Hormone Research in Paediatrics

Brief Report

Horm Res Paediatr
DOI: 10.1159/000534472

Received: July 28, 2023
Accepted: September 30, 2023
Published online: October 9, 2023

Sensitivity to Thyroid Hormones and Reduced Glomerular Filtration in Children and Adolescents with Overweight or Obesity

Procolo Di Bonito[a] Domenico Corica[b] Pierluigi Marzuillo[c] Anna Di Sessa[c] Maria Rosaria Licenziati[d] Maria Felicia Faienza[e] Valeria Calcaterra[f, g] Francesca Franco[h] Giulio Maltoni[i] Giuliana Valerio[j] Malgorzata Wasniewska[b]

[a]Department of Internal Medicine, "S. Maria delle Grazie" Hospital, Pozzuoli, Italy; [b]Department of Human Pathology of Adulthood and Childhood, University of Messina, Messina, Italy; [c]Department of Woman, Child and of General and Specialized Surgery, University of Campania "Luigi Vanvitelli," Napoli, Italy; [d]Neuro-Endocrine Diseases and Obesity Unit, Department of Neurosciences, Santobono-Pausilipon Children's Hospital, Napoli, Italy; [e]Department of Precision and Regenerative Medicine and Ionian Area, University of Bari "Aldo Moro," Bari, Italy; [f]Pediatric Department, Buzzi Children's Hospital, Milan, Italy; [g]Department of Internal Medicine, University of Pavia, Pavia, Italy; [h]Pediatric Department, Azienda Sanitaria Universitaria Friuli Centrale, Hospital of Udine, Udine, Italy; [i]Pediatric Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [j]Department of Movement Sciences and Wellbeing, University of Napoli "Parthenope," Napoli, Italy

Keywords
Estimated glomerular filtration rate · Children · Childhood obesity · Thyroid hormones · Sensitivity to thyroid hormones

Abstract

Background: Reduced central sensitivity to thyroid hormones (THs) has been observed in euthyroid adults with reduced renal function. This topic is unexplored in young people with overweight or obesity (OW/OB). ***Objective:*** The aim of this study was to evaluate the association between sensitivity to TH and mild reduced estimated glomerular filtration rate (MReGFR) in euthyroid children and adolescents with OW/OB. ***Methods:*** Data of 788 euthyroid children and adolescents with OW/OB (aged 6–16 years), recruited from seven Italian centers for the care of OW/OB, were evaluated. Peripheral sensitivity to TH was estimated through the FT3/FT4 ratio, while central sensitivity was assessed by estimating TSH index (TSHI), thyrotroph T4 resistance index, thyroid feedback quantile-based index (TFQI), parametric thyroid feedback quantile-based index (PTFQI). MReGFR was defined by an eGFR value ≥60 and <90 mL/min/1.73 m^2. ***Results:*** Subjects with MReGFR had significantly lower levels of FT3/FT4 ratio (0.43 ± 0.09 vs. 0.44 ± 0.10; $p = 0.028$) and higher levels of TSH (2.89 ± 1.00 vs. 2.68 ± 0.99; $p = 0.019$), TSHI (2.95 ± 0.45 vs. 2.85 ± 0.55; $p = 0.031$), TFQI [1.00 (0.98–1.00) versus 1.00 (0.97–1.00); $p = 0.046$], and PTFQI (0.66 ± 0.17 vs. 0.60 ± 0.23; $p = 0.006$) compared with individuals with normal eGFR. Odds ratio of

Procolo Di Bonito and Domenico Corica contributed equally to this work and shared first authorship.
Giuliana Valerio and Malgorzata Wasniewska contributed equally to this work and shared last authorship.

karger@karger.com
www.karger.com/hrp

Correspondence to:
Domenico Corica, dcorica@unime.it

MReGFR raised of 1.2–3.2-fold for each increase of 1 mIU/L in TSH, 1 unit in TSHI, and PTFQI, but not for FT3/FT4 ratio. ***Conclusion:*** MReGFR is associated with reduced indices of central sensitivity to TH in euthyroid children and adolescents with OW/OB. This preliminary observation should be confirmed in prospective studies.

Introduction

Thyroid hormones (THs) may affect renal function by influencing several mechanisms, such as renin-angiotensin system, renal perfusion, morphology, and function of the glomerular system. The available results regarding the link between TH and renal function are still conflicting [1–3]. Two independent studies recently observed that mild reduced estimated glomerular filtration rate (MReGFR) was associated with an abnormal cardiometabolic phenotype in young people with overweight/obesity (OW/OB) [4, 5]. However, the relationship between MReGFR and TH is unexplored in children and adolescents with OW/OB. This topic is intriguing since a recent study performed in a euthyroid adults Chinese population reported an association between reduced eGFR and a decreased central sensitivity to TH [6]. Based on these findings, it is possible to hypothesize that an altered sensitivity to the action of THs may be associated with reduced eGFR in euthyroid children and young people as well. The aim of this cross-sectional study was to evaluate the association between sensitivity to TH and MReGFR in euthyroid Caucasian children and adolescents with OW/OB.

Methods

Anthropometric, clinical, and biochemical data were provided from seven tertiary Italian centers for diagnosis and care of pediatric obesity. Records of 788 young people with OW/OB observed in the period 2016–2020 were analyzed. Inclusion criteria were: age 6–16 years, TH levels within normal range (according to the limit of laboratory in each center), as previously described [5]. Exclusion criteria were: thyroid diseases, genetic or endocrine obesity, chronic diseases, diabetes mellitus, and any pharmacological treatment. Moreover, to avoid the presence of children and adolescents with subclinical hypothyroidism, subjects with TSH values >4.9 mIU/L were excluded.

Peripheral sensitivity to TH was estimated as FT3/FT4 ratio, while central sensitivity was assessed by estimating TSH index (TSHI), thyrotroph T4 resistance index (TT4RI), thyroid feedback quantile-based index (TFQI), parametric thyroid feedback quantile-based index (PTFQI). TSHI was calculated as ln TSH (mIU/L) + 0.1345 × f T4 (pmol/L); TT4RI was calculated as f T4 (pmol/L) × TSH (mIU/L); TFQI was assessed as cdf f T4 – (1 – cdf TSH), where cdf is for empirical cumulative distribution function; PTFQI was assessed according to the following formula: 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 [7]. Reduced peripheral sensitivity to TH is evidenced by a reduced FT3/FT4 ratio, while reduced central sensitivity to TH is evidenced by a higher value of TSHI, TT4RI, TFQI, and PTFQI indices.

Serum creatinine (SCr) was analyzed by Jaffé method in 270 cases and by enzymatic method in 518 cases (0.57 ± 0.11 vs. 0.55 ± 0.13 mg/dL, $p = 0.012$). The difference between the two methods was compensated as previously described [8], obtaining quite comparable values (0.54 ± 0.11 vs. 0.55 ± 0.13, $p = 0.229$). eGFR was calculated using the full-spectrum eGFR equation for age: 107.3/SCr/Qcrea, where SCr was expressed in mg/dL and Qcrea was the median reference of SCr for sex and age [9]. MReGFR was defined by an eGFR value between ≥60 and <90 mL/min/1.73 m^2. OW and OB were defined as elsewhere described [7]. Prepubertal stage was defined by Tanner stage 1.

Values were expressed as mean ± standard deviation or percentage. The variables with skewed distribution (eGFR, HOMA-IR, TG/HDL ratio, TFQI) were log-transformed and expressed as median and interquartile range. The Student's *t* test was used to analyze differences between groups. χ^2 or Fisher's exact test was used to compare proportions. The associations between MReGFR and BMI-SDS were tested by linear regression analysis, as well the relationship between BMI-SDS, FT3/FT4 ratio, and PTFQI. The associations between MReGFR and indices of peripheral or central sensitivity to TH were tested by multiple logistic regression analysis, adjusted for centers, age, and prepubertal stage.

Statistical analysis was performed using the IBM SPSS Statistics, Version 20.0. The study was conducted according to the guidelines of the Declaration of Helsinki, and it was approved by the Ethics Committee of the AORN Santobono-Pausilipon (Reference number 22877/2020).

Results

Clinical and biochemical characteristics of the study population are shown in Table 1. Subjects with MReGFR were younger, more frequently prepubertal and showed higher levels of uric acid. Moreover, they had significantly lower levels of FT3/FT4 ratio and higher levels of TSH, TSHI, TFQI, and PTFQI compared with those with normal eGFR (Table 1). Linear regression analysis did not document a significant association between eGFR and BMI-SDS ($p = 0.749$). Likewise, no association was observed between BMI-SDS and FT3/FT4 ratio ($p = 0.820$) or PTFQI ($p = 0.273$). According to logistic regression analysis, the odds ratio of MReGFR raised of 1.2–3.2-fold for each increase of 1 mIU/L in TSH, 1 unit in TSHI, and PTFQI, but not for FT3/FT4 ratio, after adjustment for centers, age, and prepubertal stage (Table 2).

Table 1. Anthropometric, clinical, biochemical, and thyroid variables comparing young people with and without MReGFR

eGFR (mL/min/1.73 m^2)	eGFR ≥90	eGFR <90	*p* value
n = 788	645	143	
Age, years	11.3±2.3	10.8±2.7	0.008
Prepubertal stage, *n* (%)	86 (13.3)	34 (23.8)	0.002
Male gender, *n* (%)	333 (51.6)	67 (46.9)	0.301
BMI, kg/m^2	30.6±5.3	30.5±5.6	0.886
BMI-SDS	2.3±0.6	2.4±0.6	0.211
Fasting glucose, mg/dL	86.6±9.5	85.1±9.3	0.078
HOMA-IR	3.5 (2.4–5.0)	3.5 (2.3–5.0)	0.819
TG/HDL ratio	1.8 (1.3–2.7)	1.8 (1.3–2.6)	0.619
Uric acid, mg/dL	5.1±1.3	5.6±1.5	<0.0001
Systolic BP, mm Hg	112.3±13.6	111.1±15.1	0.353
Diastolic BP, mm Hg	66.3±9.5	66.9±9.8	0.504
FT3, pmol/L	6.22±0.92	6.06±1.03	0.061
FT4, pmol/L	14.38±2.53	14.53±2.35	0.547
FT3/FT4 ratio	0.44±0.10	0.43±0.09	0.028
TSH, mIU/L	2.68±0.99	2.89±1.00	0.019
TSH index	2.85±0.55	2.95±0.45	0.031
TT4RI	38.88±16.90	41.76±15.34	0.062
TFQI (Ln)	1.00 (0.97–1.00)	1.00 (0.98–1.00)	0.046
PTFQI	0.60±0.23	0.66±0.17	0.006

Data are expressed as mean ± standard deviation, median (IQ range), *n* (%). BMI, body mass index; SDS, standard deviation score; HOMA-IR, homeostasis model assessment of insulin resistance; TG/HDL ratio, triglycerides/HDL-cholesterol ratio; BP, blood pressure; TSHI, TSH index; TT4RI, thyrotroph T4 resistance index; TFQI, thyroid feedback quantile-based index; PTFQI, parametric thyroid feedback quantile-based index; MReGFR, mild reduced estimated glomerular filtration rate. MReGFR was defined by an eGFR value ≥60 and <90 mL/min/1.73 m^2.

Table 2. Odds ratios (95% CI) of MReGFR for 1 mIU/L increase of TSH or 1 unit of TSH index, PTFQI, or FT3/FT4 ratio

	eGFR <90 mL/min/1.73 m^2	*p* value
TSH (increase of 1 mIU/L)	1.22 (1.01–1.48)	0.042
TSH index (increase of 1 unit)	1.49 (1.01–2.21)	0.044
PTFQI (increase of 1 unit)	3.22 (1.20–8.65)	0.020
FT3/FT4 ratio	0.18 (0.02–1.74)	0.138

p value adjusted for centers, age, and prepubertal stage. PTFQI, parametric thyroid feedback quantile-based index; MReGFR, mild reduced estimated glomerular filtration rate. MReGFR was defined by an eGFR value ≥60 and <90 mL/min/1.73 m^2.

Discussion

Our study shows that MReGFR is associated with reduced central sensitivity to TH in euthyroid children and adolescents with OW/OB. To the best of our knowledge, this is the first study demonstrating this association in young people. Our finding is in agreement with Yang et al. [6]who demonstrated a reduced FT3/FT4 ratio and high levels of TSHI, TT4RI and PTFQI in euthyroid Chinese adults with reduced eGFR. Consistently, we observed an independent association between MReGFR and indices of reduced central sensitivity to TH. Conversely, although a lower FT3/FT4 ratio was observed in children and adolescents with MReGFR, this result was not confirmed by logistic regression analysis. The independent association between MReGFR and indices of reduced central sensitivity to TH we found in our cohort of euthyroid

children may add further evidence about the link between kidney and thyroid function in the context of OW and OB.

TH is involved in renal homeostasis. A condition of dysthyroidism may negatively affect renal function, although simple measurement of TH levels has not provided univocal results when evaluated with respect to changes in eGFR [1–3]. The explanation may be due to the complex interactions between the hypothalamic-pituitary-thyroid axis and peripheral tissues. Moreover, a reduction of eGFR has been found in euthyroid subjects with normal kidney function, in absence of diabetes and hypertension [6].

One explanation for these findings could result from the presence of altered tissue sensitivity to the action of TH, even within the normal range of TH serum levels. Nevertheless, the mechanisms underlying the association between TH sensitivity and renal function are not fully understood. We may speculate that the relative insufficiency of THs, caused by decreased peripheral and central sensitivity to their action, may also affect renal function because of the role THs play in directly and indirectly influencing renal activity.

A reduced central sensitivity to TH has been observed in adults with glucose dysmetabolism and metabolic syndrome even in the euthyroid subjects [10], and in euthyroid youths with OW/OB and impaired glucose tolerance [7]. Estimating central and peripheral sensitivity to the action of TH as an expression of thyroid homeostasis could therefore provide additional evidence regarding links between obesity, kidney, and thyroid function.

The close relationship between glomerular filtration and TH sensitivity in an OW/OB condition might be explained as a consequence of the occurrence of an allostatic adaptation mechanism. In conditions of energy overload, as it happens in obesity, an allostatic adaptation allows stability to be maintained (type 2 allostasis); however, changes derived from the new stability may not be favorable in the long term, such as a pro-inflammatory state [6, 11]. The significantly higher levels of the indices of central sensitivity to TH, expressing reduced central sensitivity that we found in subjects with MReGFR could be the consequence, at least in part, of a set-point change in thyroid homeostasis caused by allostatic-adaptive thyroid responses.

Although the estimation of TH sensitivity indices allows a more accurate assessment of the relationship between eGFR and thyroid homeostasis, the mechanism linking renal function and thyroid homeostasis remains to be elucidated. The cross-sectional, retrospective, design represents a limitation of our study. In addition, examining only young Caucasians with OW/OB limits the extendibility of the results to the general population.

Finally, the use of an age-based formula to calculate eGFR, because of its high sensitivity, could identify younger subjects with other possible causes of MReGFR, including anatomical and/or genetic causes that are difficult to identify in an epidemiological study. On the other hand, our study has significant strengths represented by a relatively large and well characterized sample of euthyroid Caucasian children and adolescents with OW/OB.

Conclusions

Our study documents an association between reduced indices of central sensitivity to TH and MReGFR in euthyroid children and adolescents with OW/OB. Our preliminary results support the hypothesis of a relationship between variation in sensitivity to TH action and glomerular function, suggesting a new insight to explain the relationship between renal and thyroid function.

Statement of Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the AORN Santobono-Pausilipon (Reference number 22877/2020). Consent to participate statement: Since this is a retrospective study of medical record data, consent to participate was not required. The study was exempted from Ethics Committee approval because it was confined to anonymous, non-identifiable data collected retrospectively (Ethics Committee of the AORN Santobono-Pausilipon; reference number 22877/2020).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This research received no external funding.

Author Contributions

Conceptualization: P.D.B. and D.C.; methodology: P.D.B., D.C., P.M., M.W., and G.V.; software: P.D.B.; formal analysis: P.D.B.; investigation: D.C., M.R.L., A.D.S., M.F.F., V.C., F.F., G.M. and M.W.; resources: D.C., M.R.L., A.D.S., P.M., M.F.F., V.C., F.F.,

G.M. and M.W.; data curation: P.D.B., D.C., G.V. and M.W.; writing – original draft preparation: P.D.B., D.C., P.M., G.V. and M.W.; writing – review and editing: all authors. All authors contributed to the manuscript revision, read, and approved the submitted version.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors on request, without undue reservation. Further inquiries can be directed to the corresponding author.

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