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Average pain over time, but not current pain, is associated with salivary secretory immunoglobulin a in chronic back pain: A cross-sectional study

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Adi Shani, PhD[1,2,3], Michal Granot, PhD[1], Eilam Palzur, PhD[4], Mariana Agostinho, PhD[1,5], Roi Treister, PhD[1,*], and Nimrod Rahamimov, MD[2,6,*]

Abstract

Chronic pain is accompanied by widespread physiological dysregulation, yet the mucosal immune system has received little attention. Salivary secretory-immunoglobulin-A (S-IgA) is a non-invasive biomarker of mucosal immunity modulated by sustained stress and autonomic activity. This cross-sectional secondary analysis examined whether pain intensity in chronic back pain is associated with salivary S-IgA in 57 adults enrolled in a parent interventional study (NCT05994118). Pain was assessed on a computerized visual analogue scale (CoVAS, 0–100) at the laboratory visit (current pain and 24-hour average) and via a twice-daily electronic CoVAS diary (1-week, 2-week, and 14-day averages). Two saliva samples collected ~90 minutes apart were assayed by ELISA, and baseline heart rate variability (HRV) was recorded. Spearman correlations were computed with and without partial adjustment for age, sex, and BMI; Benjamini–Hochberg correction was applied to the ten primary pain × S-IgA tests. Average 24-hour pain was negatively correlated with both S-IgA samples ($\rho \approx -.45$ for both, $p < .001$); the 1-week ($\rho \approx -.34$ to $-.35$, $p \leq .009$) and 14-day averages ($\rho \approx -.38$ for both, $p = .004$) showed similar associations. All average-pain associations survived FDR correction and partial adjustment. Current pain was not significantly associated with S-IgA. Baseline high-frequency HRV power was positively associated with S-IgA$_1$ ($\rho = .29$, $p = .033$) but not S-IgA$_2$. Sustained pain experience, rather than current pain, appears to track salivary mucosal immune function in chronic back pain. However, these hypothesis-generating findings may reflect unmeasured stress- or mood-related confounding, not a pain-specific effect.

Keywords

chronic back pain, secretory immunoglobulin A, S-IgA, mucosal immunity, heart rate variability, allostatic load

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[1]The Cheryl Spencer Department of Nursing, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa, Israel
[2]Department of Orthopedics B and Spine Surgery, Galilee Medical Center, Nahariya, Israel
[3]Oncologic Day Care Unit, Galilee Medical Center, Nahariya, Israel
[4]The Research Institute, Galilee Medical Center, Nahariya, Israel
[5]Centre for Interdisciplinary Health Research, Faculty of Health Sciences and Nursing, CIIS, Universidade Católica Portuguesa, Lisbon, Portugal
[6]Faculty of Medicine, Bar Ilan Medical School, Tsfat, Israel

*These authors contributed equally to this work.

Corresponding author:
Nimrod Rahamimov, MD, Department of Orthopedics B and Spine Surgery, Galilee Medical Center, Highway 89, 22400, Nahariya, Israel.
Emails: nim205@gmail.com, nimrodr@gmc.gov.il

Introduction

Chronic pain is increasingly recognized as a multidimensional condition[1] that extends beyond nociceptive signaling to involve widespread alterations in physiological regulation[2] across neural,[3–5] endocrine,[5] and immune systems.[5–7]

Among chronic pain conditions, chronic back pain is one of the most prevalent and disabling disorders worldwide[8–11] and represents a major source of long-term physical and psychological burden. Individuals with chronic back pain often experience sustained stress,[12] functional limitations,[9] and reduced quality of life.[13] These factors may impose a cumulative biological load on regulatory body systems.[14,15]

Growing evidence suggests that chronic pain is accompanied by alterations in immune function.[6,16–18] Most studies in this area have focused on systemic inflammatory markers such as cytokines,[17,19,20] highlighting links between chronic pain and inflammatory activity.[7,16,21] Recent reviews of neuroimmune interactions in chronic pain have examined cellular mechanisms such as microglial and T-cell contributions,[6] neuroinflammatory signaling pathways,[7] and autoimmune processes involving autoantibodies and complement activation,[21] with comparatively less attention to the mucosal immune system.[6,7,21] Mucosal tissues contain several immune components that serve as a first line of defense against external organisms and toxins. The most abundant antibody in mucosal secretions is the secretory form of immunoglobulin A (S-IgA),[22] which bathes mucosal surfaces such as the gastrointestinal, respiratory and urinary tracts, preventing pathogen adherence and entry.[22,23] Salivary glands are innervated by autonomic efferents that modulate S-IgA secretion,[24] and salivary S-IgA can be assayed non-invasively.[23,25]

Stress has been associated with bidirectional modulation of S-IgA, with acute stress typically eliciting transient increases and chronic or sustained stress more consistently associated with suppression across animal models[23,26] and adult human studies.[25,27] In community-dwelling adults, stressful life events were associated with lower salivary IgA secretion rates,[27] and caregiving stress has been linked to reduced salivary IgA secretion in case-control comparisons.[28] Engeland and colleagues reported that perceived stress, loneliness, and depressive symptoms were each associated with lower baseline IgA1/secretory-component ratios in a community sample,[25] underscoring the IgA-subclass specificity of these effects. In a small uncontrolled pre–post study of an Emotional Freedom Techniques workshop (with author-disclosed conflicts of interest), elevated S-IgA was observed alongside reductions in resting heart rate, cortisol, blood pressure, anxiety, depression, PTSD symptoms, and pain 29. Pediatric data from a systematic review of subjects under 18 years suggest a different developmental pattern, with basal S-IgA increasing in chronically stressed children.[30] Taken together, the adult literature is consistent with the view that S-IgA may be sensitive to sustained physiological burden, potentially reflecting increased allostatic load.

The autonomic nervous system, particularly vagal tone, plays a central role in regulating stress-responsive allostatic systems including immune-modulatory pathways.[31] Heart rate variability (HRV), the beat-to-beat variation in heart rate, is a well-established non-invasive index of cardiac autonomic activity.[32] The high-frequency (HF) component of HRV reflects parasympathetic activity, while the ratio of low-frequency to high-frequency power (LF/HF) has been used as an index of sympathovagal balance, although this interpretation has been debated.[33] Parasympathetic efferents innervate the salivary glands and modulate S-IgA secretion,[24] providing a candidate mechanistic link between autonomic regulation and mucosal immunity.

Chronic back pain often involves prolonged exposure to both physiological and psychological stress,[34–37] yet the salivary mucosal-immune phenotype of this population is essentially unexamined. A targeted literature search for chronic pain and immunoglobulin A yielded four directly relevant publications, none in chronic back pain. Sobas and colleagues measured salivary S-IgA alongside other candidate biomarkers in 34 healthy adults under controlled environmental conditions, framed as methodological groundwork for ocular-pain biomarker development; intra-subject reproducibility of S-IgA was modest (ICC ≈ 0.43).[38] Ye and colleagues reported altered serum immunoglobulin profiles in chronic prostatitis/chronic pelvic pain syndrome, with significantly higher serum IgG and lower CD8+ counts; serum IgA was measured but did not differ significantly between groups.[39] Imura and colleagues found reduced salivary S-IgA secretion in burning mouth syndrome compared with healthy controls.[40] In persistent orofacial pain, Sherman and colleagues demonstrated that brief progressive-relaxation training increased salivary S-IgA, linking parasympathetic engagement to mucosal immune output.[41] Across this small and heterogeneous literature, salivary S-IgA appears to vary in chronic pain populations, but the direction and magnitude of these variations are not consistent across studies.

The present study examined whether pain intensity in adults with chronic back pain is associated with salivary S-IgA. As a secondary, exploratory aim, the study examined whether baseline autonomic function, as indexed by HRV, is associated with salivary S-IgA. Because these data derive from a trial designed to study the analgesic placebo response rather than pain–immune relationships, the present analysis is hypothesis-generating rather than confirmatory.

Materials and methods

Study design

This is a cross-sectional secondary exploratory analysis of data collected as part of a larger interventional study examining physiological, psychosocial, and personal contributions to the analgesic placebo response and within-subject variability of pain reporting (https://ClinicalTrials.gov NCT05994118). The parent study included a sham placebo intervention. The present analysis uses screening and baseline data, together with saliva samples collected during the laboratory visit. The main results of the parent study have been reported elsewhere.[42–44] The reporting of this cross-sectional analysis follows the STROBE guideline (cross-sectional checklist). All procedures were approved by the Institutional Helsinki Committee of the Galilee Medical Center (0044-20-NHR) and by the Ethical Committee of the University of Haifa (240/21). All participants provided written informed consent.

Participants

Participants were adults diagnosed with chronic back pain who were recruited via the Spine Unit at the Galilee Medical Center, Israel, and through advertisements in local media and social networks. Inclusion criteria were age 18–80 years, ability to read and understand Hebrew, and a clinical diagnosis of chronic back pain defined as pain persisting for ≥3 months with an average daily pain intensity ≥ 3 on a 0–10 numeric rating scale. Exclusion criteria were back pain attributable to known malignancy or vertebral fracture, pregnancy, breastfeeding, and any cognitive impairment that would preclude informed consent or completion of study procedures. Participants who met these criteria received detailed verbal and written information about the study and were instructed to continue their usual analgesic regimens.

Pain assessment

Pain intensity was assessed throughout the study using a computerized visual analogue scale (CoVAS, 0 = no pain to 100 = worst imaginable pain). Prior to the laboratory session, participants completed a twice-daily electronic CoVAS pain diary for two consecutive weeks. From the diaries we derived average pain during the first week (APW1), the second week (APW2), and the full two-week period (AP14D). During the laboratory visit, participants reported current back pain intensity (CP) and average pain intensity during the previous 24 hours (AP24H) on the same CoVAS.

Saliva collection and S-IgA assay

Two saliva samples were collected during the laboratory session, approximately 90 minutes apart, using the passive drool technique with the SalivaBio Collection Aid (Salimetrics, State College, PA, USA), allowing for standardized collection of up to 1.8 mL per sample. To preserve sample integrity and minimize contamination, participants were asked to refrain from eating for at least one hour before the first sample; bottled water was provided for hydration. Laboratory sessions were scheduled during standard daytime working hours (08:00–17:00); the exact within-window time of day was not standardized across participants. Samples were centrifuged, the clarified supernatant aliquoted, and stored at −20 °C until assay. S-IgA concentrations were quantified using the high-sensitivity Salimetrics Salivary Secretory IgA ELISA kit (Salimetrics, State College, PA, USA; Catalog No. 1-1602) and expressed in μg/mL. Optical density was measured on a Varioskan LUX microplate reader (Thermo Scientific, Waltham, MA, USA). Final concentrations were determined by interpolation against a four-parameter logistic standard curve generated from the kit standards on each plate.

Heart rate variability

Short-term resting HRV was recorded for 5 minutes with the participant seated quietly, using the ProComp Infiniti System with BioGraph Infiniti v4 software (Thought Technology, Montreal, Quebec, Canada). Frequency-domain parameters included high-frequency power (HF; 0.15–0.40 Hz) reflecting parasympathetic activity, low-frequency power (LF; 0.04–0.15 Hz) reflecting a combination of sympathetic and parasympathetic modulation, and the LF/HF ratio of absolute spectral power, used as a global index of sympathovagal balance.[32] Baseline HRV values were available for 56 of 57 participants; one participant had missing HRV data due to equipment failure.

Statistical analysis

All analyses were conducted in Python 3.14 with pandas 3.0, NumPy 2.4, and SciPy 1.17.1. The reproducibility of partial-Spearman computations was confirmed against a separate R implementation. Normality of variable distributions was assessed using the Shapiro–Wilk test. Pain intensity variables were normally distributed (all $W \geq .975$, $p \geq .29$), while S-IgA distributions departed significantly from normality (both $W \leq .85$, $p < .001$). Normally distributed variables are presented as mean ± SD; non-normally distributed variables are presented as median with interquartile range.

Pearson correlations were used to characterize inter-correlations among the pain measures. Primary associations between pain intensity and S-IgA were examined with Spearman rank-order correlations, comprising ten primary tests (5 pain measures × 2 S-IgA samples). The Benjamini–Hochberg false discovery rate (FDR) procedure ($q = .05$) was applied to control for multiple testing across these ten tests. To assess robustness, partial Spearman correlations were computed by ranking all variables and calculating partial Pearson correlations on the ranks following Conover,[45] controlling for age, sex, and BMI. Ninety-five-percent confidence intervals for all correlations were obtained via Fisher z-transformation ($SE = 1/\sqrt{(n-3)}$ for unadjusted correlations and $SE = 1/\sqrt{(n-3-k)}$ for partial correlations, with k = number of covariates). Spearman correlations between baseline HRV parameters and S-IgA were treated as exploratory and are reported without multiplicity correction. All tests were two-tailed, with statistical significance set at $p < .05$.

Missing data were handled by complete-case analysis; participants without complete saliva data were excluded from the primary pain × S-IgA tests, and the one participant with missing HRV data was excluded from the exploratory HRV × S-IgA tests. To assess potential selection bias, participants with complete S-IgA data were compared with those excluded owing to missing samples on age, BMI, and pain intensity using Welch two-sample t-tests, and on sex using a chi-square test of independence.

Sample size was determined by participant availability in the parent study. A sensitivity analysis indicated that, with $n = 57$ and $\alpha = .05$ (two-tailed), the present analysis had 80% power to detect Spearman correlations of $|\rho| \geq 0.364$; at the more stringent Bonferroni-corrected threshold ($\alpha = .005$ for 10 tests), 80% power corresponded to $|\rho| \geq 0.459$. The Benjamini–Hochberg FDR procedure used here is less conservative than Bonferroni for multiple testing.

Results

Participant recruitment ran from March 2021 to July 2023. Of 560 individuals initially screened, 82 did not meet the predefined eligibility criteria, 271 declined to participate, and 94 could not be reached after initial contact. A total of 113 participants enrolled in and completed the parent study protocol; of these, 57 provided a complete pair of saliva samples suitable for S-IgA analysis and were included in the present analytic sample (Figure 1). Demographic and clinical characteristics of the analytic sample are summarized in Tables 1 and 2; descriptive statistics for S-IgA and HRV variables are shown in Table 3.

Participants with complete S-IgA data ($n = 57$) were compared with those excluded owing to missing saliva samples ($n = 56$). No statistically significant differences were observed in age (54.9 ± 15.3 vs 58.8 ± 15.2 yr; $t = -1.36$, $p = 0.177$), sex distribution (30/57 = 52.6% female vs 28/56 = 50.0% female; $\chi^2(1) = 0.08$, $p = 0.780$), BMI (28.0 ± 5.6 vs 26.7 ± 4.8 kg/m^2; $t = 1.33$, $p = 0.188$), or pain intensity (CP: 48.6 ± 21.1 vs 54.4 ± 24.9, $t = -1.33$, $p = 0.185$; AP24H: 49.9 ± 17.7 vs 55.2 ± 22.8, $t = -1.38$, $p = 0.171$; AP14D: 52 ± 18 vs 57 ± 22, $t = -1.32$, $p = 0.189$).

Associations between pain measures

Pearson correlations among the five pain measures were uniformly strong (Table 4): all inter-correlations were statistically significant (minimum $r = 0.606$, all $p < .001$), consistent with high convergent validity across pain-assessment methods. The two saliva S-IgA measurements obtained ~90 minutes apart were also strongly correlated (Spearman $\rho = 0.746$, 95% CI [.603, .843], $p < .001$).

Associations between pain intensity and salivary S-IgA

Average pain over the previous 24 hours was significantly and negatively correlated with both S-IgA samples to similar magnitude ($S\text{-IgA}_1$: $\rho = -0.453$, 95% CI [−.638, −.218], $p < .001$; $S\text{-IgA}_2$: $\rho = -0.452$, 95% CI [−.637, −.217], $p < .001$). The 1-week and 2-week diary averages, and the full 14-day average, were also negatively associated with both S-IgA samples (Table 5). All ten primary pain × S-IgA tests are reported in Table 5; the five tests involving an aggregated pain measure

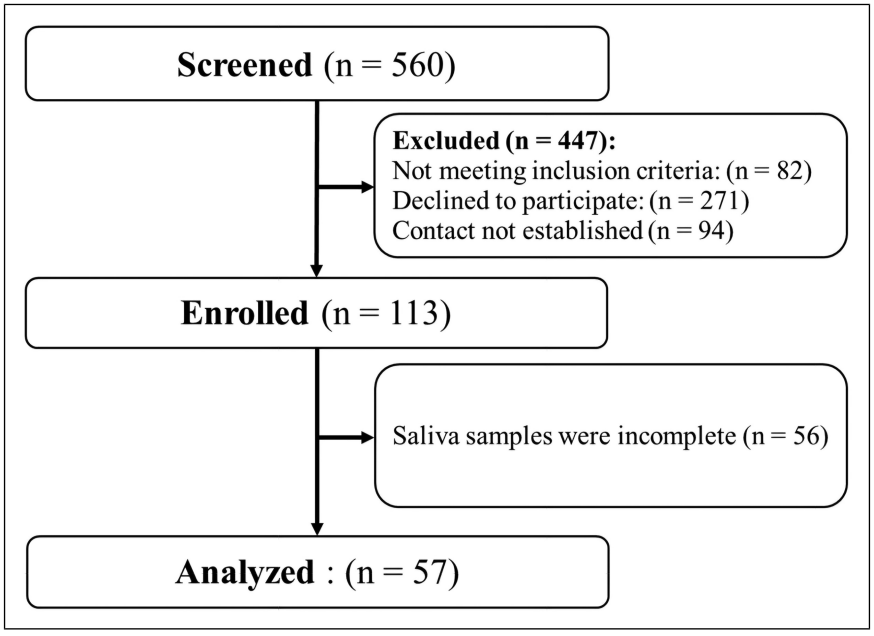

Figure 1. Participant flow diagram. Of 560 individuals screened, 82 did not meet the predefined inclusion criteria, 271 declined to participate, and 94 could not be reached following the initial screening contact. A total of 113 participants enrolled in and completed the parent study protocol. Of these, 57 provided a complete pair of saliva samples suitable for S-IgA analysis and were included in the present analytic sample. Baseline heart rate variability was available for 56 of these 57 participants.

(AP24H, APW1, APW2, AP14D) survived Benjamini–Hochberg FDR correction at $q = .05$ against both S-IgA samples. The two tests involving current pain at the visit (CP × S-IgA$_1$ and CP × S-IgA$_2$) were not statistically significant.

Adjusted analyses

Partial Spearman correlations controlling for age, sex, and BMI (Table 6) yielded a pattern of results virtually unchanged from the unadjusted analysis. The two strongest adjusted associations were observed for AP24H and APW2 ($|\rho_p|$ range 0.429–0.446, all $p \leq .002$), with comparable magnitudes across the two S-IgA samples. Adjusting for age, sex, and BMI produced only minor shifts in point estimates (maximum absolute change ≤ 0.03), suggesting that these demographic covariates were not material confounders of the pain–S-IgA association under the present design. As in the unadjusted analysis, current pain at the visit (CP) was not significantly associated with S-IgA after adjustment.

Autonomic correlates of S-IgA (exploratory)

Baseline HF power (%) was positively associated with S-IgA$_1$ ($\rho = 0.286$, 95% CI [.025, .510], $p = 0.033$) and the LF/HF ratio (absolute spectral power) was negatively associated with S-IgA$_1$ ($\rho = -0.285$, 95% CI [−.510, −.024], $p = 0.033$). The corresponding associations with S-IgA$_2$ were near zero (HF × S-IgA$_2$: $\rho = 0.034$; LF/HF × S-IgA$_2$: $\rho = -0.021$). No HRV parameter was significantly correlated with any pain measure (all $|\rho| \leq .23$, all $p \geq .23$) (Table 7).

Table 1. Categorical demographic and clinical characteristics (N = 57).

Characteristic	n (%)
Sex — Female	30 (52.6%)
Pain duration < 6 months	2 (3.5%)
Pain duration 6–12 months	5 (8.8%)
Pain duration 1–5 years	16 (28.1%)
Pain duration > 5 years	34 (59.6%)

Table 2. Continuous demographic and pain variables (N = 57).

Variable	n	Mean ± SD	Median (Q1, Q3)	Range
Age (years)	57	54.86 ± 15.26	54.00 (46.00, 66.00)	18.00–79.00
BMI (kg/m^2)	57	27.95 ± 5.56	26.73 (24.69, 30.45)	17.84–42.87
Current pain at visit (CP, 0–100)	57	48.58 ± 21.07	46.00 (34.00, 61.00)	10.00–100.00
Average pain past 24 h (AP24H, 0–100)	57	49.89 ± 17.70	50.00 (40.00, 58.00)	0.00–100.00
Average pain week 1 (APW1, 0–100)	57	52.62 ± 18.35	54.10 (39.60, 66.90)	15.00–98.10
Average pain week 2 (APW2, 0–100)	57	50.95 ± 17.47	48.10 (37.80, 65.70)	11.00–92.70
Average pain 14-day diary (AP14D, 0–100)	57	51.95 ± 17.61	53.00 (39.40, 65.70)	14.10–96.20

Discussion

The present study examined the association between pain intensity and salivary S-IgA levels in adults with chronic back pain. To our knowledge, this is the first study to test this relationship in a chronic-back-pain population.

The principal finding was a significant negative association between average pain intensity measures and salivary S-IgA, such that higher average pain was associated with lower mucosal immune output. This association was specific to pain measures capturing sustained experience: average pain over the previous 24 hours, average pain across the first and second diary weeks, and average pain across the full 14-day diary. Current pain intensity at the start of the laboratory visit was not significantly associated with S-IgA. The findings were consistent across two independently collected saliva samples obtained approximately 90 minutes apart, survived FDR correction across the 10 primary tests, and remained significant after adjustment for age, sex, and BMI.

Two non-mutually-exclusive explanations may account for the differential pattern between sustained and momentary pain measures. Biologically, salivary S-IgA secretion is regulated by the autonomic nervous system[24] and by glucocorticoid signaling associated with HPA-axis activation, both of which respond to cumulative physiological burden rather than to moment-to-moment fluctuations in nociception. Adult evidence is consistent with chronic stress being associated with suppressed salivary S-IgA secretion[25,27,28]; the strongest single dataset in adults is Deinzer and colleagues' demonstration that academic-exam stress produces prolonged S-IgA reductions.[46] Methodologically, aggregated pain measures derived from 7–28 daily diary ratings have higher measurement reliability than single-timepoint laboratory assessments, so the null current-pain association may partly reflect lower reliability and reduced statistical power rather than a qualitatively different biological process. The present design cannot fully separate these explanations, and we frame the contrast accordingly. Importantly, the mechanistic literature invoked here links sustained stress, not pain itself, to S-IgA suppression.[25,27,28] Because stress, sleep quality, and depressive or anxiety symptoms were not measured in the parent trial, the present association may reflect an unmeasured stress or mood burden correlated with both sustained pain and S-IgA rather than a pain-specific effect. The pain-specific interpretation should therefore be read as provisional and hypothesis-generating, a point developed further in the Limitations.

The exploratory finding that baseline HF power was positively associated with S-IgA$_1$ is consistent with the known role of vagal efferents in modulating salivary-gland output.[24] The concurrent negative association between the LF/HF ratio and

Table 3. Salivary S-IgA and resting HRV descriptive statistics (N = 57; n = 56 for HRV). S-IgA distributions were non-normal (Shapiro–Wilk $p < .001$); medians and IQRs are therefore the primary descriptive statistics.

Variable	n	Mean ± SD	Median (Q1, Q3)
S-IgA$_1$ (μg/mL)	57	471.39 ± 434.21	299.58 (145.03, 717.51)
S-IgA$_2$ (μg/mL)	57	344.73 ± 325.22	189.58 (110.85, 536.48)
HF power (%)	56	27.99 ± 13.32	26.57 (17.47, 35.91)
LF power (%)	56	36.59 ± 11.47	37.19 (27.82, 43.90)
LF/HF ratio (total power)	56	1.97 ± 1.73	1.39 (0.81, 2.63)

CP = current pain at visit; AP24H = average pain past 24 h; APW1/APW2 = average pain weeks 1 and 2 (CoVAS diary); AP14D = average pain across the 14-day diary. HF/LF = high/low-frequency power as percent of total spectral power; LF/HF = ratio of absolute LF to HF total power.

Table 4. Pearson correlations between pain-intensity measures (N = 57). Pearson correlations (off-diagonal upper triangle).

	CP	AP24H	APW1	APW2	AP14D
CP	—	0.718***	0.617***	0.606***	0.626***
AP24H		—	0.767***	0.783***	0.797***
APW1			—	0.887***	0.983***
APW2				—	0.952***
AP14D					—

*** $p < .001$. CP = current pain; AP24H = average pain past 24 h; APW1/APW2 = average pain weeks 1 and 2; AP14D = average pain across the 14-day diary.

$S\text{-}IgA_1$ provides tentative additional support for a sympathovagal-balance interpretation in which parasympathetic predominance facilitates mucosal immunity. However, these associations appeared only with one of the two S-IgA samples, were uncorrected for multiple comparisons, and were substantially underpowered (≈58% power at the observed effect size). The lack of replication across S-IgA samples—in contrast to the closely replicated pain–S-IgA associations—means a Type I error explanation cannot be excluded. These HRV–S-IgA findings should be interpreted cautiously and treated as hypothesis-generating.

The existing literature on chronic pain and immunoglobulin A is sparse and heterogeneous. As described in the Introduction, four publications have directly examined salivary or serum IgA in chronic pain populations, none in chronic back pain.[38–41] Of these, Imura et al.[40] reported reduced salivary S-IgA in burning mouth syndrome, consistent in direction with the present finding. Sherman et al.[41] showed that relaxation training in orofacial pain increased S-IgA, again consistent with a vagally mediated mucosal-immune pathway. The sparse and methodologically heterogeneous nature of this literature underscores the need for larger, methodologically homogeneous studies that explicitly test the steady-state hypothesis, as we have done here, rather than inferring it from intervention studies.

The observed association between average pain and reduced S-IgA is broadly compatible with the adult stress-immunology literature. Salivary S-IgA has been reported to decrease under academic-examination stress[46] and within high-demand work shifts in healthcare professionals[47]; stressful life events and caregiving stress have been associated with lower IgA secretion rates in community-dwelling adults.[27,28] Several mechanisms could underlie the present association, though each requires direct testing. First, chronic-pain-associated sympathetic activation may modulate S-IgA secretion through innervation of salivary glands and mucosa-associated lymphoid tissue,[24] a pathway with preliminary support from the exploratory HRV findings reported here. Second, sustained HPA-axis activation associated with chronic pain may affect salivary IgA via neuroendocrine pathways that regulate mucosal immune function.[25,28] Third, potential interactions between chronic pain, the oral microbiome, and mucosal immunity represent an unexplored avenue for future research. The cross-sectional design of the present study cannot test mediation. Existing intervention-and-S-IgA evidence in non-pain

Table 5. Spearman correlations between pain intensity and salivary S-IgA (N = 57). ρ = Spearman correlation coefficient. 95% CIs were computed via Fisher z-transformation.

Pain	$S\text{-}IgA_1$ ρ	95% CI	p	$S\text{-}IgA_2$ ρ	95% CI	p
CP	−.221	[−.455, .042]	.099	−.185	[−.425, .079]	.168
AP24H	−.452†	[−.638, −.218]	< .001	−.452†	[−.637, −.217]	< .001
APW1	−.343†	[−.554, −.091]	.009	−.351†	[−.561, −.100]	.007
APW2	−.426†	[−.618, −.186]	< .001	−.429†	[−.620, −.190]	< .001
AP14D	−.377†	[−.580, −.129]	.004	−.377†	[−.580, −.129]	.004

†significant after Benjamini–Hochberg FDR correction (q = .05) across 10 primary tests. CP = current pain; AP24H = average pain past 24 h; APW1/APW2 = average pain weeks 1 and 2; AP14D = average pain across the 14-day diary.

Table 6. Partial Spearman correlations between pain intensity and salivary S-IgA, controlling for age, sex, and BMI (N = 57).

Pain	S-IgA$_1$ ρ_p	95% CI	p	S-IgA$_2$ ρ_p	95% CI	p
CP	−.232	[−.471, .038]	.091	−.199	[−.443, .072]	.148
AP24H	−.446	[−.638, −.203]	< .001	−.438	[−.631, −.193]	< .001
APW1	−.353	[−.567, −.094]	.009	−.367	[−.578, −.110]	.006
APW2	−.429	[−.625, −.182]	.001	−.433	[−.628, −.186]	.001
AP14D	−.386	[−.592, −.132]	.004	−.391	[−.596, −.137]	.003

ρ_p = partial Spearman correlation coefficient (rank-then-partial-Pearson method, Conover 1999). 95% CIs computed via Fisher z-transformation on ranks with effective sample size n − k = 54 (k = 3 covariates).

populations is suggestive but not direct: changes in S-IgA have been observed alongside reductions in stress and pain in a small, uncontrolled pre–post study of an Emotional Freedom Techniques workshop (with author-disclosed conflicts of interest),[29] and a workplace mindfulness-and-self-compassion intervention in employees was associated with changes in salivary IgA.[48] Whether changes in salivary S-IgA mediate the analgesic effects of non-pharmacological interventions in chronic pain is an open question that would require dedicated intervention trials with mediation analysis.[49]

Limitations

This study has several limitations. First, it is a secondary analysis with a modest sample size (n = 57); a sensitivity analysis indicated 80% power to detect $|\rho| \geq 0.364$, so smaller effects would be missed. Second, the cross-sectional design precludes causal inference: it cannot be determined whether higher pain causes lower S-IgA, whether reduced mucosal immunity contributes to pain persistence, or whether both reflect a common upstream factor such as sustained stress. Third, 57 of 113 enrolled participants (50.4%) had complete saliva data; the included and excluded subsamples did not differ on age, sex, BMI, or pain intensity, suggesting the analytic subsample was broadly representative of the enrolled cohort. Fourth—and most consequential for interpretation—the principal alternative explanation for the observed pain–S-IgA correlation is unmeasured confounding by variables that are themselves correlated with both chronic back pain and salivary S-IgA. Time of day of saliva collection, smoking status, oral health and periodontal status, medication use (particularly corticosteroids, immunosuppressants, and long-term opioid analgesia), sleep quality, comorbid depression and anxiety, and acute infection or oral inflammation are all well-documented modulators of salivary S-IgA, and several are over-represented in chronic back pain populations. The adjustment for age, sex, and BMI used here addresses only a subset of these confounders, and the moderate observed effect could plausibly attenuate substantially under richer covariate adjustment. Future studies should pre-specify and measure these confounders. Fifth, the exploratory HRV–S-IgA associations were significant for only one of two S-IgA samples and were not corrected for multiple comparisons, limiting their interpretability. Sixth, the study included only individuals with chronic back pain, and generalizability to other chronic pain populations remains to be established. Finally, the present analysis is one of several secondary analyses of the parent study dataset[42–44]; cumulative Type I error across analyses of the same dataset should be considered when interpreting the results. More fundamentally, because the parent trial was designed to study the analgesic placebo response rather than pain–mucosal immunity, several variables needed to properly contextualize this relationship (stress, sleep, mood, medication use, oral health, and standardized time-of-

Table 7. Spearman correlations between baseline HRV parameters and salivary S-IgA (n = 56). Exploratory analyses; uncorrected p-values shown. n = 56 reflects one participant with missing HRV data.

HRV parameter	S-IgA$_1$ ρ	95% CI	p	S-IgA$_2$ ρ	95% CI	p
HF%	.286	[.025, .510]	.033	.034	[−.231, .294]	.802
LF%	−.066	[−.324, .200]	.626	.062	[−.204, .320]	.651
LF/HF	−.285	[−.510, −.024]	.033	−.021	[−.283, .243]	.875

HF % = high-frequency power as percent of total spectral power; LF % = low-frequency power as percent of total. LF/HF = ratio of absolute LF to HF total power.

day sampling) were not built into the protocol; the present analysis is therefore best regarded as hypothesis-generating rather than confirmatory.

Conclusion

In adults with chronic back pain, average pain intensity over time was negatively associated with salivary secretory immunoglobulin A. These findings contribute to the limited literature linking chronic pain to mucosal immune alterations and identify salivary S-IgA as a candidate non-invasive biomarker for further study. Confirmation in larger, longitudinal cohorts with pain-free controls, comprehensive confounder adjustment (including time of day of collection, medication use, oral health, sleep, and smoking), and intervention designs with mediation analysis are needed before any clinical inference is drawn. These associations are hypothesis-generating and may partly reflect unmeasured stress- or mood-related confounding rather than a pain-specific effect.

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ORCID iDs

Adi Shani https://orcid.org/0000-0003-3524-3128
Nimrod Rahamimov https://orcid.org/0000-0003-4712-0010

Ethical considerations

All study procedures were approved by the Institutional Helsinki Committee of the Galilee Medical Center, Nahariya, Israel (approval no. 0044-20-NHR) and by the Ethical Committee of the University of Haifa, Haifa, Israel (approval no. 240/21).

Consent to participate

Written informed consent to participate was obtained from all individual participants prior to enrollment.

Consent for publication

The manuscript does not contain identifiable individual-level data; consent for publication of de-identified group-level results was included in the informed consent provided by participants at enrollment.

Author contributions

Conceptualization: A.S., M.G., R.T., N.R.; data curation: A.S., N.R.; investigation: A.S.; methodology: A.S., M.G., E.P., M.A., R.T., N.R.; supervision: M.G., R.T., N.R.; validation: E.P., M.A.; writing—original draft: A.S., N.R.; writing—review and editing: R.T., M.G., M.A., E.P. All authors have read and approved the final manuscript.

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Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability Statement

De-identified participant-level data underlying the analyses reported here are not publicly available because the informed consent obtained from participants for the parent study (NCT05994118) did not authorize open data deposition. The data are available from the corresponding author on reasonable request and subject to a data-sharing agreement approved by the Institutional Helsinki Committee of the Galilee Medical Center.

Trial registration

The parent interventional study was registered on https://ClinicalTrials.gov (NCT05994118).

Use of generative AI

Generative AI tools were used during manuscript preparation for language polishing and to support reproducible statistical computation through script generation. All scientific content, study design, data analysis, and interpretation were carried out and validated by the authors. No AI system is listed as an author. AI-generated text was reviewed and edited by the authors prior to submission.

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