FTIR SIGNATURES OF PROTEIN CONFORMATIONAL CHANGES IN GINGIVAL CREVICULAR FLUID IN CHILDREN WITH CARIES AND GINGIVITIS

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The relevance of the study is associated with the search for minimally invasive molecular signatures of the dentogingival complex tissue condition in children. A pilot study aimed to identify spectral signatures of protein conformational changes in gingival crevicular fluid from children aged 8–14 years with dental caries and gingival inflammation (gingivitis) based on analysis of the IR spectral Amide III band in a pilot cohort. Gingival crevicular fluid samples collected from 20 children aged 8–14 years with different dental status were analyzed. FTIR spectra were acquired using synchrotron-based Fourier transform infrared spectroscopy in a Bruker Vertex 80/v spectrometer in the range of 3800–700 cm^{-1} with a focus on the Amide III region. Spectral deconvolution combined with multivariate analysis was used to estimate the contribution of protein secondary-structure elements. In the pilot cohort, dental caries was associated with a directed increase in the total contribution of components related to β-sheet structures. Based on the summed contributions of the main secondary structure elements, the β-sheet contribution exceeded 50% across the four analytical groups, the disordered component ranged approximately from 21 to 31%, and the contributions of β-turns and α-helical components remained below 10–11%. Inflammatory gingival changes showed a tendency toward a decreased contribution of β-turns and a relative increase in disordered conformations. Thus, the Amide III profile may reflect integral physicochemical changes in proteins of gingival crevicular fluid in individuals with caries and gingivitis. The reported features should be regarded as candidate spectral signatures of a hypothesis-generating nature that require further clinical validation.

Keywords: gingival crevicular fluid, Fourier transform infrared spectroscopy, Amide III band, protein secondary structure, spectral deconvolution, multivariate analysis, dental caries, gingivitis

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FTIR-ПРИЗНАКИ ПЕРЕСТРОЙКИ БЕЛКОВ ДЕСНЕВОЙ ЖИДКОСТИ У ДЕТЕЙ ПРИ КАРИЕСЕ И ГИНГИВИТЕ

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Актуальность исследования связана с поиском малоинвазивных молекулярных признаков состояния тканей зубодесневого комплекса у детей. Цель пилотного исследования — выявить в пилотной выборке спектральные признаки перестройки белков десневой жидкости у детей 8–14 лет при кариесе и воспалительных изменениях десны (гингивите) на основе анализа ИК-спектральной полосы Амид III. Проанализированы образцы десневой жидкости, полученные у 20 детей 8–14 лет с различным стоматологическим статусом. ИК-спектры регистрировали методом синхротронной ИК-Фурье-спектроскопии на спектрометре Bruker Vertex 80/v в диапазоне 3800–700 $см^{-1}$ с акцентом на область Амид III. Вклад элементов вторичной структуры белков оценивали с помощью деконволюции спектрального профиля и методов многомерного анализа. В пилотной выборке кариес ассоциировался с направленным увеличением суммарного вклада компонент, соответствующих β-складчатым структурам. По данным суммарной оценки основных элементов вторичной структуры, вклад β-складчатых компонентов во всех четырех аналитических группах превышал 50%, вклад неупорядоченных конформаций составлял примерно 21–31%, а вклад β-поворотов и α-спиральных компонент оставался менее 10–11%. При воспалительных изменениях десны отмечена тенденция к уменьшению вклада β-поворотов и относительному увеличению неупорядоченных конформаций. Таким образом, профиль полосы Амид III может отражать интегральные физико-химические изменения белков десневой жидкости при кариесе и гингивите. Выявленные особенности следует рассматривать как кандидатные спектральные признаки, имеющие гипотезо-генерирующий характер и требующие дальнейшей клинической проверки.

Ключевые слова: десневая жидкость, ИК-Фурье-спектроскопия, полоса Амид III, вторичная структура белков, деконволюция спектров, многомерный анализ, кариес, гингивит

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Gingival crevicular fluid represents a local biological medium of the gingival sulcus reflecting the dentogingival complex tissue physicochemical state. The fluid composition is determined by proteins, peptides, components of inflammatory exudate, and tissue remodeling products, therefore it is suitable for spectroscopic analysis. In contrast to targeted biochemical methods, the Fourier transform infrared (FTIR) spectroscopy allows one to obtain integral molecular characteristics of low-volume samples and assess re-distribution of the contributions of various sample protein component conformations [1–4].

The issue is especially relevant for pediatric dentistry. However, the data on local molecular markers of gingival crevicular fluid in children is still limited. Current reviews show that inflammatory gingival changes are often found in children and adolescents, and the tissue state is further affected by age, dentition stage, pubertal changes, plaque levels, and orthodontic load [5–7]. In this regard, gingival crevicular fluid is of interest as a minimally invasive test substrate that can be re-collected and correlated with a certain dentogingival complex region [1, 5–6]. In theory, microbial factors, local proteolysis, oxidative stress, and inflammatory remodeling processes that change the composition and conformational state of proteins in gingival crevicular fluid can have an effect on such spectral shifts.

The region of the Amide III band that is sensitive to the contribution of α-helical, β-sheet, β-turn, and disordered structures is of special interest for analysis of the protein component. Compared with the Amide I and Amide II regions, its interpretation is less complicated by the influence of water and hydrogen-bonded background, which is especially important when assessing low volumes of hydrogen-containing biological media, including gingival crevicular fluid [4, 8–10]. At the same time, to correctly interpret the protein system spectra in this region it is necessary to consider the IR band overlap, select the pre-processing scheme and deconvolution parameters [4, 8–10]. That is why, in complex biological media, it is reasonable to consider not single peaks as direct markers, but the integrated spectral profile as a reflection of the directed protein component changes [4, 8].

Such studies are further limited by small sample size, so it is required to use multivariate analysis methods adjusted to spectral data and the limited number of observations. Previously it was shown that multivariate analysis of the gingival crevicular fluid IR spectra allowed one to identify the underlying patterns associated with the patient's clinical status and individual characteristics [11]. This makes the combination of the Amide III band deconvolution with multivariate statistical analysis a promising approach to assessment of the directional changes in the secondary structure of proteins in gingival crevicular fluid [11].

We proceeded from the working hypothesis that in children with caries and gingival inflammation the gingival crevicular fluid Amide III band profile would change directionally through redistribution of the spectral-associated components related to various secondary protein structure elements. The study aimed to identify such directional changes in the Amide III band spectral profile and assess the possibility of considering those as candidate spectral signatures of changes in the gingival crevicular fluid protein component.

METHODS

Research design and characteristics of the sample

A total of 20 children aged 8–14 years, from whom gingival crevicular fluid was collected after the dental examination, were included in the study. Inclusion criteria: age 8–14 years; availability of the legal representative's informed consent; possibility of standard dental examination and gingival crevicular fluid collection; no antimicrobial or other therapy capable of significantly affecting the test biological medium composition at the time of examination. Exclusion criteria: other age and non-compliance with the inclusion criteria. It was a pilot single-center study. Since some patients had a combination of clinical factors, the study was focused primarily on identifying the spectral shift directional nature, not on the rigorous assessment of the independent contribution of each factor.

The dental caries status was assessed clinically; groups with no clinical signs of caries, early caries lesions, and multiple caries lesions were allocated. The gingival state was characterized based on the presence and severity of inflammatory changes as no clinically significant changes, mild or moderate inflammation. Comorbid medical conditions were taken into account based on the medical history and medical records. Four analytical groups were allocated for in-depth comparison of spectral profiles and their deconvolution (Table).

Gingival crevicular fluid sampling

The protein component of gingival crevicular fluid, the complex multicomponent biological medium locally associated with the dentogingival interface tissues, was a research object. Sampling was performed at the Department of Pediatric Dentistry and Orthodontics of the Burdenko Voronezh State Medical University (Voronezh, Russia). Gingival crevicular fluid was collected in the morning without prior stimulation using microcapillaries. Such a sampling regime minimized the effects of circadian oscillation and ensured comparability of spectrum acquisition conditions [12]. After collection samples were placed in sterile containers and stored at a temperature of 1–2 °C prior to spectroscopic analysis within the same pre-analytical regime.

Fourier transform infrared spectroscopy

IR spectra were acquired by synchrotron-based Fourier transform infrared spectroscopy using the Bruker Vertex 80/v vacuum spectrometer (Bruker Optik GmbH, Ettlingen, Germany) in the range of 3800–700 cm^{-1}. The Amide III band was considered as the main range, since it allowed one to analyze conformational features of the protein component with the less methodological dependence on the water

Table. Description of four analytical groups of gingival crevicular fluid samples included in deconvolution of Amide III spectral profiles

Internal code of the analytical group	Sex	Age subgroup	Dental caries stage	Gingival inflammation	Comorbid condition
FYNNN	F	Younger (Y)	No caries (N)	No gingival inflammation (N)	No comorbidity (N)
FAENN	F	Adolescent (A)	Early caries (E)	No gingival inflammation (N)	No comorbidity (N)
FAEMO	F	Adolescent (A)	Early caries (E)	Moderate inflammation (M)	Oncological disease (O)
MAMLG	M	Adolescent (A)	Multiple caries (M)	Mild gingival inflammation (L)	Gastrointestinal disease (F)

Note: The analytical group internal code consists of five symbols: 1st — sex, 2nd — age subgroup, 3rd — caries status, 4th — gingival state, 5th — comorbid condition.

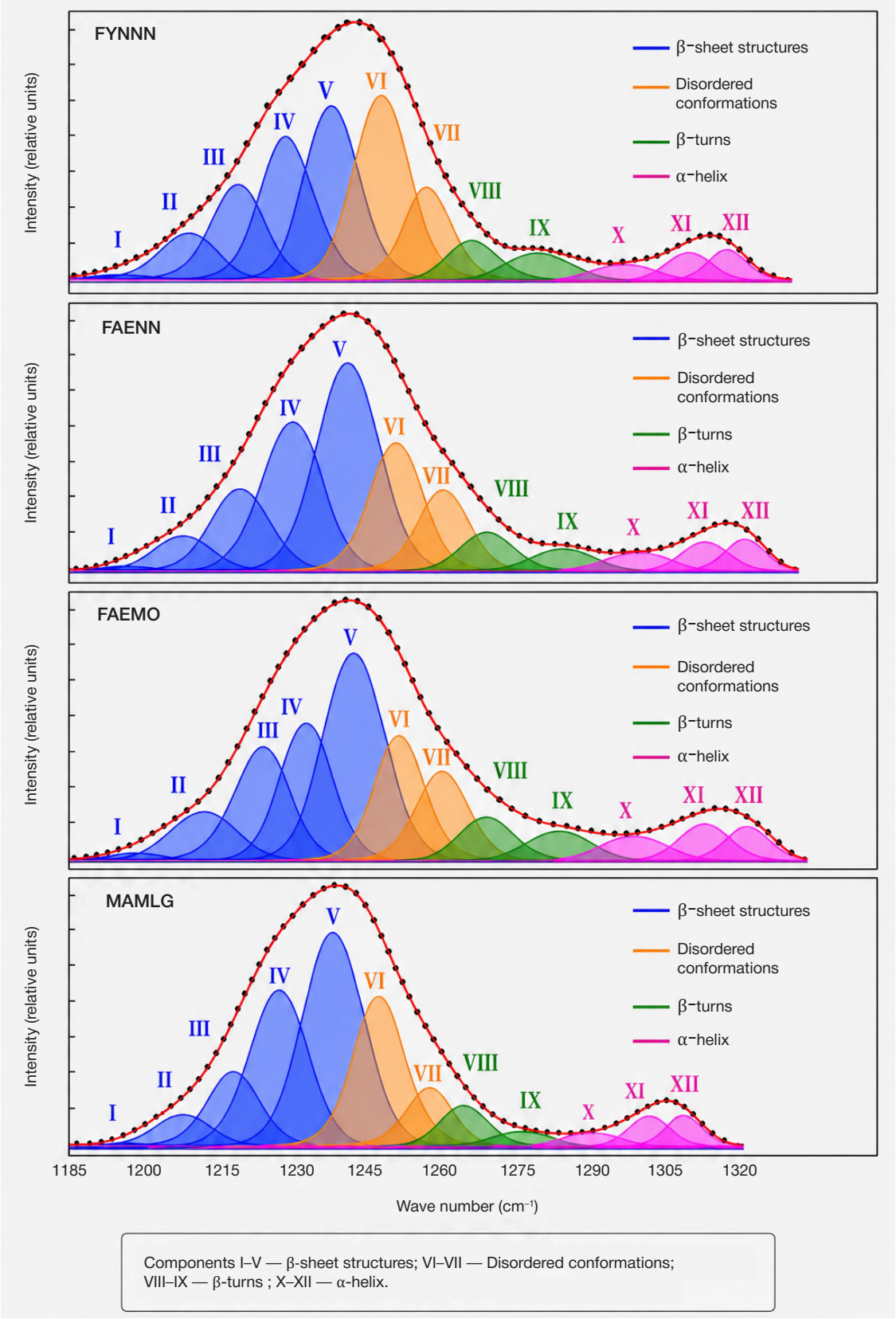

Fig. 1. Deconvolution of the gingival crevicular fluid Amide III band spectral profile in children aged 8–14 years with various clinical statuses. Internal codes of the samples are provided in Table 1. Components I–V in the spectral profile are correlated to β-sheet structures, VI–VII — to disordered conformations, VIII–IX — to β-turns, X–XII — to α-helical components

background compared to the Amide I and Amide II regions [4, 8–10]. Standard acquisition parameters were used in the initial experimental cycle: spectral resolution 4 cm^{-1}, 3-term Blackman–Harris apodization, Mertz phase correction, and the zero filling coefficient of 2. The contents of each sample were divided into ten portions, for each of which a distinct IR spectrum was acquired; the spectral profile was further characterized based on the average data.

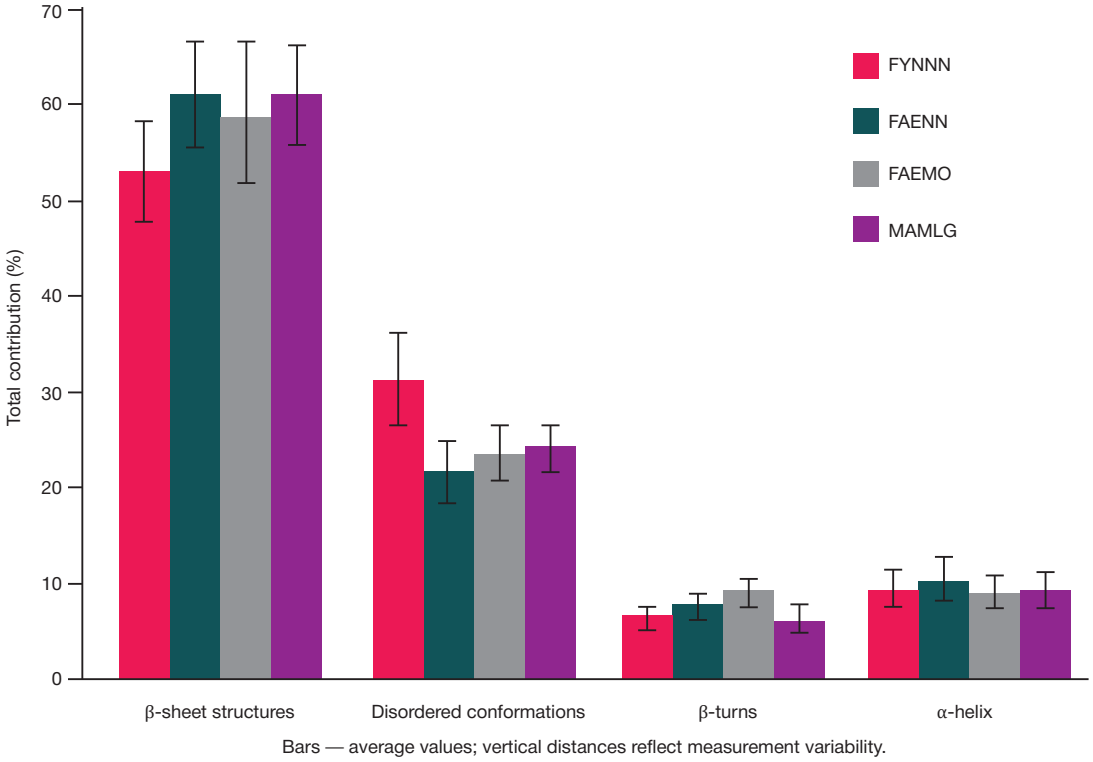

Fig. 2. Relative contribution of the main secondary structure elements of gingival crevicular fluid proteins in the integral profile of the Amide III band

Spectrum pre-processing and deconvolution

Primary processing of IR spectra included smoothing of the curves using a Savitzky–Golay filter with a polynomial order of 2 and window length of 25 points. Baseline correction was performed by the asymmetric least squares method in the range of 4000–500 cm^{-1} with the threshold value of 0.01 and asymmetry factor of about 0.001. The pre-processing parameters were selected in such a way as to reduce smoothing and baseline correction artifacts preserving sensitivity to the Amide III band shape alteration.

To quantitatively describe the Amide III band profile, deconvolution with isolation of the components correlated to α-helical, β-sheet, β-turn, and disordered conformations was performed. Gaussian functions were used for approximation. Preliminary search for balance centers and bandwidth at half-height was carried out using the 2nd and 4th derivatives of the smoothed spectra. Further modeling was accomplished in Fityk v.1.3.1 (developed by M. Wojdyr, Poland) using the Levenberg–Marquardt algorithm. To ensure comparability of results, the same number of components was maintained in all samples. Box constraints were used in the modeling: ± 2 cm^{-1} for maxima positions, 7–10 cm^{-1} for FWHM values. The best fit between theoretical and experimental curves based on the χ^2 test was used as an approximation termination criterion. The resulting components were considered as spectral-associated contributions, not direct absolute measures of the content of appropriate secondary structures [4, 8–10]. Components I–XII were correlated with the protein secondary structure elements based on the earlier published data on interpretation of the Amide III band and ranges of maxima of the corresponding IR bands [4, 8–10]. The selected box constraints were set within the ranges ensuring stability of approximation and consistence with the ranges of maxima positions and bandwidths for the Amide III band reported in the literature [4, 8–10]. The same number of components, the same box constraints, and the same approximation scheme for all samples were used to improve reproducibility and comparability of deconvolution results.

Multivariate and statistical analysis

After pre-processing the spectral data set was analyzed by the principal components method to assess relative positions of samples in the multidimensional space and interpret the correlations between spectral variability and clinical factors. Spectral intensities in the Amide III band region were used as quantitative variables, and characteristics of patients were considered as categorical traits used in the phase of interpretation. The FactoMineR software package for R was used for analysis, and the factoextra package was used for visualization. At this stage it was determined, which clinical factors were most strongly associated with the main directions of spectral variability, and the proximity of samples in the principal component space was assessed. In the phase of interpretation we also assessed how the levels of categorical clinical traits correlated with the sample positions and the main directions of spectral variability identified by the method of principal components. Categorical clinical traits were not included in the model as covariates; these were used for clinical interpretation of sample distribution in the principal component space, which was consistent with the pilot design of the study.

In the next phase, after identifying the key factors of variability, samples were selected for further deconvolution of spectral profiles, and the exploratory pairwise comparison was performed. For that the BSDA package and the tsum.test with Bonferroni correction for multiple comparisons were used. The analysis was conducted with the significance level of 0.05.

RESULTS

Amide III band spectral profile

In the Amide III band region, the gingival crevicular fluid samples were characterized by the complex multi-component contour formed by the overlapping bands belonging to different conformations (Fig. 1). That is why the integral

intensity was only partially informative, while re-distribution of the contributions of distinct spectral components within the common profile turned out to be a more meaningful parameter. The components correlated to β-sheet structures and disordered conformations were the main contributors to the integral intensity; the contribution of α-helical components was less pronounced [8–10]. Based on the summed contributions of the main secondary structure elements (Fig. 2), the β-sheet component contribution exceeded 50% across the four analytical groups, the contribution of disordered conformations was approximately 21–31%, while the contributions of β-turns and α-helical components remained below 10–11%. The key clinical characteristics of the test groups are provided in Table, and a typical deconvolution profile is presented in Fig. 1. In Fig. 2, bars represent the average values of total contributions and vertical distances represent the measurement variability. The multivariate analysis data were used to select four analytical groups; the revealed spectral heterogeneity of samples was generally consistent with the directional nature of shifts determined during further deconvolution of the Amide III band. Partial delineation of analytical groups was observed in the first principal component space, which was generally consistent with the subsequent differences in total contributions of β-sheet components and β-turns.

Internal codes of the samples are provided in Table. Components I–V in the spectral profile are correlated to β-sheet structures, VI–VII to disordered conformations, VIII–IX to β-turns, X–XII to α-helical components. Such distribution was also given in the explanatory block of Fig. 1 to make the graphic material interpretation easier.

Spectral shifts associated with caries

In the pilot cohort, the directed increase in the relative contribution of the components associated with β-sheet structures in samples from children with caries was the most stable feature. The total contribution of β-sheet components reached approximately 59–61% in the groups with caries vs. approximately 53% in the group without any clinically significant dental alterations (Fig. 2). This shift had the same direction across different combinations of associated clinical features, although its magnitude varied from comparison to comparison. In this study, it is correct to consider such a result not as a diagnostic criterion, but a candidate spectral signature of changes in the gingival crevicular fluid protein component [11, 13–14].

As for its direction, this observation is consistent with the literature data on the Fourier transform infrared spectroscopy of the Amide III band region in adults, where β-sheet components were also described as the most stable shift associated with dental caries [11, 13–14]. However, the same direction does not mean equivalent conclusions: the adult and pediatric cohorts are different in age, clinical context, and the set of confounding factors. Therefore, it is about the preliminary cross-study consistency, not the full-fledged external replication.

Spectral shifts associated with the periodontal tissue inflammatory changes

Individuals with inflammatory gingival changes showed a tendency toward a decreased contribution of β-turns and a relative increase in disordered conformations. In the research set, the share of β-turns remained low and did not exceed approximately 10%, while the contribution of disordered conformations was within the range of about 21–24% for groups with inflammatory gingival changes. From the physicochemical point of view, such a shift can reflect changes in the protein component composition, enhanced proteolytic activity, and the increased share of the structurally less organized protein states in the local inflammatory remodeling medium [2–3, 15].

International data on the gingival crevicular fluid composition analysis by molecular identification methods support this common logic: when there is periodontal disease, samples may have different molecular profiles, and changes in cytokines, metalloproteinases, and matrix proteins turn out to be significant [2–3, 15–16]. In this study, the spectral shifts identified should be interpreted as an integral signal of the inflammatory remodeling medium, not as the characteristics of distinct target proteins or protein panels.

Comorbid medical conditions

The decrease in the contribution of α-helical components was reported in some children with comorbid medical conditions. Biologically, such a shift is possible, since the "α-helix/β-sheet structure" type ratio in protein samples was described for various diseases and stress conditions [4, 17–18]. However, considering small sample size and the combination of clinical factors, such a result should be interpreted as an observational trend, not a proven independent effect of the comorbid condition. In the context of children's gingival crevicular fluid, the Fourier transform infrared analysis should be considered as an integral molecular profiling method, not a substitute for target protein panels [4, 17–18]. The distribution of contributions of the main secondary protein structure elements is presented in Fig. 2.

DISCUSSION

The data obtained suggest that the Amide III band profile in gingival crevicular fluid should be considered primarily as integral spectral characteristics of a complex protein mixture, not a direct quantitative measure of the contents of distinct secondary structures. That is why interpretation of the results should take into account the limitations associated with the band overlap, pre-processing scheme, and the deconvolution model used [4, 8–10].

The directional increase in the contribution of β-sheet components in individuals with caries is consistent with the ones earlier reported in papers about IR spectroscopy of oral biological media, it expands these results to the pediatric cohort [11, 13–14]. Such a trend can reflect changes in the ratio of more organized to less organized protein states in the context of the local caries process. In turn, the trend towards lower contribution of β-turns and relative increase in disordered conformations associated with inflammatory gingival changes is biologically credible and consistent with modern views of the gingival crevicular fluid molecular profile rearrangement in the inflammatory remodeling medium [1–3, 15–16].

Thus, in this study, multivariate analysis and deconvolution of the spectral Amide III band had mutually reinforcing functions: PCA was used to detect the general spectral heterogeneity and select analytical groups, while deconvolution made it possible to interpret such variability through rearrangement of the Amide III band component contributions. Such alignment of two approaches increases evidentiality of the identified directional shifts, but due to pilot design does not replace their further clinical testing.

Limitations of the study

Interpretation of the detected shifts is limited by the clinical heterogeneity of observations and the fact that deconvolution results depend on the spectrum pre-processing algorithms [4, 8]. Furthermore, in the cohort of children, the gingival crevicular fluid composition is potentially affected by age, dentition stage, orthodontic load, and pubertal changes [5–7]. Features of the pre-analytical phase, including material volume and time between sampling and spectrum acquisition, could be other sources of variability. Finally, in this pilot study, comorbid medical conditions were not analyzed as an independent factor. That is why the features identified should be considered as hypothesis-generating and requiring further validation using the expanded clinically stratified material. One more limitation is that in this pilot study the dental caries status and the gingival inflammation severity were described by the exploratory clinical stratification, not the expanded index assessment, which should be taken into account when interpreting the results.

CONCLUSIONS

The analysis of the gingival crevicular fluid Amide III band in children aged 8–14 years made it possible to identify differences in the protein component IR spectral profile depending on the dental status. In the pilot cohort, caries was associated with the larger contribution of β-sheet structures, and inflammatory gingival changes were associated with the trend towards growing disordered conformations and lower contribution of β-turns. Thus, the analysis of the Amide III IR spectral band can be useful as a research approach to assessment of molecular changes in gingival crevicular fluid, but its clinical significance needs to be further confirmed.

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