BMC Pediatrics

RESEARCH Open Access

Can fecal calprotectin be used as a biomarker of non-alcoholic fatty liver disease in obese adolescents?

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Abstract

Background The incidence of non-alcoholic fatty liver disease (NAFLD) is increasing with obesity, and it is believed that the ongoing low-grade inflammation in obesity and alterations in the enterohepatic axis contributing this process. This study aimed to determine the role of fecal calprotectin (FC) as inflammatory biomarker in obesity and NAFLD.

Methods Between November 2022-August 2023, 31 obese and 10 healthy adolescents aged between 10 and 18 years enrolled in this prospective controlled study. Body mass index higher than 2 standard deviation is considered as obesity. Obese adolescents were divided into two subgroups: obese adolescents ($n=11$) and Obese + NAFLD group ($n=20$). NAFLD diagnosis was made with biochemical analysis or ultrasonography. FC levels and laboratory parameters analyzed in study group, while only FC samples taken from control group. Anthropometric and laboratory parameters were compared between groups. This study was registered in ClinicalTrials.gov (NCT06229184).

Results The median (IQR P25-75) FC levels in the obese + NAFLD, obese and the healthy controls were 136.23 (43.36-332.04), 61.77 (29.70-285.92) and 38.95 (27.59–50.52) µg/g feces, respectively ($p=0.018$). Subgroup analyses revealed that the significant difference was between the obese + NAFLD group and the control group ($p=0.02$), while no significant differences were observed between the control and obese groups, or between the obese and obese + NAFLD groups. FC positivity rates were 20% ($n=2$) in the control group, 54.5% ($n=6$) in the obese group, and 75% ($n=15$) in the Obese + NAFLD group ($p=0.018$).

Conclusions FC is significantly higher in obese adolescents compared to healthy peers, but no significant difference was observed between obese and obese + NAFLD groups. Further studies needed on this subject.

Trial registration This trial is registered in ClinicalTrials.gov (Trial registration number [ClinicalTrials.gov ID] NCT06229184).

Keywords Adolescent, Fecal calprotectin, Non-alcoholic fatty liver disease, Obesity

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Introduction

Obesity is a significant public health issue worldwide. In recent years, there has been an increase in childhood obesity, leading to a rising prevalence of comorbidities such as insulin resistance, diabetes, dyslipidemia, and hypertension among adolescents. Additionally, obesity-related risks including coronary artery disease and cancer are also elevated in adulthood [1]. With the increasing prevalence of obesity, the prevalence of metabolic syndrome (MetS) in adolescents is also on the rise [2]. Literature suggests that systemic low-grade inflammation develops as a result of obesity, leading to alterations in metabolic pathways, which in turn contribute to insulin resistance and metabolic syndrome [3–5]. Insulin resistance and obesity are recognized as significant contributors to the development of non-alcoholic fatty liver disease (NAFLD), with the additional involvement of low-grade systemic inflammation in this pathway [6, 7]. NAFLD is emerging as a leading cause of chronic liver disease, being considered as the hepatic component of metabolic syndrome [8–11]. The prevalence of NAFLD is not precisely known, but in some studies, it is between 22.5% and 52.8% in children with obesity, constituting 2.6% of all children [12]. Although the mechanisms involved in the development of obesity-related metabolic complications and NAFLD are not well understood, it is believed that intestinal inflammation, changes in the microbiota, and alterations in the gut-liver axis (GLA) may play a role in the development of low-grade chronic inflammation in NAFLD associated with obesity [13]. Fecal calprotectin (FC), which has become increasingly important in demonstrating intestinal inflammation in recent years, is a widely used test, particularly in the diagnosis and monitoring of inflammatory bowel disease and various gastrointestinal disorders [14]. In our study, the utility of FC as an inflammatory biomarker in the course of NAFLD in obese adolescents has been investigated.

Methods

Subjects and design

A total of 41 adolescents (31 obese and 10 healthy adolescents) aged 10–18 years (median:14 yrs) were evaluated in this single-center, prospective controlled study. For an effect size of 0.40, 10 subjects were considered sufficient for each group with a power of 95% (beta) at a p level of <0.05. This study was conducted in the Pediatric Endocrinology and Pediatric Gastroenterology Outpatient Clinics at the Sisli Hamidiye Etfal Training and Research Hospital. Body mass index (BMI) ≥ 2 standard deviation (SD) considered as obesity criteria. BMI SD was calculated according to the Disease Centers for Disease Control and Prevention (CDC) data [15].

Adolescents aged 10–18 years without any additional diseases except metabolic syndrome attributed to obesity, BMI ≥ 2 SD, no hepatosteatosis detected by ultrasonography (USG), and alanine aminotransferase (ALT) levels within normal limits were included in the obese group. Adolescents aged 10–18 years without any additional diseases except metabolic syndrome attributed to obesity, BMI ≥ 2 SD, hepatosteatosis detected by ultrasonography (USG), and alanine aminotransferase (ALT) levels higher than normal limits(>22 U/L for girls, >26 U/L for boys) were included in the obese+NAFLD group. Hepatic USG, performed by the same physician using standard techniques, included steatosis staging based on liver brightness levels. The control group consisted of non-obese, healthy adolescents without additional diseases. BMI > 1.3 SD was considered as exclusion criteria for healthy control group [16]. For evaluation of pubertal status, Tanner staging was utilized [17].

Ethics approval and consent to participate

The study protocol was complied with Declaration of Helsinki and approved by the Şişli Hamidiye Etfal Training and Research Hospital Institutional review board (No. 2124), and an informed consent for participation in the study was obtained from all participants or their legal guardians.

Anthropometric measurements and clinical evaluation of patients

Blood pressure (BP), weight, height, BMI, waist circumference (WC) were recorded for each patient [18, 19]. Anthropometric measurements were obtained by trained personnel using Harpenden Stadiometer (Holstein Limited, Crymych, UK) and standardized methods. Body mass index (BMI) is defined as the body mass divided by the square of the body height ($kg/m^{2)}$. WC was measured at umblical level, horizontally at the end of the expirium. SD of the anthropometric measurements were calculated according to the CDC data [15]. The percentiles for WC were calculated according to the national data [20]. Patients were divided into two groups based on BMI adjusted for age and gender: subjects ($n=31$; obese $n=11$, obese+NAFLD $n=20$) and control group ($n=10$).

Systolic and diastolic BP (mm Hg) measured using a sphygmomanometer, and the measurements were repeated twice in a sitting position after 20 min of rest, using a cuff appropriate for body size, and the average measurement was recorded. The SD of the clinical BP measurements were calculated [18].

Liver and metabolic functions were assessed in the obesity groups using alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides, cholesterol, HbA1c, glucose, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and FC. HOMA-IR was determined by the formula fasting glucose (mmol/L) x fasting plasma insulin (μU/L)/22.5. HOMA-IR value

above 2.5 was considered insulin resistance [21, 22]. Abdominal ultrasound (USG) was performed for all patients to determine the presence of steatosis. Hepatosteatosis findings on USG were classified as those without hepatosteatosis, grade 1 hepatosteatosis, grade 2 hepatosteatosis and grade 3 hepatosteatosis.

Adolescents diagnosed with MetS in this study were identified based on the guidelines provided by the International Diabetes Federation. For adolescents aged 10–16 years, MetS was determined by the presence of abdominal obesity (waist circumference ≥ 90th percentile) along with two or more additional clinical features, including triglyceride levels ≥ 150 mg/dL (1.7 mmol/L), HDL-cholesterol levels < 40 mg/dL (1.03 mmol/L), systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg, and fasting blood glucose levels ≥ 100 mg/dL (5.6 mmol/L). For patients older than 16 years, the adult IDF criteria were utilized [23].

Fecal calprotectin analysis

FC levels were analyzed using the ELISA method with the Human Calprotectin kit (Fine Test, Wuhan). A 100 mg stool sample obtained from the patients was mixed with 5 ml extraction solution and vortexed for 10 min. Subsequently, the mixture was filtered through a 0.2 µm filter paper and stored at -80 degrees Celsius until further analysis. The FC values were calculated by reading absorbance at 450 nm, based on the standard curve drawn according to the absorbance values of standards. The positive threshold value was determined as 50 µg/g of stool.

Statistical analysis

In the study, the normal distribution of continuous variables was assessed using the Shapiro-Wilk test. Categorical variables were presented as frequencies (%), and continuous variables were presented as median (Interquartile Range [IQR]). Comparisons between two groups for continuous variables were performed using Mann-Whitney U test while comparisons among more than two groups were conducted using the Kruskal-Wallis test. Post-hoc tests (Dunn-Bonferroni) were employed to determine the source of differences between groups. Statistical calculations were conducted using SPSS software version 25 (IBM Corp., Armonk, NY, USA). Results were considered significant at $p < 0.05$ with a 95% confidence interval.

Results

A total of 41 patients were evaluated, with a median age of 14 years (range 10–18 years), of which 22 were male. The participants were divided into three groups: 10 in the healthy control group, 11 in the obese group, and 20 in the obese + NAFLD group. The median height was 161 cm (IQR 152–166), and the median weight was 76 kg (IQR 60–98). Notably, 51.2% of the participants were at Tanner stage 5 of puberty. Weight, BMI, WC, systolic and diastolic blood pressure were significantly higher in the study group (obese and obese + NAFLD) compared to controls ($p < 0.001$ for weight, BMI, and WC; $p = 0.049$ and $p = 0.037$ for systolic and diastolic blood pressures, respectively) (Table 1).

When evaluating the laboratory results of patients in the study group, the median ALT level was 25 IU/L (IQR 17–38). The ALT levels were statistically significantly higher in the obese + NAFLD group compared to the obese group ($p = 0.001$). Fasting hyperglycemia was found in 12.9% ($n = 4$) of the obese adolescents. Fourteen (45%) obese adolescents had IR as assessed by HOMA-IR. Four (12.9%) obese adolescents had elevated serum triglyceride levels. No significant differences were observed between the obese group and the obese + NAFLD group for other laboratory values, including CRP, glucose, HOMA-IR, HbA1c, cholesterol, triglycerides and AST/ALT ratio (Table 2).

The FC levels were calculated as follows: median (IQR P25-75): 38,95 (27.59–50.52) µg/g in the control group, median (IQR P25-75): 61,77 (29.70-285.92) µg/g in the obese group, and median (IQR P25-75): 136,23 (43.36-332.04) µg/g in the obese + NAFLD group. A statistically significant difference in FC levels was observed among research groups ($p = 0.018$). In the conducted subgroup analyses, this difference was found to be between the control group and obese + NAFLD group, with higher FC levels in the latter ($p = 0.02$) (Table 3).

To evaluate fecal calprotectin results by gender, the fecal calprotectin levels of male and female patients were compared. It was determined that there were no statistically significant differences in fecal calprotectin values between males and females in any of the control, obese, or obese + NAFLD groups (Table 4).

When comparing patients with and without positive fecal calprotectin results (> 50 µg/g feces), no statistically significant differences were observed in demographic, laboratory, and radiological findings between the two groups (Table 5).

Discussion

In the adolescents, while the developmental process of NAFLD is not clearly defined, it is reported that obesity, MetS, and changes in intestinal microbiota play a role in this process. It is believed that intestinal inflammation and microbiota alterations lead to pathological changes in the liver via the enterohepatic cycle, mediated by bacterial toxins, and contribute to the development of NAFLD [6, 7]. Although the relationship between liver disease and intestinal inflammation in this condition, also referred to as the gut-liver axis (GLA), has been

Table 1 Demographic characteristics of participants

Variables	All Patients (*N* = 41)	Control (*N* = 10)	Obese (*N* = 11)	Obese + NAFLD (*N* = 20)	*P*-value	Difference**
Age(Years, Median, Range)	14 (10–18)	13 (10–17)	12 (10–17)	15 (10–18)	0.270[a]	
Gender (N, %)					0.299[b]	
Male	22 (53.7%)	5 (12.2%)	4 (9.8%)	13 (31.7%)		
Female	19 (46.3%)	5 (12.2%)	7 (17.1%)	7 (17.1%)		
Height (cm, Median, IQR)	161 (152–166)	157 (150–161)	162 (150–166)	166 (154–174)	0.136[a]	
Weight (kg, Median, IQR)	76 (60–98)	58 (45–66)	76 (74–79)	94 (75–114)	**< 0.001***	*f = 1 < 2.3***
BMI (kg/m^2, Median, IQR)	29.7 (25.4–34)	23.1 (19.87–24.87)	29.6 (27.8–33.8)	33.2 (30.9-38.81)	**< 0.001***	*f = 1 < 2.3***
BMI SDS (Median, IQR)	2.30 (2-2.75)	0.88 (0.68–1.3)	2.5 (2.15–2.75)	2.64 (2.15–3.25)	**< 0.001***	*f = 1 < 2.3***
WC (cm, Median, IQR)	100 (91–113)	66 (50-75.5)	100 (99–113)	108 (100-117.5)	**< 0.001***	*f = 1 < 2.3***
Tanner Stage (N, %)					0.871[c]	
Stage 2	1 (2.4%)	1 (2.4%)	0 (0%)	0 (0%)		
Stage 3	8 (19.5%)	2 (4.9%)	2 (4.9%)	4 (9.8%)		
Stage 4	11 (26.8%)	3 (7.3%)	3 (7.3%)	5 (12.2%)		
Stage 5	21 (51.2%)	4 (9.8%)	6 (14.6%)	11 (26.8%)		
Blood pressure SDS (Median, IQR)						
Systolic	0.8 (0.4–1.4)	0.4 (0.2–0.6)	1.1 (0.6–1.6)	0.9 (0.2–1.6)	**0.049[a]**	*f = 1 < 2.3***
Diastolic	1 (0.5–1.5)	0.3 (0.2–0.7)	1.23 (0.7–1.8)	1 (0.4–1.6)	**0.037[a]**	*f = 1 < 2.3***

a: Kruskal Wallis Test, b: Pearson Chi-Square Test; c: Fisher's Exact Test **: Scheffe test

BMI: Body Mass Index, Cm: Centimeter, IQR: Interquartile Range, Kg: Kilogram, NAFLD: Non-Alcoholic Fatty Liver Disease, SDS: Standard Deviation Score, WC: Waist Circumference

All percentages were calculated based on the total patient population (*N* = 41)

All p-values less than 0.05 was bold

Table 2 Comparison of laboratory values among study groups

Variables	Study Group (*n* = 31)	Obese (*n* = 11)	Obese + NAFLD (*n* = 20)	*P*-value
ALT (IU/L, Median, IQR)	25 (17–38)	16 (14–22)	30 (21.25–54.25)	**0.001[a]**
CRP (mg/dL, Median, IQR)	5 (4–7)	5 (3–7)	6 (4–7)	0.416[a]
Glucose (mmol/L, Median, IQR)	4.5 (4.2–5.1)	4.5 (4.2–5.4)	4.56 (3.9–5.1)	0.573[a]
HOMA-IR (Median, IQR)	2.4 (1.77–5.75)	2.24 (1.42–4.1)	2.50 (2-6.04)	0.264[a]
HOMA-IR subgroup (N, %)				1.000[b]
< 2.5	17 (54.9%)	6 (19.4%)	11 (35.5%)	
> 2.5	14 (45.1%)	5 (16.1%)	9 (29%)	
HbA1c (%, Median, IQR)	5.5 (5.3–5.7)	5.5 (5.2–5.6)	5.5 (5.4–5.7)	0.670[a]
Cholesterol (mmol/L, Median, IQR)	8.3 (7.6–9.3)	8.9 (8.4–9.6)	7.8 (7.5-9)	0.083[a]
Triglyceride (mmol/L, Median, IQR)	6.4 (4.5–8.1)	6.33 (4-7.5)	6.5 (5.1–8.8)	0.167[a]
AST/ALT (N, %)				0.502[b]
< 1	14 (45.2%)	4 (12.9%)	10 (32.3%)	
> 1	17 (54.8%)	7 (22.5%)	10 (32.3%)	

a: Mann-Whitney U Test; b: Fisher's Exact Test

ALT: Alanine Aminotransferase, CRP: C-Reactive Protein, dL: Desiliter, IU: International Unit, IQR: Interquartile Range, L: Liter, mg: miligram, mmol: Milimol, NAFLD: Non-Alcoholic Fatty Liver Disease

All percentages were calculated based on the obese patient population (*N* = 31)

All p-values less than 0.05 was bold

suggested, studies demonstrating this correlation are limited [24, 25]. In this study, higher levels of FC were detected in the study group compared to the control group, which is consistent with the literature. Subgroup analysis revealed a higher FC level in the obese + NAFLD group compared to the obese group; however, the difference did not reach statistical significance, which could be attributed to the small sample size. Further comparison of these two groups in larger cohorts is warranted.

In studies on the pathophysiology of NAFLD, correlations have been observed between MetS, IR, type 2 diabetes mellitus (DM), obesity, and the frequency of NAFLD; however, there are differing views on which one has a causal effect [5, 26–28]. In some studies evaluating the relationship between IR and NAFLD, IR has been considered as a factor that increases the frequency of NAFLD by increasing hepatic steatosis [27, 29]. However, there are studies showing that hepatokines released as a result of NAFLD play a role in the development of IR

Table 3 Fecal Calprotectin Levels According to Study Groups

Variables	Category	Control (*n* = 10)	Obese (*n* = 11)	Obese + NAFLD (*n* = 20)	*P*-values	Difference
Fecal Calprotectin*(µg/gr feces)*	Median	38.95	61.77	136.23	**0.018**[a]	*fc=1<3*
	IQR(P_{25}-P_{75})	27.59–50.52	29.70-285.92	43.36-332.04		
	Min.-Max.	11.80-54.53	24.15-549.15	22.57-623.04		
Fecal Calprotectin*(µg/gr feces)*	≤ 50	8 (19.5%)	5 (12.2%)	5 (12.2%)	**0.019**[b]	*fb=1<3*
	> 50	2 (4.8%)	6 (14.6%)	15 (36.6%)		

a: Kruskal Wallis Test; b: Fisher's Exact Test; c: Mann-Whitney U Test

IQR: Interquartile Range, gr: gram, µg: microgram

All percentages were calculated based on the all patient population (*N* = 41)

All p-values less than 0.05 was bold

Table 4 Fecal Calprotectin Levels According to Gender

Study Groups (*N* female / *N* male)	FC levels of male patients (µg/gr feces, Median, IQR)	FC levels of female patients (µg/gr feces, Median, IQR)	*P*-values
Control (5 female / 5 male)	20.5 (1.37–31.7)	8.82 (5.32-12)	1.000[a]
Obese (7 female / 4 male)	132 (53.8–225)	40 (28.5–518)	1.000[a]
Obese + NAFLD (7 female / 13 male)	127 (38.8–378)	463 (111–551)	0.157[a]

a: Mann-Whitney U Test

FC: Fecal calprotectin, IQR: Interquartile Range, NAFLD: Non-Alcoholic Fatty Liver Disease

Table 5 Demographic, Clinical and Laboratory Findings According to Fecal Calprotectin Positivity Rate in Obese Adolescent

	Fecal Calprotectin (µg/gr feces)		
Variables	**≤ 50 (*n* = 10)**	**> 50 (*n* = 21)**	***P*-values**
Age (years, Median, Range)	14(10–18)	13 (10–17)	0.474[a]
Gender (N, %)			0.999[b]
Male	5 (16.1%)	12 (38.7%)	
Female	5 (16.1%)	9 (29.1%)	
Height(cm, Median, IQR)	162 (152.7–169)	165 (154.7-167.5)	0.846[a]
Weight(kg, Median, IQR)	88.3 (72.2-108.7)	85.8 (74.1-104.4)	0.859[a]
BMI (kg/m^2, Median, IQR)	32.94 (27.6–35.7)	31.9 (28.75–34.87)	0.164[a]
BMI SD (Median, IQR)	2.68 (2.05–2.89)	2.42 (2.26–2.87)	0.234[a]
Waist Circumference(cm, Median, IQR)	111.3 (94.2–121)	102 (96.5–115)	0.164[a]
ALT (IU/L, Median, IQR)	24 (14–59)	25 (17.5–38)	0.983[a]
HbA1c (%, Median, IQR)	5.55 (5.35–5.625)	5.5 (5.25–5.7)	0.423[a]
Glucose (mmol/L, Median, IQR)	4.3 (4.16–4.52)	4.7 (4.36–5.33)	0.667[a]
HOMA-IR (Median, IQR)	2 (1.7–2.42)	2.68 (1.86–5.27)	0.188[a]
Cholesterol (mmol/L, Median, IQR)	8.83 (7.61–9.38)	8.245 (7.35–9.25)	0.724[a]
Triglycerides (mmol/L, Median, IQR)	5.59 (3.19–8.69)	6.38 (4.81–7.62)	0.272[a]
Abdominal USG (N, %)			0.119[b]
No Hepatosteatosis	5 (16.1%)	6 (19.4%)	
Grade-I Hepatosteatosis	1 (3.2%)	10 (32.3%)	
Grade-II Hepatosteatosis	4 (12.9%)	5 (16.1%)	

a: Mann Whitney U Test; b: Fisher's Exact Test

ALT: Alanine Aminotransferase, CRP: C-Reactive Protein, dL: Desiliter, gr: gram, IU: International Unit, IQR: Interquartile Range, kg: kilogram, L: Liter, m: meter, mg: miligram, µg: microgram, mmol: Milimol, NAFLD: Non-Alcoholic Fatty Liver Disease

All percentages were calculated based on the obese patient population (*N* = 31)

and type 2 DM [5, 28]. In our study, there is no significant difference for HOMA-IR scores between obese adolescents and obese+NAFLD group. The complex interactions between IR and NAFLD etiopathogenesis need to be evaluated at the molecular level and in further studies.

While hypertriglyceridemia and increased LDL cholesterol are more commonly observed in obese individuals and associated with metabolic complications, the extent to which this elevation influences the etiopathogenesis of NAFLD is not clearly defined in the literature. Some studies suggest an association between elevated triglycerides and LDL cholesterol and the development of hepatosteatosis, but our study did not reveal a significant

difference between the obese+NAFLD group compared to the obese group [30].

In obese and NAFLD cases, it is expected that intestinal inflammation would be more advanced compared to only obese cases, and higher FC levels would be detected. Some studies in the literature also report differences in FC levels between these two groups [25]. In our study, a statistically significant increase in FC levels was observed in the study groups compared to the control group ($p=0.018$). However, in subgroup analyses, this difference was found to be between the control group and adolescents in the obese+NAFLD group. No significant difference was observed between the obese group and the obese+NAFLD group. These results, while demonstrating the impact of chronic low-grade inflammation in obese adolescents on the intestinal mucosa, do not provide a clear understanding of the use of FC in monitoring NAFLD. The limited number of patients in our study may have led to the inability to demonstrate the difference between the obese group and the obese+NAFLD group; further evaluation in larger cohorts is necessary [31, 32].

Although the prospective design of our study is an advantage, the small number of patients and the limited number of patients with obesity and NASH, which could not be evaluated as a separate group, are limitations of our study. Additionally, the slightly elevated FC values in two patients without additional diseases in the control group are limitations of our study, leading to a higher FC positivity rate than normal in the control group. Factors such as age, dietary habits, and genetic factors may have contributed to this result.

Conclusion

The significantly increased levels of FC in Obese+NAFLD group compared to the control group support the presence of low-grade inflammation in obesity and NAFLD. However, no significant difference was observed between the Obese+NAFLD and obese groups. Role of FC in NAFLD monitoring should evaluated in further studies.

Author contributions

Concept – BTD, AMU, NU; Design - BTD, AMU, AK, NU; Supervision – NU, AU, AMU; Resources - BTD, NU, AMU; Materials – BTD, NU, AMU; Data Collection and/or Processing – BTD; Analysis and/or Interpretation - BTD, NU, AK, NH, AU, AMU; Literature Search - BTD, NU, AU, AMU; Writing Manuscript - BTD, NU, AU, AMU; Critical Review – AMU, AK, NH, AU, NU. All authors read and approved the final version of the manuscript.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability

The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted under the Helsinki Declaration and approved by the local institutional review board. All participants were informed about the study and written informed consent was obtained.

Consent to publish

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 11 April 2024 / Accepted: 12 December 2024
Published online: 23 December 2024

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