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Serum soluble urokinase plasminogen activator receptor in adolescents: interaction of chronic pain and obesity

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Abstract:

Introduction: Obesity in adolescents is increasing in frequency and is associated with short-term and long-term negative consequences that include the exacerbation of co-occurring chronic pain.

Objective: To determine whether the interaction between chronic pain and obesity would be reflected in changes in serum soluble urokinase plasminogen activator receptor (suPAR) concentrations, a novel marker of systemic inflammation associated with obesity, insulin resistance, and cardiovascular disease.

Methods: We measured serum suPAR levels in 146 adolescent males and females with no pain or obesity (healthy controls; n = 40), chronic pain with healthy weight (n = 37), obesity alone (n = 41), and the combination of chronic pain and obesity (n = 28).

Results: Serum suPAR (median [interquartile range]) was not increased by chronic pain alone (2.2 [1.8–2.4] ng/mL) or obesity alone (2.2 [2.0–2.4] ng/mL) but was increased significantly with the combination of chronic pain and obesity (2.4 [2.1–2.7] ng/mL; $P < 0.019$). This finding confirms the proposition that pain and obesity are inflammatory states that display a classic augmenting interaction.

Conclusion: We propose that measurement of serum suPAR can be added to the armamentarium of serum biomarkers useful in the evaluation of mechanisms of inflammation in adolescent obesity and chronic pain.

Keywords: Children, Youth, Inflammation, Biomarkers, Body mass index, suPAR

1. Introduction

Chronic pain affects 25% to 37% of children and adolescents,[39,51] 30% of whom have co-occurring obesity.[50] These comorbid diseases are associated with impaired health-related quality of life, such that, across physical, emotional, social, and school domains, the impairment is greater than either disease alone.[21] As one example, the likelihood of experiencing impaired physical functioning is at least 2 times greater for youth with chronic pain and obesity compared with chronic pain alone, and at least 6 times greater than youth with obesity alone.[21] Furthermore, although youth with chronic pain and healthy weight show significant improvement in functional disability associated with multidisciplinary pain management, chronic pain with obesity is associated with treatment failure, such that these patients do not improve over time.[52] Obesity is a risk factor for some of the most debilitating pain conditions including osteoarthritis,[18,19,55] migraine and chronic daily headaches,[2,42] fibromyalgia,[38] and musculoskeletal pain.[56] Although less evidence exists, pediatric obesity has been identified as a risk factor for these conditions.[10,43,58] Although mechanisms for this interaction of co-occurring chronic pain and obesity are complex and multifactorial, inflammation is currently viewed as a key link in the causal pathway.[5,44] Specifically, pain- and obesity-driven elevations in inflammatory cytokines exert their effects through multiple peripheral and central pathways. As 2 primary examples, inflammatory cytokines modulate nociception and can trigger structural and biochemical changes, ultimately contributing to joint deterioration.[5,12,15,28,36,37,44,46]

Soluble urokinase plasminogen activator receptor (suPAR) has been proposed as a useful biomarker for chronic inflammation.[1,22] Soluble uPAR is a protein that is cleaved and released

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from membrane-bound uPAR, which is expressed on cells of the immune system.[24] Variations in serum suPAR have been associated with cancer, cardiovascular disease, type 2 diabetes, and mortality.[14,17,24,32,33,41,47]

Overweight and obesity, both of which have also been associated with inflammation, may have increased serum suPAR.[26,32,33,45,54] We are aware of 2 studies evaluating suPAR in children with obesity that showed conflicting results.[4,29] We are not aware of systematic studies of the independent effect of chronic pain on suPAR dynamics. Because, as described above, there are significant interactions between obesity and chronic pain in children, the purpose of this study was to perform a preliminary, exploratory study of suPAR in serum samples from a group of male and female adolescents without or with chronic pain and/or obesity that are a subset of a larger, ongoing study.

2. Methods

Adolescents (13–17 years, n = 146) were recruited for a larger trial focused on endogenous pain control. This project was approved by the Children's Wisconsin Institutional Review Board and written consent provided by participants and parents. Recruitment of 4 groups was based on presence/absence of chronic pain and presence/absence of obesity: (1) Healthy Controls (normal weight and no pain); (2) Obese (no pain); (3) Chronic Pain with Healthy Weight; and (4) Chronic Pain and Obesity. The 2 groups with chronic pain were recruited from a multidisciplinary pain clinic at Children's Wisconsin (formerly called Children's Hospital of Wisconsin). The 2 groups without chronic pain were recruited from an outpatient clinic within the Children's Wisconsin system and located in the same community.

2.1. Inclusion/exclusion criteria

Almost all criteria were extracted from information associated with the medical appointment visit in the electronic medical record before approaching participants. With the exception of diagnoses, self-reported information was confirmed with the medical provider and family before consent discussion. Medical providers inquired directly about the use of medicinal marijuana/cannabidiol and use of illicit street drugs.

2.2. Inclusion criteria

Thirteen to 17 years old, English speaking, and, if taking psychotropic or long-acting analgesics, doses had to be stable (defined as ≥ 1 week of medication use). Inclusion in the groups without obesity required a BMI of fifth to <85th percentile, based on age and sex.[30] Inclusion in the groups with obesity required a BMI ≥95th percentile, based on age and sex.[30] Subjects for the 2 nonpain groups answered screening questions before a consent discussion: (1) "Do you have any chronic illness?" Subjects who responded "yes" were excluded; (2) "Over the past 3 months, have you had pain?" Response options included "not at all," "rarely," "sometimes," "frequently," and "all the time." Subjects who responded "sometimes," "frequently," or "all the time" were excluded. Self-reported days with pain (PFSD1) and usual pain intensity (PFSD2) over the past 2 weeks were used to evaluate potential between-group differences in pain characteristics.[48]

2.3. Exclusion criteria

Type 1 or Type 2 diabetes mellitus and/or metabolic syndrome, documented hypertension, cancer-related pain, sickle cell disease, and inflammatory conditions (eg, rheumatoid arthritis, fibromyalgia, irritable bowel syndrome, celiac disease, Crohn disease, ulcerative colitis, and lupus), or the use of metformin, Accutane, corticosteroids, asthma inhalers (daily use within the past 2 weeks or ≥12 times in the past month or use within 12 hours of blood draw), medicinal marijuana/cannabidiol, immune-modulating medications, or self-reported use of illicit "street drugs."

A total of 179 subjects were consented, with 33 lost to follow-up, resulting in 146 subjects who completed the study. A total of 339 were excluded for the following reasons: Weight status (43.1%, with all but 3 of these adolescents having an overweight status), excluded medications (18.0%), chronic pain in the no pain groups (11.2%), a subset with medical complications, untreated mental health concerns, or other reasons (10.6%), excluded pain/medical condition (10.0%), physically unable to participate in the larger trial (6.2%), or other drug use (0.9%). Seven adolescents declined to hear about the study (8.3%), and 77 declined participation after being approached. Most of these declinations were due to the blood draw required (35.1%), followed by disinterest in research, distance to travel or other reasons (33.8%), with a subset of passive declines (31.1%).

2.4. Serum soluble urokinase plasminogen activator receptor assay

Blood (12 mL) was drawn from an arm vein into serum separating tubes, allowed to clot at room temperature for 30 to 60 minutes, and centrifuged (4°C) for 15 minutes at 1000 g and serum frozen at −80°C until analysis. Serum suPAR was measured by enzyme immunoassay from R&D Systems (DUP00; Minneapolis, MN) as described previously.[54] The samples were diluted 5-fold before assay and assayed in duplicate. The sensitivity of the assay without dilution of the serum is <33 pg/mL, which translates to <0.2 ng/mL with the 5-fold dilution of serum. The intraassay and interassay precisions are 2% to 8%.

2.5. Statistical analysis

Data were analyzed using nonparametric Kruskal–Wallis one-way analysis of variance, exact Mann–Whitney tests for pairwise comparisons, and Fisher–Freeman–Halton exact test (SPSS v26, IBM Corporation, Somers, NY, and Cytel StatXact v8, Cambridge, MA). Cohen's d was calculated to estimate effect size, based on the Kruskal–Wallis H[31](with d = 0.20, 0.50, or 0.80 interpreted as a small, medium, or large effect size, respectively).[7] No adjustments were made for multiple comparisons. $P < 0.05$ was considered significant; unadjusted values are given. Data are presented as mean (SD) or median (25%-75%).

3. Results

Table 1 shows the demographic and anthropometric data for the 4 groups of subjects. There was no significant difference in the ages ($P > 0.39$) or sex ($P > 0.29$) between the 4 groups. There was a significant difference in the racial distribution of the groups with significantly more African Americans and Native Americans in the Chronic Pain & Obese group compared to Healthy Controls and Obese Alone groups ($P < 0.009$). As expected, BMI was significantly greater in the Obese and Chronic Pain & Obese Groups compared to the Healthy Controls and Chronic Pain/Healthy Weight groups, but there was no difference within the nonobese groups and within the obese groups. Self-reported days with pain and worst pain intensity over the past 2 weeks (PFSD1 and PFSD2, respectively) were significantly greater in the Chronic Pain/Healthy Weight and Chronic

Table 1

Demographic and anthropomorphic data.

	Healthy controls	Pain/healthy weight	Obese alone	Pain & obese	*P*
N	40	37	41	28	
Age (y)	14.9 [1.3]	14.8 [1.4]	14.6 [1.4]	14.9 [1.4]	>0.39
Race				§‖	0.009
White	38	32	36	20	
African American	0	4	0	3	
Native American	0	0	0	2	
More than 1	2	1	5	3	
Hispanic					>0.11
No	37	30	37	21	
Yes	2	5	4	7	
No answer	1	2	0	0	
Sex (F/M)	20/20	20/17	21/20	20/8	>0.29
BMI (percentile)	56 [37–71]	55 [36–72]	97 [95–99]*	98 [96–99]*	<0.001
Pain location (n, %)					>0.07
Headache/migraine		27 (73.0)		25 (89.3)	
Extremities		6 (16.2)		0	
Abdomen		2 (5.4)		3 (10.7)	
Other		2 (5.4)		0	
Pain duration (mo)		24 [12–36]		36 [12–60]	>0.18
PFSD1 (d)	1.0 [0.0–2.0]	6.0 [4.0–13.5]†	2.0 [0.0–3.0]	7.0 [3.3–12.8]†	<0.001
PFSD2 (pain intensity)	2.0 [1.3–4.0]	5.0 [3.5–6.0]‡	2.0 [2.0–3.0]	5.0 [3.0–6.0]‡	<0.001

Data are shown as mean [SD] or median [25th–75th%] where appropriate.
* Different from Healthy Controls and Pain/Healthy Weight groups.
† Different from Healthy Controls and Obese Alone groups ($P < 0.002$).
‡ Different from Healthy Controls and Obese Alone groups ($P < 0.001$).
§ $P = 0.030$ vs Healthy Controls.
‖ $P = 0.048$ vs Obese Alone.
BMI, body mass index; PFSD1, Pain Frequency Severity Duration Scale-1 (days with pain in the past 2 weeks); PFSD2, Pain Frequency Severity Duration Scale-2 (usual pain intensity in the past 2 weeks).

Pain & Obese groups compared to the Healthy Controls and Obese Alone groups, but not different within the no chronic pain groups or within the chronic pain groups. Pain location was condensed to best represent between group differences. The majority of participants in both chronic pain groups presented with headache/migraine pain, followed by extremity pain (Chronic Pain group) and abdominal pain. "Other" pain conditions were condensed into a single category (included back pain and joint pain).

Serum suPAR (**Fig. 1**) concentration was in the expected range in the Healthy Control group.[4,29] Serum suPAR was not related to either chronic pain alone or obesity alone. However, there was a significant, classic interaction between pain and obesity on suPAR ($P = 0.046$) reflected in a significant increase in serum suPAR in the Chronic Pain & Obese group compared to the other 3 groups (*P* values shown in **Fig. 1**). The differences in suPAR are characterized as a small-medium (Cohen's $d = 0.4$) effect size. There was no difference between males and females with respect to chronic pain/obesity on serum suPAR ($P > 0.17$), although pain intensity (PFSD1) seemed to differ between males and females for the chronic pain only group (data not shown; unadjusted $P = 0.003$). We also did a subanalysis in the Pain/Healthy Weight and Pain & Obese groups to explore whether headache/migraine could be a covariate. We found no such interaction with suPAR in the Pain/Healthy group with vs without headache (2.2 [1.8–2.4] ng/mL (n = 27) vs 2.2 [2.0–2.3] ng/mL (n = 10), respectively $P = 0.918$) or with suPAR in the Pain & Obese group with vs without headache (2.4 [2.1–2.7] ng/mL (n = 25) vs 2.9 [2.0–3.2] ng/mL (n = 3), respectively; $P = 0.391$).

4. Discussion

The purpose of this study was to perform an exploratory study of serum suPAR in male and female adolescents without and with chronic pain and/or obesity. We found a classic, significant interaction between chronic pain and obesity in that neither condition increased suPAR, but the combination of chronic pain and obesity did. This augmentation of suPAR by the combination of pain and obesity was subtle with an increase in the median of 0.3 ng/mL. Although the effect size was small-medium, given that even small differences in levels of various biomarkers can make critical differences to health, the implications of this augmentation cannot be determined until future research defines cutoff values for the effects of suPAR.

As a biomarker of inflammation and immune system activation, increases in suPAR have been associated with obesity and insulin resistance.[17,24,26,32,33,45] Furthermore, it is considered a marker and may be a predictor of outcomes in a variety of cardiovascular diseases associated with inflammation.[1,14,17,22,32,41,47,54]

It is possible that the higher percentage of non-White subjects in the Pain & Obese group (29%) compared to the other groups (5%–14%) could have been a contributing factor to the subtle augmentation of serum suPAR observed. Many more subjects are needed to evaluate this novel conjecture. That said, there is no evidence in the literature so far of any relationship of race/ethnicity with serum suPAR concentration in adult and pediatric patients with kidney disease or peripheral artery disease.[3,25,49] In a comprehensive study using the Framingham Risk Score for cardiovascular disease prediction, the authors bemoan the lack of information on ethnicity and socioeconomic status in the evaluation of suPAR.[32] In fact, evaluation of serum suPAR in a very large cohort of subjects from different racial and ethnic groups may provide insight in potential mechanisms for differences in the interaction of obesity and pain. This is particularly so because other biomarkers may be altered by and reflect differences in race and ethnicity with respect to pain and obesity.[11,20,23]

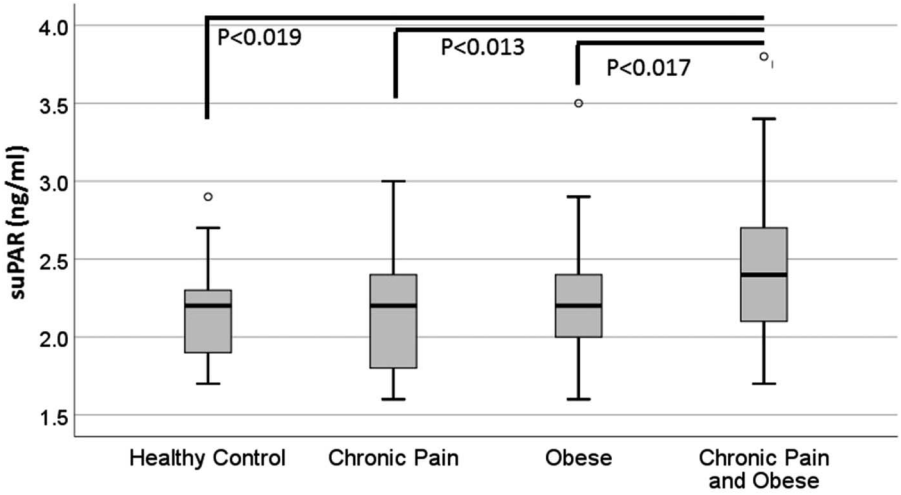

Figure 1. Serum suPAR concentrations in healthy controls (n = 40), chronic pain with healthy weight (n = 37), obesity alone (n = 41), and the combination of chronic pain and obesity (n = 28). For each group, the box represents values between 25% and 75% of the values in that group (the interquartile range [IQR]), the horizontal line in the box represents the median, the whiskers represent the usual range, and outliers that are more than 1.5 times the IQR of the median are shown by the o. The *P* values shown were obtained with a Bonferroni correction. suPAR, soluble urokinase plasminogen activator receptor.

Obesity in adolescents is increasing in frequency and severity.[8] Furthermore, we have shown that adolescents with obesity and chronic pain have a higher incidence of impaired functioning in multiple domains.[21] Therefore, we hypothesized that serum suPAR may be useful as a marker of the interaction between these 2 conditions. The 2 studies of which we are aware that measured serum suPAR in adolescents with obesity alone have been conflicting.[4,29] More importantly, we are unaware of systematic studies of suPAR in conditions of chronic pain in any age group.

Inflammatory biomarkers, now including suPAR, may provide insight into the mechanisms underlying the co-occurrence of chronic pain and obesity.[5,9,42] For example, serum biomarkers have been used to characterize pain conditions and their symptomatology,[13,40] predict pain intensity,[34] diagnose pain conditions,[6] identify the etiology of painful conditions,[57] identify relationships between pain, obesity, and comorbid psychobehavioral conditions[35] and, critically, distinguish between groups based on the presence of pain.[53] Such advancements are needed because we know little about adequate management of chronic pain with comorbid obesity.[27] Of note, we did not find an association of headache/migraine with suPAR in the 2 pain groups. It is also important to point out that we excluded fibromyalgia and inflammatory bowel disease from our cohort, primarily to avoid confounds due to inflammation associated with these conditions. Furthermore, these conditions can be difficult to quickly diagnose, and difficult to distinguish whether these conditions have any underlying autoimmune components. One of the ways that suPAR may be useful is as an additional biomarker in the evaluation and diagnosis of these complex pain conditions. More research is necessary to further explore the potential of suPAR as a biomarker in pediatric populations.

Given our results, suPAR shows promise as a new inflammatory biomarker of the co-occurrence of chronic pain and obesity. Because it is possible that suPAR may be more stable than C-reactive protein, it may serve as a more reliable, less volatile integrated index of treatment response, particularly in children. As an example of its potential to assess treatment response, it has been suggested that obesity-driven inflammation in those with chronic pain may respond to nutritional interventions.[15,16]

In conclusion, we have demonstrated in this initial, exploratory study an interaction of chronic pain and obesity to increase serum suPAR in male and female adolescents. This is further evidence that these 2 conditions have an inflammatory process as a characteristic. We plan to add suPAR to our panel of inflammatory biomarkers in adolescents and to determine whether suPAR can be used to evaluate the effectiveness of therapeutic approaches such as nutritional interventions as well as to evaluate mechanisms of racial and ethnic differences in the interaction of obesity and pain.

Disclosures

The authors have no conflicts of interest to declare.

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