

**Carlos Enrique Ramos Urrea**

**Influência do eixo hormonal tireoidiano sobre a recuperação  
nutricional de crianças e adolescentes com excesso de peso**

Tese apresentada à Universidade Federal de  
São Paulo - Escola Paulista de Medicina, para  
obtenção do Título de Doutor em Ciências.

SÃO PAULO  
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**Orientadora:**

Profa. Dra. Eliane Beraldí Ribeiro

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**CARLOS ENRIQUE RAMOS URREA**

**INFLUÊNCIA DO EIXO HORMONAL TIREOIDIANO SOBRE A  
RECUPERAÇÃO NUTRICIONAL DE CRIANÇAS E ADOLESCENTES COM  
EXCESSO DE PESO**

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## **RESUMO**

Os hormônios tireoidianos desempenham múltiplos efeitos fisiológicos essenciais para a manutenção da taxa metabólica basal (TMB), termogênese adaptativa, metabolismo da gordura, crescimento e apetite. As relações entre obesidade e os hormônios do eixo tireoidiano, ou seja, triiodotironina (T3), tiroxina (T4) e tireotropina (TSH), ainda são controversas, principalmente quando se trata de crianças e adolescentes. Esta população apresenta altas taxas de sobrepeso e obesidade e diversas abordagens de tratamento, incluindo intervenções nutricionais, psicológicas e de exercícios físicos têm sido utilizadas. Compreender a importância dos hormônios do eixo tireoidiano na recuperação do sobrepeso e da obesidade pode auxiliar no direcionamento de medidas para a manutenção de uma composição corporal saudável.

Realizamos uma revisão de escopo para analisar estudos avaliando esses níveis hormonais em resposta a intervenções direcionadas ao tratamento de sobrepeso e obesidade em crianças e adolescentes. O objetivo principal foi verificar se os níveis hormonais variam durante a perda de peso. Selecionei 19 estudos publicados entre 1999 e 2022. A maioria dos estudos mostrou que alterações em diferentes indicadores antropométricos em resposta às intervenções multidisciplinares correlacionaram-se positivamente com T3 livre (fT3) | T3 total (TT3) / TSH. Com relação ao T4 livre (fT4) | T4 total (TT4), o achado mais comum foi de níveis inalterados e, assim, ausência de associação significante com perda de peso. É importante ressaltar que a resposta à intervenção não foi afetada pela suplementação de fT4. Mais estudos são necessários para elucidar a relevância das variações nos níveis hormonais para o estabelecimento do sobrepeso/obesidade e para a recuperação dessas condições em crianças/adolescentes.

Também examinamos o estado do eixo dos hormônios tireoidianos (TSH, fT3 e fT4) de 71 crianças com excesso de peso, antes e após uma intervenção multicomponente de longo prazo (aconselhamento nutricional e para atividade física, 27-29 meses). Nas crianças que obtiveram sucesso (grupo recuperado) ou falharam na normalização do IMC (grupo não-recuperado) em resposta à intervenção, avaliamos as relações entre os níveis hormonais e as medidas antropométricas.

No momento basal, os grupos tinham um Z-score de IMC/Idade semelhante, mas o grupo não-recuperado ( $n=44$ ) teve um Z-score de Altura/Idade maior do que o grupo recuperado ( $n=27$ ). No grupo recuperado, os níveis de fT3 foram menores do que no grupo não-recuperado, enquanto os níveis de fT4 e TSH foram semelhantes entre os grupos. Após a intervenção, os níveis de fT3 caíram no grupo recuperado, enquanto os níveis de fT4 e o Z-score de Altura/Idade caíram no grupo não-recuperado. O TSH não variou em ambos os grupos. Considerando os 2 grupos em conjunto, os níveis de fT3 correlacionaram-se positivamente com os Z-score de Altura/Idade basais e pós-intervenção e com o Z-score de IMC/Idade pós-intervenção. O teste do qui-quadrado ou o teste exato de Fisher (de acordo com os graus de liberdade) foi aplicado para analisar a associação do eixo hormonal tireoidiano com a recuperação do excesso de peso. A presença de níveis basais de fT3 na faixa baixa favoreceu a recuperação, conforme indicado por uma maior porcentagem de crianças com níveis de fT3 na faixa baixa no grupo recuperado do que no grupo não-recuperado. Após a intervenção, o percentual de crianças com níveis de fT3 na faixa de normalidade foi maior no grupo não-recuperado do que no grupo recuperado, indicando que níveis normais de fT3 não favoreceram a recuperação. O modelo de regressão logística mostrou que, tanto na linha de base quanto após a intervenção, a presença de valores de fT3 na faixa baixa aumentou cerca de 29,9 vezes e 47,2 vezes, respectivamente, a chance de recuperação. Não foram encontradas associações significantes entre recuperação e IMC/Idade, Altura/Idade, fT4 ou TSH.

Esses resultados indicaram que baixos níveis de fT3 associaram-se positivamente com a capacidade de se recuperar do excesso de peso, enquanto os níveis na faixa normal não foram tão eficazes. A comparação realizada no presente estudo, examinando as diferenças hormonais associadas à capacidade de recuperação do excesso de peso versus a resposta malsucedida, indica que as flutuações de fT3 podem ser vistas como um fator causal. Se essas associações estão relacionadas à existência de resistência às ações do T3 ou a outros distúrbios do eixo dos hormônios tireoidianos necessita de mais estudos.

#### Palavras-chave:

Z-escore de IMC/Idade, Z-escore de Altura/Idade, T3 livre, T4 livre, TSH, intervenção multicomponente.

## **ABSTRACT**

Thyroid hormones play multiple physiological effects essential for the maintenance of basal metabolic rate (BMR), adaptive thermogenesis, fat metabolism, growth, and appetite. The links between obesity and the hormones of the thyroid axis, i.e., triiodothyronine (T3), thyroxine (T4), and thyrotropin (TSH), are still controversial, especially when considering children and adolescents. This population has high rates of overweight and obesity and several treatment approaches, including nutritional, psychological, and physical exercise interventions have been used. Understanding the importance of the hormones of the thyroid axis in the recovery from overweight and obesity may help directing measures to the maintenance of a healthy body composition. We performed a scoping review to analyze studies evaluating these hormonal levels throughout interventions directed at treating overweight and obesity in children and adolescents. The main purpose was to ascertain whether the hormones levels vary during weight loss. We selected for analysis 19 studies published between 1999 and 2022. Most of the studies showed that changes in different anthropometric indicators in response to the multidisciplinary interventions correlated positively with free T3 (fT3)/ total T3 (TT3)/TSH. With respect to free T4 (fT4) / total T4 (TT4), the most common finding was of unchanged levels and hence, no significant association with weight loss. Importantly, the response to the intervention has even been found to not be affected by fT4 supplementation. Further studies are necessary to elucidate the relevance of the variations in hormone levels to the establishment of overweight/obesity and to the recovery from these conditions in children/adolescents.

We also examined the status of the thyroid hormones axis (TSH, free T3 and free T4) of 71 overweight children, both before and after a long-term multicomponent intervention (physical activity and nutritional counseling, 27-29 months). In children who were either successful (recovery group) or failed to achieve normalization of BMI (non-recovery group) in response to the intervention, we evaluated the relationships of hormonal levels and anthropometric measures.

At baseline, the groups had a similar BMI/Age Z-score but the non-recovery group (n=44) had a Height/Age Z-score higher than that of the recovery group (n=27). In the recovery group, fT3 levels were lower than in the non-recovery one while fT4 and TSH levels were similar between the groups. After the intervention, fT3 levels fell in the recovery group while fT4 levels and Height/Age Z-score fell in the non-recovery group. TSH failed to

vary in both groups. Considering the 2 groups together, fT3 levels correlated positively with baseline and post-intervention Height/Age Z-scores and with post-intervention BMI/Age Z-score. Chi-square test or the Fisher's exact test (according to the degrees of freedom) was applied to analyze the association of the thyroid hormone axis with recovery from overweight. The presence of fT3 levels in the low range at baseline favored the recovery from overweight, as indicated by a higher percentage of children with low-range fT3 levels in the recovery than in the non-recovery group. After the intervention, the percentage of children with fT3 levels in the normal range was higher in the non-recovery than in the recovery group, indicating that normal fT3 levels did not favor recovery. The logistic regression model showed that, both at baseline and after the intervention, the presence of fT3 values in the low range increased by around 29.9 times and 47.2 times, respectively, the chance to recover from overweight. No significant associations were found between recovery and BMI/Age, H/Age, fT4, or TSH.

These results indicated that low fT3 levels associated positively with the ability to recover from overweight while having levels in the normal range was not as effective. The comparison performed in the present study, examining the hormonal differences associated with the ability to recover from overweight versus the unsuccessful response indicate that fT3 fluctuations may be viewed as a causative factor. Whether these associations are related to the existence of resistance to T3 actions or to other disturbances of the thyroid hormones axis needs further studies.

**Keywords:**

BMI/Age Z-score, Height/Age Z-score, free T3, free T4, TSH, multicomponent intervention.

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## **LISTA DE ABREVIATURAS**

AgRP: proteína *agouti*

BC: composição corporal (do inglês “body composition”)

BMI: índice de massa corporal (do inglês “body mass index”)

BMR: taxa metabólica basal (do inglês “basal metabolic rate”)

CART: neurônios do transcrito regulado pela cocaína e anfetamina

CREN: Centro de Recuperação e Educação Nutricional

Cm: centímetros

DNA: ácido desoxirribonucleico

EM: entrevista Motivacional

EUT: eutireoideo

F: feminino

fT3: triiodotironina livre

fT4: tiroxina (tetraiodotironina) livre

GAB: Guia Alimentar Brasileiro

GH: hormônio do crescimento (do inglês “Growth hormone”)

H: Horas

HIIT: treinamento de alta intensidade (do inglês “High-intensity interval training”)

HTTR: hyperthyrotropinemia

IMC: índice de massa corporal

IOTF: força-Tarefa Internacional de Obesidade (do inglês “International Obesity Task Force”)

ISCOLE: International Study of Childhood Obesity Lifestyle and the Environment

L: Litros

M: masculino

Min: minutos

mil: Miliunidades

MII: treinamento de moderada intensidade (do inglês “Moderate-intensity interval training”)

MSH: hormônio melanócito-estimulante

NPY: neuropeptídeo Y

OB: crianças com obesidade

OMS: Organização Mundial da Saúde

OW: sobrepeso

Pmol: picomol

RMR: taxa metabólica em repouso (do inglês “resting metabolic rate”)

TRH: hormônio liberador de tireotrofina

TR: receptor tireoidiano (do inglês “Thyroid receptor”)

TSH: hormônio estimulante da tireoide

TTM: teste do Modelo Transteórico

TT3: triiodotironina total

TT4: tiroxina (tetraiodotironina) total

T3: triiodotironina

T4: tetraiodotironina

Y: ano (do inglês “year”)

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## **1. INTRODUÇÃO**

A obesidade resulta do desequilíbrio entre o consumo e o gasto de energia, tanto em adultos quanto em crianças. Essa condição complexa que entrelaça fatores biológicos, ambientais, comportamentais e genéticos, atingiu proporções epidêmicas e seus efeitos resultam em significativos custos à saúde pública (Agnihotri et al., 2014; Colquitt et al., 2016). A obesidade na infância também se associa a risco aumentado de distúrbios cardiovasculares e metabólicos na vida adulta (Enes & Slater, 2010; Torun et al., 2013).

De acordo com o International Obesity Task Force (IOTF), nos últimos 30 anos a prevalência de sobrepeso e obesidade em crianças e adolescentes aumentou tanto em países desenvolvidos quanto naqueles em desenvolvimento (Colquitt et al., 2016). Segundo publicação do Ministério da Saúde, a prevalência de obesidade no Brasil nos últimos 20 anos, referente à faixa etária entre 5 e 9 anos, passou de 4,1% para 16,6% entre os meninos e de 2,4% para 11,8% entre as meninas (Brasil, 2014). Já entre os adolescentes, aproximadamente 20% estão com excesso de peso, sendo que em torno de 6% destes já se encontram com obesidade (Victorino et al., 2014).

Nos últimos anos, tem havido um interesse crescente na relação entre a função da tireoide e o desenvolvimento da obesidade (Aeberli et al., 2010; Eliakim et al., 2006; Kumar et al., 2019; Licenziati et al., 2019; Longhi & Radetti, 2013; Marras et al., 2010; Martins et al., 2020; Reinehr, 2010; Rijks et al., 2017; Wolters et al., 2013). É sabido que os hormônios tireoidianos desempenham papel importante na regulação do metabolismo basal, termogênese, no metabolismo da glicose e dos lipídios (Longhi & Radetti, 2013). A tireoide produz dois hormônios importantes, a 3,5,3',5'-l-tetraiodotironina (T4) e a 3,5,3'-l-tri-iodotironina (T3), ambos relacionados à regulação do crescimento, metabolismo e desenvolvimento corporal, desempenhando papel fundamental na produção de proteínas estruturais, enzimas e outros hormônios (Barra et al., 2004; Mezzomo & Nadal, 2016). A deficiência de hormônios tiroidiano sé promove diversas alterações fisiológicas que podem levar ao desenvolvimento da obesidade (Santini et al., 2014).

Dadas as sérias comorbidades associadas à obesidade infantil, a eficácia do seu tratamento torna-se imperativa. Embora os princípios fundamentais do controle de peso em crianças sejam os mesmos que em adultos, ou seja, redução da ingestão de energia associada ao aumento do seu gasto, estudos recentes têm demonstrado que a adoção de uma abordagem multidisciplinar, caracterizada por intervenções na dieta, prática de atividade física e mudança de aspectos comportamentais e psicológicos têm se mostrado eficaz no

tratamento da obesidade infantil (Colquitt et al., 2016). Dentro deste contexto, o presente estudo tem como objetivo avaliar a influência do eixo hormonal tireoidiano sobre a recuperação nutricional de crianças e adolescentes com excesso de peso atendidos em um centro que utiliza abordagem multidisciplinar para o tratamento da obesidade.

## **2. REVISÃO DA LITERATURA**

### **2.1 Obesidade infantil – Conceito e aspectos epidemiológicos**

A obesidade é uma doença multifatorial que se beneficia de terapia interdisciplinar e estratégias preventivas. Comorbidades relacionadas à obesidade, como diabetes mellitus do tipo 2 e doenças cardiovasculares, representam atualmente os principais custos incorridos pelos sistemas de saúde (Brown et al., 2019; Finkelstein et al., 2014). Estudo realizado nos Estados Unidos estimou aumento de dezenove mil dólares americanos durante a vida nos custos médicos de uma criança com obesidade em comparação àquela eutrófica que se mantenha no peso adequado durante a vida adulta (Finkelstein et al., 2014). Por outro lado, estudo realizado na Austrália demonstrou que a redução nos valores de índice de massa corporal (IMC) em uma população de crianças com idade entre 2 a 5 anos poderia economizar, aproximadamente, de trezentos a um milhão de dólares australianos em custos de assistência à saúde, desde que essa redução se mantivesse no decorrer dos anos (Brown et al., 2019).

A prevalência de obesidade em crianças e adolescentes está aumentando em todo o mundo. Entre os anos 2000 e 2016, observou-se que a prevalência de sobrepeso na faixa etária dos cinco aos dezenove anos subiu de 10,3% para 19,2% em meninos e de 10,3% para 17,5% em meninas. Já a prevalência de obesidade nessa faixa etária subiu de 3,3% para 7,8% no sexo masculino e de 2,5% para 5,6% no sexo feminino (NCD, 2017). Em 2019, constatou-se que aproximadamente 38 milhões (5,6%) da população mundial de crianças abaixo de cinco anos estavam acima do peso (UNICEF/WHO/World Bank Group, 2020). Infelizmente, no Brasil há uma carência de grandes estudos populacionais com crianças e adolescentes para avaliação da prevalência do excesso de peso. As informações mais recentes de estudos indicam uma prevalência de excesso de peso na ordem de 15,3 e 29,1% (Sociedade Brasileira de Pediatria – Departamento de Nutrologia Obesidade na infância e adolescência, 2019). Um estudo realizado em creches no Piauí revelou prevalência de 4,2% de sobrepeso e obesidade em crianças com idade entre 2 e 5 anos (De Araujo et al., 2017). Já a Pesquisa de Orçamentos Familiares (POF) realizada entre os anos de 2008-2009 encontrou prevalência de sobrepeso em indivíduos entre 5-9 anos entre 32 e 40% na região Sul, Sudeste e Centro-Oeste do país, e entre 25 a 30% nas regiões Norte e Nordeste (IBGE, 2019). Um estudo realizado no município de São Caetano do Sul que fez parte do International Study of Childhood Obesity Lifestyle and the Environment (ISCOLE) com 584 crianças de 9 a 11 anos de idade revelou que 51.8% dessas crianças apresentavam sobrepeso ou obesidade (Ferrari et

al., 2017). Esse cenário deixa evidente a importância do diagnóstico precoce e do seu acompanhamento adequado, visando assim a redução do número de casos e possíveis agravos à saúde da criança. O desequilíbrio entre as calorias ingeridas e gastas, a susceptibilidade genética e a inatividade física somam-se a outros fatores de risco socioambientais como escola, família, comunidade e políticas públicas para explicar o recente aumento da prevalência de sobrepeso e obesidade entre crianças e adolescentes (Lee & Yoon, 2018).

Em 2007, a obesidade foi definida para crianças menores de cinco anos como um peso para a estatura maior do que três desvios padrões acima da mediana estabelecida (de Onis et al., 2007). Já para aquelas com idade entre cinco e dezenove anos foi determinada por dois desvios padrões acima da mediana para o IMC (de Onis et al., 2007). Essa classificação tem sido a mais usada em nosso meio. Há ainda a classificação proposta pelo IOTF, que baseia-se em uma curva de IMC para cada idade que corresponde aos valores de corte para obesidade na vida adulta (IMC maior ou igual a 30 kg/m<sup>2</sup>) (Cole & Lobstein, 2012).

A fisiopatologia da obesidade é complexa, sendo o resultado da combinação de diversos fatores metabólicos, genéticos, comportamentais, sociais e culturais (Kolotkin et al., 2001). Esses fatores não agem isoladamente, mas interagem propiciando um estado favorável para o desenvolvimento dessa enfermidade já nos primeiros anos de vida. A presença de um ambiente obesogênico, ou seja, altamente favorecedor de um estilo de vida sedentário e com o consumo excessivo de energia, associado à suscetibilidade genética, pode levar ao desenvolvimento precoce da obesidade (Lobstein et al., 2004; Wang & Lobstein, 2006). Assim, a etiologia da obesidade não é facilmente identificada na maioria dos casos, já que diversos fatores estão envolvidos no desenvolvimento e na manutenção dessa enfermidade.

## 2.2 Hormônios tireoidianos e seus aspectos fisiológicos

Os hormônios tireoidianos desempenham papel essencial na regulação do metabolismo energético, sendo a sua produção regulada pelo eixo hipotalâmico-hipofisário-tireoidiano (Yen, 2001). Em resposta a diversos estímulos periféricos e centrais, o hipotálamo libera o hormônio liberador de tireotrofina (TRH), que estimula as células tireotróficas da hipófise anterior a secretarem o hormônio estimulante da tireoide (TSH). Esse último ganha a circulação periférica e, na tireoide, liga-se a receptores específicos estimulando a síntese de T4 e T3, bem como a sua liberação pela glândula. Por outro lado, a síntese e a secreção do TRH e do TSH são inibidas pelos hormônios tireoidianos caracterizando, assim, um importante mecanismo de retroalimentação negativa (Agnihothri et al., 2014; Yen, 2001).

O T4 é o hormônio secretado principalmente pela tireoide, sendo apenas 20% do T3 circulante produzido diretamente por essa glândula. A maior parte do T3 presente na circulação é oriundo da desiodação periférica do T4, devido à ação das desiodases dos tipos 1 e 2 (Yen, 2001). É sabido que grande parte da atividade biológica dos hormônios tireoidianos decorre dos efeitos celulares do T3, uma vez que esse possui maior afinidade pelo receptor do hormônio tireoidiano e é pelo menos 10 vezes mais potente que o T4 (Agnihothri et al., 2014; Yen, 2001). Esses hormônios são pouco solúveis em água, portanto, uma vez liberados na circulação ligam-se reversivelmente as proteínas plasmáticas e, dessa forma, aumentam suas meias-vidas assegurando uma distribuição regular e homogênea nos diferentes tecidos-alvo. A globulina ligadora da tiroxina é uma glicoproteína que apresenta maior afinidade pelos hormônios tireoidianos carreando de 70 a 80%. Já a transtirretina se liga a 10%, a albumina em torno de 15% e o restante do T3 e do T4 plasmáticos (3-6%) estão ligados a lipoproteínas (Barra et al., 2004; Mullur et al., 2014).

A atividade biológica dos hormônios tireoidianos se dá pela ligação da fração livre desses hormônios (0,03% do T4 e 0,3% do T3) aos receptores específicos presentes no núcleo celular desencadeando a regulação da transcrição gênica nos tecidos-alvo (Friesema et al., 2005; Hennemann et al., 2001). Os hormônios tireoidianos entram nas células por transporte ativo utilizando transportadores específicos que incluem diversas famílias de proteínas carreadoras de solutos, ânions orgânicos, aminoácidos e transportadores monocarboxilato. Por outro lado, apenas pequena parcela é transportada por difusão passiva (Friesema et al., 2005; Hennemann et al., 2001).

Os receptores para os hormônios tireoidianos (TR) são fatores de transcrição ligante-dependentes que apresentam três domínios principais: 1) amino-terminal, 2) ligação ao ácido desoxirribonucleic (DNA), 3) ligação ao ligante (LBD) que é a porção carboxi-terminal, além de uma região de rotação da porção DNA em relação ao LBD denominada de “dobradiça” (Barra et al., 2004; Lazar, 1993). Existem dois subtipos de receptores,  $\alpha$  e  $\beta$ , que são codificados por dois genes distintos. Estudos na literatura demonstraram que as isoformas  $\alpha 1$ ,  $\beta 1$ ,  $\beta 2$  e  $\beta 3$  estão distribuídos de forma heterogênea nos diversos tecidos-alvo. Foi descrito maior abundância dos  $TR\beta 1$  no cérebro, fígado e rins, sendo a expressão do  $TR\beta 2$  observada, quase que exclusivamente, na hipófise anterior e em outras áreas do cérebro (Barra et al., 2004; Cheng, 2005; Lazar, 1993). Por outro lado, a expressão  $TR\alpha 1$  é bastante observada em músculos esqueléticos e no miocárdio (Cheng, 2005; Lazar, 1993). Um aspecto interessante dos hormônios tireoidianos é que eles apresentam a mesma afinidade pelas diferentes isoformas dos TR, portanto, a expressão variada dessas isoformas parece

constituir um dos mecanismos usados pelo T3 para a regulação dos tecidos de forma seletiva (Brent, 1994). Os hormônios tireoidianos podem também exercer suas ações na membrana plasmática e no citosol, independentemente da ligação ao receptor. Esse mecanismo envolveria a interação desses hormônios com segundos mensageiros, canais iônicos e a fosforilação oxidativa. É sabido que os hormônios tireoidianos ativam cinases e calmodulina, estimulando a captação de glicose em diversos tecidos e modulando o transporte intracelular do cálcio, via essa ação não-genômica. Contudo, a importância desses efeitos para o organismo é reconhecidamente menos significante que as ações mediadas pelos receptores (Bassett et al., 2003; Lin et al., 2003).

### 2.3 Hormônios Tireoidianos e a Obesidade

A composição corporal e os níveis de hormônios tireoidianos parecem estar intimamente correlacionados, uma vez que esses hormônios desempenham papel importante na regulação do metabolismo energético e da termogênese (Bjergved et al., 2014). O TSH é considerado o primeiro mecanismo regulatório do gasto energético total, pois estimula o gasto energético de repouso e modula tanto a termogênese quanto o metabolismo muscular (Agnihothri et al., 2014). Sabe-se que o T3 regula o metabolismo energético e a termogênese exercendo papel importante no controle da ingestão alimentar, oxidação de ácidos graxos e nas vias metabólicas da glicose e dos lipídios (Reinehr, 2010). A atividade termogênica desse hormônio é devida a sua ação sobre os receptores do tipo TR $\alpha$  (Reinehr, 2010; Silva, 2006). O tecido adiposo branco expressa as isoformas  $\alpha 1$  e  $\alpha 2$ , portanto a ligação do T3 a esses receptores afeta a atividade lipolítica (Santini et al., 2014). Por outro lado, a ligação do T3 aos receptores TR $\beta$  modula o metabolismo do colesterol (Silva, 2006).

Nas últimas décadas, diversos estudos na literatura têm avaliado a associação existente entre obesidade e a presença de disfunções tireoidianas (Bétry et al., 2015; Biondi, 2010; Eliakim et al., 2006; Golden et al., 2009; Knudsen et al., 2005; Lobotková et al., 2014; Reinehr, 2010). Foi relatada correlação positiva entre os níveis circulantes de TSH e o IMC em indivíduos adultos (Knudsen et al., 2005; Laurberg et al., 2006, 2012) e em crianças e adolescentes (Lobotková et al., 2014; Reinehr & Andler, 2002). Vale ressaltar que nesses estudos os valores de TSH encontravam-se dentro dos limites determinados de normalidade. Além disso, os níveis circulantes de T3 e T4 livres tendem a ser maiores em indivíduos obesos e isso foi descrito tanto na população adulta quanto na pediátrica (De Pergola et al., 2007; Reinehr, 2010; Reinehr & Andler, 2002; Rotondi et al., 2009). Além disso, foi observado em indivíduos com obesidade que a razão T3/T4 está

diminuída, sendo consistente com uma menor taxa de conversão devida a redução do processo de desiodação (Krotkiewski, 2002). Um aspecto interessante é que a redução de peso, seja ela resultado de mudanças de estilo de vida, dieta ou cirurgia, tende a melhorar as alterações de função tireoidiana observada na maioria dos indivíduos com obesidade (Dall'Asta et al., 2010; Fazylov et al., 2008; Reinehr et al., 2006; Reinehr & Andler, 2002).

Por outro lado, estudos descreveram níveis elevados de TSH na obesidade, achado interpretado como uma resposta adaptativa, destinada a aumentar atividade tireoidiana e a taxa metabólica. Já outros autores indicaram que a presença de resistência aos hormônios tireoidianos contribuiria como um fator causal da obesidade (Jaivinder et al., 2018; Witkowska-Sędek et al., 2017).

Os mecanismos envolvidos no aumento de TSH e dos hormônios tiroidianos periféricos são complexos e ainda não foram totalmente elucidados. A elevação de T3 e T4 pode ser indício de resistência à ação desses hormônios. De fato, tanto os receptores para o T3 quanto o processo de retroalimentação negativa entre o TSH e o T3 estão diminuídos na obesidade (Reinehr & Andler, 2002). Outra possível causa da ativação da tireoide relacionada ao excesso de peso pode estar relacionada com os níveis de leptina (Biondi, 2010; De Moura Souza & Sichieri, 2011; Isozaki et al., 2004; Rotondi et al., 2011; Vendrell et al., 2004). De fato, a leptina pode ser considerada um importante modulador da função tireoidiana em pacientes obesos que não apresentam quadro clínico de disfunção da tireoide (Isozaki et al., 2004). É sabido que, em estado de jejum, a função tireoidiana diminui promovendo redução do gasto energético. Por outro lado, a secreção de leptina também reduz com a restrição de alimentos, sugerindo que tanto a leptina quanto a tireoide podem responder paralelamente (Pinkney et al., 1998).

A leptina é secretada de acordo com adiposidade e atua estimulando o catabolismo (Barsh & Schwartz, 2002; Lustig, 2001). Esse hormônio inibe os neurônios orexigênicos hipotalâmicos de neuropeptídeo relacionado à proteína *agouti* (AgRP) e de neuropeptídeo Y (NPY), que estimulam a ingestão alimentar e inibem o gasto energético. Por outro lado, estimula neurônios anorexigênicos de hormônio melanocito-estimulante (MSH), um derivado pós- translacional da pro-opiomelanocortina (POMC), e neurônios do transcripto regulado pela cocaína e anfetamina (CART) que atuam como inibidores da ingestão alimentar e promovem o aumento do gasto energético (Barsh & Schwartz, 2002; Lustig, 2001). Portanto, alterações na neurobiologia desses grupamentos de neurônios podem levar ao desenvolvimento da obesidade (Barsh & Schwartz, 2002).

O exato mecanismo de ação da leptina sobre a função tireoidiana ainda não foi totalmente elucidado. Existe uma interação complexa entre os hormônios tireoidianos e o tecido adiposo, onde o TSH e os hormônios tireoidianos podem participar da diferenciação dos adipócitos (Obregon, 2008) e da regulação da lipólise (Endo & Kobayashi, 2012), enquanto várias citocinas liberadas pelos adipócitos podem interagir com o eixo hipotálamo-hipófise-tireoide (Boelen et al., 2008; Feldt-Rasmussen, 2007; Sainsbury & Zhang, 2012). Acredita-se que redução dos níveis circulantes de leptina é capaz de gerar um sinal periférico que atua inibindo diretamente o eixo hipotálamo-hipófise-tireóide. Tem sido descrito que a leptina também age a nível hipotalâmico modulando a estimulação da secreção hipofisária de TSH (Ghamari-Langroudi et al., 2010; Pearce, 2012; Reinehr & Andler, 2002). Além disso, foi observada correlação inversa entre T3 e leptina (Krotkiewski, 2002). É sabido que a leptina inibe a expressão e secreção de TRH no núcleo paraventricular do hipotálamo. Esse papel regulatório pode ser caracterizado como uma resposta ancestral, objetivando a economia de energia durante períodos de escassez de alimentos (Ghamari-Langroudi et al., 2010; Iacobellis et al., 2005).

Os dados acima expostos mostraram que o sobrepeso e a obesidade em crianças e adolescentes constitui um importante problema de saúde pública. A reversão destas condições é difícil, mas crucial para prevenir suas consequências a longo prazo. Várias abordagens têm sido utilizadas para este fim, incluindo as nutricionais, psicológicas e programas de exercício físico. Os estudos apontaram que as intervenções multidisciplinares são o método mais efetivo para alcançar a recuperação antropométrica (Hoelscher et al., 2013; NCD, 2017).

Foi abordado também que os hormônios tireoidianos têm importante papel fisiológico na regulação da homeostase energética e do crescimento. No sobrepeso/obesidade de crianças e adolescentes, foram relatados desarranjos dos hormônios do eixo tireoidiano, mas os dados não são conclusivos. O entendimento destes aspectos bem como da importância destes hormônios na recuperação do sobrepeso e obesidade pode contribuir para o direcionamento de medidas para a manutenção de uma composição corporal saudável.

### **3. OBJETIVOS**

#### **3.1 Objetivo geral**

Avaliar a influência do eixo hormonal tireoidiano sobre a recuperação nutricional de crianças e adolescentes com excesso de peso.

#### **3.2 Objetivos específicos**

- Realizar uma revisão de escopo sobre estudos que avaliaram as variações dos níveis dos hormônios do eixo tireoidiano em resposta a intervenções destinadas a tratar sobre peso e obesidade em crianças e adolescentes.
- Em crianças com sobre peso, verificar se a capacidade de recuperação antropométrica em resposta a uma intervenção multidisciplinar tem relação com os hormônios do eixo tireoidiano. Em crianças que mostraram recuperação ou que não se recuperaram, avaliaremos os níveis de TSH e de T3 e T4 livres (fT3 e fT4).

## **4. MÉTODOS**

### **4.1 Artigo 1 - Revisão de Escopo**

A revisão de escopo foi registrada no International Prospective Register of Systematic Reviews (PROSPERO, CRD42020203359) e realizada segundo as recomendações do Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).

Os critérios de elegibilidade foram: artigos originais publicados em periódicos com revisão por pares, escritos em inglês, português ou espanhol, que tinham crianças e/ou adolescentes com sobrepeso ou obesidade como participantes e que realizaram algum tipo de intervenção para controle de peso, incluindo nutricional e/ou psicológica e/ou médica e/ou exercício físico. Os critérios de exclusão foram: estudos em animais, em humanos adultos, uso de hormônio de crescimento ou esteroides, diagnóstico de doenças da tireoide, rins, coração ou neurológicas. Os tipos de estudos foram: ensaios clínicos e estudos longitudinais.

A busca da literatura foi realizada em janeiro de 2022, nas bases de dados MEDLINE (via Pubmed), Latin American and Caribbean Literature in Health Sciences (LILACS), Scopus (Elsevier) e Cochrane Library. Não houve determinação do período de publicação. O desenvolvimento das estratégias de busca seguiu as recomendações do Peer Review of Electronic Search Strategies (PRESS) (Mcgowan et al. 2016).

As estratégias de busca utilizadas foram:

Pubmed e Cochrane: (((((obesity OR overweight OR obese OR excess weight OR weight gain) AND (child OR children OR adolescents) AND (thyroid hormones OR Thyroid concentrations OR Thyroid Stimulating Hormone OR triiodothyronine OR Thyroxine OR Thyroid Gland OR T3 OR T4 OR TSH))) AND (humans[Filter])))

Scopus: (obesity OR overnutrition OR 'excess weight loss' OR 'excess weight' OR 'body weight gain' OR malnutrition OR 'obese patient') AND (('thyroid hormone' OR 'thyroid concentrations' OR thyroid) AND stimulations OR triiodothyronine OR thyroxine OR 'thyroid gland') AND (child OR adolescent) AND [humans]/lim

Lilacs: tw:((tw:(obesity OR overweight OR obese OR "excess weight" OR "weight gain" OR malnutrition)) AND (tw:(("thyroid hormones" OR "Thyroid concentrations" OR "Thyroid Stimulating Hormone" OR triiodothyronine OR thyroxine OR "Thyroid Gland")) AND (tw:(child\*))) AND ( db:( "LILACS" OR "IBECS" OR "MedCarib" OR "BINACIS" OR "CUMED" OR "colecionaSUS" )))

A seleção e análise dos estudos foi realizada por 3 pesquisadores independentes usando a ferramenta Rayyan. A primeira seleção foi baseada no título e sumário. Artigos duplicados ou cujo texto completo não estava disponível foram excluídos. Os conflitos quanto à inclusão dos artigos foram resolvidos por consenso. Os artigos selecionados para análise foram lidos integralmente por 3 pesquisadores independentes para identificação dos dados relevantes à análise.

Para caracterizar os achados foram considerados idade, gênero, tipo de intervenção, efeito da intervenção sobre parâmetros antropométricos e níveis hormonais, tanto no momento basal quanto no pós-intervenção. Os artigos foram agrupados por tipo de comparação realizada, isto é, intra-grupo ou com indivíduos eutróficos. Dois estudos envolvendo suplementação com tiroxina constituíram a terceira categoria.

## 4.2 Artigo 2

### Amostra

Esta pesquisa utilizou dados secundários de crianças portadoras de sobrepeso, atendidas no Centro de Recuperação e Educação Nutricional-CREN no período compreendido 2007 e 2018. O CREN é um centro que oferece atendimento ambulatorial a crianças com desnutrição. Situa-se na região sul da cidade de São Paulo e é vinculado à Universidade Federal de São Paulo (UNIFESP).

Foi levantada no banco de dados do CREN uma amostra de conveniência que incluiu 71 crianças com sobrepeso. Foram incluídas crianças de ambos os sexos, que no momento inicial (pré-intervenção) tinham idade entre 2 e 7 anos. As crianças tinham Z-score IMC/Idade entre 2 e 3 e Z-score Estatura/Idade maior que -2.

### Desenho do estudo

Para este estudo longitudinal, foram levantados os dados constantes dos prontuários eletrônicos e físicos, em dois momentos. No momento inicial, as crianças foram avaliadas por um médico e um nutricionista, passaram por avaliação antropométrica e receberam as orientações que deveriam ser seguidas para o tratamento. No momento final, que aconteceu entre 20 e 35 meses mais tarde, foi realizada nova avaliação antropométrica. Nos dois momentos, houve realização de exames sanguíneos para determinação dos níveis de triiodotironina livre (fT3), tiroxina livre (fT4) e hormônio tireoide estimulante (TSH).

### Protocolo de tratamento

A assistência incluiu monitoramento contínuo da saúde e intervenção em casos de infecções, parasitas e anemia. Pediatras, nutricionistas, assistentes sociais, educadores físicos e psicólogos participaram da elaboração dos regimes de tratamento e do manejo das crianças. O estado clínico, os achados laboratoriais e a evolução antropométrica foram monitorados pelo pediatra e nutricionista. A dieta da criança é seguida e ajustada, se necessário, durante o tratamento. Os exames laboratoriais para sangue e fezes são realizados em intervalos de 5 ou 6 meses. As crianças também receberam doses profiláticas de ferro e vitaminas A, B, C e D. O tratamento visa a recuperação do peso e da estatura, o melhor impacto na saúde em longo prazo e a recuperação da desnutrição e inclui:

a) Aconselhamento Nutricional. No primeiro encontro, o nutricionista identificou a prontidão para mudança do paciente, de acordo com a metodologia do Teste do Modelo Transteórico (TTM) para Mudança de Comportamento. Após a classificação do estágio de mudança, o foco da consulta passou a ser o aconselhamento nutricional por meio da estratégia de Entrevista Motivacional (EM). EM é um aconselhamento diretivo centrado no cliente que visa estimular a mudança de comportamento, ajudando os participantes a explorar e resolver sua ambivalência (conflito entre dois caminhos a seguir, neste caso, hábitos alimentares saudáveis ou não saudáveis). O nutricionista, portanto, não prescreve planos ou estratégias alimentares para controle de calorias, mas foca na identificação do estado de prontidão para mudar, intervir para reforçar as medidas positivas tomadas pelos pacientes e seus familiares, e estabelecer novas metas, fornecendo novas informações sobre estilo de vida saudável. Essas metas baseiam-se nas Diretrizes para o Tratamento da Obesidade Infantil, bem como nas recomendações da Organização Mundial da Saúde (OMS) e no Guia Alimentar Brasileiro (GAB). Os objetivos da estratégia foram os seguintes: reduzir o consumo de bebidas açucaradas com aumento progressivo na ingestão de água potável, reduzir o consumo de alimentos fritos e ultra processados substituindo-os por opções de alimentos crus ou minimamente processados, aumentar o consumo de frutas e vegetais (meta de 3 a 5 porções / dia), evitar o sedentarismo (diminuir o tempo de tela para menos de 2 h / dia) e aumentar a atividade física regular (meta de 60 min por dia / 5 dias a semana). Essas metas foram reavaliadas a cada nova visita e redefinidas ou reforçadas para o período seguinte. Além disso, foi realizado recordatório alimentar de 24 horas durante a consulta, como ferramenta para orientar o aconselhamento e estabelecer metas mensais para o paciente. A duração desta consulta foi de 40 minutos (primeira consulta) e 30 minutos (visitas de retorno).

- b) Cuidados Clínicos. A avaliação clínica foi baseada na avaliação geral do paciente, incluindo exame físico para definição do estágio puberal, da pressão arterial, e avaliação de parâmetros laboratoriais. Participantes com comorbidades, como por exemplo, diabetes, dislipidemias, hipertensão, resistência à insulina, hiperinsulinemia ou hiperglicemia foram tratadas de acordo com as Diretrizes da Sociedade Brasileira de Pediatria. Os participantes com alterações ortopédicas, dermatológicas, renais, hepáticas, respiratórias ou psicológicas foram encaminhadas aos especialistas adequados. Pacientes com diagnóstico de deficiência / insuficiência de vitamina D ( $25\text{OHD} <20 \text{ ng/ml}$  e  $<30 \text{ ng/ml}$ , respectivamente) foram tratados com suplementação adequada. Os participantes com  $25\text{OHD}$  sérico, concentrações de  $\geq 30 \text{ ng/ml}$ , recebem suplemento de colecalciferol (D3) de 600 UI/dia para manutenção por três meses consecutivos. Os participantes que não recuperam a deficiência de vitamina D após esse período recebem suplementação adicional de 50.000 UI de colecalciferol, uma vez por semana, por outras 6 semanas, seguida de avaliação repetida de D  $25\text{OH}$  após esse período.
- c) Aconselhamento Psicológico. As crianças identificadas com algum sofrimento psicológico significativo durante as consultas nutricionais ou médicas e mesmo aqueles que procuram ajuda ativamente foram atendidos individualmente por meio de sessões de aconselhamento psicológico. Nessas sessões, o terapeuta buscou em conjunto com as crianças um entendimento da demanda e problema de vida, bem como uma forma possível de resolvê-los (Patriota, 2017).

### **Avaliação antropométrica.**

As crianças foram pesadas sem roupas e calçadas, em balança digital (capacidade máxima de 15 kg, precisão de 65 g; Kratos, Embu, SP, Brasil) para crianças com peso inferior a 15 kg ou balança plataforma (capacidade máxima de 150 kg, precisão de 6100 g; Filizola, São Paulo, SP, Brasil) para maiores de 15 kg. A estatura foi medida com estadiômetro de parede vertical (Wiso, Curitiba, PR, Brasil) com dimensão máxima de 200 cm e precisão aproximada de 0,1 cm (Alves Vieira, Ferraro, Nascimento Souza, Fernandes, & Sawaya, 2010). Os indicadores Z-score IMC/Idade e Z-scores E/Idade foram calculados utilizando-se o software *Anthro* (para as crianças menores de 5 anos) e *Anthro plus* (para crianças maiores de 5 anos) (versão 1.0.4) (OMS, 2009).

### **Hormônios tireoidianos**

Para definição da adequação dos níveis hormonais foram utilizados os valores de referência pediátricos descritos no estudo CALIPER (Adeli, Higgins, Trajcevski, & White-Al Habeeb, 2017), segundo a tabela abaixo.

Tabela 1. Valores de referência de fT3 (pmol/L)

Intervalo de referência				
Feminino			Masculino	
Idade	Limite mínimo	Limite máximo	Limite mínimo	Limite máximo
4 dias a 1 ano	3.56	7.48	3.56	7.48
De 1 a 12 anos	4.29	6.79	4.29	6.79
De 12 a 15 anos	3.84	6.06	4.44	6.65
De 15 a 19 anos	3.55	5.70	3.46	5.92

Tabela 2. Valores de referência de fT4 (pmol/L)

Intervalo de referência (Ambos os sexos)		
Idade	Limite mínimo	Limite máximo
5 a 14 dias	13.5	41.3
De 15 a 29 dias	8.7	32.5
De 30 dias a 1 ano	11.4	21.9
De 1 a 19 anos	11.4	17.6

Tabela 3. Valores de referência de TSH (mIU/L)

Intervalo de referência (Ambos os sexos)		
Idade	Limite mínimo	Limite máximo
4 dias a 6 meses	0.73	4.77
De 6 meses a 14 anos	0.70	4.17
De 14 a 19 anos	0.47	3.41

## Análises estatísticas

Foram inicialmente realizadas análises estatísticas descritivas univariadas. A normalidade e a homogeneidade das variáveis foram avaliadas pelo teste de Shapiro-Wilk e Levene, respectivamente.

As variáveis qualitativas foram apresentadas em número de casos, absoluto e percentual, e analisadas pelo teste do Qui quadrado ou teste exato do Fisher, de acordo com os graus de liberdade.

As variáveis quantitativas paramétricas foram apresentadas como média e desvio padrão e analisadas pelo teste t de Student para amostras independentes. As variáveis quantitativas não-paramétricas foram apresentadas como mediana e intervalo interquartil e analisadas pelo teste de Mann Whitney.

Os coeficientes de correlação de Person e Spearman foram utilizados para detecção de associações entre as variáveis quantitativas paramétricas e não paramétricas, respectivamente.

Modelos de regressão logística foram construídos para avaliar a existência de influência dos hormônios do eixo tireoidiano sobre a recuperação nutricional.

O poder estatístico foi calculado pelo Gpower 3.1.9.7 (Universidade do Kiel) e foi determinado uma amostra de 138 crianças em total, com um poder estatístico de 95% para o teste F usando Mann-Whitney Test (2 grupos) e um tamanho do efeito de 0.5 baseado nestes cálculos o total da amostra foi estatisticamente adequada para cumprir as hipóteses apresentadas e as análises feitas.

Os dados foram digitados em Excel e processados pelo software SPSS versão 24. Em todas as análises, foi adotado  $p \leq 0,05$  como nível mínimo de significância.

## **5. RESULTADOS E DISCUSSÃO**

Os resultados e discussão estão apresentados na forma de dois artigos científicos:

Artigo 1- Thyroid axis hormones and anthropometric recovery of children/adolescents with overweight/obesity: a scoping review

Artigo 2 – Low T3 levels favor anthropometric recovery in prepubertal children with overweight

# Thyroid axis hormones and anthropometric recovery of children/adolescents with overweight/obesity: a scoping review

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**Abstract:** Thyroid hormones exert multiple physiological effects essential to the maintenance of basal metabolic rate (BMR), adaptive thermogenesis, fat metabolism, growth, and appetite. The links between obesity and the hormones of the thyroid axis, i.e., triiodothyronine (T3), thyroxine (T4), and thyrotropin (TSH), are still controversial, especially when considering children and adolescents. This population has high rates of overweight and obesity and several treatment approaches, including nutritional, psychological, and physical exercise interventions have been used. Understanding the importance of the hormones of the thyroid axis in the recovery from overweight and obesity may help directing measures to the maintenance of a healthy body composition. The present scoping review was carried out to analyze studies evaluating these hormonal levels throughout interventions directed at treating overweight and obesity in children and adolescents. The main purpose was to ascertain whether the hormones levels vary during weight loss. We selected for analysis 19 studies published between 1999 and 2022. Most of the studies showed that changes in different anthropometric indicators, in response to the multidisciplinary interventions, correlated positively with free T3 (fT3), total T3 (TT3), and TSH. With respect to free T4 (fT4) and total T4 (TT4), the most common finding was of unchanged levels and, hence, no significant association with weight loss. Moreover, thyroxine supplementation has failed to affect the response to the interventions. Further studies are necessary to elucidate the relevance of the variations in hormone levels to the establishment of overweight/obesity and to the recovery from these conditions in children/adolescents.

**Keywords:** Thyroid hormones; multidisciplinary intervention; obesity

## 1. Introduction

Globally, obesity is a well-recognized public health problem affecting both adults and children (1). In children/adolescents, the prevalence of overweight/obesity is high (2) and associates with increased risk to develop diabetes and other co-morbidities (3).

The pathophysiology of overweight/obesity includes genetic, environmental, behavioral, metabolic, psychological factors, and hormonal factors. The thyroid hormones exert multiple physiological effects essential to the maintenance of basal metabolic rate (BMR), adaptive thermogenesis, fat metabolism, growth, and appetite (4). The participation of the levels of the hormones of the thyroid axis, i.e., thyrotropin-releasing hormone (TRH), thyrotropin (TSH), triiodothyronine (T3), and thyroxine (T4), and has been studied with no conclusive results, especially when

considering children and adolescents. They have indicated either that thyroid-hormones resistance is a causal factor of obesity or that elevated hormone levels may represent an adaptive response to obesity (5).

The treatment of children and adolescents with overweight or obesity is a very relevant issue, and several approaches, including nutritional, psychological, and physical exercise interventions have been used (6). Understanding the importance of the hormones of the thyroid axis in the recovery from overweight and obesity may help directing measures to the maintenance of a healthy body composition.

The present scoping review was carried out to analyze studies evaluating these hormonal levels throughout interventions directed at treating overweight and obesity in children and adolescents.

## **2. Materials and Methods**

This scoping review was registered on the International Prospective Register of Systematic Reviews (PROSPERO, CRD42020203359) and performed in accordance with the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).

### *2.1. Eligibility criteria*

We included original articles published in peer-reviewed journals, written in English, Portuguese, or Spanish, that had children and/or adolescents with overweight or obesity as participants and that performed some intervention for weight management, including, nutritional and/or psychological, and/or medical, and/or exercise.

The exclusion criteria were studies in animals or adults, use of growth hormone or steroid hormones, diagnostic of thyroid, kidney, heart, or neurological illness. The types of studies included were clinical trials and longitudinal studies. Review articles were excluded.

### *2.2. Literature search*

Data collection and analysis were performed in January 2022. Electronic searches were conducted using the following databases: MEDLINE via Pubmed, Latin American and Caribbean Literature in Health Sciences (LILACS), Scopus (Elsevier) and Cochrane Library. All articles appearing in the searches were included, with no pre-determined period. The following descriptors were extracted from the Health Science Descriptors database: obesity, overweight, obese, excess weight, weight gain, malnutrition, thyroid hormones, thyroid concentrations, thyroid-stimulating hormone,

triiodothyronine, thyroxine, thyroid gland, child, children, adolescents, humans. The development of the search strategy followed the recommendations of the checklist Peer Review of Electronic Search Strategies (PRESS) (7).

### *2.3. Study selection and appraisal*

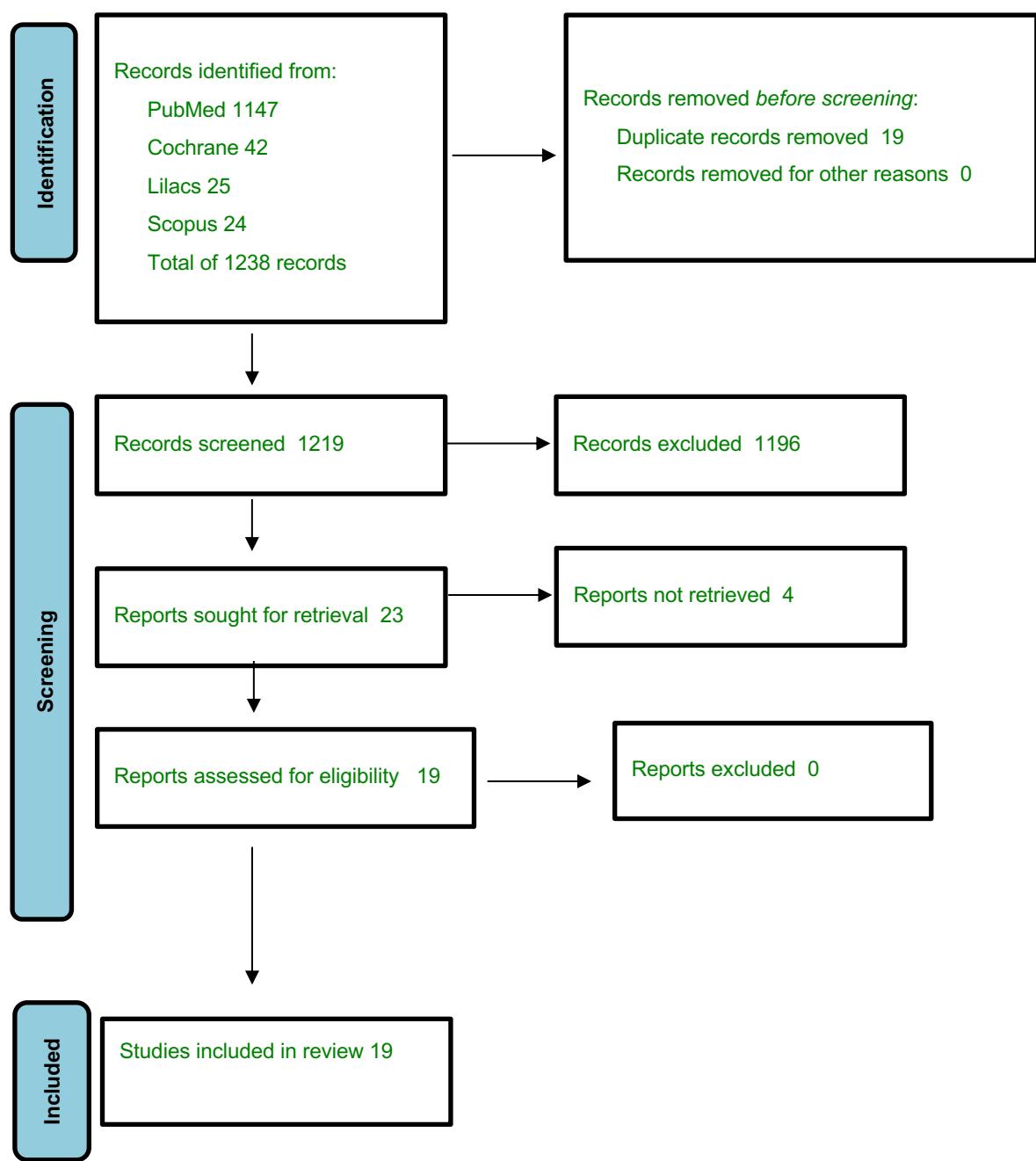
Three authors performed independent selection and analysis of the studies, using the Rayyan tool. The first selection was based on the title and summary of the studies. Duplicates and articles whose full texts were not available were excluded. Conflicts were resolved by consensus. After selection according to the inclusion criteria, the 3 authors independently analyzed the full texts to identify the relevant outcomes.

#### Data extraction and synthesis of results

To characterize the findings, the following variables were considered: age, sex, type of intervention, effect of the intervention on body composition and on hormone levels, both at baseline and after the intervention. The articles were grouped by type of comparisons performed (intra-group or between obese and eutrophic). Two studies involving thyroxine supplementation constituted a third category.

## **3. Results**

A total of 1219 articles were screened, leading to 23 eligible articles, of which 4 were excluded due to absence of full texts. Nineteen articles were thus included in the qualitative analysis. Figure 1 describes the selection process and Table 1 shows the results of each selected articles.



**Figure 1.** Flow diagram of the studies' selection.

**Table 1.** Summary of the characteristics and results of the 19 studies included in the analysis.

Reference	Sample (Age)	Groups/Gender	Intervention type and duration	Effect of Intervention n*	Hormones		Authors' conclusion	Our observation
					Baseline	After intervention		
<b>Studies allowing intra-group comparisons</b>								
Martins et al. 2020 (8)	School 1: 73 School 2: 103 (8-11y)	School 1: OW/ OB (BMI ≥ 1 Z-score) School 2: OW/ OB (BMI ≥ 1 Z-score)	School 1: Nutrition education workshops at school (10 months) followed by outpatient clinical care and nutritional counseling (16 months)  School 2: Nutrition education, supervised physical activity and reflective meetings at school (16 months) followed by outpatient clinical care and nutritional counseling (16 months)	ft3: both schools had normal levels (School 2: 8% above normal range). School 2 levels lower than School 1  BMI Z-score decreased in both schools  TSH: normal levels in both schools.  School 2 levels lower than School 1	ft3: both schools had normal levels (School 2: 8% above normal range). School 2 levels lower than School 1  ft4: normal levels in both schools.  School 2 levels lower than School 1  TSH: decreased levels in School 1	ft3: decreased levels in both Schools.  School 1 levels lower than School 2  ft4: decreased levels in both schools.  School 1 levels lower than School 2  TSH: decreased levels in School 1	The decrease in delta BMI/Age was similar in both schools and was accompanied by a decrease in TSH and ft3 concentrations	The different multidisciplinary interventions were effective in reducing BMI, ft3, ft4 and TSH
Lass et al. 2020 (9)	28 (10.2 ± 2.2 y)	28 OW 14 M; 14 F (BMI > 90th percentile)	Lifestyle intervention (physical exercise, nutrition education, and psychological therapy) (1 year)	BMI Z-score decreased*	ft3: normal range  ft4: normal range  TSH: high range	ft3: decreased  ft4: unchanged  TSH: decreased	Thyroid volume correlates positively to weight status in childhood obesity. Change reverts after weight loss independently of	Weight loss induced by multidisciplinary intervention for 1 year decreased ft3 and TSH levels

								thyroid function parameters
Abasi et al. 2020 (10)	16 (15 – 17y)	16 OW/OB girls (No information on criteria)	Moderate- or High-intensity interval training (MIIT or HIIT) (3 months)	BMI Z-score decreased in both groups*	fT4: normal range TSH: normal range	fT4: decreased only in HIIT TSH: decreased only in HIIT	Pituitary-thyroid function is more sensitive to training intensity than training duration	Although both MIIT and HIIT decreased BMI similarly, only HIIT was effective in lowering fT4 and TSH
Kiortsis et al. 1999 (11)	64 (10 – 14y)	64 OB (RBW>120%) 22 M; 42 F	Caloric restriction, including a 24h recall method (6 weeks)	BMI decreased*	Baseline values not reported	TT3: decreased TT4: unchanged TSH: unchanged	The decline in TT3 levels seems to play an important role in the decrease of RMR in children	TT3 levels decreased along with weight loss
Rijks et al. 2017 (12)	330 (2.6 – 18.9y)	66 OW (BMI Z-score >75<90), 148 OB (BMI Z-score=90<97), 115 MO ( $\geq$ 97) 142 M; 188 F	Tailored lifestyle intervention (nutritional education and physical activity (1 year)	BMI Z-score decreased*	fT4: no differences among the subgroups OW, OB and MO  TSH: no differences among the subgroups OW, OB and MO	fT4: decreased in children with decreased BMI Z-score (n = 62), but unchanged in children with increased BMI Z-score (n = 37)  TSH: unchanged children showing weight loss	In OW and OB, TSH is positively associated with CVD markers. Changes in TSH are also associated with changes in lipid concentrations in children showing weight loss	fT4 levels decreased along with weight loss
Aeberli et al. 2010 (13)	206 (10 – 18y)	206 OB (BMI- SDS >98 percentile) 119 M; 87 F	Hypocaloric diet, physical activity, and psychological treatment	BMI-SDS decreased*	fT3: normal range fT4: normal range	fT3: decreased fT4: unchanged	TSH concentrations tend to be higher in OB	fT3 and TSH levels decreased along with weight loss

			(8 weeks)	TSH: normal range (52% in the high normal range and 1.9% had HTTR)	TSH: decreased (but 44% in the high normal range and 0.5% had HTTR)	
Shalitin et al. 2009 (14)	207 (5 – 18y)	197 OB completed the intervention	Hypocaloric diet (12 weeks)	TT3: normal range fT4: normal range TSH: 161 subject showed normal range levels; 46 subjects showed levels above the normal range	TT3: not reported <b>fT4:</b> $\Delta 0.18 \pm 1.9$ in the 125 children with decreased BMI-SDS; <b>TSH:</b> $\Delta -0.28 \pm 1.12$ in the 125 children with decreased BMI-SDS; $0.06 \pm 2.13$ in the 16 children with no BMI-SDS changes	No significant differences regarding fT4 and TSH between the children showing decreased BMI-SDS and those showing no BMI-SDS changes
Bas et al. 2013 (15)	150 (3 – 17y)	150 OB (BMI Z-score >percentile 95) 67 M; 83 F Only 21 OB who had TSH	Nutrition education and physical activity (6 months)	BMI Z-score decreased Baseline values not reported BMI Z-score unchanged	<b>fT3:</b> decreased <b>fT4:</b> unchanged <b>TSH:</b> decreased <b>fT3:</b> unchanged <b>fT4:</b> unchanged <b>TSH:</b> unchanged	TSH and fT3 levels are significantly increased in childhood obesity with weight loss

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levels above the  
normal range at  
baseline were  
evaluated after  
the intervention

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Wolters et al. 2013 (16)	477 (10.6 ± 2.7y)	477 OB (BMI- SDS >97 percentile) 219 M; 258 F	Lifestyle intervention (physical exercise, nutrition education, and psychological therapy) (1 year)	BMI-SDS decreased *	<b>fT3:</b> normal range <b>fT4:</b> normal range <b>TSH:</b> High range	<b>fT3:</b> unchanged <b>fT4:</b> unchanged <b>TSH:</b> unchanged	Moderately increased TSH and fT3 concentrations in OB, which normalized after substantial weight loss	No changes in fT3, fT4 and TSH levels along with weight loss
Licenziati et al. 2019 (17)	96 (4.7 – 16.4y)	96 OB (BMI- SDS >75 percentile) 49 M; 47 F	Dietary recommendations, physical activity, and behavioral strategies (0.8 ± 0.3 year)	BMI-SDS decreased *	<b>fT4:</b> normal range <b>TSH:</b> High range - TSH levels exceeded the normal range in 83.3% of the OB	<b>fT4:</b> unchanged <b>TSH:</b> decreased - TSH levels exceeded the normal range in 57.3% of OB	The alterations of thyroid function and structure in OB are reversible after weight loss	OB with alterations of thyroid structure (volume, echogenicity, homogeneity of parenchima) showed decreased TSH levels along with weight loss
Bouglé et al. 2014 (18)	528 (4.1 – 17.9y)	528 OW + OB (BMI Z-score >2 SDS) 238 M; 290 F  79 subjects completed the intervention	Nutritional education and physical activity (52 ± 15 weeks)	BMI Z-score decreased	<b>fT3:</b> normal range <b>fT4:</b> normal range  <b>TSH:</b> in the group with normal TSH at baseline, 26 and 42 subjects showed decrease and increased TSH levels, respectively. TSH decreased in all patients	<b>fT3:</b> unchanged <b>fT4:</b> unchanged  <b>TSH:</b> normal range levels, but 69 showed levels above the normal range	Increased TSH may be predictive of decreased insulin resistance; fT4 was associated with a low metabolic risk. Changes in thyroid function could protect against obesity-associated metabolic diseases	Non-significant decrease of fT3, fT4, TSH and BMI Z-score

							with initial values above the normal range
Radetti et al. 2012 (19)	72 (8 – 14y)	72 OW/OB (BMI-SDS >85 percentile) 41 M; 31 F	Meetings with dietician and instructions on physical activity at 3-month intervals (1.8 ± 1.0 year)	BMI-SDS decreased	<b>fT3:</b> normal range <b>fT4:</b> normal range <b>TSH:</b> normal range (17.2% high range)	<b>fT3:</b> decreased <b>fT4:</b> unchanged <b>TSH:</b> decreased. 6.2% of the children showed a TSH above the normal range	A yet slightly reduced body fat can be followed by an improvement in biochemical parameters such as TSH and fT3  <b>fT3 and TSH levels decreased along with a non-significant weight loss</b>

#### Studies conducted with comparisons between excess weight and euthrophic groups

Marras et al. 2010 (20)	520 (3.7 – 17.9y)	Intervention group 468 OB (BMI- SDS >95 percentile) 213 M; 255 F	Educational program: Dietary guidelines and decreased in physical activity (6 months)	BMI-SDS decreased in the OB group	<b>fT3:</b> no difference (17.9% above the normal range) <b>fT4:</b> no differences (1.28% above normal range) <b>TSH:</b> no differences (3.2% above normal range)	<b>fT3 and fT4 normalized in 63% of the patients who showed abnormal concentrations at baseline</b>	In OB, an increased fT3 concentration is the most frequent thyroid function abnormality. Serum fT3 and TSH correlate with BMI-SDS. Moderate weight loss frequently restores these abnormalities  <b>fT3 levels were higher in only 17.9% of OB. 63% of OB who had abnormal thyroid hormone levels presented normalization of these hormones along with weight loss</b>
Control Group 52 EUT 24 M; 28 F							

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		<b>Between-groups comparison (n = 50)</b>	
		<b>fT3:</b> no differences	
		<b>fT4:</b> no differences	
		between boys, but OB girls had higher levels than EUT girls	
Cayir et al. 2014 (21)	109 (5 – 18y)	<b>TSH:</b> no differences	Normal thyroid function in OB, not influenced by a prolonged period of caloric restriction
		<b>In-group comparison (n = 36)</b>	higher in OB girls than in EUT girls, reaching normal levels along with weight loss induced by caloric restriction
		<b>fT3:</b> unchanged	
		<b>fT4:</b> no changes among the boys. OB girls showed decreased levels (became like the EUT girls)	
		<b>TSH:</b> unchanged	
		Control Group: 24 EUT 13 M; 11 F	

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		Intervention group: 246 OB (BMI Z-score >97 percentile) 109 M; 137 F 49 OB	<b>fT3:</b> OB had higher levels than EUT (normal range)	<b>fT3:</b> OB with substantial weight loss showed decreased levels
Reinehr et al. 2006 (22)	317 (9.5 – 12y)	completed the intervention	<b>fT4:</b> no differences (normal range)	<b>fT4:</b> unchanged fT3 and TSH were moderately increased in OB and weight loss
		Control group: 71 EUT (30 M; 41 F) (Information about the treatment or intervention performed for this group is not described)	<b>BMI Z-score</b> decreased with substantial weight loss	<b>TSH:</b> OB had higher levels than EUT (17% above normal range) led to a reduction. Substantial weight loss decreased fT3 and TSH. The elevation of these hormones seems to be rather a consequence of obesity than a cause of obesity

		Intervention group: 118 OB (BMI Z-score >97 percentile) 63M; 55 F - 68 OB completed the intervention	BMI Z-score decreased (n=55) Baseline values not reported	<b>TT3:</b> decreased <b>TT4:</b> decreased <b>TSH:</b> unchanged	<b>TT3, TT4 and TSH levels were moderately increased in OB at baseline.</b> A normal energy diet induces a long-term decrease in the peripheral thyroid hormones as opposed to TSH
Reinehr et al. 2002 (23)	225 (4.5 – 16y)	Control group: 107 EUT (61 M; 46 F) (No information about intervention in the control group)	Physical exercise, nutrition education, and psychological therapy (12 months)		levels moderately increased in OB than in controls TT3 and TT4 levels decreased along with intervention-induced weight loss in OB

		Intervention group: 11 MO (BMI >50 or ≥40 with comorbidities) 3 M; 2 F	Roux-en-Y gastric bypass surgery (RYGB). The subjects were reevaluated 12 months after surgery	BMI decreased after RYGB*	<b>TT3:</b> decreased <b>fT3:</b> unchanged <b>TT4:</b> unchanged <b>fT4:</b> unchanged <b>TSH:</b> decreased	Energy adaptations that occur in adolescents following RYGB possibly involves TT3 mediation	TT3 and TSH levels decreased along with BMI decrease induced by RYGB
Butte et al. 2015 (24)	16 (12 – 17y)	Control group: 5 MO who rejected bariatric surgery		Baseline values not reported			

Studies involving thyroxine supplementation							
Eliakim et al. 2006 (25)	41 OB (5 – 17y) with HTTR	Intervention group: 26 OB (BMI >85 percentile), with HTTR, supplementatio n	BMI decreased in both supplemented and not supplemented groups	<b>fT4:</b> normal range	<b>fT4:</b> no differences between supplemented and non-supplemented groups	HTTR is relatively common in OB. TSH levels returned to normal in the majority of patients even without thyroid hormone administration. No beneficial effects on body weight and BMI were found in treated subjects, suggesting that thyroid substitution is not necessary in most cases	TSH levels decreased independent of thyroxine supplementation
Kumar et al. 2019 (26)	51 OB with HTTR (6 – 12y)	Control group: 15 OB, with HTTR, without thyroxine supplementatio n	thyroxine supplementation (1-2 µg/kg) for 6 months	<b>TSH:</b> HTTR	<b>TSH:</b> decreased in both supplemented and not supplemented groups	Supplementation of levothyroxine during weight management interventions, and should not be prescribed to children with obesity associated	Supplementation with levothyroxine has no effect on weight loss

Control group: 25 OB without levothyroxine supplementatio n	<b>TSH:</b> decreased in both groups. No differences between groups.	thyroid dysfunction
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\* p<0.05 versus baseline according to the effect of the intervention in relation to the body mass index.

T3 = triiodothyronine; T4 = thyroxine; TSH = thyrotropin; TT3 = total T3; TT4 = total T4; fT3 = free T3; fT4 = free T4

M = male; F = female; BC = body composition; EUT = eutrophic; OW = children with overweight; OB: children with obesity; MO = children with morbid obesity; MIIT = Moderate-intensity interval training; HIIT: High-intensity interval training; HTTR = hyperthyrotropinemia; RMR = resting metabolic rate.

RBW = Relative body weight: child's weight divided by the expected weight for height and multiplied by 100.x

**Table 2.** Correlations between anthropometric recovery and hormonal levels.

Reference / correlation test	Significant Correlations	
	Baseline	After intervention
Marras et al. 2010 (20) Pearson correlation	TSH and fT3 correlated positively with BMI-SDS	
Bouglé et al. 2014 (18) Simple correlations	TSH correlated positively with BMI Z-score	
Aeberli et al. 2010 (13) Pearson analysis	Body weight correlated negatively with fT3 Percentage body fat correlated positively with fT4	Delta fT3 correlated positively with body weight, BMI-SDS, fat mass, and percentage body fat and negatively with lean body mass. Delta fT4 correlated negatively with percentage body fat
Lizziati et al. 2019 (17) Bivariate correlation	TSH correlated positively with BMI-SDS	TSH correlated positively with BMI-SDS
Martins et al. 2020 (8) Pearson and Spearman correlations	fT3 correlated positively with BMI/Age Z-score	fT3 correlated positively with BMI/Age Z-score
Kiortsis et al. 1999 (11) Pearson correlation	TT3 correlated positively with BMI	
Bas et al. 2013 (15) Pearson correlation		TSH and fT3 correlated positively with BMI Z-score
Reinehr & Andler 2002 (23) Pearson correlation		TT3 and TT4 correlated positively with BMI Z-score
Butte et al. 2015 (24) Pearson correlation		TT3 and TSH correlated positively with BMI

### 3.1. Description of the included studies

The literature search identified 1219 references (Figure 1) and 19 articles met all the inclusion criteria.

Table 1 summarizes the characteristics of the studies included in the analysis. There are studies performed with subjects from Germany (9,16,22,23), Italy (17,19,20), France (11,18), Israel (14,25), Turkey (15,21), Netherlands (12), Switzerland (13), United States (24), Brazil (8), Tunisia (10), and India (26).

Thirteen studies analyzed only obese children and adolescents (9,11,13–17,20,22–26) while the other 6 studies targeted both overweight and obese children and/or adolescents (8,10,12,18,19,21).

In 4 studies (11, 15, 23, 24) the baseline hormonal values were not informed but the authors reported the changes induced by the interventions, hence they were included in the analysis.

Table 2 describes the correlations between the thyroid hormonal axis and body composition parameters in the 9 studies that performed this calculation. At baseline, body weight was negatively correlated with fT3 (13), the percentage of fat mass was positively correlated with fT4 (13), and BMI was positively correlated with TSH (17,18,20) and fT3 (8,20). After intervention, BMI correlated positively with fT3, and/or TSH, TT3, and TT4 (8,15,17,23,24). When considering the baseline/after intervention changes, the authors reported positive correlations of BMI and TT3 (11,23,24), fT3 (8,13,15), TT4 (23), and TSH (15,17,24). Also, fT3 correlated positively with body weight, fat mass, and percentage body fat (13). Negative correlations were seen between lean body mass and fT3 and percentage body fat and fT4 (13).

### *3.2. Interventions*

The duration of the interventions varied from 6 weeks to 18 months. One study utilized only a nutritional intervention (11) and one study applied only exercise intervention (10). Six studies performed nutritional intervention plus exercise intervention (14,15,18–21). One study allied nutritional and exercise interventions to administration of thyroxine (25).

In 7 studies, a psychological intervention was added to the nutritional plus exercise intervention (8,9,13,16,17,22,23). One study performed the 3 interventions plus levothyroxine supplementation (26). One study performed psychological and exercise interventions (12) and 1 study used only a surgical intervention (24).

### *3.3. Nutritional Interventions*

Seventeen studies used nutritional interventions (8,9,11-23,25,26). In many studies, the characteristics of the intervention were not detailed. The descriptions of the nutrition interventions performed included: dietary recommendations (17), meetings with dietitian (19), diet list based on the ideal body weight (21), behavioral modification and diet plans (26). Four

studies used a calorie restriction approach, with varying energy levels and macronutrient combinations (11,13,14,25). Two studies used 1200 kcal/day (11,14). One study adapted the caloric restriction to the subject's weight, using 1200, 1400, or 1600 kcal/day for the subjects with less than 50 Kg, 50-80 Kg, or more than 80 Kg of body weight, respectively (13). One study decreased the restriction throughout the duration of the intervention, using 600 (up to 1.5 month), 1100 (1.5 to 6 months), or 1400 kcal/day (6-12 months) (25). Nine studies reported the use of a nutrition education approach (8,9,12,15,16,18,20,22,23). Professionals in nutrition and dietetics performed sessions relaying information on food selection, diet, food habits, and food macronutrients composition and energetic densities. The sessions were directed to the children/adolescents only (9,15,16,22,23) or included also their parents (20) and school teachers (8). In two studies only the parents were addressed (12,18).

### 3.4. Exercise Interventions

Sixteen studies utilized physical exercise interventions. Eleven studies conducted supervised training sessions with no specific routine or duration, with varying types and intensities (8,9,12,15–19,22,23,26), 1 involved two daily group endurance exercise sessions to improve aerobic performance, with a typical session lasting 60–90 min (13), and 3 performed aerobic exercise 3–5 times/week for at least 45–60 min (20), 30 minutes per day (21), or 90 minutes per day (14). One study involved either high- or moderate-intensity interval training for 45 min 3 times/week (10).

### 3.5. *Psychological intervention*

This type of intervention was used in 9 studies and included individual psychological care of the child/adolescent (8,9,13,17,26) or of them and their family (12,16,22,23). In the 2 studies detailing the psychological intervention, it consisted of techniques focusing on increasing self-esteem, responsibilities, and problem-solving strategies (12), relaxation techniques and breathing therapy (13).

#### **4. Discussion**

All the 19 studies included in this analysis, published between 1999 and 2020, achieved anthropometric recovery of the overweight/obese children/adolescents in response to the interventions, which, as depicted in table 1, varied largely with respect to the type and duration.

Among the 17 studies utilizing nutritional interventions (8,9,11-23,25,26), 9 studies stated the use of a nutrition education approach (8,9,12,15,16,18,20,22,23). There was no mention about a distinction between nutrition education and nutrition counseling (51) in any of these 9 studies.

One study (8) performed a nutrition intervention based on consultations focused on a "Motivational Interviewing", aimed at stimulating behavioral change (52). Four studies utilized a 1-year lifestyle intervention called Obeldicks, in which the nutritional intervention consisted of individual coaching on the concept of prevention through an "optimized mixed diet" (9,16,22,23).

One study reported the use of an educational program in which normocaloric dietary guidelines were proposed to children and parents, based on the adoption of the Mediterranean diet and considering the dietary habits and age of the children (20). One study reported that "the dietary intervention consisted of 6 months of meetings with a dietitian, where the participants received nutritional education, and information about food choices, diet, cooking and eating habits" (15).

One study reported that an individual food plan was developed for each child/family, based on their specific needs and possibilities. They stated that: "The behavior change strategies used were motivational interviewing, goal setting, positive reinforcement, social support, and relapse prevention" (12). One study explained the nutrition intervention as follows: "Attempts to understand the causes of unhealthy habits and to obtain changes from the family; imply parents in these changes; obtaining the disappearance of junk foods from family shelves; decreasing the caloric density of cooking and the quantities served, without any prohibition except fried foods and chocolate spreads" (18).

Concerning the baseline levels (before intervention) of the thyroid hormones (fT3, fT4, TT3 or TT4), 6 studies did not report these data (11,12,15,23,24,26). Among the 13 studies in which this

information was available, the majority (11 studies) reported no significant alterations in baseline levels, either in relation to the normality ranges (8-10,13,14,16–19,22,25) or in comparison to eutrophic individuals (20,21), although one of these latter studies reported higher levels of fT4 in obese than in eutrophic girls (21) and the other study reported small percentages of subjects with levels of fT3 (17.9%) or fT4 (1.28%) above normal range (20). Only one study reported higher mean fT3 values in the obese than in the eutrophic subjects, although still in the normal range (22). These results show that the most common status of thyroid hormones is of levels in the normal range.

TSH levels at baseline were not reported in 5 studies (11,12,15,23,24) while 2 studies selected only individuals with hyperthyrotropinemia (25,26). Among the remaining 12 studies, the mean levels were normal in 9 studies (8, 10, 13,14,18–22), although some of these studies found mean values in the high normal range and highlighted the presence of elevated levels in variable percentages of their cohorts, namely 1.9% (13), 28.6% (14), 13.1% (18), 17.2% (19), 3.2% (20), and 17% (22). Elevated baseline levels of TSH were reported in 3 studies (9,16,17). These data demonstrate that the most common status of TSH among the studies analyzed fell into normal levels, although the finding of values in the high normal range was frequent.

Six studies reported correlations between body measures and hormone levels at baseline. Two studies reported a positive association of fT3 with BMI-SDS, or BMI/Age Z-score (8,20) while another study found a positive association of fT3 and body weight and a negative association of fT4 and percentage body fat (13). In 3 studies, TSH correlated positively with BMI-SDS (17,20) and BMI Z-score (18).

We searched other studies reporting levels of the hormones of the thyroid axis in children/adolescents with overweight/obesity. In one study, no differences were found in the levels of fT4 and TSH between children/adolescents with excess weight and the eutrophic ones (16). Many studies showed that these levels fell into the normal range, although a common

finding was that they were higher than those of eutrophic children/adolescents, concerning TT3 (27), TT4 (28), and TSH (27–31), fT3 and fT4 (5).

Similar findings have been found in adults, with respect to fT3 (32) and TT4 (32,33), i.e., levels in the normal range but higher than the eutrophic levels. There are also reports that the hormone levels were in the normal range but lower in obese than in eutrophic adults, concerning TSH (32–34), fT3 and fT4 (34).

Examining studies performing correlation analysis of hormone levels and body composition parameters in overweight/obese children/adolescents, we observed one study reporting no significant associations of fT3, fT4, and TSH levels with body composition parameters (35). In contrast, we found reports of a positive correlation between fT3 and BMI (5) and of a negative correlation of fT4 and BMI (28). There are also studies showing a positive correlation of TSH and body measures (5,36). These latter results agree with the findings of the studies analyzed in this scoping review.

These findings are like some reports in adults, finding positive associations between BMI and TT3 (37) and fT3 (32,34,37–41), and a negative correlation with fT4 (41). With respect to TSH, the studies found achieved a negative (33) or positive (41–44) association of BMI and TSH.

Concerning the response to the interventions, 12 of the studies included in this scoping review reported a decrease in at least one thyroid hormone measured (TT3, TT4, fT3, fT4) in relation to the respective baseline values (8,9,11–15,19,20,22–24). Six studies did not find any significant change between the baseline and the post-intervention values (10,16–18,21,26). One study did not report these data (25).

In relation to TSH, 12 studies reported a decrease after the intervention (8–10,13,15,17–19,22,24–26) and 5 studies showed no changes (11,12,16,21,23). It is important to point out that 2 of these studies (25, 26) included only subjects with hyperthyrotropinemia. In 2 studies, this information was not reported (14,20).

The relation of hormonal levels and anthropometric recovery was evaluated in 6 studies by a correlation analysis. Positive associations were found between delta of fT3 and body weight, BMI-SDS, fat mass, and percentage of fat mass (13), fT3 and BMI Z-score (8,15) and TT3 and BMI (24). TT4 correlated positively with BMI Z-score (23) while delta fT4 correlated negatively with percentage of fat mass (13). TSH correlated positively with BMI-SDS (17), BMI Z-score (15) and BMI (24). Studies performed in adults submitted to multidisciplinary interventions to treat obesity corroborate the above results, as they have found positive associations of fT3 or TT3 with BMI and body weight (37,45,46) and of TSH with body weight (46–49). However, we found one study in which body and fat mass losses were not accompanied by changes in TSH levels (50). The main purpose of this scoping review was to ascertain whether the hormones of the thyroid axis vary during weight loss in overweight/obese children/adolescents. The examination of the 19 selected studies allowed us to conclude that most of the results pointed to the absence of elevated levels at baseline, in agreement with a previous review (5). Also, most of the studies showed that the changes in body composition parameters in response to the multidisciplinary interventions correlated positively with fT3 , TT3, or TSH. Further studies are necessary to elucidate the relevance of the variations in hormone levels to the establishment of overweight/obesity and to the recovery from these conditions in children/adolescents. With respect to fT4 and TT4, the most common finding was of unchanged levels and hence, no significant association with weight loss. Importantly, the response to the intervention has even been found to not be affected by fT4 supplementation.

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## **Artigo 2**

### **Low fT3 levels favor anthropometric recovery in prepubertal children with overweight**

#### **Abstract**

The thyroid hormones have an important physiological role in the regulation of energy homeostasis and growth. Concerning childhood overweight/obesity, disorders of the thyroid axis have been described but the data are not conclusive.

In this study, we examined the status of the thyroid hormones axis (TSH, free T3 and free T4) of 71 overweight children, both before and after a long-term multicomponent intervention (physical activity and nutritional counseling, 27-29 months). In children who were either successful (recovery group) or failed to achieve normalization of BMI (non-recovery group) in response to the intervention, we evaluated the relationships of hormonal levels and anthropometric measures.

At baseline, the groups had a similar BMI/Age Z-score but the non-recovery group ( $n=44$ ) had a Height/Age Z-score higher than that of the recovery group ( $n=27$ ). In the recovery group, fT3 levels were lower than in the non-recovery one while fT4 and TSH levels were similar between the groups. After the intervention, fT3 levels fell in the recovery group while fT4 levels and Height/Age Z-score fell in the non-recovery group. TSH failed to vary in both groups. Considering the 2 groups together, fT3 levels correlated positively with baseline and post-intervention Height/Age Z-scores and with post-intervention BMI/Age Z-score. Chi-square test or the Fisher's exact test (according to the degrees of freedom) was applied to analyze the association of the thyroid hormone axis with recovery from overweight. The presence of fT3 levels in the low range at baseline favored the recovery from overweight, as indicated by a higher percentage of children with low-range fT3 levels in the recovery than in the non-recovery group. After the intervention, the percentage of children with fT3 levels in the normal range was higher in the non-recovery than in the recovery group, indicating that normal fT3 levels did not favor recovery. The logistic regression model showed that, both at baseline and after the intervention, the presence of fT3 values in the low range increased by around 29.9 times and 47.2 times, respectively, the chance to recover from overweight. No significant associations were found between recovery and BMI/Age, H/Age, fT4, or TSH.

The present results indicated that low fT3 levels associated positively with the ability to recover from overweight while having levels in the normal range was not as effective. The comparison performed in the present study, examining the hormonal differences associated with the ability to recover from overweight versus the unsuccessful response indicate that fT3 fluctuations may be viewed as a causative factor. Whether these associations are related to the existence of resistance to T3 actions or to other disturbances of the thyroid hormones axis needs further studies.

**Keywords:**

BMI/Age Z-score, Height/Age Z-score, free T3, free T4, TSH, multicomponent intervention

## **Introduction**

High rates of overweight and obesity in children and adolescents constitute an important public health issue worldwide. Reversing these conditions is key to prevent their long-lasting associated complications and multicomponent interventions have been shown to be the most effective method to achieve anthropometric recovery (Hoelscher et al., 2013; NCD, 2017)

Although hormonal derangements play a recognized role in overweight/obesity, and they are not completely understood. Moreover, the effects of weight loss on the hormonal derangements associated with overweight/obesity and, conversely, the hormonal influences on the ability to achieve success in response to strategies aimed at producing weight loss, are certainly complex and need proper elucidation.

The thyroid hormones have an important physiological role in the regulation of energy homeostasis and growth. Concerning childhood overweight/obesity, disorders of the thyroid axis have been described but the data are not conclusive. Increased TSH levels have been described and interpreted as representing an adaptive response, aimed at stimulating thyroid function and metabolic rate. Conversely, thyroid hormones resistance has been suggested to contribute as a causal factor of obesity (Jaivinder et al., 2018; Witkowska-Sędek et al., 2017).

In this study, we examined the status of the thyroid hormones axis (thyroid stimulating hormone (TSH), free T3 (fT3) and free T4 (fT4) in overweight children, both before and after a long-term multicomponent intervention. In children who were either successful or failed to achieve normalization of BMI we evaluated the relationships of hormonal levels and anthropometric measures.

## **Methods**

This retrospective research used secondary data of children with overweight, treated at the Center for Nutritional Recovery and Education-CREN, in the period between 2007 and 2018. The CREN is a center that offers outpatient care to children with malnutrition. It is in the southern region of the city of São Paulo, Brazil, and is linked to the Federal University of São Paulo (UNIFESP).

A convenience sample was searched in the CREN database, which included 497 children of both sexes, with 2 months to 17 years of age. The exclusion criteria included the presence of obesity ( $\text{BMI}/\text{Age Z-score} \geq 3$ ), stunting ( $\text{Height}/\text{Age Z-score}$  lower than -2), diabetes, hypertension, dyslipidemia, dermatological diseases, liver, kidney or respiratory diseases and psychological disorders. Additionally, the initial age of 2-7 years was chosen to ensure that the children had passed the initial phase of thyroid hormones fluctuations (Hübner et al., 2002) and that none reached the pubertal transition during the multidisciplinary intervention.

### Study design

For this longitudinal study, data from electronic and physical records were collected in two moments. At baseline, the children were evaluated by a physician and a nutritionist, underwent anthropometric assessment, and received the guidelines that should be followed for treatment. At the final, post-intervention moment, which took place between 20 and 35 months later, a new anthropometric assessment was carried out. Both at baseline and at the post-intervention moment, the families were referred to a clinical laboratory for blood sampling, for determination of fasting serum levels of free fT3, fT4 and thyroid stimulating hormone TSH. The adequacy of hormonal levels (low,

normal or high) was determined according to the pediatric reference values described in the CALIPER study (Adeli et al., 2017)

#### Intervention protocol

At the first meeting, the dietitian identified the readiness for behavioral change, using the Transtheoretical Model Test (TTM) (Prochaska et al., 1992). The nutritional intervention was then based on the Motivational Interviewing (MI) method (Borrello et al., 2015) in which, rather than prescribing eating plans, the counseling aims at stimulating behavioral change, through reinforcement of the positive achievements of the patients and their families, and establishment of consecutive goals of lifestyle change. The established targets were based on the Guidelines for the Treatment of Childhood Obesity (Puder & Munsch, 2010; Russell-Mayhew et al., 2012; Spear et al., 2007), the recommendations of the World Health Organization (WHO, 2016) and the Brazilian Food Guide (Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Básica, 2014). The general objectives were to minimize the consumption of sugary drinks and ultra-processed and fried foods and to increase fruits and vegetables intakes. The physical activity program was based on counseling to avoid a sedentary lifestyle by, among other aspects, reducing the screen time to less than 2 h/ day, and increasing the regular physical activity to at least 60 minutes/day and 5 days/week. These aspects were reinforced every 6 months, during 30-minutes consultations.

#### Anthropometric evaluation

The children were weighed without clothes and shoes on a platform scale (maximum capacity of 150 kg, accuracy of 6100 g: Filizola, São Paulo, SP, Brazil). Height was measured with a vertical wall stadiometer (Wiso, Curitiba, PR, Brazil) with an approximate accuracy of 0.1 cm. The Z-scores of BMI/Age and H/Age were calculated

using the software Anthro (for children under 5 years) and Anthro plus (for children older than 5 years) (version 1.0.4) (WHO, 2009).

### Statistical analysis

Initially, univariate descriptive statistical analyzes were performed. The normality and homogeneity of the variables were assessed by the Shapiro-Wilk and Levene tests, respectively. The parametric quantitative variables were presented as mean and standard deviation and analyzed by Analysis of Variance for repeated measures with Tukey Post Hoc Test.

The hormonal levels were categorized as falling in the low, normal, or high ranges and analyzed as qualitative variables. They were then presented in number of cases, absolute and percentual, and compared using the Chi-square test or the Fisher's exact test, according to the degrees of freedom. To detect significant differences among sub-groups, the partitioning of Chi-Square was performed.

Pearson correlation analysis was used to detect associations between the parametric quantitative variables.

Stepwise binary logistic regression models were performed to identify, among the hormones of the thyroid axis, significant predictors of the chance for anthropometrical recovery.

The data were entered in Excel and processed by SPSS version 24 software. In all analyzes,  $p \leq 0.05$  was adopted as the minimum level of significance.

## **Results**

### ***Anthropometric Parameters at Baseline and After Intervention***

The analyses of variance showed that the BMI/Age Z-score varied significantly among the groups ( $F: 104.2; p<0.001$ ). Among the 71 children treated with the multicomponent intervention, 27 achieved recovery of the BMI/Age Z-score (recovery group) while 44 children failed to do so (non-recovery group). At baseline, the BMI/Age Z-score was similar between the recovery and the non-recovery groups ( $p=0.767$ ). After the intervention, the BMI/Age Z-score of the recovery group was significantly lower than its value at baseline ( $p<0.001$ ) and then the value of the non-recovery group ( $p<0.001$ ) (Table 1).

The Height/Age Z-score varied significantly among the groups ( $F: 3.272; p=0.022$ ). At baseline, the non-recovery children had H/Age Z-score significantly higher than that of the recovery group ( $p=0.037$ ) but the values were similar among the groups after the intervention ( $p=0.312$ ) (Table 1).

### ***Thyroid Hormone Axis Association with Anthropometric Parameters***

Analysis of variance showed that fT3 levels varied significantly among the groups ( $F: 59.73; p<0.001$ ). At baseline, fT3 levels were lower in the recovery than in the non-recovery group ( $p<0.001$ ). After the intervention, the fT3 levels of the recovered children were slightly but significantly lower than their baseline values ( $p<0.001$ ). They were also lower than the levels of the non-recovered children ( $p<0.001$ ) (Table 1).

The analysis of variance showed that the fT4 levels varied significantly between groups ( $F: 6.893; p=0.011$ ). After the intervention, fT4 levels of the non-recovery group were lower than at baseline ( $p=0.009$ ). TSH levels did not show any significant differences among the groups ( $F: 0.290; p=0.592$ ) (Table 1).

The levels of fT3 correlated positively with baseline and post-intervention H/Age Z-scores and with post-intervention BMI/Age Z-score (Table 2).

The presence of low fT3 levels at baseline favored the recovery from overweight, as indicated by a higher percentage of children with low fT3 levels in the recovery than in the non-recovery group. After the intervention, the percentage of children with fT3 levels in the normal range was higher in the non-recovery than in the recovery group, indicating that normal fT3 levels did not favor recovery. Concerning TSH, the recovery and the non-recovery values differed significantly, but the specific comparisons of low, normal, and high ranges frequencies failed to show significant differences between the recovery and non-recovery values (Table 3).

The logistic regression model showed that, both at baseline and after the intervention, the presence of fT3 values in the low range increased by around 29.9 times and 47.2 times, respectively, the chance to recover from overweight. No significant associations were found between recovery and BMI/Age, H/Age, fT4, or TSH (Table 4).

Table 1: Anthropometric and hormonal parameters, at baseline and after multidisciplinary intervention, of children with overweight at baseline.

Variable	Baseline				After Intervention†			
	Recovery N= 27		Non-recovery N= 44		Recovery N= 27		Non-recovery N= 44	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	4.73	1.5	4.64	1.4	6.75	1.6	6.94	1.5
BMI/Age	2.70	0.3	2.78	0.2	1.81*	0.3	2.70#	0.3
H/Age	0.79	0.8	1.40#	1.1	1.01	0.8	1.33	0.9
fT3 (pmol/L)	4.77	0.9	5.99#	1.0	4.08*	1.2	5.55#	0.7
fT4 (pmol/L)	14.07	2.1	14.82	2.4	13.83	2.5	13.64*	3.0
TSH (mIU/L)	3.16	1.1	3.08	1.4	3.04	0.6	3.08	1.4

BMI/Age and H/Age are Presented as mean Z-scores.

†Months of intervention (Means  $\pm$  SD): Recovery:  $(27.27 \pm 4.02)$ ; Non recovery:  $(28.97 \pm 3.05)$ .

# p<0.005 vs. recovery according to Tukey Post Hoc Test

\*p<0.005 vs. baseline according to Tukey Post Hoc Test

Table 2. Pearson correlations of thyroid hormones and anthropometric parameters, in children with overweight.

Variable	fT3		fT4		TSH	
	r	p	r	p	r	p
<b>Baseline</b>						
BMI/Age	0.006	0.963	0.063	0.599	0.126	0.293
H/Age	0.257	0.030	0.103	0.393	0.035	0.771
<b>After intervention</b>						
BMI/Age	0.481	<0.001	0.020	0.871	0.061	0.612
H/Age	0.252	0.034	0.103	0.939	0.042	0.725

N = 71

Table 3. Association of the thyroid hormone axis with recovery from overweight.

Variable	Baseline						<i>p</i>	After Intervention						
	Recovery (N= 27)			Non Recovery (N= 44)				Recovery (N= 27)			Non Recovery (N= 44)			
Variable	Low	Normal	High	Low	Normal	High	Low	Normal	High	Low	Normal	High	Low	Hi
fT3	12 (44.4)*	14 (51.9)	1 (3.7)	2 (4.5)	33 (75)	9 (20.5)	<0.001 <sup>a</sup>	15 (55.6)	12 (44.4)*	0 (0)	4 (9.1)	38 (86.4)	2(4.5)	
fT4	4 (14.8)	22 (81.5)	1 (3.7)	4 (9.1)	33 (75)	7 (15.9)	0.257 <sup>b</sup>	6 (22.2)	20 (74.1)	1 (3.7)	12 (27.3)	29 (65.9)	3 (6.9)	
TSH	1 (3.7)	21 (77.8)	5 (18.5)	0 (0)	36 (81.8)	8 (18.2)	0.593 <sup>a</sup>	0 (0)	26 (96.3)	1 (3.7)	0 (0)	34 (77.3)	10 (22.7)	

Values represent N (%)

<sup>a</sup> Chi-square test

<sup>b</sup> Fisher's Exact test

\* *p* < 0.05 Recovery vs. Non Recovery, according to Chi-Square Partitioning Test

Table 4. Binary logistic regression analyses of the association of thyroid hormone axis and recovery from overweight

Variable	Dependent Variable: Recovery		
	OR	(95% CI)	p
<b>Baseline</b>			
fT3 (Low)	29.9	(1.65, 54.39)	0.022
<b>After intervention</b>			
fT3 (Low)	47.2	(8.93, 124.94)	<0.001

## **Discussion**

In the present study, we applied a multicomponent intervention to treat 71 children with overweight. The adhesion to the intervention was similar for all participants but only 27 children succeeded in achieving normalization of the BMI/Age Z-score after the treatment (recovery group) while 44 children failed to do so (non-recovery group). At baseline, the recovery and the non-recovery groups had similar ages and BMI/Age Z-score.

The mean duration of the multicomponent intervention was similar between the recovery (27 months) and the non-recovery (29 months) groups both groups. Interventions lasting 6-12 months, with 6-8 months of follow-up, have been shown to be effective in reducing BMI in pediatric samples (Colquitt et al., 2016; Ells et al., 2018).

In response to the intervention, the recovery group had a substantial decrease in BMI/Age Z-score (approximately 0.89 units). Studies evaluating the beneficial consequences of weight loss have reported improvement of metabolic health in children (mean age of 12.4 years) after a 0.25 unit decrease of BMI SDS (Ford et al., 2010), improvement of insulin sensitivity in obese children and adolescents (5-19 years of age) after a 0.15 unit decrease of BMI/Age Z-score (Kirk et al., 2005), improvement of arterial blood pressure in obese children and adolescents (7-17 years of age) after a decrease of 0.1 unit of BMI/Age Z-score (Kolsgaard et al., 2011). The benefits of even small BMI reductions to public health issues have been recognized, emphasizing the importance of interventions aimed at reducing body mass and adiposity (Copley et al., 2017; Mead et al., 2017).

None of the children were stunted, as the presence of stunting was an exclusion criterion, and their Height/Age Z-score fell in the normal range (WHO, 2017). However,

the non-recovery group had a baseline Height/Age Z-score higher than that of the recovery group. This may indicate a more pronounced deranged condition in comparison to the recovery-group, which, despite a similar BMI, had a lower Height/Age Z-score. The intervention was effective in decreasing this parameter, which became similar between the two groups after the intervention. Excess weight gain during childhood has been demonstrated to increase height gain and induce taller stature during this period. A precocious induction of growth hormone (GH) receptors and, hence of insulin-like growth factor 1 (IGF-1) has been implicated. The risk to develop obesity is increased in these children (Dunger et al., 2006; O'Keeffe et al., 2020). Thus, although not able to normalize BMI/Age Z-score in the non-recovered children, the fact that the intervention did improve the Height/Age Z-score was probably beneficial for their future health, despite not getting association between this indicator and anthropometric recovery capacity.

Because thyroid hormones are relevant to the regulation of both energy homeostasis and growth, we analyzed whether the levels of TSH, fT3 and fT4 were related to recovery from overweight in response to the multicomponent intervention. Our results showed that fT3 variations were the most important factor.

The mean basal levels of TSH, fT3 and fT4 fell into the normal range in both the recovery and the non-recovery groups, corroborating data from several studies in children/adolescents with overweight/obesity (Aeberli et al., 2010; Bouglé et al., 2014; Eliakim et al., 2006; Lass & Reinehr, 2020; Licenziati et al., 2019; Martins et al., 2020; Radetti et al., 2012; Reinehr et al., 2006; Shalitin et al., 2009; Wolters et al., 2013). The TSH levels showed no significant differences between the recovery and the non-recovery groups at baseline and most of the children had levels in the normal range. TSH failed to associate with the body composition parameters. We found one paper reporting absence of an association of TSH and BMI in 10 years-old obese children (Soydan et al., 2019).

Contrarily, other authors reported a positive association of TSH and BMI, in different pediatric populations including overweight 10 years-old children (Ayala-Moreno et al., 2018; Bouglé et al., 2014; Fontenelle et al., 2016; Ghergherehchi & Hazhir, 2015; Langrock et al., 2018; Licenziati et al., 2019; Marras et al., 2010). We hypothesize that the age of the children in the present study (4-7 years) was a factor relevant to our results, as all the studies finding an association of TSH, and BMI analyzed older individuals.

The post-intervention TSH values were similar between the groups and in relation to the basal levels. This agrees with some data (Kiortsis et al., 1999; Rijks et al., 2017; Wolters et al., 2013) but contrasts with more numerous reports showing decrease of TSH levels after weight loss, (Aeberli et al., 2010; Baş et al., 2013; Eliakim et al., 2006; Kumar et al., 2019; Licenziati et al., 2019; Radetti et al., 2012; Reinehr et al., 2015; Reinehr & Andler, 2002). Although our mean values were similar, in the recovery group the percentage of levels in the high range were lower after the intervention than at baseline. Indeed, most of the recovered children had TSH levels in the normal range while, among the non-recovered children, high-range levels also appeared.

Our findings with respect to fT4 showed similar basal values between the groups, a finding corroborating other studies in similar populations (Bouglé et al., 2014; Dursun et al., 2019; Langrock et al., 2018; Licenziati et al., 2019; Marras et al., 2010; Martins et al., 2020; Reinehr et al., 2008; Soydan et al., 2019). Also, no associations of these hormonal levels and the anthropometric measures were found.

The post-intervention levels of fT4 were also similar between the groups. In the recovery group, the levels did not vary in relation to the basal ones. Although some authors have found similar results (Aeberli et al., 2010; Baş et al., 2013; Bouglé et al., 2014; Butte et al., 2015; Eliakim et al., 2006; Licenziati et al., 2019; Radetti et al., 2012; Reinehr & Andler, 2002; Wolters et al., 2013), there are reports of diminished levels in

response to weight loss (Marras et al., 2010; Rijks et al., 2017; Shalitin et al., 2009), a finding we observed only in the non-recovery group and that has been associated to reduction of sympathetic tone and leptin levels after weight loss (Vella, 2018).

We observed that the non-recovery group had higher fT3 levels in comparison to the recovery group, both at baseline and after the intervention. We also found a positive correlation between fT3 and Height/Age at baseline. The thyroid hormones influence growth through a stimulatory effect on several aspects of GH function, such as GH gene transcription, GH response to hypothalamic GH releasing hormone (GHRH), GH release, and hepatic IGF-1 response to GH (Leung & Brent, 2016). It is thus likely that the higher fT3 levels of the non-recovery group, in relation to the recovery group, contributed to the increased height of the former.

A diminution of T3 levels after weight loss has been described (Aeberli et al., 2010; Baş et al., 2013; Bouglé et al., 2014; Lass & Reinehr, 2020; Radetti et al., 2012; Reinehr et al., 2006; Wolters et al., 2013), what was interpreted as reflecting an adaptive process (Reinehr et al., 2006; Vella, 2018). Here, we found that the levels of fT3 decreased significantly in response to the intervention in the recovery group but not in the non-recovery group. This comparison, not performed in the other studies, revealed that this distinct behavior may be of significance to the understanding of the conditions associated with the failure to successfully lose weight.

In the recovery group, fT3 levels also correlated positively with BMI/Age at the post-intervention moment. Other authors have described such a positive association (Baş et al., 2013; Marras et al., 2010; Martins et al., 2020). In adults, it has also been demonstrated that fT3 associated positively with weight loss and decreased leptin levels (Vella, 2018).

Additionally, the totality of the children in the recovery group had basal fT3 levels in the low and normal ranges. We found somewhat contrasting data in two studies in obese children/adolescents showing that, although mean fT3 levels were normal, 18% (Marras et al., 2010) or 8% (Martins et al., 2020) of the studied individuals presented high range levels.

Importantly, the logistic regression analysis revealed that the presence of fT3 levels in the low range favored recovery, both before and after the intervention. Thus, low fT3 levels associated positively with the ability to recover while having levels in the normal range was not as effective. The comparison performed in the present study, examining the hormonal differences associated with the ability to recover from overweight versus the unsuccessful response indicate that fT3 fluctuations may be viewed as a causative factor. Whether these associations are related to the existence of resistance to T3 actions or to other disturbances of the thyroid hormones axis needs further studies.

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## 6. CONCLUSÕES

1. Realizamos uma revisão de escopo para analisar estudos avaliando os níveis de hormônios do eixo tireoidiano em resposta a intervenções direcionadas ao tratamento de sobrepeso e obesidade em crianças e adolescentes. O objetivo principal foi verificar se os níveis hormonais variam durante a perda de peso. Selecionamos para análise 19 estudos publicados entre 1999 e 2022.

A maioria dos estudos mostrou que alterações em diferentes indicadores antropométricos em resposta às intervenções multidisciplinares correlacionaram-se positivamente com T3 livre (fT3) / T3 total (TT3) / TSH. Com relação ao T4 livre (fT4)/T4 total (TT4), o achado mais comum foi de níveis inalterados e, assim, ausência de associação significante com perda de peso. É importante ressaltar que a resposta à intervenção não foi afetada pela suplementação de fT4. Mais estudos são necessários para elucidar a relevância das variações nos níveis hormonais para o estabelecimento do sobrepeso/obesidade e para a recuperação dessas condições em crianças/adolescentes.

2. Também examinamos o estado do eixo dos hormônios tireoidianos (TSH, fT3 e fT4) de 71 crianças com excesso de peso, antes e após uma intervenção multicomponente de longo prazo (aconselhamento nutricional e para atividade física, 27-29 meses). Nas crianças que obtiveram sucesso (grupo recuperado) ou falharam na normalização do IMC (grupo não-recuperado) em resposta à intervenção, avaliamos as relações entre os níveis hormonais e as medidas antropométricas.

Os resultados indicaram que baixos níveis de fT3 associaram-se positivamente com a capacidade de se recuperar do excesso de peso, enquanto os níveis na faixa normal não foram tão eficazes. A comparação realizada no presente estudo, examinando as diferenças hormonais associadas à capacidade de recuperação do excesso de peso versus a resposta malsucedida, indica que as flutuações de fT3 podem ser vistas como um fator causal. Se essas associações estão relacionadas à existência de resistência às ações do T3 ou a outros distúrbios do eixo dos hormônios tireoidianos necessita de mais estudos.

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