ± 7.1 | 31.3% (10/32) | - | - | 40.0% (14/35) | - |
| Yoo et al. 2014 | 23 (13/10) | - | 35 (13/22) | - | - | 53.9 | - | 51.8 | - | 34.8% (8/23) | - | 40.0% (14/35) | - |
| Zhang et al. 2014 | 46 (22/24) | - | - | 71 (30/41) | - | 1 level 55.04 ± 11.09; 2 level 57.81 ± 11.50 | 1 level 56.56 ± 12.13; 2 level 57.00 ± 10.95 | - | - | NR | - | NR | - |

*NR = not reported

Ti = titanium
PEEK = polyetheretherketone
Si$_3$N$_4$ = silicon nitride
n-HA/PA66 = nano-hydroxyapatite/polyamide66
Table 3
Summary of Subsidence Definition, Follow-up, Modality Used for Assessment, Events:

| Study            | Definition                          | Mean Follow-up | Modality                          | Results (Events) |
|------------------|-------------------------------------|----------------|-----------------------------------|------------------|
| Arts et al. 2017 | [≥2 mm] multiple measurements      | 24 months (last)| CT and Medical Metrics, Inc. (MMI, Houston, TX, USA) software | -                |
|                  | *                                    |                |                                   | 52.2% (24/46)    | 50.0% (23/46)    |
| Cabraja et al. 2012 | ≥2 mm                           | 28.4 months | NR                                | 20.5% (9/44)    | 14.3% (6/42)    |
| Chen et al. 2013 | ≥3 mm                               | 99.7 months   | NR                                | 34.5% (17/50)   | 5.4% (5/93)     |
| McIntire et al. 2020 | ≥3 mm                          | 24 months (last) | X-Ray and CT                       | -                | 0.0% (0/53)     |
| Nemoto et al. 2014 | ≥2 mm                           | 24 months (last) | CT                              | 34.8% (8/23)    | 28.0% (7/25)    |
| Niu et al. 2010 | ≥3 mm                               | Ti 31.9 ± 3.4; PEEK 30.4 ± 3.3 | NR                               | 16.2% (6/37)    | 0% (0/34)      |
| Wrangel et al. 2017 | NR                               | Ti 32 ± 13; PEEK 39 ± 12 | CT                               | 0.0% (0/15)    | 0.0% (0/25)     |
| Deng et al. 2016 | >3 mm                               | PEEK 14.61 ± 4.08; n-HA/PA66 14.69 ± 4.13; Ti 102.4 ± 4.6; n-HA/PA66 103.6 ± 6.3; PEEK 95.4 ± 8.4; n-HA/PA66 98.6 ± 11.3 | X-Ray and CT | 40.4% (22/52) | 18.2% (10/55) |
| Hu et al. 2019a | ≥3 mm; radiographic >2 mm           | 48 months (last) | CT                                | 21.9% (7/32)    | 5.7% (2/35)     |
| Hu et al. 2019b | ≥3 mm; radiographic >2 mm           | 24 months (last) | MRI                              | 26.1% (6/23)    | 34.3% (12/35)   |
| Yang et al. 2013 | >3 mm                               | 45.28 ± 12.83 months | CT                               | 30.4% (14/46)   | 4.2% (3/71)     |

* NR = not reported

The selection process included identifying and excluding duplicate entries, followed by reviews of titles and abstract for relevance, and finally full-text review. Manuscripts selected for review and final inclusion were based on MINORS criteria for quality.[11]

Study elements (metadata, abstract, full text, PICO elements) were managed using the Zotero reference management software.

Inclusion and Exclusion Criteria

Studies were selected if subsidence rates were reported and feasible for data extraction; and if the study evaluated at least two different types of biomaterials. Studies were excluded if the focus was on novel device design only (i.e., 3D printed cages) or involved solely metallic-polymer composite biomaterial devices (i.e., Ti/PEEK or Ti-coated PEEK).

Quality Assessment

Quality was assessed according to the Newcastle-Ottawa Scale,[12] which scores studies under three main categories: selection, comparability, and outcome. The maximum score was nine, and studies meeting seven or more of the items were considered of good quality in this analysis.

Data Synthesis and Statistical Methods

Once the structured literature review was deemed adequate and representative, a formal meta-analysis was conducted. Outcomes of interest were reported as odds ratios with 95% confidence intervals. A network meta-analysis was chosen since it allowed for direct and indirect comparisons for multiple treatments using a Bayesian hierarchical framework and Markov chain Monte Carlo methods. Heterogeneity between studies was evaluated using the I² test. The I² statistic determined suitability for fixed effect (I² <50%) or random effect (I² >50%) method. A pairwise meta-analysis was also produced to compare the results of the network analysis for consistency and tendency. Publication bias was assessed using a funnel plot, Egger test, and Begg test. All analyses were conducted using R (ver. 4.0.4; R Project for Statistical Computing, Vi-
ennan, Austria; the packages used include: tidyverse, metafor, gmeta, and igraph).

Results

Study Network

The initial search yielded a total of 821 articles (Figure 1). After removal of duplicates and preliminary title and abstract screening, the collection was reduced to 140 articles. A second round of screening based on inclusion and exclusion criteria on full paper readings resulted in 64 articles for review and 17 for consideration (Table 1)[13–31].

Quality Assessment

A total of 65% of the included studies (11/17) scored above six (“good”); 18% (3/17) of the studies scored six or five (“fair”) and 24% (4/17) studies scored lower than five (“poor”). These 4 “poor” studies were excluded from the final meta-analysis.

Baseline Characteristics

The biomaterial assessed from the final selected studies included: silicon nitride (Si₃N₄), polyetherketone (PEEK), titanium (Ti), nanohydroxyapatite/polyamide 66 (n-HA/PA66), and a carbon fiber reinforced polymer composite (i.e., polyether-ketone-ether-ketone-ketone composite (CFRP)). A total of 1,192 patients were included in this analysis – 419 with titanium implants, 460 with PEEK, 96 with Si₃N₄, 332 with n-HA/PA66, and 35 with CFRP (Table 2). The definition of subsidence, by individual study, is summarized in Table 3.

Network Meta-Analysis

The models were tuned according to tests for convergence, node-split, and Gelman diagnostics. The final parameters used were chains = 4; burn-in = 5,000; iterations = 14,000, thinning interval = 5.

A fixed effect model (I² <50%) was found to be suitable for our study selection. The multivariate potential scale reduction factor (PSRF) value for the model was 1.00 - 1.01 indicating acceptable model convergence; node-splitting results were all p > 0.05 indicating acceptable network consistency (Figure 2).

In our analysis, titanium had the highest rate of subsidence compared to other biomaterials. Notably, PEEK, Si₃N₄, and N-HA/PA66 all had significantly lower rates. CFRP also had a lower subsidence rate than titanium, though the difference was not statistically significant. Compared to titanium the estimate for subsidence in ascending order were nHA/PA66 (OR=0.236, 95% CI 0.137 to 0.394), followed by Si₃N₄ (OR=0.287, 95% CI 0.106 to 0.770), then PEEK (OR=0.314, 95% CI 0.182 to 0.521), and lastly, CFRP (OR = 0.477, 95% CI 0.134 to 1.83).

For the network analyses comparing subsidence risks in titanium, PEEK, and Si₃N₄ – PEEK and Si₃N₄ were on par, and titanium ranked last (Figure 3). Subsidence risk rankings were also expressed as a bar chart (Figure 4). In the extended network analysis, treatment performance was summarized as Surface Under the Cumulative Ranking (SUCRA) scores, which illustrates the probability of a treatment being most effective. The SUCRA values were nHA/PA66 0.84, Si₃N₄ 0.67, CFRP 0.38, PEEK 0.58, and titanium 0.03.

Forest plot results for subgroups of pair-wise studies are presented in Figure 5a-c. Arts et al., 2017, compared Si₃N₄ versus PEEK. Point estimate favors Si₃N₄ (OR=0.92, 95% CI 0.41 to 2.08), but this did not attain statistical significance. In a pair-wise comparison involving titanium, there is favorability towards alternative biomaterials: PEEK (OR = 0.45, 95% CI 0.25 to 0.78) and nHA/PA66 (OR = 0.22, 95% CI 0.11 to 0.42).

Publication Bias

Both the Egger test (p = 0.28) and the Begg test (p = 0.37) were found to be non-significant for publication bias. This is illustrated by the funnel plot with points symmetrically distributed around the effect mean (Figure 6).

Discussion

This analysis focuses on biomaterial type and its relation to subsidence in spinal fusion. Other studies have discussed the relative importance of biomaterial modulus of elasticity compared to other factors, such as cage height, bone quality, cage shape, cage footprint. For example, Igarashi et al. 2017 did not find a significant difference in subsidence rates between PEEK and titanium cages when restricting cage heights to less than 5mm.[32] They did, however, conclude that increasing general cage height was associated with increased subsidence risk.

| Table 4 | Ranking Probabilities (Extended Model): |
| --- | --- |
| | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 |
| Carbon | 0.14 | 0.12 | 0.15 | 0.42 | 0.17 |
| nHA/PA66 | 0.45 | 0.32 | 0.16 | 0.07 | 0.00 |
| PEEK | 0.06 | 0.35 | 0.46 | 0.13 | 0.00 |
| Si₃N₄ | 0.35 | 0.21 | 0.22 | 0.18 | 0.04 |
| Titanium | 0.00 | 0.00 | 0.02 | 0.19 | 0.79 |
Cabraja et al. 2012, compared PEEK and titanium and determined that biomaterial modulus did not appear to be a major factor in cage subsidence and instead surmised that patient bone quality may be more critical.[33] A notable and potential bias in their paper was a tendency for surgeons to select PEEK implants for older patients. Similarly, Campbell et al. 2020 identified that an increase in age directly correlated with an increase in subsidence risk.[34] Kim et al. 2012 studied curved and wedged shaped PEEK cages and suggested that implant shape was an important risk factor.[35] Similarly, Le et al. 2012 found that wider cages significantly mitigated the risk of subsidence while length was not significant.[36] Suh et al. 2017 identified substrate density and cage footprint as being greater contributors to subsidence than biomaterial when comparing titanium, PEEK, and silicon nitride.[37] Recently, Fiani et al., 2021, found that Si$_3$N$_4$ and other biomaterials can act as suitable fusion expanders given their favorable properties.[38]

Significant limitations must be considered while assessing the generalizability of the results. The literature is inconsistent in its definitions of subsidence and the lack of randomized control trials remains pervasive. Also, despite acceptable levels of statistical heterogeneity, many of the studies evaluated in this analysis introduce potentially significant disparate clinical variables, such as implants of varying footprints/sizes, the inclusion of cervical and lumbar patients, and biomaterials with

| Author(s) and Year | Events | Total | Events | Total | Odds Ratio [95% CI] |
|-------------------|--------|-------|--------|-------|--------------------|
| Hu et al. a, 2019 | 10     | 55    | 22     | 52    | 0.30 [0.13, 0.73] |
| Yang et al., 2013 | 2      | 36    | 7      | 32    | 0.22 [0.04, 1.13] |
| Zhang et al., 2014| 3      | 71    | 14     | 46    | 0.10 [0.03, 0.38] |

RE Model (Q = 1.86, df = 2, p = 0.40; $\hat{r}^2 = 0.0\%$)

Odds Ratio (log scale)

| Author(s) and Year | Events | Total | Events | Total | Odds Ratio [95% CI] |
|-------------------|--------|-------|--------|-------|--------------------|
| Deng et al., 2016  | 12     | 159   | 16     | 178   | 0.83 [0.38, 1.80] |
| Hu et al. b, 2019  | 5      | 47    | 5      | 51    | 1.10 [0.30, 4.05] |

RE Model (Q = 0.13, df = 1, p = 0.72; $\hat{r}^2 = 0.0\%$)

Odds Ratio (log scale)

Figure 5. a. Forest Plot: n-HA/PA66 vs Ti
b. Forest Plot: n-HA/PA66 vs PEEK
c. Forest Plot: PEEK vs Ti
d. Forest Plot: Si$_3$N$_4$ vs PEEK
e. Forest Plot: CFRP vs PEEK
Figure 5. Continued
mesh/porous designs. Despite this, the authors contend that some level of clinical heterogeneity was necessary to attain sufficient power for the analysis. It is also unclear how this would bias our results although it may affect the generalizability of our conclusion. We continue to believe that this meta-analysis represents the most complete clinical assessment of Si₃N₄ and its associated subsidence risk compared to other readily implanted biomaterial for spinal fusion. Given the additional benefits of Si₃N₄, it seems reasonable to consider their more widespread adoption in spinal fusion surgery.

Conclusion

Taken in context of the limitations of this analysis, the subsidence risk of Si₃N₄ appears most similar to PEEK, while both appear to fare better than titanium. The true risk of subsidence may therefore not be related to modulus of elasticity alone and is likely multifaceted and nuanced, requiring further investigation.

Author Contributions

(I) Conception and design: JA, RS
(II) Administrative support: JA, AV, RS, JPJ
(III) Provision of study materials or patients: JA
(IV) Collection and assembly of data: JA, RS
(V) Data analysis and interpretation: JA, AV, RS, JPJ
(VI) Manuscript writing: All authors
(VII) Final approval of manuscript: All authors

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding Disclosure

SINTX LLC provided research funding support for the project but had no role in the analysis or the production

Footnote

The authors have completed the PRISMA reporting checklist.

Conflict of Interest

All authors have completed the ICMJE uniform disclosure form. JA is the president/CEO of a research think-tank organization (Neuronomics) that received funding from SINTX to conduct this research. SINTX was not involved in the data acquisition, data analysis, or creation of this manuscript. RS is an employee of Neuronomics. The other authors have no conflicts of interest to declare."

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