

Serum Periostin Level Has Limited Usefulness as a Biomarker for Allergic Disease in 7-Year-Old Children

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Keywords

Allergen · Pediatrics · Periostin · Polysensitization

Abstract

Background: Previous studies have used serum periostin levels as a biomarker of Th2-driven inflammatory responses. However, no population-based study has yet examined the association of serum periostin levels with the allergic status of children. **Objectives:** The aim of this study was to determine the usefulness of periostin as a biomarker for allergy in a group of 7-year-old Korean children. **Method:** This prospective cross-sectional study examined 451 children (aged 7 years to 7 years and 11 months) from the general pediatric population who attended 6 different schools between June and July 2016. A total of 249 children, all of whom completed the questionnaire and skin prick test and provided blood samples, were included in the final analysis. **Results:** The geometric mean serum periostin level was 107.6 ng/mL (95% CI 104.5–110.7). After adjustment for confounding, se-

rum periostin levels were significantly associated with sensitization to poly-allergens (adjusted odds ratio, aOR 1.032, 95% CI 1.006–1.059, $p = 0.016$) and pollen (aOR 1.020, 95% CI 1.002–1.039, $p = 0.026$). Serum periostin levels were also associated with eosinophil levels (adjusted $\beta = 0.023$, SE = 0.009, $p = 0.010$), but were unrelated to body mass index, sex, obesity, or presence of an allergic disease. **Conclusions:** Our results suggest that serum periostin level may have limited usefulness as a biomarker of allergic disease in children.

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Introduction

The level of serum periostin, which is highly induced by Th2-related cytokines, has clinical significance for numerous diseases [1–3]. Recent studies showed that serum periostin can be used as a biomarker for the severity and

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phenotype classification of asthma [4–6], atopic dermatitis (AD) [7, 8], and allergic rhinitis (AR) [9]. Meanwhile, it is well established that poly-sensitization is associated with the severity of allergic disease, and that poly-sensitization during infancy can be considered a risk factor for later development of asthma and rhinitis [10–13]. Furthermore, poly-sensitization may reflect allergic subtypes, because children with mono- and poly-sensitization have different IgE-mediated allergic phenotypes [10–13]. Previous studies suggested that early sensitization to an allergen may predict allergic multimorbidity in childhood, and that early poly-sensitization is associated with multimorbidity [12, 13]. Thus, poly-sensitization and multimorbidity appear to reflect allergic subtypes, as well as the level of serum periostin. Therefore, to determine whether serum periostin can be used as a biomarker for allergic diseases, its association with poly-sensitization and multimorbidity must be established.

Previous studies suggested that the serum periostin level in children depends on age (especially during adolescence), sex, body mass index (BMI), and allergic diseases. Age may have an effect, because children have more rapid rates of bone turnover and growth than adults [5, 6, 14]. Thus, the role of serum periostin as an allergy biomarker in children may have been underestimated. Additionally, the lack of reliable reference values derived from children of the same age limits the potential utility of serum periostin. In this regard, when establishing a reference range for serum periostin for children of the same age, allergic disease and sensitization to allergens must be considered. Therefore, we evaluated the usefulness of periostin as a biomarker for allergy in a group of children of the same age to exclude the impact of age, and also examined the effect of various clinical factors on the level and reference range of serum periostin.

Materials and Methods

Subjects

This prospective cross-sectional study enrolled children from the general pediatric population who were in the first grade (age 7 years to 7 years and 11 months) and attended 6 different elementary schools between June and July 2016. Questionnaires were distributed to the parents of 618 children, and 451 completed questionnaires were returned (response rate 73.0%). Each participant's parents were asked to respond to the questionnaires prior to physical examination and blood sampling. A total of 249 children provided questionnaire data and data on the skin prick test (SPT) and blood samples for determination of serum periostin, 25-hydroxyvitamin D₃ [25(OH)D₃], and eosinophil levels. The 202 children who only provided questionnaire data were excluded (Fig. 1).

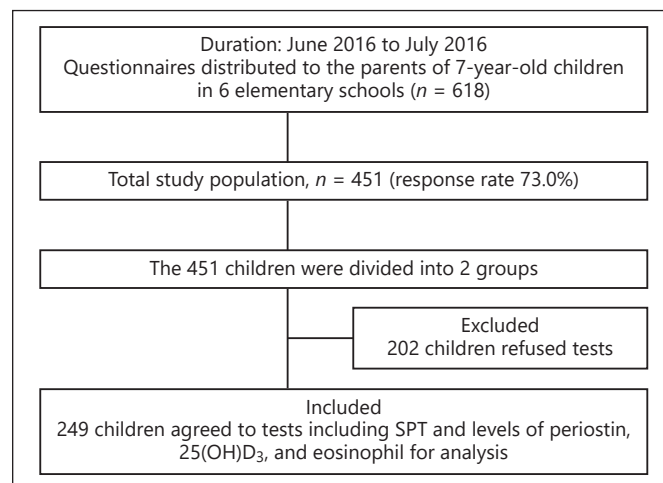


Fig. 1. Enrollment and classification of the study subjects.

Clinical Definitions

The diagnosis of allergic diseases was based on the Korean International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, according to the 12-month history of each subject [15]. Allergic multimorbidity was defined as the co-existence of at least two of the following conditions: asthma, AR, and AD [16]. The questionnaire provided data on the general characteristics of the children. Among the questionnaire items, we selected items that had documented associations with allergic diseases (*p* values <0.05 in simple linear regression analysis) or items with significant associations according to previous studies for further analysis [2–7].

Measurements

Blood sampling was used to determine the eosinophil count, serum 25(OH)D₃, and serum periostin. The serum periostin level was measured using an enzyme-linked immunosorbent assay (ELISA) at Shino Test Corp. (Kanagawa, Japan), as previously described [17]. Blood eosinophil counts are presented as percentages. The serum 25(OH)D₃ level was determined using an ELISA kit (Immunodiagnostic Systems, COBAS 6000 Roche, Mannheim, Germany). The SPT was performed using standardized allergen extracts and control solutions from LaForma (Milan, Italy) on the volar surface of both arms. Subjects were tested for sensitivity to the following 13 common aeroallergens: house-dust mites (HDM; *Dermatophagoides pteronyssinus*, *D. farinae*), animal dander (cat and dog), cockroach, *Alternaria*, pollen (elm, birch, oak, ragweed, mugwort, Japanese hop, and orchard grass), and 9 common food allergens (eggs, milk, shrimp, apple, kiwi, peanut, walnut, wheat, and celery). A positive SPT was defined as one with a mean wheal diameter that was 3 mm or greater than the positive control. Allergic sensitization was defined as the presence of one or more positive reactions in an SPT. Non-sensitization was defined as having no positive allergenic reactions, oligo-sensitization as having 1 or 2 positive reactions, and poly-sensitization as having 3 or more positive reactions. Sensitization to pollen was defined as having positive sensitization to elm, birch, oak, ragweed, mugwort, Japanese hop, or orchard grass.

Table 1. Demographic and clinical characteristics of the total study population

	Included children (<i>n</i> = 249)		Excluded children (<i>n</i> = 202)		<i>p</i> value
	<i>N</i> ¹	value	<i>N</i> ¹	value	
Demographics					
Male	249	138 (55.4)	201	98 (48.8)	0.159
Anthropometrics					
BMI <i>z</i> -score	240	0.03±1.09	179	−0.16±1.18	0.101
Height, cm	240	121.62±5.25	182	120.57±9.90	0.140
Prenatal history					
Vaginal delivery	248	172 (69.4)	202	142 (70.3)	0.829
Prematurity (gestational age <37 weeks)	231	25 (10.8)	187	12 (6.4)	0.115
Low birth weight (<2.5 kg)	247	13 (5.3)	199	5 (2.5)	0.142
Allergic history					
Asthma	247	19 (7.7)	199	11 (5.5)	0.364
AR	249	140 (56.2)	201	123 (61.2)	0.288
AD	248	69 (27.8)	196	34 (17.3)	0.009*
Parental allergic history					
Asthma	208	18 (8.7)	178	17 (9.6)	0.760
AR	230	137 (59.6)	188	92 (48.9)	0.030*
AD	248	38 (15.3)	178	23 (12.9)	0.485

Values are presented as *n* (%) or mean ± SD. *p* values are from a χ^2 test or Student's *t* test, * *p* < 0.05. AR, allergic rhinitis; AD, atopic dermatitis.

¹ Number of completed questionnaires or of appropriate responses to questions in the questionnaire.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA). Values are reported as medians (interquartile range; IQR), unless otherwise stated. Frequencies and continuous variables were compared using the χ^2 test and Student's *t* test, respectively. Levels of periostin and eosinophil counts were log₁₀-transformed before analysis, because they had non-normal distributions; the least-squares means on the log scale were back-transformed and presented as geometric means (GM) and 95% confidence intervals (CIs). Generalized linear models with the logit function were used to determine the odds ratio between serum periostin level and poly-sensitization and multimorbidity. Statistical significance was defined as values of *p* < 0.05.

Results

Demographic Characteristics

Table 1 shows the characteristics of the children who were included (*n* = 249 provided questionnaire data and blood samples) and excluded (*n* = 202 provided questionnaire data only). The enrolled group (55.4% males) had a significantly greater prevalence of AD (*p* = 0.009), and their parents had a significantly greater prevalence of AR

(*p* = 0.030). Among the enrolled children, the prevalence of asthma was 7.7% (*n* = 9), the prevalence of AR was 56.2% (*n* = 140), and the prevalence of AD was 27.8% (*n* = 69). Among the parents of the enrolled children, the prevalence of asthma was 8.7% (*n* = 18), the prevalence of AR was 59.6% (*n* = 137), and the prevalence of AD was 15.3% (*n* = 38).

Association of Serum Periostin Level with Demographic Parameters

We log₁₀-transformed the serum periostin levels before statistical analysis, because the distribution had a non-normal distribution. The GM serum periostin level was 107.6 ng/mL (95% CI 104.5–110.7), and the 5th and 95th percentiles were 76.0 and 154.0 ng/mL, respectively. Analysis of the association of serum periostin level with demographic factors indicated no significant relationships with height, BMI *z*-score, sex, or presence of obesity (*p* > 0.05; Table 2).

After adjusting for gender, height, and BMI, we found that the serum periostin level was significantly associated with eosinophil count (adjusted β = 0.023, standard error = 0.009, *p* = 0.010) and white blood cell count (ad-

Table 2. Continuous and binary factors that are potential confounders in the analysis of serum periostin levels (ng/mL) among the included children ($n = 249$)

Continuous variables		N (%) ¹	β (SE)	p value
Height (cm)		240 (96.4)	0.193 (0.344)	0.574
BMI z-score		240 (96.4)	-0.183 (1.660)	0.270
Binary variables		N (%) ¹	GM (95% CI)	p value
Gender	male	138 (55.4)	107.6 (103.4–111.8)	0.984
	female	111 (44.6)	107.5 (102.9–112.3)	
Obesity	normal	222 (92.5)	106.7 (103.5–110.1)	0.401
	obese	18 (7.5)	112.0 (102.7–122.0)	

Obesity was defined as a BMI z-score >1.63 . p values are from linear regression or Student's t test. GM, geometric mean.

¹ Number of completed questionnaires or of appropriate responses to questions in the questionnaire.

Table 3. Association of serum periostin level (ng/mL) with laboratory parameters among the included children ($n = 249$)

Hematological factor	Crude β (SE)	p value	Adjusted β (SE)	p value
25(OH)D ₃ , ng/mL	0.180 (0.400)	0.654	0.076 (0.410)	0.852
Hemoglobin, g/L	0.094 (2.342)	0.968	1.195 (2.382)	0.616
White blood cell count, $\times 10^9$ /L	1.795 (1.073)	0.096	2.233 (1.095)	0.043*
Lymphocytes, $\times 10^9$ /L	0.002 (0.002)	0.354	0.002 (0.003)	0.432
Eosinophils, $\times 10^9$ /L	0.021 (0.009)	0.018*	0.023 (0.009)	0.010*

p values are from linear regression after adjusting for gender, height, and BMI. * $p < 0.05$.

justed $\beta = 2.233$, standard error = 1.095, $p = 0.043$). The levels of 25(OH)D₃, hemoglobin, and lymphocytes were not significantly related to the serum periostin level ($p > 0.05$; Table 3).

Association of Serum Periostin Level with Allergic Multimorbidity and Sensitization to Allergens

The serum periostin levels were similar for children without ($n = 228$, GM = 107.4, 95% CI 104.1–110.7) and with asthma ($n = 19$, GM = 106.5, 95% CI 97.1–116.8, $p = 0.881$), for children without ($n = 109$, GM = 107.4, 95% CI 103.4–111.6) and with AR ($n = 140$, GM = 107.6, 95% CI 103.2–112.3, $p = 0.945$), and for children without ($n = 179$, GM = 106.1, 95% CI 102.6–109.8) and with AD ($n = 69$, GM = 116.7, 95% CI 105.1–118.0, $p = 0.143$). There were also similar serum periostin levels among those who had no allergy, mono-allergy, and multiple allergies ($p = 0.415$; Fig. 2a). In addition, allergic multimorbidity (asthma, AR, and AD) was unrelated to the serum periostin

level after adjusting for sex, height, and BMI ($p > 0.05$; Table 4).

There were positive SPT results to at least 1 allergen in 99 children (42.9%); 83 children (35.9%) had oligo-sensitization and 16 children (6.9%) had polysensitization. Sensitization to HDM was most common ($n = 87$, 37.7%), followed by pollen ($n = 29$, 12.9%). Children with polysensitization had a significantly greater serum periostin level (GM = 121.2 ± 1.15) than non-sensitized children (GM = 106.3 ± 1.24 , $p = 0.033$) or those with oligo-sensitization (GM = 107.1 ± 1.3 , $p = 0.050$; Fig. 2b). After adjusting for confounding, poly-sensitization remained associated with a greater serum periostin level (adjusted odds ratio, aOR 1.032, 95% CI 1.006–1.059, $p = 0.016$). After dividing the children into two serum periostin quantiles, there was increased poly-sensitization in quantile 2 relative to quantile 1 (aOR 8.269, 95% CI 1.763–38.793, $p = 0.007$; Table 4).

Table 4. Association of serum periostin level with allergic multimorbidity, pollen sensitization, and poly-sensitization among the included children with an SPT result ($n = 231$)

	Multimorbidity				Pollen sensitization				Poly-sensitization			
	OR (95% CI)	<i>p</i> value	aOR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	aOR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	aOR (95% CI)	<i>p</i> value
Periostin (ng/mL) ¹	0.991 (0.979–1.002)	0.121	0.990 (0.978–1.002)	0.105	1.018 (1.002–1.034)	0.032*	1.020 (1.002–1.039)	0.026*	1.024 (1.002–1.046)	0.029*	1.032 (1.006–1.059)	0.016*
Periostin quantile ¹												
1	Reference		Reference		Reference		Reference		Reference		Reference	
2	1.071 (0.491–2.338)	0.862	0.924 (0.409–2.084)	0.848	2.794 (1.153–6.771)	0.023*	2.582 (1.141–7.129)	0.025*	7.452 (1.627–34.125)	0.010*	8.269 (1.763–38.793)	0.007*

Multimorbidity was defined as co-existence of at least two allergic diseases (AR, asthma, and/or AD). Pollen sensitization was defined as positive sensitization to elm, birch, oak, ragweed, mugwort, Japanese hop, or orchard grass. Poly-sensitization was defined as having 3 or more reactions to allergens. * $p < 0.05$. SPT, skin prick test.

¹ Generalized linear regression with logit function, after adjusting for sex, height, and BMI.

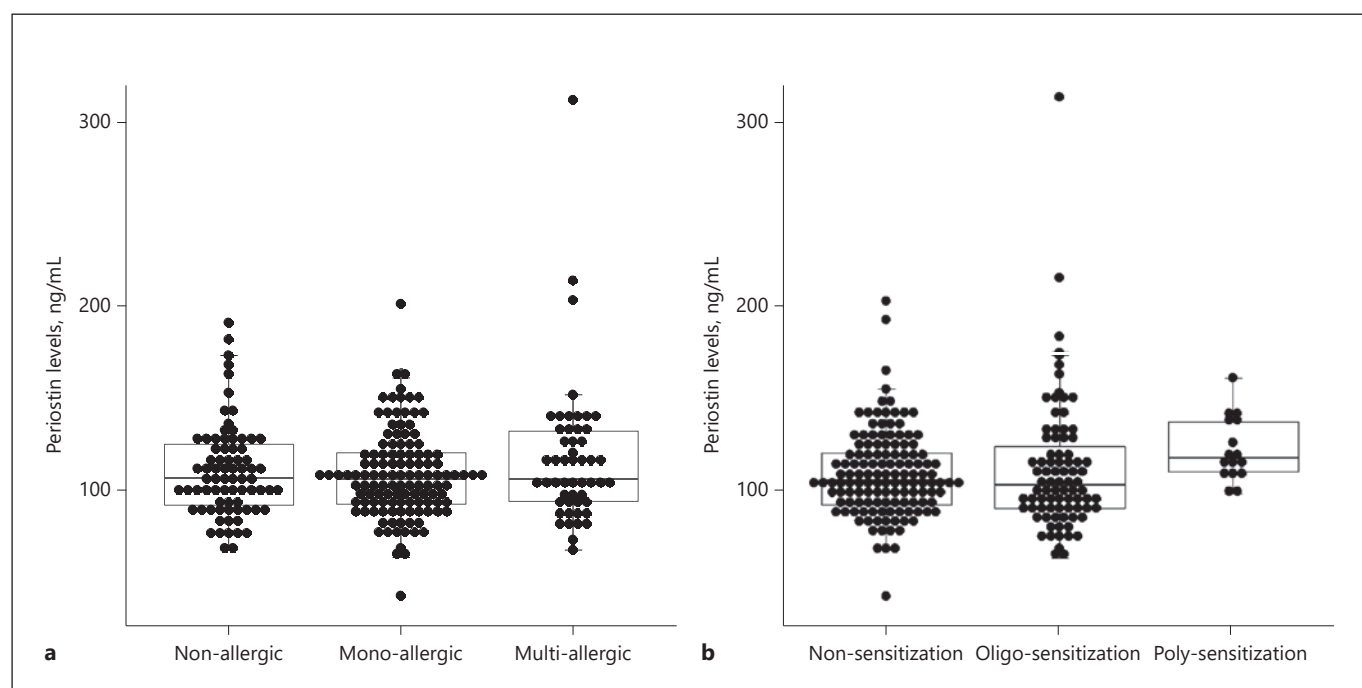


Fig. 2. **a** Serum periostin levels in children who were non-allergic, mono-allergic, and multi-allergic. **b** Serum periostin levels in children who were non-sensitized, oligo-sensitized, and poly-sensitized.

Children with sensitization to pollen ($n = 29$, $GM = 117.2 \pm 1.22$) had a significantly higher level of serum periostin than those without sensitization ($n = 132$, $GM = 106.0 \pm 1.23$, $p = 0.024$). After adjustment for confounding, sensitization to pollen was also associated with an increased serum periostin level (aOR 1.020, 95% CI 1.002–1.039, $p = 0.026$), but not with sensitization to HDM or animal dander. There was a significantly increased pollen sensitization in quantile 2 relative to quantile 1 (aOR 2.582, 95% CI 1.141–7.129, $p = 0.025$; Table 4).

Discussion

The current epidemiological study evaluated the association of serum periostin level with sensitization to allergens, level of blood eosinophils, and the presence of allergic disease in 7-year-old Korean children. We demonstrated that children with poly-sensitization had the highest levels of periostin, and that this association remained after adjustment for confounding. The IgE sensitization is a heterogeneous phenomenon, and individuals

who are mono- and poly-sensitized have different clinical and immunological characteristics [18, 19]. Thus, poly-sensitized individuals have high levels of total IgE or eosinophils, poor quality of life due to AR or asthma, and more severe asthma symptom scores [18, 19]. Therefore, our findings indicate that an elevated serum periostin level may indicate a more severe allergic disease or a subset of allergic diseases in children; similarly, poly-sensitization indicates a more severe allergic disease or a subset of allergic diseases. Our results indicated no association of serum periostin with allergic multimorbidity or with the presence of an allergic disease, in contrast to some previous studies [4–6]. However, our findings are in agreement with several other studies which reported no relationship of serum periostin level with allergic diseases or AR in children [15, 20]. Additionally, previous studies have already demonstrated that serum periostin levels are higher in healthy children than healthy adults, suggesting limited utility as a biomarker for allergic diseases in children [5, 14]. Moreover, a recent study examined children aged younger than 5 years and showed that serum periostin levels were higher in non-allergic (control) children than allergic children, suggesting it is not useful as a biomarker for allergic diseases in children of this age [21]. In agreement, our results showed that the periostin level has limited usefulness as a biomarker for allergic diseases in 7-year-old children.

Interestingly, we found that children with high levels of blood eosinophils or with pollen-sensitization, but not HDM sensitization, had increased serum periostin levels. The positive association between serum periostin and eosinophil levels may be because both of these are induced by IL-5 and IL-13, the key cytokines of Th2 immune responses [5–7, 22]. It is well-known that pollen and HDM allergens induce Th2 immune responses. However, pollen grains contain other immunomodulatory substances that differentiate them from HDM, and pollen-derived non-allergenic substances might contribute to B cell-dependent activation of IgE-mediated allergy [23, 24]. Thus, our finding of a difference between pollen and HDM may be explained by the different immunopathophysiological responses to these aeroallergens. Additionally, this study was conducted from June to July, and studies conducted during other months could produce different results.

The median serum periostin level in our 7-year-old children was 107.6 ng/mL, higher than reported in a previous Korean study of children with asthma (76.0 ng/mL, mean age 8.7 ± 1.8 years) and healthy controls (71.0 ng/mL, mean age 8.6 ± 1.5 years) [25]. However, our serum periostin levels were lower than reported for children in

the USA (128 ng/mL, mean age 4 years; 130 ng/mL, mean age 11 years) [5]. These differences may be due to a difference of race, sex, prevalence of allergic diseases, manufacturer of the ELISA kit used for analysis, and/or selection bias.

Additionally, our study showed no significant association of serum periostin level with obesity or sex, in contrast to previous studies [14, 26]. In contrast, multiple studies of adults have reported an inverse association between serum periostin level and BMI [9, 27, 28]. These differences of adults and children suggest that serum periostin has different functions in children and adults, and the need for more studies of pediatric populations of well-defined age groups.

There were several limitations to this study. All of the 249 children lived in one urban area in Korea, so this study could be subject to selection bias and may have limited generalizability. This study was a cross-sectional analysis using questionnaires, thus there is the possibility of recall bias by the parents. Nonetheless, the present study had numerous strengths. To eliminate age bias, we only examined children of the same age category from 6 different elementary schools. Furthermore, we analyzed the relationships of serum periostin with sensitization to allergens by use of SPTs and using a comprehensive and stringent questionnaire.

Overall, our study of 7-year-old Korean children indicated that the serum periostin level was significantly and positively associated with sensitization to poly-allergens and pollen, but was unrelated to BMI, sex, obesity, or presence of an allergic disease. These results suggest that the serum periostin level may have limited usefulness as a biomarker of allergy in children. Future prospective studies of children representative of the whole population are needed to corroborate our findings.

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Statement of Ethics

The study protocol was approved by the Institutional Review Board of the CHA Bundang Medical Center (IRB No. 2016-04-032). Written informed consent was obtained from the parents or guardians of all participants following a detailed explanation of the study.

Disclosure Statement

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contributions

M.S., H.S.B., and M.Y.H. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: M.S., H.S.B., M.Y.H. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: M.S., Y.H.S. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: S.W.L., D.K.Y., K.S.L., M.Y.H. Obtained funding: H.M.J. Study supervision: H.S.B., M.Y.H.

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