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Sensitivity to thyroid hormones in children developing acute kidney injury at the onset of type 1 diabetes mellitus

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Abstract

Background Thyroid hormone (TH) sensitivity at type 1 diabetes mellitus (T1DM) onset and its connection with acute kidney injury (AKI) has not been investigated. We aimed to evaluate changes in TH sensitivity in children with and without AKI at T1DM onset and to assess the role of euthyroid sick syndrome (ESS) in this relationship.

Methods We included 161 children with new-onset T1DM and followed them until renal function normalized. The free triiodothyronine (FT3)/free thyroxine (FT4) ratio was used to assess peripheral TH sensitivity, while the TSH index (TSHI), thyrotroph T4 resistance index (TT4RI), thyrotroph T3 resistance index (TT3RI), Thyroid Feedback Quantile-based Index (TFQI), and parametric TFQI (PTFQI) were used for central sensitivity.

Results Patients with AKI exhibited greater weight loss, higher serum ketones, creatinine, corrected sodium, and glycated hemoglobin, but lower bicarbonate and estimated glomerular filtration rate compared to those without AKI. Logistic regression showed that the odds of AKI increased by 11.5-fold for each unit decrease in TFQI, 4.0-fold per unit decrease in PTFQI, and 1.7-fold per unit decrease in TSHI, adjusting for age and gender. After adjusting for age, gender, and ESS, the odds for AKI significantly increased (4.8-fold for each 1-unit decrease) only for TFQI.

Conclusions AKI at the onset of T1DM has a dual effect on TH. It reduces peripheral sensitivity while increasing central sensitivity. This effect appears to be largely driven by ESS, with the exception of the association between AKI and TFQI, which remains independent of ESS.

Keywords Type 1 diabetes mellitus, Acute kidney injury, Thyroid hormones, Euthyroid sick syndrome, Sensitivity

Background

The onset of type 1 diabetes mellitus (T1DM) can be complicated by diabetic ketoacidosis (DKA) [1] and acute kidney injury (AKI) [2]. AKI affects up to 65% of the patients at T1DM onset [3, 4] and increases the risk of developing chronic kidney disease (CKD) during follow-up [5, 6].

There is a well-documented intricate and bidirectional relationship between kidney and thyroid function. Kidney dysfunction can influence the metabolism, clearance, and levels of thyroid hormones (TH), while THs, both

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directly and indirectly, impact renal development, structure, hemodynamics, glomerular filtration rate, and the regulation of water and electrolyte balance [7]. The interactions between free thyroxine (FT4), free triiodothyronine (FT3), and thyroid-stimulating hormone (TSH) can be assessed using TH sensitivity indices, with various indices appearing to correlate with organ dysfunction, including kidney function [7].

TH sensitivity is a newly proposed functional concept. It refers to the responsiveness of the body's tissues to THs [8, 9]. Evaluating TH sensitivity can be valuable as it offers insights into how effectively these hormones regulate various physiological processes in the body [10]. Subsequently, researchers have proposed indices representing impaired sensitivity to TH [8, 9].

As reported, a reduced central sensitivity to TH has been observed in euthyroid adults with reduced renal function [11] and in euthyroid children and adolescents with overweight/obesity [12].

To our knowledge, a potential role of THs in maintaining metabolic equilibrium in T1DM has been proposed [13]; however, the sensitivity to TH at T1DM onset and its relationship with AKI have not yet been explored in detail.

So far, only the euthyroid sick syndrome (ESS) has been studied in the context of T1DM onset [14–16]. ESS develops in approximately 37% of the children at T1DM onset [15], rising to 57% in those with DKA [14, 16], indicating thyroid involvement during T1DM onset.

Based on our previous findings that patients with EES at T1DM onset experienced more severe kidney complications [15], we hypothesized that sensitivity to TH could be influenced by both ESS and AKI in children with T1DM onset. Therefore, our aims were (i) to evaluate how TH sensitivity changes in children with and without AKI at T1DM onset, and (ii) to analyze the impact of ESS on the relationship between TH sensitivity and AKI. To achieve these aims we analyzed the DiAKIdney cohort [4].

Methods

The DiAKIdney cohort was enrolled consecutively from December 2017 to August 2019 [4]. The study was approved by the Research Ethics Committee of Università degli Studi della Campania "Luigi Vanvitelli" (approval number 368), and written informed consent was obtained from all parents. As previously described [4], participants were eligible if they had onset of T1DM before the age of 18 and were not receiving any medication other than intravenous 0.9% NaCl infusion. Participants were excluded if they had been on medication for chronic conditions prior to T1DM onset, failed to return for scheduled follow-ups, or had congenital anomalies of the kidney and urinary tract.

All participants had autoimmune T1DM, confirmed at diagnosis by the presence of glutamic acid decarboxylase, islet antigen 2, insulin, and/or Zinc transporter 8 antibodies at diagnosis. Consistent insulin therapy was required for all following diagnoses.

After discharge, participants were followed up after 14 days. Those who had not recovered from AKI by that time returned after 30 days and, if necessary, after 60 days.

For the analyses of this manuscript, we used data on age, weight, serum creatinine (measured by the Jaffe method [17, 18]), ketones, Na, Cl, bicarbonates, glycated hemoglobin (HbA1c) at T1DM onset and follow-up visits. Additionally, we collected data on TSH, FT4, and FT3 concentrations at T1DM onset. Anti-thyroglobulin and anti-thyroid peroxidase antibodies were also measured in all participants. Thyroid hormones were reassessed after 6–12 months.

The Jaffe creatinine method is based on the reaction with alkaline picrate. At an alkaline pH, creatinine in the sample reacts with picrate to form a creatinine-picrate complex [17, 18]. The rate of increase in absorbance at 500 nm, due to the formation of this complex, is directly proportional to the concentration of creatinine in the sample [17].

We corrected the Na levels for blood glucose levels using the following formula: ([glucose (mg/dL)/18] − 5.6) × 0.36 + serum Na [3, 4].

The original DiAKIdney cohort included 185 participants. One participant was excluded due to autoimmune thyroiditis and overt severe hypothyroidism, and 23 were excluded due to the unavailability of thyroid hormone data at T1DM onset.

Definitions

ESS was defined as decreased FT3 and/or FT4 levels with normal or reduced TSH concentrations [15].

DKA was defined by blood glucose levels ≥ 200 mg/dL, pH ≤ 7.3, or bicarbonates ≤ 15 mEq/L, along with elevated serum ketones [4].

AKI was defined based on Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine and/or urine output criteria [19].

Baseline creatinine values were taken from the most recent follow-up when all biochemical parameters had normalized and the estimated glomerular filtration rate (eGFR) was within the normal range for age [20].

Calculations of parameters indicating sensitivity to TH

The sensitivity to TH can be evaluated both at the peripheral and central levels.

Peripheral sensitivity to TH

The FT3/FT4 ratio reflects the peripheral metabolism of thyroid hormones and serves as a tool to assess peripheral sensitivity to these hormones [21, 22]. An elevated FT3/FT4 ratio indicates heightened peripheral sensitivity to thyroid hormones, whereas a lower ratio suggests reduced sensitivity [21, 22].

Central sensitivity to TH

Indexes of central sensitivity included the TSH index (TSHI), thyrotroph T4 resistance index (TT4RI) and thyrotroph T3 resistance index (TT3RI), Thyroid Feedback Quantile-based Index (TFQI), parametric TFQI (PTFQI), which were calculated as follows:

- TSHI = ln TSH (mIU/L) + 0.1345 * FT4 (pmol/L).

Higher values suggest reduced sensitivity of the pituitary–hypothalamic–thyroid axis (HPT) to TH, indicating that more TSH is required to achieve a given FT4 level. Conversely, lower values reflect increased sensitivity to TH [9, 23].

- TT4RI = FT4 (pmol/L) * TSH (mIU/L)
- TT3RI = FT3 (pmol/L) * TSH (mIU/L).

Both TT4RI and TT3RI reflect the pituitary's sensitivity to T4 and T3 feedback, respectively. Higher values indicate reduced sensitivity, potentially suggesting altered regulation or resistance to T4 or T3 at the central level [9].

- TFQI = cumulative distribution function (cdf) − (1 − cdf TSH) [8, 21, 23].

The TFQI serves as a more effective indicator of the HPT response to variations in peripheral serum FT4 or FT3 levels. It continuously measures deviations from the typical pituitary response (inhibition) to thyroid hormones [8, 21, 23]. TFQI uses the cdf of thyroid hormones and TSH. This ensures that individual values are interpreted relative to the specific population's distribution. By normalizing values to the reference population, TFQI allows direct comparison of HPT axis sensitivity between different populations, even if their absolute hormone levels differ [8, 21, 23].

The index ranges from − 1 to 1, with positive values indicating reduced sensitivity to TH, negative values indicating increased sensitivity, and a value of 0 representing normal sensitivity to TH.

- PTFQI = Φ ([FT4 − μFT4/σ FT4] − (1 − Φ [ln TSH − μ ln TSH/σ ln TSH]), where μFT4 = 10.075, σ FT4 = 2.155, μ ln TSH = 0.4654, σ ln TSH = 0.7744.

The PTFQI was developed as an approximation to be applied across various populations, and its interpretation is similar to that of the TFQI [23]. It offers a standardized approach for evaluating central sensitivity to thyroid hormones, particularly useful in studies involving multiple populations because it incorporates population-based statistical parameters (mean, μ, and standard deviation, σ) for FT4 and TSH distributions [23].

Statistical analysis

P values < 0.05 were considered statistically significant. Differences in continuous variables were analyzed using the independent-sample t-test for normally distributed variables and with the Mann–Whitney test in case of non-normality. Qualitative variables were compared using the chi-square test. Logistic regression was used to assess the association between TH sensitivity and AKI and TH sensitivity and ESS. The SPSS 29 software was used for all statistical analyses.

Results

General characteristics

One hundred and sixty-one patients met the inclusion criteria and were included in the analyses of this study. As previously described [15], the enrolled patients had a mean age of 9.1 years ± 4.0 standard deviation. Seventy-three patients (45.3%) developed AKI at the onset of T1DM. All patients who developed AKI achieved creatinine normalization within 14 days of its onset. Among the participants, ESS was identified in 60 out of 161 cases (37.3%). ESS resolved in all affected participants when thyroid hormone levels were reassessed after a median of 12 months following T1DM onset (range: 6–12 months) [15].

Comparing the characteristics of patients with and without AKI, we found that those with AKI presented with greater weight loss, higher serum ketones, creatinine, corrected serum Na, and HbA1c levels, and lower serum bicarbonate and eGFR levels compared to patients without AKI (Table 1). Furthermore, patients with AKI had a higher prevalence of DKA than those without AKI (76.7% vs 32.9%; $p < 0.001$) (Table 1).

Thyroidal status

Sensitivity to TH according based on the presence or absence of AKI

Analyzing the thyroidal status, patients with AKI had a higher prevalence of ESS and lower FT3, TSH, TFQI,

Table 1 Clinical characteristics of enrolled patients classified on the basis of presence or absence of AKI at T1DM onset

		AKI (yes) No. = 73	AKI (no) No. = 88	*p*
At T1DM onset	**Age, year**	8.9 (4.4)	9.2 (3.8)	0.66
	Male sex, No. (%)	37 (50.7)	37 (42.0)	0.27
	Weight loss, %	10.5 (7.8)	6.1 (5.4)	< 0.001
	DKA, No. (%)	56 (76.7)	29 (32.9)	< 0.001
	ESS, No. (%)	20 (27.4)	40 (45.5)	< 0.001
	Serum bicarbonate level, mEq/L, mean (SDS)	12.7 (5.9)	19.1 (5.8)	< 0.001
	Serum ketones, mmol/L, mean (SDS)	5.6 (2.5)	3.2 (2.6)	< 0.001
	eGFR, mL/min/1.73m^2, mean (SDS)	76.3 (18.6)	110.1 (21.6)	< 0.001
	Creatinine, mg/dL, median (IQR)	1.0 (0.42)	0.69 (0.16)	< 0.001
	Corrected serum Na level, mEq/L, mean (SDS)	141.0 (4.4)	139.3 (2.9)	0.005
	Serum chloride levels, mEq/L, median (IQR)	104.0 (8.0)	102.0 (5.0)	0.17
	HbA1c, %, mean (SDS)	11.9 (1.6)	11.1 (2.2)	0.01
	TSH, mIU/L, median (IQR)	2.5 (1.3)	2.8 (1.6)	0.09
	FT3, pmol/L, mean (SDS)	2.1 (0.93)	2.8 (0.69)	< 0.001
	FT4, pmol/L, mean (SDS)	10.3 (2.7)	12.0 (1.8)	< 0.001
	TFQI, mean (SDS)	− 0.13 (0.32)	0.08 (0.26)	< 0.001
	PTFQI, mean (SDS)	− 0.12 (0.43)	0.11 (0.38)	< 0.001
	FT3/Ft4 ratio, mean (SDS)	0.20 (0.08)	0.23 (0.06)	0.004
	TSH index, mean (SDS)	2.3 (0.69)	2.6 (0.66)	0.02
	TT4RI, median (IQR)	25.9 (15.6)	33.9 (22.5)	0.02
	TT3RI, median (IQR)	5.2 (4.7)	7.8 (6.5)	0.001
At follow-up	**BMI, SDS**	19.4 (3.6)	18.9 (4.0)	0.37
	eGFR, mL/min/1.73m^2, mean (SDS)	131.1 (18.8)	126.6 (16.4)	0.10
	Creatinine, mg/dL, median (IQR)	0.58 (0.15)	0.58 (0.1)	0.13
	TSH, mIU/L, median (IQR)	2.5 (1.6)	2.4 (1.2)	0.33
	FT3, pmol/L, mean (SDS)	3.3 (0.41)	3.5 (0.43)	0.002
	FT4, pmol/L, mean (SDS)	11.2 (1.88)	11.1 (2.46)	0.75
	TFQI, mean (SDS)	− 0.001 (0.32)	− 0.08 (0.29)	0.10
	PTFQI, mean (SDS)	0.03 (0.35)	− 0.06 (0.34)	0.10
	FT3/Ft4 ratio, median (IQR)	0.30 (0.08)	0.32 (0.08)	0.05
	TSH index, mean (SDS)	2.5 (0.54)	2.3 (0.55)	0.04
	TT4RI, median (IQR)	27.4 (18.8)	24.7 (13.3)	0.07
	TT3RI, median (IQR)	8.8 (5.6)	8.4 (4.8)	0.30

Abbreviations: AKI, acute kidney injury; *DKA*, diabetic ketoacidosis; *eGFR*, estimated glomerular filtration rate; *ESS*; euthyroid sick syndrome; *FT3*, free triiodothyronine; *FT4*, free thyroxine; *HbA1c*, glycated hemoglobin; *TFQI*, parametric TFQI; *T1DM*, type 1 diabetes mellitus; *TFQI*, Thyroid Feedback Quantile-based Index; *TSH*, thyroid-stimulating hormone; *TSHI*, TSH index; *TT3RI*, thyrotroph T3 resistance index; *TT4RI*, thyrotroph T4 resistance index

PTFQI, FT3/FT4 ratio, TSH index, TT4RI, and TT3RI compared to those without AKI (Table 1). At follow-up, patients who had presented with AKI continued to have lower FT3 and FT3/FT4 ratio, along with a higher TSH index compared to those who had not developed AKI.

Sensitivity to TH based on the presence or absence of ESS

When comparing the TH and sensitivity between patients with and without ESS, we found that those with ESS had lower FT3, FT4, TFQI, PTFQI, FT3/FT4 ratio, TSH index, TT4RI, and TT3RI values compared with patients without ESS (Table 2). At follow-up, patients with ESS had persistently lower FT3 values, with no significant differences in FT4, TFQI, PTFQI, Ft3/Ft4 ratio, TSH index, TT4RI, and TT3RI compared to those without ESS (Table 2).

Association between TH sensitivity and AKI at logistic regression analyses

According to logistic regression analysis, the OR for AKI increased by 11.5-fold for each 1-unit decrease in TFQI, by 4.0-fold for each 1-unit decrease in PTFQI, by 1.1-fold

Table 2 Thyroidal status of enrolled patients classified on the basis of presence or absence of ESS at T1DM onset

		ESS (yes) No. = 60	ESS (no) No. = 101	*p*
At T1DM onset	**TSH, mIU/L, median (IQR)**	2.54 (1.16)	2.78 (1.67)	0.058
	FT3, pmol/L, mean (SDS)	1.55 (0.52)	3.02 (0.52)	< 0.001
	FT4, pmol/L, mean (SDS)	9.4 (2.35)	12.3 (1.69)	< 0.001
	TFQI, mean (SDS)	− 0.24 (0.37)	0.12 (0.24)	< 0.001
	PTFQI, mean (SDS)	− 0.26 (0.37)	0.16 (0.37)	< 0.001
	FT3/Ft4 ratio, mean (SDS)	0.17 (0.06)	0.25 (0.05)	< 0.001
	TSH index, mean (SDS)	2.2 (0.72)	2.7 (0.60)	< 0.001
	TT4RI, median (IQR)	23.8 (19.1)	34.2 (27.8)	< 0.001
	TT3RI, median (IQR)	3.74 (3.4)	8.4 (6.8)	< 0.001
At follow-up	**TSH, mIU/L, median (IQR)**	2.4 (1.4)	2.4 (1.5)	0.68
	FT3, pmol/L, mean (SDS)	3.3 (0.32)	3.5 (0.47)	< 0.001
	FT4, pmol/L, mean (SDS)	11.0 (1.9)	11.3 (2.4)	0.47
	TFQI, mean (SDS)	− 0.06 (0.31)	− 0.33 (0.31)	0.53
	PTFQI, mean (SDS)	− 0.03 (0.36)	− 0.004 (0.34)	0.59
	FT3/Ft4 ratio, median (IQR)	0.30 (0.09)	0.31 (0.08)	0.24
	TSH index, mean (SDS)	2.4 (0.54)	2.4 (0.56)	0.81
	TT4RI, median (IQR)	25.7 (17.5)	26.6 (17.1)	0.95
	TT3RI, median (IQR)	7.9 (5.0)	8.8 (5.5)	0.80

Abbreviations: ESS; euthyroid sick syndrome; *FT3*, free triiodothyronine; *FT4*, free thyroxine; *TFQI*, parametric TFQI; *T1DM*, type 1 diabetes mellitus; TFQI, Thyroid Feedback Quantile-based Index; *TSH*, thyroid-stimulating hormone; *TSHI*, TSH index; *TT3RI*, thyrotroph T3 resistance index; *TT4RI*, thyrotroph T4 resistance index

for each 0.1-unit decrease in the FT3/FT4 ratio, and by 1.7-fold for each 1-unit decrease in the TSH index, after adjusting for age and gender (Fig. 1A).

After adjusting for age, gender, and ESS, the OR for AKI significantly increased (4.8-fold for each 1-unit decrease) only for TFQI (Fig. 1B).

Discussion

Our study investigates the association between AKI and sensitivity to THs, as well as the impact of ESS on this relationship. We found that patients with AKI at the onset of T1DM exhibit increased sensitivity to TH at the central level. This is demonstrated by the reduction in indices such as TFQI, PTFQI, TSH index, TT4RI, and TT3RI in patients with AKI compared to those without, as well as by the association of these indices with AKI in the logistic regression model adjusted for age and gender. These indices reflect the regulatory interaction between the pituitary gland and the thyroid, which governs the feedback loop of hormone production [24]. A reduction in these values heightened the sensitivity of the HPT axis to thyroid hormone fluctuations, indicating a more pronounced feedback response to changing hormone levels [9, 21–23].

Conversely, the study shows a reduced sensitivity to TH at the peripheral level, as evidenced by a lower FT3/FT4 ratio in patients with AKI compared to those without, and by the significant association between a reduced FT3/FT4 ratio and AKI in multiple logistic regression analysis corrected for age and gender. This aligns with the findings of Zeng et al., who reported that in euthyroid adults undergoing elective percutaneous coronary intervention, low FT3/FT4 ratio was independently associated with an increased risk of contrast-associated AKI [25].

The FT3/FT4 ratio reflects the efficiency of the conversion of FT4 to its more active form, FT3, in peripheral tissues [26]. A lower ratio may indicate reduced peripheral tissue responsiveness or efficiency in this conversion

(See figure on next page.)

Fig. 1 Odds ratio of AKI at T1DM onset based on thyroid sensitivity indices, adjusted for age and gender (**A**) and adjusted for age, gender, and ESS (**B**). The displayed OR represents a reduction of 1 unit for each parameter, except for the FT3/FT4 ratio, where it reflects a reduction of 0.1 unit. *Abbreviations:* AKI, acute kidney injury; ESS, euthyroid sick syndrome; FT3, free triiodothyronine; FT4, free thyroxine; TFQI, parametric TFQI; T1DM, type 1 diabetes mellitus; TFQI, Thyroid Feedback Quantile-based Index; TSH, thyroid-stimulating hormone; TSHI, TSH index; TT3RI, thyrotroph T3 resistance index; TT4RI, thyrotroph T4 resistance index

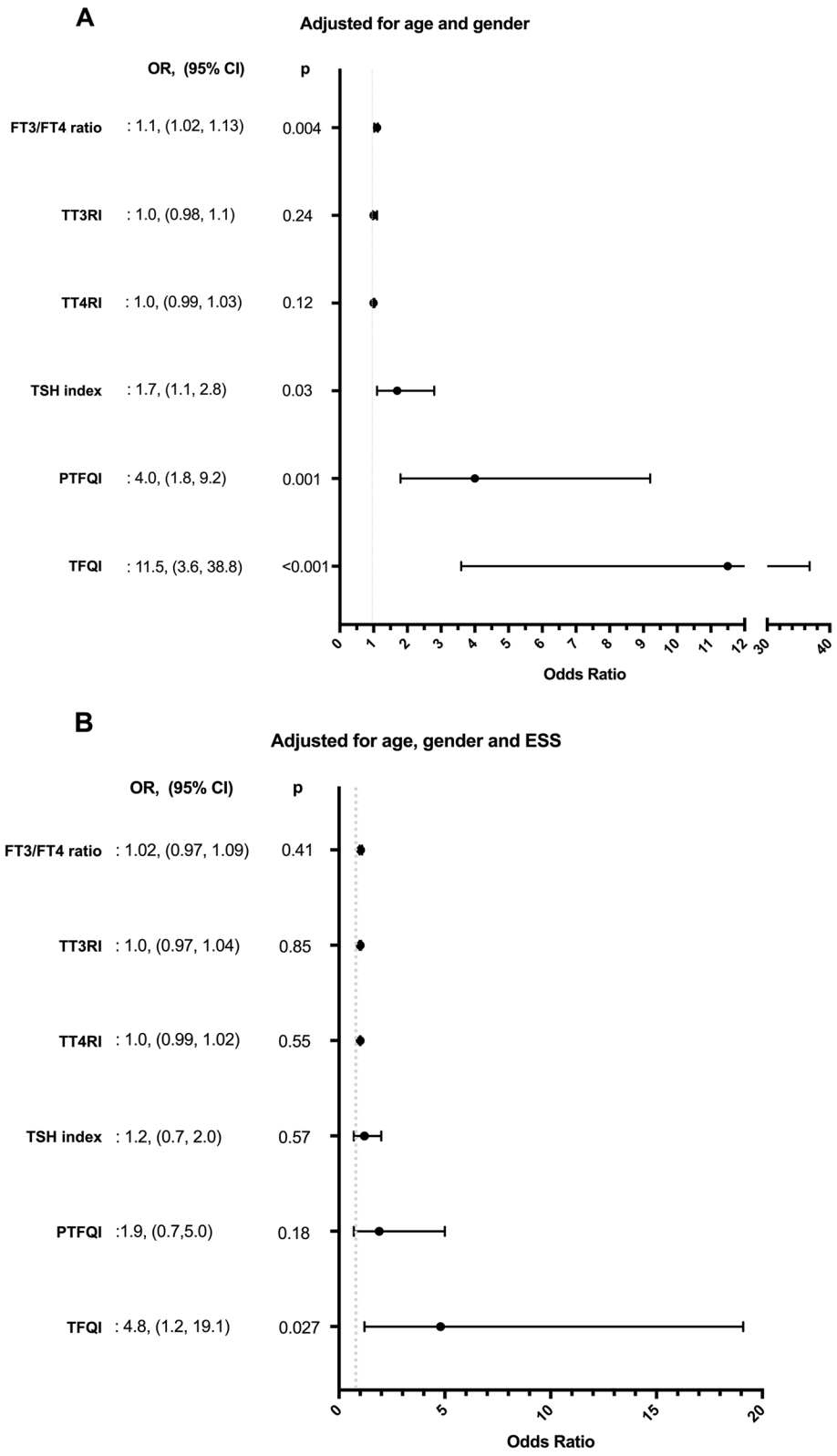

Fig. 1 (See legend on previous page.)

process, leading to diminished peripheral thyroid hormone action [22].

One possible explanation for these seemingly contrasting findings is that peripheral resistance to TH may represent a protective adaptation to reduce metabolic stress and energy consumption, especially in tissues affected by inflammation, oxidative stress, or energy shortages, as often seen in AKI [27, 28] and at the onset of T1DM [28–30]. As a consequence of this peripheral resistance, the central hypersensitivity could be a compensatory response by the HPT axis to maintain thyroid hormone levels and feedback control in the face of peripheral inefficiency.

These associations appear to be driven by ESS, a condition characterized by altered TH metabolism during acute illness without underlying thyroid dysfunction [15]. In ESS, alterations such as reduced FT3 production—closely associated with disease severity—are common and reflect impaired peripheral TH activity [31]. Thus, the increased central sensitivity may serve as a compensatory mechanism in response to peripheral resistance, ensuring adequate central TH production to meet the body's needs under altered conditions. Our findings partly support this hypothesis. With the exception of the association between AKI and TFQI, which remained significant in logistic regression analysis even after adjusting for ESS, the other associations lost their significance after adjustment for ESS.

From a pathophysiological perspective, one of the key mechanisms may involve the increase in pro-inflammatory cytokines (e.g., IL-6 and IL-8), which are commonly observed in children with DKA [32] or AKI [33]. These and other pro-inflammatory cytokines can impair thyroid function, contributing to the development of ESS and correlated changes in sensitivity to TH [34–36].

At the follow-up, we found that these differences in TH sensitivity between patients with and without AKI either completely disappeared (for TFQI, PTFQI, TT4RI, and TT3RI) or were mitigated (for TSHI and FT3/FT4 ratio).

To the best of our knowledge, no studies have previously investigated the relationship between TH sensitivity and AKI in the context of T1DM onset. TH sensitivity has only been studied in children with T1DM during the follow-up, compared with controls, and no differences in central sensitivity to TH were found between the groups [13]. However, patients with T1DM did exhibit a higher FT3/FT4 ratio, indicating increased peripheral sensitivity to TH [13].

Patients who experience an episode of AKI, particularly in its severe forms, are inherently at increased risk of developing CKD [5, 37]. Furthermore, evidence has shown that a longer timing of functional recovery from AKI is strongly associated with future adverse outcomes [38]. This highlights the necessity for clinicians managing patients with AKI to carefully consider both the severity of the condition and its progression, tailoring diagnostic and therapeutic strategies to promote rapid and complete recovery of kidney function [39].

In a previous study, we demonstrated that patients with both AKI and ESS required a longer time to recover kidney function compared to those with AKI alone [15]. Given that ESS is closely associated with altered TH sensitivity, it is plausible that patients with both AKI and ESS—along with their associated TH dysfunction—may face an additional risk of developing CKD in the long term compared to those with AKI alone. Long-term follow-up studies are necessary to confirm this hypothesis.

The observation that ESS and AKI, along with their impaired TH sensitivity, resolved in all participants suggests that treating thyroid dysfunction in these cases may not be necessary. It may simply reflect the greater severity of T1DM onset, which itself is associated with an elevated risk of complications such as AKI. However, whether a short course of TH treatment could accelerate AKI recovery and thereby reduce the risk of CKD remains an open question that warrants further investigation.

A limitation of our study is the single-center enrollment of the patients. However, this may be mitigated by the homogenous management of patients and their prospective enrollment.

Another limitation, applicable to all studies evaluating kidney function at the onset of T1DM, is that patients with DKA may exhibit elevated serum creatinine levels not only due to dehydration but also due to potential interference from ketoacids with the plasma creatinine assay, leading to falsely elevated plasma creatinine concentrations [40, 41]. Nevertheless, serum creatinine remains the primary marker of renal function used in routine clinical practice, even in patients with DKA. Therefore, there is a need to explore and adopt alternative markers of kidney function to enhance clinical practice.

Conclusions

In conclusion, we showed that AKI at the onset of T1DM has a dual effect on TH. It reduces peripheral sensitivity while increasing central sensitivity. This effect appears to be largely driven by ESS, with the exception of the association between AKI and TFQI, which remains independent of ESS. Future research could focus on evaluating whether these changes in TH sensitivity have long-term effects on kidney function.

Abbreviations

AKI	Acute kidney injury
CKD	Chronic kidney disease
DKA	Diabetic ketoacidosis

eGFR	Estimated glomerular filtration rate
ESS	Euthyroid sick syndrome
FT3	Free triiodothyronine
FT4	Free thyroxine
HbA1c	Glycated hemoglobin
HPT	Pituitary–hypothalamic–thyroid axis
PTFQI	Parametric TFQI
T1DM	Type 1 diabetes mellitus
TFQI	Thyroid Feedback Quantile-based Index
TH	Thyroid hormones
TSH	Thyroid-stimulating hormone
TSHI	TSH index
TT3RI	Thyrotroph T3 resistance index
TT4RI	Thyrotroph T4 resistance index

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None.

Authors' Contribution
PM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and conceptualized and designed the study, participated in the acquisition, analysis and interpretation of data, drafted the manuscript, critically revised the manuscript for important intellectual content, participated to statistical analysis and supervised the study. SG, VC, and ADS conceptualized and designed the study, participated in the acquisition, analysis and interpretation of data, critically revised the manuscript for important intellectual content. LL, MMM, AG, AZ, GZ, DI, and EMDG participated in the acquisition, analysis and interpretation of data, critically revised the manuscript for important intellectual content, participated to statistical analysis and participated in the statistical analysis. All authors approved the final version of the paper and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The Research Ethics Committee of Università degli Studi della Campania "Luigi Vanvitelli" (approval number 368). The investigation conforms to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from the parents of the patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Rabbone I, Maltoni G, Tinti D, Zucchini S, Cherubini V, Bonfanti R, et al. Diabetic ketoacidosis at the onset of disease during a national awareness campaign: a 2-year observational study in children aged 0–18 years. Arch Dis Child. 2020;105:363–6.
2. Rivetti G, Hursh BE, Miraglia del Giudice E, Marzuillo P. Acute and chronic kidney complications in children with type 1 diabetes mellitus. Pediatric Nephrology. 2023;38:1449–58.
3. Hursh BE, Ronsley R, Islam N, Mammen C, Panagiotopoulos C. Acute Kidney Injury in Children With Type 1 Diabetes Hospitalized for Diabetic Ketoacidosis. JAMA Pediatr. 2017;171: e170020.
4. Marzuillo P, Iafusco D, Zanfardino A, Guarino S, Piscopo A, Casaburo F, et al. Acute kidney injury and renal tubular damage in children with type 1 diabetes mellitus onset. J Clin Endocrinol Metab. 2021;106:e2720–37.
5. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81:442–8.
6. Huang JX, Casper TC, Pitts C, Myers S, Loomba L, Ramesh J, et al. Association of Acute Kidney Injury during Diabetic Ketoacidosis with Risk of Microalbuminuria in Children with Type 1 Diabetes. JAMA Pediatr. 2022;176:169–75.
7. Amiri FS. Bidirectional Interaction of Thyroid-Kidney Organs in Disease States. Int J Nephrol. 2020;2020:5248365.
8. Laclaustra M, Moreno-Franco B, Lou-Bonafonte JM, Mateo-Gallego R, Casasnovas JA, Guallar-Castillon P, et al. Impaired Sensitivity to Thyroid Hormones Is Associated With Diabetes and Metabolic Syndrome. Diabetes Care. 2019;42:303–10.
9. Jostel A, Ryder WDJ, Shalet SM. The use of thyroid function tests in the diagnosis of hypopituitarism: definition and evaluation of the TSH Index. Clin Endocrinol. 2009;71:529–34.
10. Wu Z, Jiang Y, Li P, Wang Y, Zhang H, Li Z, et al. Association of impaired sensitivity to thyroid hormones with hyperuricemia through obesity in the euthyroid population. J Transl Med. 2023;21:1–10.
11. Anderson JLC, Gruppen EG, van Tienhoven-Wind L, Eisenga MF, de Vries H, Gansevoort RT, et al. Glomerular filtration rate is associated with free triiodothyronine in euthyroid subjects: Comparison between various equations to estimate renal function and creatinine clearance. Eur J Intern Med. 2018;48:94–9.
12. Di Bonito P, Corica D, Marzuillo P, Di Sessa A, Licenziati MR, Faienza MF, et al. Sensitivity to Thyroid Hormones and Reduced Glomerular Filtration in Children and Adolescents with Overweight or Obesity. Horm Res Paediatr. 2024;97:383–7.
13. Calcaterra V, Mameli C, Macedoni M, De SA, Sgambetterra L, Nosenzo F, et al. Investigating the connection among thyroid function, sensitivity to thyroid hormones, and metabolic syndrome in euthyroid children and adolescents affected by type 1 diabetes. J Pediatr Endocrinol Metab. 2024;37:347–52.
14. Hu YY, Li GM, Wang W. Euthyroid sick syndrome in children with diabetic ketoacidosis. Saudi Med J. 2015;36:243–7.
15. Marzuillo P, Iafusco D, Guarino S, Di Sessa A, Zanfardino A, Piscopo A, et al. Euthyroid sick syndrome and its association with complications of type 1 diabetes mellitus onset. Pediatr Res. 2023;94:632–42.
16. Shao P, Guo S, Li G, Qin D, Li S, Luan Y. Determinants of deranged thyroid function parameters in children admitted for management of diabetic ketoacidosis/diabetic ketosis. BMC Endocr Disord. 2020;20:135.
17. Küme T, Sağlam B, Ergon C, Sisman AR. Evaluation and comparison of Abbott Jaffe and enzymatic creatinine methods: Could the old method meet the new requirements? J Clin Lab Anal. 2018;32: e22168.
18. Jaffe M. Ueber den Niederschlag, welchen Pikrinsäure in normalem Harn erzeugt und über eine neue Reaction des Kreatinins. bchm. 1886;10:391–400.
19. Kellum JA, Lameire N. KDIGO AKI Guideline Work Group Diagnosis, Evaluation, and Management of Acute Kidney Injury: A KDIGO Summary (Part 1) Crit. Care. 2013;17:204.
20. Schwartz GJ, Furth SL. Glomerular filtration rate measurement and estimation in chronic kidney disease. Pediatr Nephrol. 2007;22:1839–48.
21. Wang XJ, Qian XW, Zhang X, Han L, Zheng YQ, Wu T, et al. Association of serum uric acid with thyroid function in health check-up participants. Chin Med J (Engl). 2020;133:1409–14.
22. Dietrich JW, Landgrafe-Mende G, Wiora E, Chatzitomaris A, Klein HH, Midgley JEM, et al. Calculated Parameters of Thyroid Homeostasis: Emerging Tools for Differential Diagnosis and Clinical Research. Front Endocrinol (Lausanne). 2016;7:57.
23. Xie H, Li N, Zhou G, He Z, Xu X, Liu Q, et al. The association between the thyroid feedback quantile-based index and serum uric acid in U.S. adults. Eur J Med Res. 2023;28:1–14.
24. Fitzgerald SP, Bean NG, Falhammar H, Hoermann R. Physiological linkage of thyroid and pituitary sensitivities. Endocrine. 2023;79:143.

25. Zeng JL, Zhang LW, Liang WJ, You Z, Chen JH, Chen LC, et al. Predictive value of free triiodothyronine to free thyroxine ratio on contrast-associated acute kidney injury and poor prognosis in euthyroid patients after percutaneous coronary intervention. Int Urol Nephrol. 2024;56:3023–30.
26. Lang X, Li Y, Zhang D, Zhang Y, Wu N, Zhang Y. FT3/FT4 ratio is correlated with all-cause mortality, cardiovascular mortality, and cardiovascular disease risk: NHANES 2007–2012. Front Endocrinol (Lausanne). 2022;13: 964822.
27. Rashid H, Jali A, Akhter MS, Abdi SAH. Molecular Mechanisms of Oxidative Stress in Acute Kidney Injury: Targeting the Loci by Resveratrol. Int J Mol Sci. 2024;25:3.
28. McWilliam SJ, Wright RD, Welsh GI, Tuffin J, Budge KL, Swan L, et al. The complex interplay between kidney injury and inflammation. Clin Kidney J. 2021;14:780–8.
29. Elendu C, David JA, Udoyen A-O, Egbunu EO, Ogbuiyi-Chima IC, Unakalamba LO, et al. Comprehensive review of diabetic ketoacidosis: an update. Annals of Medicine and Surgery. 2023;85:2802.
30. Chaudhuri A, Umpierrez GE. Oxidative stress and inflammation in hyperglycemic crises and resolution with insulin: implications for the acute and chronic complications of hyperglycemia. J Diabetes Complications. 2012;26:257.
31. Ganesan K, Wadud K. Euthyroid Sick Syndrome. Treasure Island (FL): StatPearls Publishing; 2021.
32. Karavanaki K, Karanika E, Georga S, Bartzeliotou A, Tsouvalas M, Konstantopoulos I, et al. Cytokine response to diabetic ketoacidosis (DKA) in children with type 1 diabetes (T1DM). Endocr J. 2011;58:1045–53.
33. Liu KD, Altmann C, Smits G, Krawczeski CD, Edelstein CL, Devarajan P, et al. Serum Interleukin-6 and interleukin-8 are early biomarkers of acute kidney injury and predict prolonged mechanical ventilation in children undergoing cardiac surgery: a case-control study. Crit Care. 2009;13:R104.
34. Bartalena L, Bogazzi F, Brogioni S, Grasso L, Martino E. Role of cytokines in the pathogenesis of the euthyroid sick syndrome. Eur J Endocrinol. 1998;138:603–14.
35. Papanicolaou DA. Euthyroid Sick Syndrome and the Role of Cytokines. Rev Endocr Metab Disord. 2000;1:43–8.
36. Croce L, Gangemi D, Ancona G, Liboà F, Bendotti G, Minelli L, et al. The cytokine storm and thyroid hormone changes in COVID-19. J Endocrinol Invest. 2021;44:891–904.
37. Mammen C, Al Abbas A, Skippen P, Nadel H, Levine D, Collet JP, et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: A prospective cohort study. Am J Kidney Dis. 2012;59:523–30.
38. Bhatraju PK, Zelnick LR, Chinchilli VM, Moledina DG, Coca SG, Parikh CR, et al. Association Between Early Recovery of Kidney Function After Acute Kidney Injury and Long-term Clinical Outcomes. JAMA Netw Open. 2020;3: e202682.
39. Mehta RL. Renal Recovery After Acute Kidney Injury and Long-term Outcomes: Is Time of the Essence? JAMA Netw Open. 2020;3: e202676.
40. Kemperman FAW, Weber JA, Gorgels J, Van Zanten AP, Krediet RT, Arisz L. The influence of ketoacids on plasma creatinine assays in diabetic ketoacidosis. J Intern Med. 2000;248:511–7.
41. Greenberg N, Roberts WL, Bachmann LM, Wright EC, Dalton RN, Zakowski JJ, et al. Specificity characteristics of 7 commercial creatinine measurement procedures by enzymatic and jaffe method principles. Clin Chem. 2012;58:391–401.

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