Author's response to reviews

Title: Candida spp. and gingivitis in children with nephrotic syndrome or type 1 diabetes

Authors:

Dorota Olczak-Kowalczyk (do-k@o2.pl)
Beata Pyrzak (bpyrzak@wum.edu.pl)
Maria Dabkowska (m.dabkowska@wp.pl)
Malgorzata Panczyk-Tomaszewska (m.panczyk@czd.edu.pl)
Grazyna Miszkurka (g.miszkurka@czd.edu.pl)
Izabela Rogozińska (i.rogozinska@wum.edu.pl)
Ewa Swoboda-Kopec (ewa.swoboda@gmail.com)
Dariusz Gozdowski (dariusz.gozdowski@sggw.pl)
Angelika Kaminska (angelikakalinska@gmail.com)
Anna Pirog (aniapirog@gmail.com)
Malgorzata Mizerska-Wasiak (wasiaczki@wp.pl)
Maria Roszkowska-Blaim (dblaim@o2.pl)

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Author's response to reviews: see over
Thank you for the valuable reviews.

The authors were the only people involved in the study. The study is part of the Warsaw Medical University scientific programme, without any additional funding. The role of scientific writer was performed by the first author of the paper (D.O-K).

Following the editor's and reviewers' suggestions the following modifications were made:

- Additional statistical analysis was performed (however, I should like to emphasise that some confounders, such as tobacco smoking, excluded from the study - none of the study participants smoked); tables with statistical data were placed in the supplemental material section for the work to be clearer; the table from the old manuscript, presenting the added analysis of the correlation between GI, age, and sex was incorporated in the body text, and so were the crucial multiple regression and $R^2$ – coefficient of determination data (reviewer CRS),

- Full names were used in the abstract (reviewer CMF),

- The study objective section informs that it is to assess plaque related gingivitis and the conclusion states that "Poor hygiene control is the main cause of gingivitis". The authors fully agree with the reviewer. However, they attempted to determine whether and what systemic factors increased inflammation. In many systemic diseases, including obesity, the correlation between gingivitis severity and the amount of dental plaque varies when compared to healthy individuals (not only in immunodeficiencies). It would be interesting to know what systemic disorders may cause that. It is also important to determine the role of Candida spp. According to our studies (previous and current) and those of other authors, Candida spp. does not occur significantly more frequently in children with diabetes or under immunosuppressive treatment. However, it is known to cause more lesions in these two groups. It may also manifest as copathogen in gingivitis, which has an impact on treatment selection.

- Patient qualification and trial blinding were explained in the method section and the added table 1 presents the examined patients (reviewers CRS and LP).

- Fig 1 and 2 were removed (reviewer LP)

- Tables were modified (a comparison of NS and C1 was removed, among others, as it did not present any crucial information) (reviewer CRS);

- According to the authors, removing the part of the table on diabetes patients (currently tab 4, tab 3 in the old manuscript) would have a negative impact on the quality of the work.

- Comments on the correlation between GI and the assessed systemic factors were removed from the results section since, as the reviewer CMF rightly noted, they should not be presented in this section of the work.

- Since the correlation between GI and age was assessed, this notion was added to the discussion and to the references. The quotation mistake was also corrected (reviewer CMF).
on plaque-related gingivitis severity was added;

38 and 39 ((old manuscript – 37 and 38) – full names for BMI, BM/SDS GI, PLI were addend: Body mass index (BMI), BMI standard deviation score, and oral cavity (Plaque Index -PLI, Gingival Index - GI,

39 (old manuscript – 38) – direct mycological assessment, API20C AUX, and API ZYM tests was deleted

42 –(old manuscript – 41) HbA1c level was changed into glycated haemoglobin,

44 – (old manuscript – 43) NS treatment (drugs, dosage, duration)” was changed into diseases duration and treatment,

46 - (old manuscript –44) and multiple regression analysis was added,

47 - (old manuscript –46) was found was added

49 - (old manuscript –48) was correlated to was changed into was correlated with

52 – (old manuscript –50) to blood glucose and HbA1c level >8% levels in diabetes

was changed into in diabetes – to blood glucose and glycated haemoglobin >8% levels.

53 – 56 (old manuscript –50-54) - Candida spp. in the oral cavity of children with uncompensated diabetes/under multi-drug immunosuppressive treatment might intensify plaque-related gingivitis. Gingivitis severity is most probably related to lipid disorders and increases in body mass was changed into Poor hygiene control is the main cause of gingivitis. Gingivitis severity is most likely related to age, lipid disorders and increase in body mass. Candida spp., in uncompensated diabetes and in those using immunosuppressive treatment, might intensify plaque-related gingivitis.

Background

64 in children predispose was changed into predispose children

65 (old manuscript – 66) promoting was changed into that promote

66 Decreased salivary slow was changed into Reduced salivary flow

71 (old manuscript – 71) with a proteinuria exceeding the body’s compensating abilities was changed into with a proteinuria level exceeding the body’s

76-80 candidiasis symptoms prevail in defence ..... Yeast-like fungi also often prevail in non candidiasis-related oral mucosal lesions [20, 21]. ......independently of plaque
presence, such as linear gingival erythema (LGE), which manifests as gingival margin erythema, sometimes also of the related … was changed into candidiasis symptoms also occur in defence…. Yeast-like fungi also often occur in non-candidiasis related oral mucosal lesions [20, 21]. ….. independently out of plaque, such as linear gingival erythema (LGE) manifesting as gingival margin erythema. It may also sometimes develop from the related …. 

85 – (old manuscript – 85) also proved to facilitate P. gingivalis was changed into has also been shown to facilitate P. gingivalis’

88 -- (old manuscript – 87) which is reflected by the activity was changed into reflected in the activity

93 - (old manuscript – 92) the was added

95 - (old manuscript – 93) and under was changed into and with NS under

97 - - (old manuscript – 95) occurred was changed into occurs

97 -(old manuscript – 95) In the present study was changed into In the previous study

101 -(old manuscript – 99) be intensifying was changed into intensify

103 -104 -(old manuscript – 101-102) on gingivitis was changed into on plaque-related gingivitis

107-108 - -(old manuscript – 105-106) that were was added;

108 -(old manuscript – 105-106) ones was changed into (Tab.1 ); The was added.

109 -(old manuscript – 107) and; was changed into as well as:

114 --(old manuscript – 112) The was added

116 - --(old manuscript – 114) The NS and diabetes groups included patients referred to the dentists by paediatricians and those who presented themselves for a check up at a nephrology or diabetes clinic. Patients who presented themselves for the first time at the Department of Paediatric Dentistry were qualified to participate in the control group - was added

120 -(old manuscript – 115) The study was approved by the Warsaw Medical University Committee for Ethics was changed into The Warsaw Medical University Committee for Ethics approved the study.

120-128 -(old manuscript – 116) The study was prospective and included a general medical and oral examination (clinical assessment and laboratory tests) and a medical history analysis. The oral examination was performed after a general medical examination
(clinical and sampling for the scheduled laboratory tests) on the same or following day. A dentist, just prior to the clinical examination, took swabs for mycological testing. The dentists were only aware of the disease (diabetes or nephrotic syndrome) occurrence. They did not know the general medical details of the NS and diabetes patients, including the main disease course and treatment plan, as well as the occurrence of other diseases - was added.

129 - (old manuscript – 118)  **Clinical evaluation** was changed into **General medical examination**

133 - (old manuscript – 122)  *The* was added

134 - (old manuscript – 123)  administered drug with dosage was changed into information on the administered drugs with dosage

137-138 - (old manuscript – 126-127)  Twenty-four hour urinary protein excretion was measured using the Elton turbidimetric method was changed into A 24-hour urinary protein excretion was measured using turbidimetry.

148 -149 (old manuscript – 136)  The and was based on the were added; assessing plaque deposits was changed into deposits were assessed

154-155 (old manuscript – 142-143)  Gingivae score: Silness and Löe Gingival Index (GI): gingival tissues around all scored teeth, were assessed with PLI with criteria: was changed into *The* gingival score was based on the Silness and Löe Gingival Index (GI). The gingival tissues were assessed around the same teeth according to the following criteria:

Mild inflammation – slight change in colour and slight change in tissue structure; no bleeding on probing

Severe inflammation – marked redness and hypertrophy; tendency towards spontaneous bleeding; ulceration.

162 - (old manuscript – 150)  groups was deleted

169 - (old manuscript – 157)  control; the second was changed into control. The second

170-173 - (old manuscript – 159-161)  ); micro-vials 6-10 contain substrates for proteases; and micro-vials 13-20 contain substrates for glycosidases. Micro-vials were filled with 65 µL of urine and incubated for 4-4.5h at 37°C. After incubation, 1 drop was changed into ). Micro-vials 6–10 contained substrates for proteases. Finally, micro-vials 13–20 contained substrates for glycosidases. The micro-vials were filled with 65 µL of urine and incubated for 4–4.5h at 37°C. After incubation, one drop

177- (old manuscript 165)  to the reaction was changed into to a reaction
178-179 (old manuscript 166) 8 strains ….for potential identicality was changed into eight cultured strains…. for potentially identical

182 -184 (old manuscript 170-171) Relationships between selected variables were evaluated using the Kendall Tau correlation coefficient (significance level P<0.05). was changed into The t-test was used to compare means in the examined groups, and the chi-squared test was used to compare fractions. Correlations between the selected variables were assessed using the Kendall rank correlation coefficient (significance level P<0.05).

188 (old manuscript 174) ill was changed into sick

191 (old manuscript 178) Moreover, a multiple regression analysis was used to assess the simultaneous effect of many independent variables on the GI. Partial standardised regression coefficients were presented.

102- plaque related was added

106  i 107 - (Tab. 1) was added , which resulted in shifting the sentence: Inclusion criteria …. previous weeks from line 106-114 to line 108 -116

117-112 –The NS and diabetes groups included …at the Department of Paediatric Dentistry were qualified to the control group was added

123 – Oral examination was performed after … and treatment and the occurrence of other diseases was added

131– change: (old manuscript – 118): Clinical evaluation into: General medical examination

182 – change: The t-test was used to compare means in the examined groups, and the chi-squared test to compare fractions. Correlations between the selected variables were assessed using the Kendall rank correlation coefficient (significance level P<0.05) (old manuscript line 170: Relationships between selected variables were evaluated using the Kendall Tau correlation coefficient (significance level P<0.05). Statistical analysis was performed using the Statistica 10.0 software

192- (old manuscript – 178) Moreover, multiple regression analysis was used to assess the simultaneous effect of many independent variables on the GI. Partial standardized regression coefficients were presented was added
196 (old manuscript – 181-183) Subject age ranged from 3 to 18 years for patients with NS (mean 10.05±4.8 years); from 6 to 17.9 for patients with diabetes (mean 13.24±2.64 years); and from 3 to 17.1 years for healthy controls (mean 11.52±4.01 years) – deleted

201- In the NS group, disease duration oscillated between 0.5 and 15.67 years (mean duration: 5.06±4.95 years) was added (196 old manuscript – the sentence: Mean duration of disease was 5.06±4.95 years was deleted
204 and 205 (old manuscript – 191) 7 and 4 were changed into seven and four
210-211 (old manuscript – 198) decreased serum total protein levels in 10 patients was changed into decreased serum total protein levels in 10 patients
215 (old manuscript – 202) duration of disease was changed into the duration of the disease
216 (old manuscript – 203) with diabetes was added
219 (old manuscript – 206) and in four patients (11.4%), it was lower than 7% was added

220 – the number of the table was changed into 2 (line 207 old manuscript - tab 1)
225 (old manuscript – 211) of patients from the control group (41.37% subjects), and less often in that of patients’ with NS (34.37%, all under immunosuppressive treatment), and in that of patients was changed into of the controls (41.37% subjects), and less often in patients with NS (34.37%, all under immunosuppressive treatment) and those

228 i 232 - the number of the table was changed into 3 (line 214 i 218 old manuscript – tab 2)
230-231 (old manuscript – 217-218) A considerably more frequently higher E16 activity was discovered only by comparing the NS group with the control group was changed into A considerably higher level of E16 activity was discovered only when comparing the NS group to the control group
239 (old manuscript – 226) those from the control group was changed into controls
239-240 (old manuscript – 226 and 227) A statistically significant difference occurred only between D1 and C (Tab. 3). was changed into There existed a statistically significant difference only between D1 and C (Tab. 4).
241 (old manuscript – 228) a was added (in a single)
243 (old manuscript – 230) Both patients with diabetes and with NS was changed into Patients with both diabetes and NS
240 i 244- the number of the table was changed into 4 (lines 227 and 232 old manuscript – tab3)
247 (old manuscript – 237) control groups was changed into controls
247 (old manuscript – 237-238 ) the activity of yeast enzymes was changed into yeast enzyme activity
248 (old manuscript – 238) the sole occurrence of yeasts was changed into the occurrence of only yeasts
248 and 258- the number of the table was changed into 5 (lines 239 and 254 old manuscript – tab 4)
248 (old manuscript lines 239) However was deleted
253 (old manuscript lines 242-245) the fragment However, the correlation with the lipid profile remains doubtful, because there existed a positive correlation with a higher blood cholesterol level (mg/dL) only in the assessment of the NS and control groups combined together was deleted. Additionally was added
255 - change: were also correlated with the GI (old manuscript 247 -248 proved to be crucial in patients with nephrotic syndrome) and deleted: Proteinuria, hypoalbuminemia, hypoproteinaemia, decreased haemoglobin level, elevated hematocrit, elevated white cell count, and elevated triglyceride level had no impact on gingiva condition in the NS group (old manuscript 247-250)
256 (old manuscript 251) and was changed into as well as
258 (old manuscript 253-254) for HbA1c <7%, which indicates gingivitis is less severe when diabetes is compensated, together with a positive coefficient for HbA1c>8% (Tab. 4) was changed into for HbA1c <7%, and positive for HbA1c>8%
259-263– The results of multiple regression only confirmed the correlation between GI, immunosuppressive treatment and blood cholesterol levels in NS. The coefficient of determination ($R^2$) was between 0.309 - 0.662 (in NS group: 0.662, in NS and controls: 0.468, in D1 group: 0.520, in D1and controls: 0.309) was added (old manuscript - 255)
264 before Since the analysis (old manuscript line 256) - deleted There was no correlation between GI and BMI and BMI SDS in patients with diabetes.
265 (old manuscript line 258) between gingivitis was changed into between the GI
266 (old manuscript line 259) the analysis was changed into The analysis

Discussion
as in patients who are organ recipients under immunosuppressive treatment, cancer patients under cytotoxic treatment, as in organ recipients receiving immunosuppressive treatment, cancer patients receiving cytotoxic treatment.

had a more severe course than in generally healthy children. had a more severe course compared to the generally healthy children

276 -285 (old manuscript line 272 – before Gingivae in children with) Dental plaque was the main cause behind gingivitis. The present study confirmed a correlation between GI, PLI, and child and adolescent age. Romero et al. also established that GI increased with child age, even though PLI decreased [39]. The present study, assessing the impact of the respective factors, including the occurrence if Candida spp. in the oral cavity, and the systemic disorders in diabetes and NS, points to factors related to the general disease and its treatment that may intensify gingivitis. The assessment of the simultaneous impact of factors (multiple regression) was not statistically significant for most of them. It was caused of their mutual correlations. However, the coefficients of determination ($R^2$) indicated a significant impact of the assessed factors on GI (Tab. 5).

nephrotic syndrome had not been assessed until now; with NS has not been previously assessed and, the

indicated there existed a correlation indicated a correlation

came to the same conclusions in diabetes, independently of the way periodontal disease was defined [12, 39-41]. concluded the same in diabetes, independent of the definition of periodontal disease [12, 40–42].

did

that

and basing their assessment on the with the results based on the
than the group ……. [41] was changed into than did the group…… [42].

in adults [40, 41]. was changed into by others authors that used adults in their studies [12, 44,45].

however, they were evident only . was changed into . However, it was only evident

, for the control, and above all, for the nephrotic syndrome group. was changed into and in controls and NS.

[45]. was changed into [46].

[46]. was changed into [47].

glucose level was well-managed. was changed into glucose level was well-managed.

increase was changed into increased

There are many factors was changed into There exist many factors

and under immunosuppressive treatment was changed into and in those receiving immunosuppressive treatment

than of generally healthy ones, but they caused more often candidiasis. No difference was found was changed into compared to the generally healthy participants, but Candida spp. more often led to candidiasis. There was no difference

that of generally healthy control subjects, was changed into that of the controls.

[47]. was changed into [48].

Interestingly, the present study noted a correlation between gingivitis and local was changed into It is also interesting to note that the present study established a correlation between gingivitis and the local

In the Kurnatowska was changed into In Kurnatowska

[48]. was changed into [49].
Conclusions

346 – 349 (old manuscript lines 332-335) added: The main cause of gingivitis is poor oral hygiene. The order of the next two sentences was changed. There most probably was changed into. There most likely.

352 and 353- changed into: came up with the study idea (old manuscript line 339- conceived of the study), took part in sequence alignment (old manuscript line 339- participated in the sequence alignment and),

354, 356, 358, 369, 362, 364, 367, 369, 371,373 changed into - took part in the drafting of the manuscript (old manuscript lines - 341, 343, 345, 347, 349, 351, 355, 358 : participated in the sequence alignment

366 (old manuscript lines 353-354) participated in the sequence alignment, participated in the design of the study and was changed into took part in sequence alignment and study design and performed the statistical analysis

References


501 – added: Taylor G. Bi-directional interrelationships….. - nr 43 (old manuscript line 486, nr 44), which resulted in changes:

Wood N, Johnson RB, Streckfus CF: Comparison….. line 488, nr 44 (old manuscript line 492, nr 42)

Saito T, Shimazaki Y, Kiyohara Y, Kato I, Kubo M,….. line 491, nr 45 (old manuscript line 495, nr 43)

Mérouani A, Lévy E, Mongeau JG, Robitaille line 494, nr 46 (old manuscript line 500, nr 45)

Mahmud S, Jahan S, Hossain MM: Hyperlipidemia.. line 497, nr 47 (old manuscript line 503, nr 46)

Plomer-Niezgoda E, Hrynczewicz-Gwóźdź A, Maj J, Baran.. line 500, nr 48 (old manuscript line 507, nr 47)
Fig. 1. Moderate gingivitis in a girl aged 15.0 years with NS and proteinuria, treated with three immunosuppressants (Corticosteroid, Cyclosporine A, and Mycophenolate mofetil), E16 and E18 activity in oral cavity.

Fig. 2. Moderate gingivitis in a girl aged 13.6 years with type 1 diabetes with HbA1c >8%, without Candida spp. in oral cavity.

List of abbreviations: lines 58 -531 (old manuscript lines 529-552)

Competing interests: lines 533 -535 (old manuscript lines 562-564)

539 – Table 1 added.
Change in tables numbers - lines : 542 – Table 2 (old manuscript line 565 – table 1), 549 – Table 3 (old manuscript line 570 – Table 2 ), 556 – Table 4 (old manuscript line 580 – Table 3), 667 – Table 5 (old manuscript line 607 – Table 4)

Tab 2. - the last row was deleted
Tab 4 – rows SN vs D1 were deleted in the column P-value
Tab 5 – change in the table content: added rows: age and sex
To whom it may concern,

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Author(s): Dorota Olczak-Kowalczuk, Beata Pyrza, Maria Dąbrowska, Małgorzata Palińska-Tomaszewska, Grażyna Miszurkowa, Iwona Rogozińska, Ewa Swoboda-Kopeć, Dariusz Gozdowski, Angelika Kalisz, Anne Piring, Małgorzata Mizerowska-Wasiew, Maria Roszkowska-Blaim

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