Combined effect of pancreatic lipid content and gene variants (TCF7L2, WFS1 and 11BHSD1) on B-cell function in Middle Aged Women in a Post Hoc Analysis

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Abstract

Background: TCF7L2 rs7903146 and PNPLA3 rs738409 gene variants confer the strongest risk for type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD), respectively. Pancreatic triacylglycerol content (PTGC) was reported to have a role in T2DM development. We aimed to assess the correlation between PTGC and hepatic triacylglycerol content (HTGC) stratified by PNPLA3 rs738409 genotype and subsequently interactions between PTGC and gene variants associated with β-cell dysfunction (TCF7L2, WFS1) and visceral adiposity (11BHSD1) on β-cell function were also tested.

Methods: PTGC and HTGC were assessed using MR in a post-hoc analysis of a genotype-based (PNPLA3 rs738409) recall study of 39 (lipid- and glucose lowering) drug-naïve women. Oral glucose tolerance test, HbA1c, insulin indices, anthropometric data were evaluated. The effect of minor allele carrying of TCF7L2 (rs7903146); WFS1 (rs1801214) and 11BHSD1 (rs4844880) variants in combination with PTGC was studied on surrogate markers of β-cell function. We used Spearman's rank-order, Mann-Whitney-U tests, and linear regression models.

Results: PTGC and HTGC values were correlated after stratification by the rs738409 variant (only in CC genotype group R² = 0.67, p = 10^-4). PTGC and HbA1c values correlated in the entire study population (R² = 0.58, p = 10^-4). Insulin resistance, sensitivity and disposition indices were correlated with PTGC (HOMA2-IR: R² = 0.42, p = 0.008; TyG: R² = 0.38, p = 0.018; Matsuda: R² = 0.48, p = 0.002; DIbasal: R² = 0.33, p = 0.039; ISSI-2: R² = 0.35, p = 0.028). Surrogate markers of β-cell function (HOMA2-B, AUC_insulin/AUC_glucose) correlated significantly with PTGC in subjects with the following genotypes rs7903146: CC R² = 0.51, p = 0.022; rs18001214: CT + CC R² = 0.55, p = 0.013; rs4844880: TA + AA R² = 0.56, p = 0.016. The strongest interactions were found between PTGC and TCF7L2 rs7903146 effect on HOMA2-B (p = 0.001) and AUC_insulin/AUC_glucose (p = 0.013).

Conclusions: The PNPLA3 rs738409 genotype has a major effect on the correlation between PTGC and HTGC. Furthermore we first report the combined effect of PTGC and individual risk gene variants of TCF7L2, WFS1 and 11BHSD1

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1. Introduction

Fatty pancreas was first reported by Ogilvie in 1933 in patients with obesity including a few individuals with type 2 diabetes mellitus (T2DM) [1].

Despite the global burden of obesity and related diseases including T2DM and non-alcoholic fatty liver disease (NAFLD) the role of fatty pancreas regained interest in the study of the development of metabolic diseases recently [2, 3]. There is an increasing number of supporting data that the accumulation of pancreatic fat has a role in the development of T2DM and related metabolic disorders [4]. Moderate evidence suggests that the reduction in pancreatic fat improves the metabolic condition, including the improvement of beta cell function and even potential reversal of T2DM after bariatric surgery [4, 5].

In contrast to NAFLD that is characterized with an internationally accepted cut-off value of 5.5% liver lipid content determined by magnetic resonance (MR) based methods [6, 7], currently there is a lack of both clinically meaningful standardized examination methods and internationally or even nationally accepted normal reference range and cut-off value of the intrapancreatic lipid content and pancreatic steatosis, respectively. There is a remarkable variability (3.6–10%) in reported pancreatic lipid contents of control groups in different studies [5, 8–17]. Therefore, there are neither diagnostic recommendations, nor treatment guidelines of pancreatic steatosis despite that there is accumulating evidence that it might have a significant role in the development of T2DM.

A few studies raised that the association between liver and pancreatic fat content could be confounded by major factors [9, 10] therefore we aimed to assess this association stratified by PNPLA3 rs738409 (missense variant), a major genetic risk factor for NAFLD development.

Pancreatic lipid accumulation is associated with beta-cell dysfunction [12, 16], particularly in patients with increased susceptibility to impaired beta-cell function due to the presence of T2DM risk gene variants [18]. It is likely that the islet pathology and subsequent metabolic consequences also depend on the infiltrating (pre)adipocyte induced pro-inflammatory changes [19].

To the best of our knowledge there is no available public report on the effect of individual T2DM risk gene variants in combination with pancreatic fat on beta-cell function. We selected TCF7L2 rs7903146 (intron variant) as the strongest T2DM associated genetic risk factor to date that is also associated with higher fasting and post-challenge glucose levels in Caucasians and another beta-cell dysfunction associated T2DM risk variant (WFS1 rs1801214, missense) and also 11BHSID1 rs4844880 as a reported visceral obesity associated intron variant for further analysis from a prior gestational diabetes mellitus (GDM)-genetic study [20–29].

2. Methods

2.1 Study population

This study was focused on the pancreatic lipid accumulation and was conducted complementary to a recently completed post-GDM genetic based recall study on metabolic (dysfunction) associated fatty liver disease (MAFLD) [30]. Thirty-nine Hungarian women prone to T2DM were enrolled based on the PNPLA3 rs738409 genotype (only homozygotes included) to the study focused primarily on the liver lipid accumulation and all of them underwent a detailed metabolic phenotyping between 2016 and 2020.

None of the participants were previously diagnosed with type 2 diabetes mellitus or treated with a glucose or a lipid lowering medication at the enrolment.

2.2 Exclusion criteria

MR incompatible metal implants and a maximum body weight of 200 kg, waist/hip circumference <135 cm/148 cm, drug treatment with known impact on the glycaemic traits, significant alcohol consumption (>20 g/day), and presence of a malignant disease were considered as exclusion criteria. In addition, patients with other major chronic/acute diseases, ongoing pregnancy/breastfeeding or with contraindication for OGTT were also excluded.

2.3 Genotyping

The genotypes of the gene variants: PNPLA3 rs738409; TCF7L2 rs7903146; WFS1 rs1801214; 11BHSID1 rs4844880 were extracted for this analysis from larger genotype database established during a preceding study [29]. These gene variants were selected based on their previously reported associations with relevant traits rs738409: NAFLD development; rs7903146, rs1801214: T2DM development, beta-cell dysfunction; and rs4844880: visceral obesity. All the gene variants assessed occurred with a minor allele frequency (MAF) of at least 0.20 in the Hungarian population [29].
2.4 Clinical data
Anthropometric data (weight [kg], height [m], waist/hip circumferences [cm], BMI, waist/hip ratio [W/H]), age, medical history (including GDM) were recorded. Based on the result of 75 g OGTT and/or HemoglobinA1c (HbA1c) the diagnosis of diabetes mellitus (DM) or prediabetes (IFG/IGT) was established according to the WHO, 2016 ADA and the Hungarian guidelines [31–33]. MAFLD was diagnosed based on the recently proposed criteria [30, 34].

2.5 75 g OGTT, metabolic phenotyping and measurement of β-cell function
Seventy-five gramm OGTT (0′-30′-120′) was performed after an overnight fasting period of at least 10 h. Plasma glucose (PG), HbA1c, and other routine laboratory parameters were determined according to standard protocols and the International Federation of Clinical Chemistry (IFCC) standards. Serum insulin levels were measured using Liaison analyser (DiaSorin, Saluggia, Italy). HOMA2-IR, Triglyceride-Glucose index (TyG) as surrogate measures of insulin resistance and HOMA2-B values as marker of β-cell function were calculated [35]. TyG index was calculated as: TyG = ln[38.67×Tg(mg/dl)/18×glucose(mg/dl)/2] [36–38]. In order to assess the future T2DM development risk we used the following markers: Disposition Index basal (DIbasal: HOMA2-B x 1/HOMA2-IR) [39, 40], Insulin Secretion and Sensitivity Index-2 (ISSI-2: using the formula: AUC_{Insulin}/AUC_{Glucose} x Matsuda) [41].

2.6 Determination of intrapancreatic and intrahepatic lipid content
Hepatic and pancreatic triglyceride contents (HTGC and PTGC, respectively) were determined as follows: All MR imaging (MRI) sessions were acquired on a clinical 3T MRI system (Prisma, Siemens Healthineers, Erlangen, Germany) with the subject in a supine position. For MRI protocol, standard body-array 18 channel flexible coils were positioned on the liver and pancreatic region and combined with the spine array coil located below the subject. Imaging proton density fat-fraction (PDFF), unenhanced axial images were obtained by using a low-flip-angle, six-echo two-dimensional spoiled gradient-recalled-echo sequence with all array coil elements (TE = 2.4, 1.6, 2.8, 2.10.2 and 12.3 ms). The repetition time and flip angle were chosen to avoid T1 weighting: TR: 15 ms; Flip-angle: 11°; FOV = 240 × 400 mm in plane; matrix = 240 × 130; slice thickness = 3.5 mm, space between slices 4.3 mm. Phase and magnitude images were systematically saved.

MR imaging: Multi-section PDFF maps were generated offline from the source images via joint estimation of water and fat images and field maps using custom made MATLAB routines [29]. The method used complex signal model similar to advanced multipoint DIXON/IDEAL algorithms (incorporating multiprobe/multifrequency fat model and T2* decay) analysing six-echo FLASH complex images. Voxels representing pancreas tissue were delineated with a freehand ROI defining tool by an expert radiologist on multi-section PDFF maps excluding ill-defined edges (due to macroscopic fatty infiltration e.g.), vessels, the pancreatic duct, and artifacts. In each subject the mean value of the selected voxels was calculated and this value represented the average pancreatic fat fraction.

2.7 Statistical analysis
Data distributions and comparisons between two or more cohorts were assessed using the Shapiro-Wilk’s, Mann-Whitney-U and Kruskal-Wallis tests, respectively. Spearman’s rank-correlation was also used. Linear regression model was employed for interaction analysis. Genotype based subgroups of T2DM associated genes were assessed using the dominant model for the minor allele. Case data were deleted in the given analysis when data were missing. Benjamini-Hochberg p-value correction was used to control false discovery rate in multiple testing. “R” (version 4.0.4, R Foundation for Statistical Computing, Vienna, Austria, 2021) and TIBCO Statistica (version 13.4.0.14, TIBCO Software Inc.) softwares were used.

Genotype distributions were non-deviant from the Hardy-Weinberg equilibrium (HWE) in the original study [29], and HWE was not assessed in this analysis.

3. Results
3.1 Study population characteristic
Clinical characteristics of the study population are presented in Table 1. Continuous data are presented as medians and 25–75th percentiles due to that most of the variables were non-normally distributed and due to the low sample size. None of the participants had pancreatitis in their personal medical history. All patients were naïve for antidiabetic and lipid lowering drug therapy.

3.2 PTGC vs. BMI, age
A significant correlation was observed between PTGC and BMI (R = 0.40, p = 0.012), in contrast to that of between PTGC and age (R = 0.12, p = 0.440). Waist circumference also correlated with PTGC (R = 0.50, p = 0.002).
3.3 PTGC vs. HTGC and its stratification by PNPLA3 rs738409 genotype

We found a significant correlation between HTGC and PTGC values in the entire study population ($R = 0.46 \ p = 0.004$), and in the PNPLA3 rs738409 CC genotype group after stratification by the genotype ($R = 0.67 \ p = 10^{-6}$) but not in the GG group ($R = -0.08 \ p = 0.80$) (Fig. 1).

3.4 IPCL vs. HbA1c, OGTT derived markers of insulin resistance and disposition indices

PTGC and HbA1c values were highly correlated ($R = 0.58 \ p = 10^{-4}$, Fig. 2A). No significant correlations were found between HbA1c and HTGC levels, BMI or waist circumference.

| Table 1  | Population characteristic |
|----------|----------------------------|
| Age (years) | 37.0 (34.0–40.0) |
| BMI (kg/m²)  | 26.2 (22.8–32.4) |
| Overweight + obesity | 24 (61.5%) |
| GDM history  | 22 (56.4%) |
| HbA1c % (mmol/mol) | 5.5[37] (5.2[33]-5.6[38]) |
| Prediabetes* + T2DM | 14 (35.9%) |
| PTGC (%) | 8.2 (5.4–10.2) |
| HTGC (%)  | 3.9 (2.8–8.4) |
| MAFLD  | 14 (35.9%) |

**Fig. 1** Correlation between PTGC and HTGC values stratified by PNPLA3 rs738409 genotype. Abbreviations: PTGC: pancreatic triacylglycerol content, HTGC: hepatic triacylglycerol content

**Fig. 2** Correlations among PTGC and HbA1c and disposition indices. A Between PTGC and HbA1c values, B PTGC and DIBasal, C PTGC and ISSI-2. Abbreviations: PTGC: pancreatic triacylglycerol content, DIBasal: disposition index basal, ISSI-2: insulin secretion sensitivity index − 2

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GDM gestational diabetes mellitus, T2DM type 2 diabetes mellitus, PTGC pancreatic triacylglycerol content, HTGC hepatic triacylglycerol content, MAFLD metabolic (dysfunction) associated fatty liver disease

* Diagnosed by using HbA1c and/or glucose values from OGTT (IFG, IGT)
Negative correlations were observed between PTGC and disposition indices: DI basal value \( (R = -0.33, p = 0.039) \) derived from fasting steady state insulin and glucose values (Fig. 2B) and ISSI-2 value \( (R = -0.35, p = 0.028) \) derived from OGTT (Fig. 2C).

PTGC values were also correlated with surrogate markers of insulin resistance \( (\text{HOMA2-IR}: R = 0.42, p = 0.008, \text{TyG}: R = 0.38, p = 0.018, \text{Fig. 3 A, B, respectively}) \), and inversely with the “whole body” sensitivity index \( (\text{Matsuda index}: R = -0.48, p = 0.002; \text{indicated on Fig. 3C}) \).

In addition, there was a correlation between PTGC and serum triglyceride levels with borderline significance \( (R = 0.34, p = 0.035) \). In contrast no correlations were found between PTGC and total cholesterol levels or its fractions (HDL, LDL).

3.5 Effect of intrapancreatic lipid content in combination with risk gene variants on surrogate markers of insulin secretion

Although we could not detect any correlation between the pancreatic fat content and surrogate markers of β-cell function \( (\text{HOMA2-B, AUC}_{\text{insulin}}/\text{AUC}_{\text{glucose}}) \) in the entire study population a specific pattern of correlations was identified when the results were stratified by the genotypes (Table 2; Fig. 4 A, B, and C). Subsequently we performed an interaction analysis between pancreatic lipid values and T2DM / visceral obesity risk genotypes on β-cell function indices. We found significant interactions between the PTGC and variants of \textit{TCF7L2} and \textit{11BHSD1} (Table 2). Higher PTGC values were found in patients carrying the risk \( (T) \) allele of the \textit{TCF7L2} variant \( (\text{rs7903146 dominant model p} = 0.050) \), and subjects with the “TT” genotype tended to have the highest values \( (\text{additive model: Kruskal-Wallis p} = 0.089) \) without any difference in BMI values.

In case of the \textit{TCF7L2} gene variant we observed a statistically significant correlation and interaction indicating that the β-cell function is increased in parallel with the increasing PTGC in patients without the risk allele indicating a preserved β-cell compensatory mechanism for the increased insulin resistance. The other studied gene variants \( (\textit{WFS-1}, \textit{11BHSD1}) \) also displayed correlation patterns referring to a loss of β-cell compensatory mechanism in patients homozygous for the risk alleles.

4. Discussion

In this study we recalled middle aged female participants from a prior GDM genetic association study [29]. All participants underwent detailed clinical phenotyping and MRI assessment of liver and whole pancreatic proton density fat fractions. A significant correlation was found between HTGC and PTGC values in the entire study population, notably in participants with the \textit{PNPLA3}
rs738409 CC genotype. We first report a strong correlation between the pancreatic lipid content and the HbA1c values in antidiabetic drug naïve individuals who are prone to type 2 diabetes mellitus development. We also observed significant correlations between PTGC and BMI, waist circumference, surrogate markers of insulin resistance (HOMA2-IR, TyG) and indices indicative for future T2DM development (Diabetes mellitus and metabolic syndrome: Homeostasis Model Assessment 2-B, AUC Area Under the Curve). We first report a strong correlation between PTGC and anthropometric data

| Indices of β-cell function | Gene       | Variant ID | Genotypea (n) | Correlation | Interaction analysisb |
|---------------------------|------------|------------|----------------|--------------|-----------------------|
|                           |            |            |                |              |                       |
| HOMA2-B                   | TCF7L2     | rs7903146  | CC (20)        | 0.51         | 0.022/0.044 0.664     |
|                           |            |            | CT + TT (18)   | -0.32        | 0.20/0.20 0.263      |
|                           | WFS1       | rs1801214  | TT* (18)       | 0.09         | 0.71/0.71 0.065      |
|                           |            |            | CT* + CC (20)  | 0.55         | 0.013/0.044 0.745    |
|                           | 11BHS1D1   | rs4844880  | TT (20)        | -0.05        | 0.82/0.82 0.055      |
|                           |            |            | TA + AA (18)   | 0.56         | 0.016/0.044 0.714    |
| AUCinsulin/AUCglucose     | TCF7L2     | rs7903146  | CC (20)        | 0.39         | 0.087/0.17 0.415     |
|                           |            |            | CT + TT (18)   | -0.21        | 0.40/0.60 0.136      |
|                           | WFS1       | rs1801214  | TT* (18)       | 0.13         | 0.61/0.73 0.082      |
|                           |            |            | CT* + CC (20)  | 0.51         | 0.021/0.13 0.664     |
|                           | 11BHS1D1   | rs4844880  | TT (20)        | -0.04        | 0.87/0.87 0.053      |
|                           |            |            | TA + AA (18)   | 0.47         | 0.048/0.14 0.530     |

PTGC Pancreatic Triacylglycerol Content, T2DM type 2 diabetes mellitus, HOMA2-B Homeostasis Model Assessment 2-B, AUC Area Under the Curve

a Major allele homozygous vs. minor allele carriers;
b Linear regression model. Outcome: insulin secretion marker, genotype in a dominant model (for minor allele) as a categorical and PTGC as a continuous variable. Interaction: categorical x continuous variable;

Only C and T alleles detected in the Hungarian-Austrian cohort; multiallelic in GRCh38 assembly using the Ensembl browser “1000 Genomes” database [55].

A prior study already reported a step-wise consecutive increase in PTGC in subjects with normal glucose tolerance (NGT) vs. prediabetes vs. T2DM in an European population with over 350 participants [17]. Smaller studies reported similar findings [9, 16, 42]. Furthermore, bariatric surgery studies indicated that the loss of pancreatic fat is significantly associated with the reversal of T2DM [5, 8]. More specifically, the presurgery PTGC was increased in patients with T2DM and the PTGC reduced to similar levels that was observed in the NGT group and this was associated with the improvement in the first phase insulin response 8 weeks after surgery [5]. There were inconsistent reports on the associations between PTGC and HbA1c, due to that two prior studies [8, 9] reported associations, but another study [42] with higher sample size did not observe any correlation. The inconsistency in prior reports may be related to the potential glucose and lipid lowering drug use, in contrast to our study where only drug-naïve participants were enrolled. This study design enabled us to assess the natural disease course of type 2 diabetes mellitus (NGT-prediabetes-T2DM) in early stages in a diabetes prone population due to the enriched presence of participants with prior GDM. The clinical relevance is that HbA1c is a well-known, stable blood based marker used in diabetes care
for monitoring and also to establish the diagnosis of both prediabetes and diabetes [43]. Disposition indices (DLbasal and ISSI-2) that are known predictors of future T2DM development [44–46] were also correlated with PTGC. Although all three correlations were statistically significant, the correlation between PTGC and HbA1c was stronger compared to that of with the disposition indices. This may be related to that HbA1c is indicative for the mean glucose value in the prior 2–3 months, in contrast to disposition indices that are calculated from the glucose and insulin levels characterized with a lower reproducibility during OGTT [46, 47].

The current understanding of T2DM development is that increased insulin resistance is a key pathologic step in early stages when the β-cell dysfunction is not yet preponderant and the insulin overproduction can still cope with the higher demand. Subsequently the β-cell dysfunction turns into the major drive of the disease progression and as a consequence the glycaemic control is lost [48].

The observed associations between the higher BMI, HOMA2-IR, TyG values and higher pancreatic lipid content indicated a higher insulin need and the related compensatory increase in β-cell function in these individuals. A recent multi-organ and multi-trait GWAS reported associations between a few gene variants and pancreatic fat content derived from abdominal MRI scans [49]. We could assess the effect of other gene variants (TCF7L2 rs7903146, WFS1 rs1801214 and 11ΒHSD1 rs4844880) that were available from our prior study [29] and including core gene variants associated with T2DM, β-cell dysfunction and visceral adiposity [20–26, 28].

Although the general concept of the combined effect of T2DM genetic risk factors and pancreatic lipid content on insulin secretion was successfully proposed [18] to our best knowledge no direct interaction between TCF7L2 rs7903146 risk variant and pancreatic fat content was described earlier. Our results first indicate that the β-cell function (HOMA2-B) increase observed in the TCF7L2 rs7903146 “CC” homozygotes as part of an adequate adaptation process becomes disrupted in “T” risk allele carriers and this difference develops to be higher along with the increase of PTGC early during the course of T2DM development.

Pancreatic fat accumulation could be an auxiliary factor for the genetic susceptibility linked to the rs7903146 variant which until date shows the strongest association with T2DM across different populations [20]. The TCF7L2 gene encodes a transcription factor in the WNT signalling pathway and it is involved in vital functions in the pancreatic islets: pancreas development, β cell mass maintenance, secretory functions of matured β-cells, regulation of insulin production and processing [21, 22]. It was reported that the rs7903146
“T” (risk) allele carriers had an elevated TCF7L2 mRNA expression in the human pancreatic islets [21].

One explanation could be that the excess pancreatic lipid deposition is occuring in parallel with the intra-islet fat accumulation and this may alter the islet cells’ microenvironment by increasing the exposure of β-cells to free fatty acids and proinflammatory cytokines resulting in a direct pathological effect. The combined effect of WFS1 gene variant and PTGC on HOMA2-B may potentially be explained by a similar pathology on β cell survival [26].

This mechanism might be particularly relevant when the β-cells are prone to dysfunction due to the genetic susceptibility [50]. The effect of the I1BHSDS1 gene variant on β-cells is less well characterized, however it is one of the “disallowed” genes in β-cells and the variant’s effect on the function and maintenance cannot be excluded [51].

Based on the result with borderline statistical significance, it may also be raised that the rs7903146, the strongest confirmed T2DM risk gene variant [20, 52] might have a direct effect on the pancreatic lipid content, however, our results are not yet fully conclusive, and should be replicated in studies with larger sample sizes. Nevertheless, it was already reported that the TCF7L2 rs7903146 risk (“T”) allele had a negative effect on BMI, total body fat and visceral fat reductions after lifestyle intervention in a human trial and this result is consistent with baseline observations made in a heterozygous TCF7L2 knock out animal model (Tcf7l2−/−) [53, 54].

The limitations of our findings include the post-hoc nature of our study, the limited sample size and also that the diet, physical activity, family history, and hormonal fluctuations were not considered.

Abbreviations
T2DM: Type 2 diabetes mellitus; NAFLD: Non-alcoholic fatty liver disease; MR: Magnetic resonance; GDM: Gestational diabetes mellitus; BMI: Body Mass Index; MAF: Minor allele frequency; W/H: Waist to Hip ratio; OGTT: Oral glucose tolerance test; HbA1c: Hemoglobin A1c; DM: Diabetes mellitus; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; WHO: World Health Organisation; ADA: American Diabetes Association; NAFLD: Metabolic (disfunction) associated fatty liver disease; PG: Plasma glucose; IFCC: International Federation of Clinical Chemistry; HOMA: Homeostasis Model Assessment; TyG: Tyglyceride-Glucose Index; Di: Disposition Index; IS2: Insulin Secretion and Sensitivity Index – 2; AUC: Area Under the Curve; HTGC: Hepatic triacylglycerol content; PTGC: Pancreatic triacylglycerol content; MR: MR imaging; PDF: Proton density fat fraction; HWE: Hardy-Weinberg equilibrium; NGT: Normal glucose tolerance.

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Authors contributions
Conceptualization, GF; Formal analysis, ÁN and GF; Funding acquisition GF; Investigation, ÁN, VG, and GF; Patient recruitment, AN, AS and GF; Project administration, AS and GF; Resources, PI, TM, Supervision, AS and GF; Validation, GF; Writing—original draft, ÁN, VG and GF; Writing—review and editing, AP, PI and AS. All the authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
The study was approved by the relevant institutional bodies (Semmelweis University, Regional and Institutional Committee of Science; the Medical Research Council Scientific and Research Committee of Hungary) and conducted according to the Declaration of Helsinki. Participants had previously given informed consent for the whole project [20].

Consent for publication
All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Competing interests
The authors declare that they have no competing interests.

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