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# Maintaining the gluten-free diet: The key to improve glycemic metrics in youths with type 1 diabetes and celiac disease

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ABSTRACT

*Aims:* Gluten-free diets (GFD) were considered as high glycemic index and/or high content of saturated fats; this could affect keeping good metabolic control in individuals with both type 1 diabetes (T1D) and celiac disease (CD). Our objective was to analyze time in range and other continuous glucose monitoring (CGM) metrics with real-time CGM systems, in youths with T1D and CD, compared to those with T1D only.
*Methods:* An observational case-control study, comparing youths aged 8–18 years with T1D and CD, with people with T1D only was performed. The degree of maintaining GFD was assessed through anti-tissue transglutaminase antibodies and dietary interview, and maintaining Mediterranean diet through the KIDMED questionnaire.
*Results:* 86 youths with T1D and CD, 167 controls with T1D only, were included in the study and the two groups reported similar real-time CGM metrics. Among the first group, 29 % were not completely maintaining GFD and compared to people with T1D only they showed higher hyperglycemia rates (% time above range: 38.72 ± 20.94 vs 34.34 ± 20.94; P = 0.039).
*Conclusions:* Individuals with T1D and CD who maintain GFD presented similar glucose metrics compared to youths with T1D only. Individuals not strictly maintaining GFD presented higher hyperglycemia rates.

## 1. Introduction

In youths with type 1 diabetes (T1D), the diagnosis of celiac disease (CD) involves the initiation of a gluten-free diet (GFD) and a lifelong, burdensome change. Maintaining GFD represents the only possible therapy for individuals with CD and, at the same time, a challenging task for individuals with T1D and CD. GFD added to a dietary regimen in youths with T1D might impose practical limitations and lead to considerable restrictions in lifestyle, especially in youths. As a matter of the fact, only 60 % of individuals with T1D and CD could be considered

*Abbreviations:* T1D, type 1 diabetes; CD, celiac disease; GFD, gluten free diet; CGM, continuous glucose monitoring; tTG, Anti-transglutaminase level; ULN, upper limit of normal; EMA, IgA endomysial antibody; MDI, multiple daily injections; IP, insulin pump; SAP, sensor augmented pump; HCL, hybrid closed loop; AHCL, advanced hybrid closed loop; BMI, body mass index; TIR, Time in range; TBR, Time below range; TAR, Time above range; CV, Coefficient of variation; GRI, Glycemia Risk Index; GMI, Glucose management indicator.

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adequately compliant with a strict GFD compared to a compliance rate of about 78 % of youths with CD only [1,2]. Assessment of GFD maintaining could be challenging, as the transglutaminase antibodies (tTG) titer is not enough sensitive to detect infrequent transgression of GFD [3]. Child-adapted questionnaires could be a valid screening tool [4] and, due to the absence of a gold standard to assess diet maintaining, dietary evaluation by a trained dietitian is nowadays considered the method of choice, requiring a close relationship between the examiner and the youth [4,5].

Instituting and maintaining GFD could be a significant hurdle for individuals with T1D and CD, indeed many gluten-free foods have a high glycemic index [6] and this may have an impact on glycemic measures, insulin requirement, lipid profiles, and even the incidence of chronic diabetic complications [7]. However, in a recent systematic review, we reported that youth with T1D and CD who maintain GFD, compared to those with T1D only, show no significant differences in growth parameters, glucose control (HbA1c), number of episodes of hypoglycemia, total daily insulin doses and quality of life (QoL) [8]. Similarly, studies assessing the effect of GFD introduction have shown no differences before and after the diet in terms of BMI, HbA1c and QoL [8].

In youths with T1D, HbA1c reflects average glucose over the last 2–3 months, but it does not show information about acute glycemic excursions; indeed, analysis of continuous glucose monitoring (CGM) metrics allows for the direct observation of glycemic excursions, and time in range 70–180 mg/dl (3.9–10 mmol/L) (TIR) $>$ 70 % strongly corresponds with an HbA1C of approximately 7 % [9,10]. Controlling postprandial blood glucose levels (BGLs) in individuals with T1D and CD, compared to those with T1D only, has been reported as more challenging, with higher and more rapid postprandial peaks [11]; one more study confirmed this data on retrospective CGM data, in individuals maintaining GFD [12]. There are no studies analyzing glucose control metrics with real-time CGM (rt-CGM) systems in youths with T1D and CD, who are maintaining or not GFD, compared to those with T1D only.

The aims of this study were: i) to evaluate the percentage of Time in Range (%TIR, primary endpoint) and other CGM metrics in youths with T1D and CD compared with T1D only individuals; ii) to analyze glucose metrics in youths with T1D and CD who are strictly maintaining or not GFD.

## 2. Subjects, materials and methods

### 2.1. Participants and procedure

This was a cross-sectional study of youth with T1D, and CD compared to individuals with T1D only. The pediatric diabetes centers participating in the study belonged to the Italian Pediatric Diabetes Study Group [13] and included Messina, Napoli Federico II, Napoli G. Stoppoloni, Trento and Verona. The Clinical Research Ethics Committee (128/2023) of the coordinating center of Naples approved the study, which followed the Declaration of Helsinki. Written informed assents and consents were obtained by minors aged $\geq$ 12 years and all parents prior to study entry. Inclusion criteria were: (1) age 8–18 years at the time of recruitment, with a diagnosis of T1D and diabetes duration $>$ 1 year for both T1D and CD group and T1D only group; (2) multiple daily injections (MDI) or insulin pump (IP) therapy for at least 2 months; (3) to wear a rt-CGM system; (4) diagnosis of CD demonstrated by performing small bowel biopsy or by a biopsy sparing approach according to ESPGHAN guidelines in effect at the time of diagnosis of CD [14,15]; (5) to be on a GFD for at least 12 months; (6) availability of data download with identification of rt-CGM sensor metrics; (7) signature of the informed consent. Exclusion criteria were: (1) fail to meet the inclusion criteria; (2) presence of complications related to diabetes (peripheral nerve abnormality, retinopathy, renal disease); (3) presence of other autoimmune diseases.

Youths with T1D only were enrolled consecutively with the proportion 2:1 and youths were matched for age, gender, type of therapy (MDI or IP) technology worn [Sensor Augmented Pump (SAP), Hybrid Closed Loop (HCL), Advanced Hybrid Closed Loop (AHCL)], and HbA1c level.

The study was conducted from June 2023 to August 2023. Written informed consent was obtained from each participant and parent or legal guardian as appropriate, prior to consecutive enrollment at a quarterly follow-up visit.

### 2.2. Outcomes

The following data were collected from medical records about CD diagnosis:

- data of CD diagnosis, presence of symptoms, total IgA value, IgA tTG and IgA endomysial antibody (EMA) levels, small bowel biopsy histology, HbA1c. We considered T1D and CD as diagnosed "at the same time" if the time between two diseases onset was within 4 months.

The following data were collected at the enrollment visit:

- anthropometric data, ethnic background, waist circumference, blood pressure, albumin excretion rate, HbA1c, full blood count, serum traditional lipid profile, microalbuminuria, tTG, total daily insulin dose. Moreover, the following rt-CGM metrics were calculated (last 14 days): mean and standard deviation (SD) of sensor glucose levels, percentage of time below 54 mg/dl (3.0 mmol/L) (%TBR2), percentage of time between 54 and 70 mg/dl (3.0 and 3.9 mmol/L) (%TBR1), percentage of time below 70 mg/dl (3.9 mmol/L) (%TBR), percentage of time between 70 and 180 mg/dl (3.9 and 10 mmol/L) (%TIR), percentage of time above 180 mg/dl (10 mmol/L) (% TAR), percentage of time between 180 and 250 mg/dl (10 and 13.9 mmol/L) (%TAR1), percentage of time above 250 mg/dl (13.9 mmol/L) (%TAR2), glucose management indicator (GMI), percentage of coefficient of variation (%CV) expressed in percentage, glycemia risk index (GRI);

### 2.3. Assessment of GFD and Mediterranean diet maintaining in T1D and CD group

1) we considered as expression of maintaining GFD these cut-offs of tTG [16]: "poor maintaining": positivity for tTG titers higher than 3 times the upper limit of reference for each local laboratory; "partial maintaining": titers between 1x and 3x the upper limit of reference; "complete maintaining": titers within normal values;

2) A structured interview on GFD maintaining, considering currently available questionnaire for children) [4,17], was produced by expert dietitians from the tertiary-level pediatric diabetes centers participating in the study. The results of the interview conducted by the same dieticians, each in their own center, were classified as Score 1 (strictly maintaining), Score 2 (maintaining but with lapses), Score 3 (not-maintaining).

3) dietician's interview was also conducted to assess Mediterranean diet maintaining, using the validated Italian version of the Mediterranean Diet Quality Index (KIDMED) score, which is composed of 16 dichotomous (positive/negative) items on eating habits [18]. The test is divided into 4 questions with negative connotations (−1) and 12 questions evaluated with a positive score (+1). A total score is calculated, ranging from 4 to 12. The assessment of the test is interpreted according to the following classification: low maintaining (total score $\leq$ 3), average maintaining (total score between 4 and 7), high maintaining (total score $\geq$ 8).

Youths aging $\geq$ 12 years were asked to independently complete the questionnaires and for individuals aging $<$ 12 years parents completed the questionnaires.

### 2.4. Laboratory assays

Serum total cholesterol, LDL cholesterol and triglycerides were measured by an enzymatic colorimetric method on an automated analyzer at both diagnosis of CD and at the follow-up visit. The tTG level

**Table 1**
Descriptive statistics of the people with T1D and CD (N. 86) at the CD diagnosis. ULN: upper limit of normal.

| | N. (%) |
|---|---|
| Female | 47 (55 %) |
| First diagnosed with T1D and then with CD | 49 |
| | 12 |
| First diagnosed with CD and then with T1D | 25 |
| T1D and CD diagnosis within 4 months | |
| Symptoms at the CD diagnosis | 31 % |
| Anti-transglutaminase level at the CD diagnosis | |
| | 3 % |
| <3 ULN | 25 % |
| 3–10 ULN | 72 % |
| >3 ULN | |
| Intestinal biopsy | 62 % |
| | 38 % |
| Biopsy sparing approach | |

was measured in each center using a commercially available enzyme-linked immunosorbent assay, based on a human recombinant antigen (Eu-tTg IgA; Eurospital, Trieste, Italy). EMA was detected by standardized indirect immunofluorescence techniques (using monkey esophagus as the substrate). HbA1c values were measured by high-performance liquid chromatography.

### 2.5. Statistical analysis

In order to determine the number of individuals to be consecutively enrolled in the study, the sample size was calculated in collaboration with biostatisticians during the planning of this clinical study. The main outcome of the study is the difference in terms of %TIR, in the two groups (group 1 vs group 2). We considered a minimum %TIR difference of 10 % (62.4 ± 9.9 to 72.7 ± 5.6, $P < 0.001$) as previously observed, to be clinically relevant [19]. Accepting a two-tailed α error of 5 % and a study power of 90 % (1-β), we obtain a number (n) of 18 for each group. Statistical analyzes were performed with the SAS System 9.4 statistical program (SAS Institute Inc., Cary, NC, USA). Variables of metabolic risk were evaluated in the two groups. Shapiro's test was used to evaluate which variables are normally distributed. Data were expressed as mean ± SD for normally distributed variables and with medians (interquartile range) for non-normally distributed variables. Differences between groups of continuous variables were analyzed with student's *t*-test for paired samples (for normally distributed variables) or with Mann-Whitney test (for non-normally distributed variables). Chi-squared test with Fisher test has been used to evaluate differences in categorical data. ANOVA test, followed by Duncan post-hoc analysis, was used for comparisons between groups for normally distributed variables, alternatively the not-parametric Kruskal-Wallis' test in case of variables not normally distributed.

Spearman's correlations have been used to analyze the correlations between the different variables. The significance of the test is fixed at $P < 0.05$. Data processing has been entrusted to the Governance Department of the Clinical and Evaluation Epidemiology Service of APSS.

## 3. Results

### 3.1. Outcomes in youths with T1D and CD compared to those with T1D only

Out of 1458 youths with T1D aged 8–18 years, followed up in the

**Table 2**
Descriptive statistics and glucose metrics of people with T1D and CD compared to ones with T1D only, at the study enrollment. Data are reported as [mean ± SD (Median)]. MDI: multiple daily injections, SAP: sensor augmented pump, HCL: hybrid closed loop, AHCL: advanced hybrid closed loop. BMI: body mass index.

| | Type 1 diabetes and celiac disease | Type 1 diabetes | p-value |
|---|---|---|---|
| **Sample size** | 86 | 167 | |
| **Female n (%)** | 47 (55 %) | 76 (45.5 %) | 0.168◊ |
| **Age at study enrollment (years)** | 13.8 ± 2.6 (14.2) | 13.6 ± 2.9 (13.7) | 0.750* |
| **Age at diabetes onset (years)** | 6.2 ± 4.0 (5.9) | 7.7 ± 3.6 (7.4) | **0.003**‡ |
| **Diabetes duration (years)** | 7.6 ± 4.4 (7.8) | 5.95 ± 3.6 (5.6) | **0.006*** |
| **Insulin treatment n (%)** | 47 | 86 | 0.960◊ |
| | (54 %)16 | (52 %)32 | |
| MDI | (19 %)6 | (19 %)14 | |
| SAP | (7 %)17 | (8 %)35 | |
| HCL | (20 %) | (21 %) | |
| AHCL | | | |
| **Weight (Kg)** [mean ± SD (Median)] | 52.1 ± 13.8 (53.0) | 53.3 ± 15.3 (53.0) | 0.537‡ |
| **Height (m)** [mean ± SD (Median)] | 157.1 ± 13.5 (157.7) | 158.9 ± 13.6 (160.0) | 0.310‡ |
| **BMI z-score** | 0.3 ± 1.0 (0.3) | 0.3 ± 1.0 (0.3) | 0.725‡ |
| **Stage of Puberty n (%)** | 11 | 34 | 0.280◊ |
| Prepubertal | (13 %) | (20 %)50 | |
| Pubertal | 27 | (30 %)83 | |
| Postpubertal | (31 %)48 | (50 %) | |
| | (56 %) | | |
| **% HbA1c** [mean ± SD (Median)] | 7.2 ± 1.2 (7.1) | 7.03 ± 0.8 (7.0) | 0.417* |
| **Total daily insulin dose (U/Kg)** [mean ± SD (Median)] | 0.8 ± 0.2 (0.8) | 0.7 ± 0.3 (0.7) | 0.093* |
| **% of time with active sensor** | 88.9 ± 12.0 (93.0) | 88.9 ± 14.2 (93.3) | 0.342 |
| **% of time below range < 3.0 mmol/L (%TBR2)** | 0.6 ± 1.3 (0.0) | 0.7 ± 1.3 (0.0) | 0.328 |
| **% of time below range 3.9–3.0 mmol/L (%TBR1)** | 2.9 ± 5.7 (1.0) | 2.4 ± 2.4 (2.0) | 0.465 |
| **% of time below range < 3.9 mmol/l (%TBR)** | 3.41 ± 4.98 (2.0) | 3.05 ± 4.98 (2.0) | 0.308 |
| **% of time in range 3.9–10 mmol/L (%TIR)** | 60.6 ± 19.6 (61.0) | 63.8 ± 18.3 (68.0) | 0.155 |
| **% of time above range > 10 mmol/L (%TAR)** | 35.04 ± 20.94 (33.0) | 34.34 ± 20.94 (33.0) | 0.401 |
| **% of time above range 10–13.9 mmol/L (%TAR1)** | 22.1 ± 9.6 (23.0) | 23.7 ± 11.8 (23.0) | 0.975 |
| **% of time above range > 13.9 mmol/L (%TAR2)** | 14.2 ± 14.0 (10.0) | 11.3 ± 12.1 (7.0) | 0.130 |
| **Mean glucose (mmol/L)** | 9.3 ± 2.0 (8.9) | 9.0 ± 1.5 (8.7) | 0.346 |
| **% Coefficient of variation (CV)** | 36.8 ± 6.9 (34.9) | 35.8 ± 5.6 (35.4) | 0.231 |
| **Glycemia Risk Index (GRI)** | 47.6 ± 25.5 (44.0) | 44.2 ± 24.5 (39.0) | 0.307 |
| **% Glucose management indicator (GMI)** | 7.3 ± 1.0 (7.2) | 7.2 ± 0.6 (7.0) | 0.166 |

◊ Chi squared test.
* Non parametric Kruskal-Wallis' test
‡ Student's *t* test with equal variances between groups.

**Table 3**
Clinical, laboratory and CGM metrics in people with type 1 diabetes and celiac disease strictly maintaining GFD (GFD+) vs maintaining with lapses or not maintaining GFD (GFD−), according to the standardized dietary interview (score 1 vs score 2–3), and individuals with type 1 diabetes only. [mean ± SD (Median)]. tTG: transglutaminase, ULN: upper limit of normal, CGM: continuous glucose monitoring, n.a.: not applicable.

| | T1 + CD strictly adherent (GFD + ) | T1 + CD Not strictly adherent (GFD-) | T1D only | *p*-value | Significant differences between groups |
|---|---|---|---|---|---|
| **Sample size** | 61 | 25 | 167 | | |
| **Female n (%)** | 35 (57.4 %) | 12 (48.0 %) | 76 (45.5 %) | 0.283◊ | |
| **Age at diabetes onset (years)** | 5.5 ± 3.8 (4.6) | 8.0 ± 4.2 (7.1) | 7.7 ± 3.6 (7.4) | **0.0003*** | 0.009*GFD + vs. GFD-<0.0001‡ GFD + vs. T1D only |
| **Age at CD onset (years)** | 6.3 ± 3.3 (5.6) | 7.8 ± 3.8 (7.4) | n.a. | 0.118* | |
| **Symptoms at diagnosis (%)** | 31 % | 32 % | n.a. | 0.977◊ | |
| **tTG at the diagnosis** | | | n.a. | 0.605◊ | |
| | 2 % | 5 % | | | |
| **< 3 ULN** | 28 % | 19 % | | | |
| **3–10 ULN** | 70 % | 76 % | | | |
| **> 10 ULN** | | | | | |
| **Bowel biopsy** | 73 % | 57 % | n.a. | 0.162◊ | |
| **HbA1c at CD diagnosis** | 8.6 ± 2.4 (8.0) | 10.5 ± 2.8 (10.0) | n.a. | **0.004*** | GFD + vs. GFD- |
| **Age at study enrollment (years)** | 13.9 ± 2.5 (14.0) | 13.6 ± 3.0 (15.0) | 13.6 ± 2.9 (13.7) | 0.950* | |
| **T1D first** | 66 % | 36 % | n.a. | **0.042**◊ | GFD + vs. GFD- |
| **CD first** | 11 % | 20 % | | | |
| **T1D and CD at the same time** | 23 % | 44 % | | | |
| **Data at the study enrollment** | | | | | |
| **Diabetes duration (years)** | 8.4 ± 4.1 (8.5) | 5.6 ± 4.6 (3.4) | 6.0 ± 3.6 (5.6) | **0.0003*** | GFD + vs. GFD- GFD + vs. T1D only |
| **CD duration (years)** | 7.6 ± 3.5 (7.9) | 5.6 ± 4.8 (2.7) | n.a. | **0.034*** | GFD + vs. GFD- |
| **BMI z-score** | 0.4 ± 0.9 (0.4) | 0.2 ± 1.1 (0.2) | 0.3 ± 1.1 (0.3) | 0.808‡ | |
| **HbA1c (%)** | 7.1 ± 1.2 (7.0) | 7.5 ± 1.0 (7.2) | 7.0 ± 0.8 (7.0) | 0.117* **0.039** ¶ | ¶GFD-vs T1D only (paired comparison) |
| **Total daily insulin dose (U/Kg)** | 0.8 ± 0.3 (0.8) | 0.8 ± 0.3 (0.8) | 0.7 ± 0.3 (0.7) | 0.231* | |
| **% of time with active sensor** | 90.1 ± 11.1 (94.0) | 85.6 ± 13.8 (88.0) | 88.9 ± 14.2 (93.3) | 0.311* | |
| **% of time below range < 54 mg/dL** | 0.7 ± 1.4 (0.0) | 0.4 ± 0.7 (0.0) | 0.7 ± 1.3 (0.0) | 0.315* | |
| **% of time below range 70–54 mg/dL** | 3.3 ± 6.5 (2.0) | 1.8 ± 2.2 (1.0) | 2.4 ± 2.4 (2.0) | 0.307* | |
| **% of time in range (70–180 mg/dL)** | 61.4 ± 20.4 (62.5) | 55.3 ± 19.7 (53.0) | 64.1 ± 17.8 (68.0) | 0.070* **0.039*** ¶ | ¶GFD-vs T1D only (paired comparison) |
| **% of time above range 180–250 mg/dL** | 21.5 ± 10.4 (22.0) | 23.8 ± 7.2 (26.0) | 23.5 ± 11.7 (23.0) | 0.352* | |
| **% of time above range > 250 mg/dL** | 12.6 ± 12.9 (9.0) | 18.3 ± 16.1 (16.0) | 11.3 ± 12.1 (7.0) | 0.120* **0.046*** ¶ | ¶GFD-vs T1D only (paired comparison) |
| **Mean glucose (mg/dL)** | 9.0 ± 1.8 (8.9) | 9.9 ± 2.4 (9.1) | 9.0 ± 1.5 (8.7) | 0.147* **0.048*** ¶ | ¶GFD-vs T1D only (paired comparison) |
| **% Coefficient of variation (CV)** | 36.3 ± 7.3 (35.0) | 35.4 ± 7.8 (34.8) | 36.7 ± 9.3 (35.5) | 0.928* | |
| **% Glucose management indicator (GMI)** | 7.2 ± 0.9 (7.1) | 7.6 ± 1.0 (7.5) | 7.2 ± 0.6 (7.0) | 0.092* **0.027*** ¶ | ¶GFD-vs T1D only (paired comparison) |

◊ Chi squared test.
* Not parametric Kruskal-Wallis' test (¶ paired comparison).
‡ ANOVA.

four Pediatric Diabetology Clinics, 159 presented with coexisting T1D + CD (10.9 %). Fifty-one were excluded based on the inclusion and exclusion criteria, 22 did not accept to participate in the study, and finally 86 accepted to be included in this study. Ethnic background was Caucasian for all the individuals enrolled, age at CD diagnosis was 6.75 ± 3.48 years and other descriptive statistics of the youths with T1D and CD at diagnosis of CD, are reported in Table 1.

Data of the T1D and CD group and T1D group at the time of the study enrollment are reported in Table 2. In our study the two groups were different for age at diabetes onset and for diabetes duration, youths with T1D and CD manifested onset of T1D at an earlier age than those with T1D only (P = 0.003); consequently, they also had a longer duration of diabetes at the time of the study enrollment (P = 0.006). However, they presented similar growth parameters (weight, height, BMI z-score), pubertal score, total daily insulin dose per Kg body weight (Table 2); moreover, there was no significant correlation between age at onset or duration of diabetes, and the main analyzed variables (BMI-z score, HbA1c, total daily insulin dose, glucose control CGM metrics) in both groups (T1D only and those with T1D and CD) (data not shown). Laboratory investigations including cardio-metabolic risk factors in individuals with T1D and CD at the study enrollment, are reported in Supplemental Table S1. The two groups were similar in terms of % of time with active sensor; no differences were found in %TIR, %TBR, % TAR, mean glucose, CV, Glycemia Risk Index (GRI), and GMI in group 1 compared to group 2 (Table 2).

### 3.2. Outcomes related to maintaining GFD

According to the tTG titer, individuals with T1D and CD were strictly maintaining GFD in a percentage of 87.3 %, whereas dietary interview was more sensitive to detect lapses: 71 % of individuals were strictly maintaining GFD; 24.4 % of youths were maintaining GFD but with

lapses and with normal tTG in most of these youths (Supplemental Table S2); 4.6 % of individuals were not maintaining GFD. The lack of maintaining GFD was identified by dietician interview and by the tTG titer in the same percentage of individuals (4.6 %), and the most frequent occasions were reported with friends, or on special occasions such as birthdays, parties, when dining outside, or due to the failure to use personal utensils and dishes. The most contaminated foods consumed were bars, sweets and chips. According to these results we classified individuals as "strictly maintaining GFD" (No. 61) and "not strictly maintaining GFD" (No. 25) according to the dietary interview criteria.

Maintaining of the Mediterranean diet was on average-high in 80,55 % of the youths (Supplemental Table S3.).

Youths with T1D and CD considered as "not strictly maintaining GFD", have developed T1D at an older age (P = 0.009) and in most of them T1D and CD was diagnosed at the same time, compared to the strictly maintaining individuals (Table 3). At the study enrollment they had less T1D and CD duration (P = 0.013 and P = 0.034 respectively), higher tTG serum levels of 27.9 ± 29.2 (18.1) vs 5.0 ± 2.9 (4.2) (P < 0.0001). BMI z-score, total daily insulin and lipid profile were similar between the two groups (data not shown). Youths not strictly maintaining GFD had lower %TIR, higher %TAR2, and higher GRI (Supplemental Figure S1) even if with no significant differences compared to those GFD maintaining; moreover, an almost significant difference has been described for HbA1c (P = 0.082) (OR = 1.383, Supplemental Table S4). Compared to youths with T1D only, they showed higher HbA1c (P = 0.039) and glucose management indicator (GMI, P = 0.027), worst glucose metrics [higher %TAR2 (P = 0.046), higher mean glucose (P = 0.048), lower %TIR (P = 0.039)] as shown in Fig. 1, with no differences in glycemic variability (CV), GRI, and diabetes duration. Comparison between youths with T1D and CD who were strictly maintaining and those with T1D only, revealed no differences in glucose metrics and HbA1c, but they showed a significant difference for diabetes duration (P = 0.0001) (Table 3). Multivariate analysis that included age at diabetes onset and diabetes duration found only the latter variable as an independent predictor of being strictly maintaining GFD (OR = 1.25, C.I. 1.08–1.46).

## 4. Discussion

Our study presents for the first time in literature real-world data on glucose metrics registered with rt-CGM, in a large cohort of youths with T1D and CD, compared to one well-matched with T1D only. Good maintaining of GFD leads to the regression of both clinical symptoms and intestinal mucosal damage [20], nevertheless, represents an onerous task for individuals with CD and even more for those with T1D and CD. Previously the GFD has been reported as a high glycemic index, higher glycemic load, and low-fiber content diet [21,22] potentially influencing glycemic excursions. Two studies [11,12] reported in youth with T1D and CD treated with GFD a shorter time-to-peak BGL, higher peak, and higher postprandial BGLs than individuals with T1D only, without differences in time spent in hypoglycemic, euglycemic or hyperglycemic ranges measured with blinded CGM in a smaller cohort [12]. However, newer gluten free products have been improved, the glycemic index and glycemic load are not reported as different between gluten free and gluten containing food, but they may have higher intake of saturated fat and a lower intake of fibers [23].

In our study %TIR and the other glucometabolic control metrics were similar when the group with T1D only was compared with the one with T1D and CD and with the group of patients with T1D and CD strictly maintaining GFD. The metrics were significantly different when the T1D only group was compared to the not strictly maintaining T1D and CD group with higher HbA1c, more time spent in hyperglycemia (%TAR2), higher mean glucose value and GMI, and lower Time spent in the target range (%TIR). In contrast to another Italian study [23], we found a significant difference for HbA1c of the not strictly maintaining group which was significantly different from the one with T1D only, and tending towards a significant difference, also compared to the strictly maintaining GFD group. The cross-sectional design of the study precludes conclusions about mechanisms influencing glucose metrics in the not strictly maintaining GFD group. Disrupted absorption could be expected to cause hypoglycemia (TBR%) or increased CV, but interestingly in our study youths with poor GFD maintaining, did not seem to increase hypoglycemia. We cannot exclude that who are non– maintaining strictly GFD, may be less likely adherent to diabetes care and self-management. Similar to our finding, a previous study by Pham Short

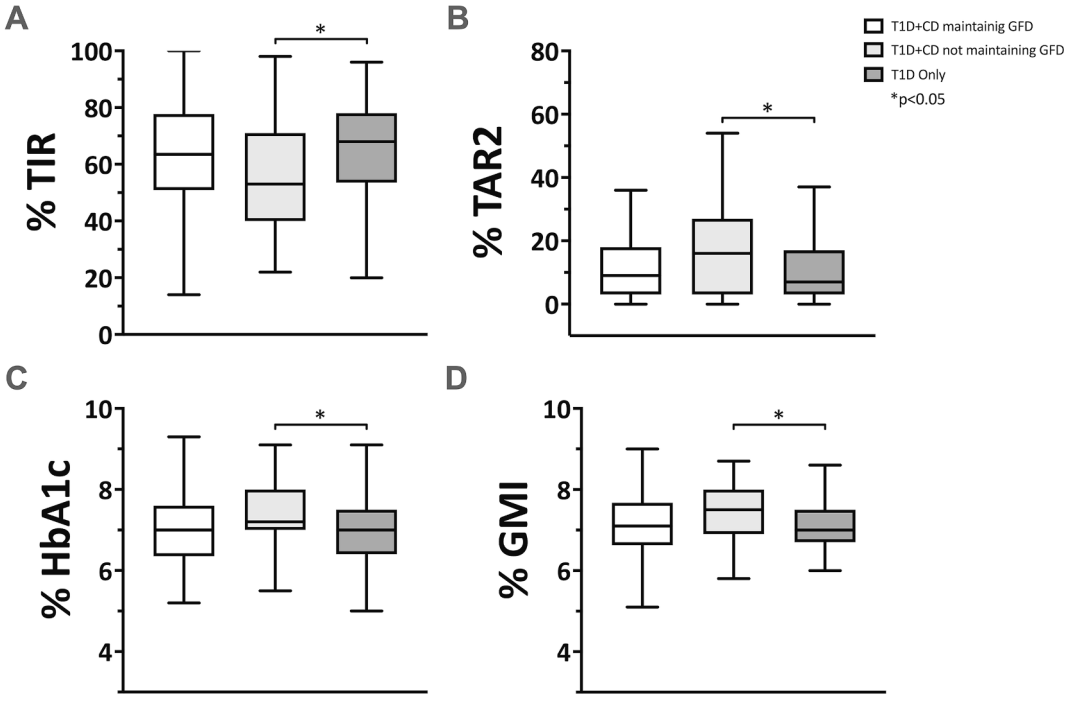


**Fig. 1.** People with type 1 diabetes and celiac disease not maintaining gluten free diet (GFD), compared to maintaining and to people with type 1 diabetes only.

et al. reported that individuals not maintaining the GFD had higher HbA1c, indicating youth may be struggling with both conditions [24]. In our study, dietitians found some special occasions when dining outside or the failure to use personal utensils as the main causes of lack of maintaining GFD. Some factors have been previously reported to improve GFD maintaining in patients with CD, as improving knowledge of GFD and practitioners' abilities to educate patients on CD, providing follow-up appointments, a telephone clinic, online courses, cooking sessions, dietary and psychological support [25,26], but according to our results, not maintaining GFD is probably related to the difficulties and sadness having to follow a GFD.

The maintaining of the Mediterranean diet in our youths was overall good, as in our cohort 81 % of the individuals with T1D and CD had an average-high score at the questionnaire, and this could represent a protective factor against obesity in both groups, differently from that reported in literature, with higher BMI z-score in youths with T1D and CD after GFD initiation [24].

In our study, the dietary interview, conducted by dietitians with experience in GFD who were working in tertiary-level diabetes clinics, found more no– maintaining individuals than tTG titles; as already known the tTg dosage is not sensitive enough to detect infrequent gluten exposures [5]. According to the dietician interview, we know that none of the patients "strictly maintaining" was on a naturally GFD, but we have no indicators on how this group found easier to maintain the GFD.

In our cohort, individuals with T1D and CD not strictly maintaining GFD, were older than those maintaining GFD, at CD diagnosis. Diagnosis of CD later in life could likely influence the unwillingness to get used to a GFD, and according to these results, clinicians should consider this subgroup as more at risk to be not strictly maintaining, and it is important to appropriately counsel them.

Potential limitations of this study are: the cross-sectional design, which cannot determine causality; inflammation parameters were not collected; we did not quantify the quality of the diets in terms of fiber or saturated fats; small number of not strictly maintaining individuals. However, it is difficult to pick out not strictly maintaining individuals with T1D and CD in children, because parental supervision has an important role in promoting maintaining GFD. Strengths are: we report rt-CGM data of youths with T1D and CD in a larger cohort than previously reported, compared to a well match cohort of individuals with T1D only; the sample size allowed us to analyze differences also in the secondary outcomes (GFD- vs GFD+); the assessment of maintaining GFD with a structured interview, in the absence of validated pediatric questionnaires, shared by GFD expert dietitians belonging to the participating tertiary pediatric diabetes centers; the assessment of maintaining the Mediterranean diet; the novelty that no- maintaining to GFD could affect glucometabolic control. In addition, the enrolling centers were tertiary care centers experienced in both the treatment of T1D and the diagnosis and treatment of CD.

For clinical practice, to reach a better control in patients with T1D and CD, it is important to identify individuals not strictly maintaining GFD, to improve knowledge about the importance of following this diet, and provide psychological support to encourage acceptance of this diet, that imposes practical limitations and leads to considerable restrictions in lifestyle.

## 5. Conclusion

In conclusion, youths with T1D and CD strictly maintaining the diet, show similar glucose metrics compared to those with T1D only, and this may be due to the quality of gluten free food. On the contrary, individuals not strictly maintaining GFD presented higher hyperglycemia rates with worst glucose control. Longitudinal studies in larger samples are needed to confirm our results and to explore the underlying mechanisms.

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## CRediT authorship contribution statement

**Enza Mozzillo:** Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing, Investigation, Visualization. **Marco Marigliano:** Conceptualization, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, Investigation, Project administration. **Irene Cuccurullo:** Data curation, Validation, Visualization. **Federica Berchielli:** Data curation, Validation. **Renata Auricchio:** Data curation, Validation, Visualization. **Claudio Maffeis:** Data curation, Validation, Visualization. **Francesco Maria Rosanio:** Data curation, Supervision, Validation, Visualization. **Dario Iafusco:** Data curation, Validation, Visualization. **Carlo Pedrolli:** Data curation, Validation, Visualization. **Riccardo Pertile:** Formal analysis. **Maurizio Delvecchio:** Data curation, Validation. **Stefano Passanisi:** Data curation, Validation, Visualization. **Giuseppina Salzano:** Data curation, Validation, Visualization. **Francesca Di Candia:** Data curation, Supervision, Validation, Visualization. **Roberto Franceschi:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.111074.

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