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Circulating leptin levels in thyroid dysfunction: a systematic review and meta-analysis

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Abstract

Purpose Leptin is an important regulator of energy homeostasis, analogous to thyroid hormone (TH). The purpose of this study was to investigate circulating leptin levels in thyroid dysfunction (TD) patients and the role of TH levels.

Methods The electronic databases PubMed, Embase, Cochrane Library, and Web of Science were independently searched by two researchers, from inception until February 3, 2024, and updated on February 15, 2025. Pooled standardized mean difference (SMD) with a 95% confidence interval (CI) was calculated by the random effects model.

Results Thirty-eight studies reported circulating leptin levels in TD and control with euthyroidism, 4295 subjects were included in total, of which 1277 were hypothyroidism, 540 were hyperthyroidism, and 2478 were control. Compared to euthyroidism, leptin levels were significantly higher in hypothyroidism, and not significantly altered in hyperthyroidism (SMD [95%CI] = 0.71 [0.38, 1.04] and -0.03 [-0.57, 0.51], respectively). The subgroup analysis indicated that, compared to euthyroidism, leptin levels were significantly higher in subjects regardless of overt and subclinical hypothyroidism (SMD [95%CI] = 0.76 [0.25, 1.26] and 0.41 [0.11, 0.70], respectively), and not significantly different in overt hyperthyroidism (SMD [95%CI] = -0.14 [-0.74, 0.45]). Furthermore, when compared to age-, gender-, and body mass index (BMI)-matched euthyroidism, leptin levels were significantly higher in hypothyroidism and had no significant difference in hyperthyroidism (SMD [95%CI] = 0.66 [0.24, 1.07] and -0.43 [-1.13, 0.27], respectively). A total of 16 studies analyzed the correlations between leptin levels and TH levels in TD, 488 were hypothyroidism and 206 were hyperthyroidism. Following correlation analysis, leptin levels displayed a positive correlation with thyroid-stimulating hormone (TSH) levels (r = 0.19) and a negative correlation with triiodothyronine (T3) levels (r = -0.40) in TD.

Conclusion Compared to euthyroidism, circulating leptin levels were significantly higher in hypothyroidism, and not significantly altered in hyperthyroidism. Besides, leptin levels in TD may be directly regulated by TSH and T3 levels, independent of BMI.

Trial registration CRD42024561055.

Keywords Leptin, Thyroid dysfunction, Thyroid hormone, Meta-analysis

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Introduction

Thyroid dysfunction (TD) is a common chronic endocrine disease, primarily including hypothyroidism and hyperthyroidism [1]. According to statistics, the prevalence of hypothyroidism and hyperthyroidism is about 0.25–4.2% and 0.1–1.25% worldwide, separately [2]. Depending on the etiology, TD is categorized into primary and secondary, which can be effectively differentiated following the location of the lesion and peripheral thyroid hormone (TH) levels. Primary TD is due to lesions of the thyroid gland itself, with elevated and decreased thyroid-stimulating hormone (TSH) levels in hypothyroidism and hyperthyroidism, respectively [3, 4]. Secondary TD is due to hypothalamic or pituitary pathology, with reduced or low normal TSH levels in secondary hypothyroidism and elevated or high normal TSH levels in secondary hyperthyroidism [5]. Besides, TD was categorized into clinical and subclinical forms according to whether free thyroxine (FT4) levels were abnormal [1]. TH is a key molecule in the regulation of metabolism and energy homeostasis [6, 7]. There are widespread systemic metabolic abnormalities and disturbances in energy balance in TD. Hypothyroidism typically presents with a decreased basal metabolic rate (BMR), fear of cold, loss of appetite, and weight gain, whereas in hyperthyroidism there is an increased BMR, fear of heat, excessive sweating, hyperphagia, and weight loss [8].

Leptin, a product of the obesity (ob) gene, produced and secreted by adipose tissue, maintains energy homeostasis by controlling appetite, energy expenditure, and fat metabolism primarily through binding to leptin receptors (ObRb) in the hypothalamus [9–11]. Leptin plays a key role in the negative feedback loop that regulates energy homeostasis. Circulating leptin levels increase during periods of increased body fat or high energy states, which suppresses appetite and accelerates metabolism; conversely, circulating leptin levels decrease during periods of decreased body fat or low energy states, triggering foraging behavior and reduced energy expenditure [10, 12]. Since its discovery, leptin has attracted considerable interest due to its wide range of physiological and pathological roles in various metabolic diseases [10]. Available evidence suggests that leptin maintains a complex dual relationship with the hypothalamic-pituitary-thyroid (HPT) axis [13]. However, whether leptin is involved in the pathogenesis of TD remains largely unknown. Several studies have explored leptin levels in primary TD, but no consensus has been achieved. Current studies have concluded that circulating leptin levels were elevated [14], decreased [15], or even unchanged [16] in hypothyroidism compared to euthyroid individuals. Similarly, compared to euthyroidism, circulating leptin levels in hyperthyroid patients were noted to be elevated by Dutta et al. [17], decreased by Oge et al. [14], and unchanged by Braclik et al. [16]. What's more, it has not been determined whether TH is directly involved in the regulation of leptin levels in TD [7]. Therefore, the present study aimed to investigate circulating leptin levels in TD patients and the role of TH levels.

Methods

The present study complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [18]. It has been registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/), a platform for the International Prospective Register of Systematic Reviews, under the identifier CRD42024561055.

Search strategy

The electronic databases PubMed, Embase, Cochrane Library, and Web of Science were independently searched by two researchers, without language restrictions, from inception until February 3, 2024, and updated on February 15, 2025. The strategy for searching MeSH terms was as follows: (hypothyroidism OR hyperthyroidism OR thyroid diseases) AND (leptin). Additionally, we conducted a manual review of references from pertinent literature to prevent any exclusions. The detailed search strategy is demonstrated in Table S1.

Inclusion criteria and exclusion criteria

The TD patients were hypothyroid and hyperthyroid, respectively. Hypothyroidism was considered as serum TSH levels above the upper limit of the reference range with (overt hypothyroidism) or without (subclinical hypothyroidism) FT4 levels below the lower limit of the reference range. Hyperthyroidism is described as serum TSH levels below the lower limit of the reference range with (overt hyperthyroidism) or without (subclinical hyperthyroidism) FT4 levels above the upper limit of the reference range. Euthyroidism is defined as a healthy population without any thyroid disease, whose serum TSH and FT4 levels are within the reference range.

The criteria for inclusion entailed: (1) studies comparing circulating leptin levels in TD and controls with euthyroidism or analyzed the correlations between leptin levels and TH levels in TD; (2) leptin levels were presented as mean ± standard deviation (or can be calculated); (3) the study was made available in English.

The criteria for exclusion entailed: (1) reviews, conference abstracts, letters, editorial, commentary, case reports, and meta-analyses; (2) animal experiments; (3) taking medicine that affects thyroid function or body composition, such as levothyroxine, lithium; (4) the study

conducted during pregnancy or lactation; (5) absence of data or complete texts.

In studies with more than one control group, we included those with characteristics more similar to the TD group for meta-analysis, prioritizing body mass index (BMI).

Data extraction and quality assessment

The literature was organized using EndNote 21 software. Two reviewers extracted data independently using a predesigned form, and any disagreements were resolved by talking with the third reviewer. The first author, publication year, region, study type, thyroid state, sample size, gender, age, BMI, TSH, FT4, and detection method were among the details that were gathered and included in the data.

The quality assessment of prospective studies using the Newcastle–Ottawa Scale (NOS) [19] and cross-sectional studies using the Agency for Healthcare Research and Quality Scale (AHRQ) [20], of 0–3, 4–6, 7–9 stars in NOS and 0–3, 4–7, 8–11 in AHRQ scores represent the highest, medium, and lowest risk of bias, respectively. The above was implemented independently by two reviewers and any disagreements were resolved by a third reviewer.

Data synthesis and analysis

Meta-analyses were performed in STATA/MP 15. Standardized mean difference (SMD) with a 95% confidence interval (CI) to combine effect sizes for continuous variables. Effect size (ES) with a 95% CI to calculate the correlation coefficient (r). The chi-squared-based Q test and the I^2 test assessed the size of heterogeneity. Studies with an I^2 value of $<25\%$, 25%-75%, and $>75\%$ were considered low, moderate, and high heterogeneity, respectively. A random effects model was selected to combine effect size, irrespective of heterogeneity. Subgroup analyses were performed following subtypes of TD (overt, subclinical, and mixed). Meta-regression analyses were conducted by characteristics of the TD patients (age, gender, BMI), detection method, sample type, study region, and publication date. Sensitivity analysis was conducted to determine the robustness of the pooled data by removing each study in turn. Additionally, we only included those studies that explicitly showed TD and euthyroidism were matched for age, gender, and BMI for sensitivity analysis. The funnel plot (the number of studies should be at least 10) and Egger's test were used to test publication bias. If publication bias existed, the trim-and-fill method was used to reconfirmation the stability of statistical results. Two-sided P values <0.05 were considered statistically significant.

Result

Study search and inclusion

Figure 1 displays the screening process of the study. After excluding duplicate studies, titles and abstracts were filtered and 69 studies were obtained. By full-text review, 28 studies were eliminated for the following reasons: reviews ($n=1$), letters ($n=1$), conference abstracts ($n=7$), with medicine ($n=1$), no control ($n=5$), no extractable data ($n=4$), no full text ($n=9$). Finally, 41 studies were included in the systematic review and meta-analysis.

Study characteristics and quality assessment

Table 1 presents the characteristics of the included studies reporting circulating leptin levels in TD and euthyroidism. Of these 38 studies, 4295 subjects were included in total, of which 1277 were hypothyroidism, 540 were hyperthyroidism, and 2478 were euthyroidism. Table 2 displays the characteristics of the included studies reporting the correlations between leptin levels and TH levels in TD. Among these 16 studies, 694 TD were included, of which 488 were hypothyroidism and 206 were hyperthyroidism. The study sites included Kyrgyzstan, Egypt, Iran, Iraq, India, Turkey, Japan, China, Kuwait, Bulgaria, Romania, Greece, Mexico, Brazil, Poland, Italy, Spain, Sweden, United Kingdom, Austria, Denmark, Germany, and America. The main methods of leptin detection included RIA and ELISA.

The results of quality assessment by NOS for prospective studies showed a minimum of 6 stars and a maximum of 9 stars (Table S3), and AHRQ for cross-sectional studies showed a minimum quality score of 5 and a maximum quality score of 8 (Table S4). Overall, the included studies were of medium to high quality.

Meta-analysis

Comparison of circulating leptin levels in hypothyroidism than in euthyroidism

Thirty-six studies analyzed circulating leptin levels in hypothyroidism and euthyroidism. The pooled result demonstrated that leptin levels were significantly higher in hypothyroidism than in euthyroidism (SMD [95%CI] = 0.71 [0.38, 1.04], $I^2=93.30\%$, $P=0.000$, Fig. 2). Furthermore, the subgroup analysis indicated that leptin levels were significantly higher in subjects regardless of overt (SMD [95%CI] = 0.76 [0.25, 1.26], $I^2=93.90\%$, $P=0.003$, Fig. 2) and subclinical (SMD [95%CI] = 0.41 [0.11, 0.70], $I^2=75.10\%$, $P=0.006$, Fig. 2) hypothyroidism than in euthyroid subjects.

In the sensitivity analysis, when compared to age-, gender-, and BMI-matched euthyroidism,

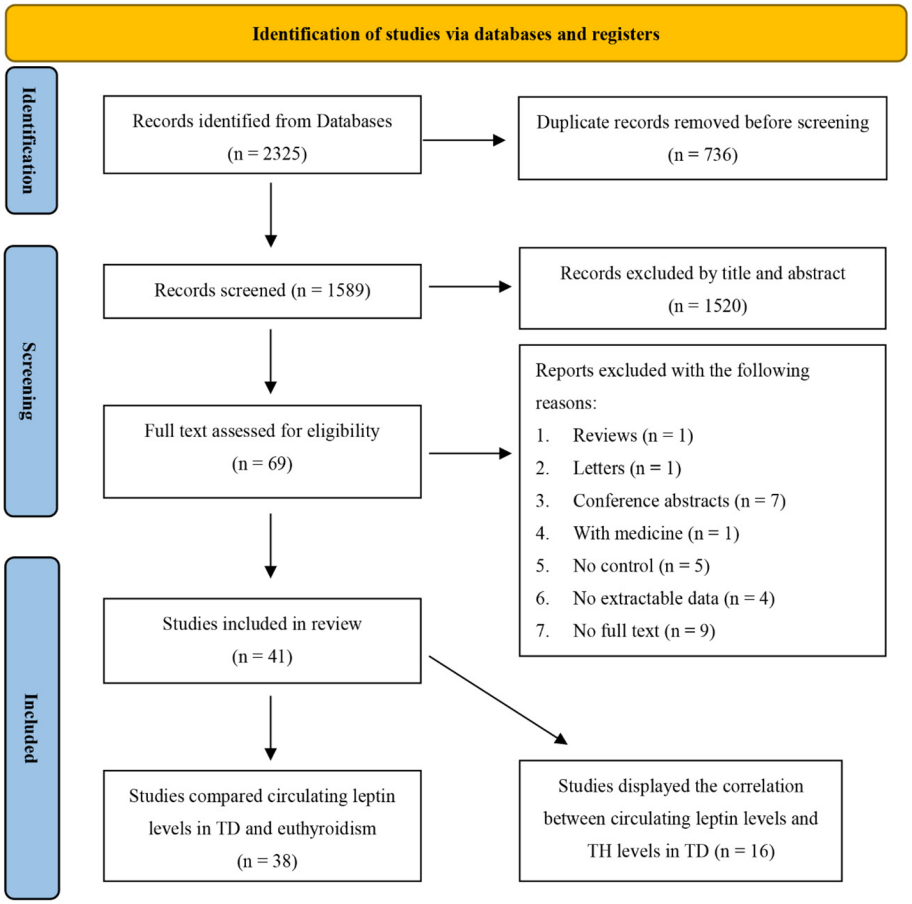

Fig. 1 Flow chart of study screening

leptin levels were significantly higher in hypothyroidism (SMD [95%CI] = 0.66 [0.24, 1.07], I^2 = 91.30%, P = 0.002, Fig. 3).

Comparison of circulating leptin levels in hyperthyroidism than in euthyroidism

Twenty-seven studies analyzed circulating leptin levels in hyperthyroidism and euthyroidism. The pooled result indicated that leptin levels in hyperthyroidism were not significantly different from euthyroidism (SMD [95%CI] = -0.03 [-0.57, 0.51], I^2 = 94.40%, P = 0.904, Fig. 4). Furthermore, the subgroup analysis indicated that leptin levels had no significant difference in subjects with overt hyperthyroidism than in euthyroid subjects (SMD [95%CI] = -0.14 [-0.74, 0.45], I^2 = 94.70%, P = 0.631, Fig. 4).

In the sensitivity analysis, when compared to age-, gender-, and BMI-matched euthyroidism, leptin levels had no significant difference in hyperthyroidism (SMD [95%CI] = -0.43 [-1.13, 0.27], I^2 = 94.50%, P = 0.230, Fig. 5).

Correlations between leptin levels and TH levels in TD

Sixteen studies demonstrated the correlations between leptin levels and TH levels, including TSH, thyroxine (T4), triiodothyronine (T3), FT4, and free triiodothyronine (FT3). As shown in Table 3, leptin levels displayed a positive correlation with TSH levels (r = 0.19, P = 0.015) and a negative correlation with T3 levels (r = -0.40, P = 0.010) in TD.

Meta-regression analysis

As presented in Table 4, meta-regression analyses were conducted by age, gender, BMI, detection method, sample type, study region, and publication date indicating that these factors were not a source of heterogeneity among studies (P > 0.05).

Sensitivity analysis and publication bias

Sensitivity analyses showed that the pooled results remained unchanged before and after excluding each study in turn, indicating relatively stable (Figure S1). The funnel plot and Egger's test showed that publication bias was absent (Figure S2 and Table S2).

Table 1 Characteristics of studies reporting circulating leptin levels in TD patients and euthyroidism

Study	Region	Study type	Case						Control					Case–control match	Measurement type (sample type)
			State	N (F/M)	Age (M ± SD)	BMI (M ± SD)	TSH (M ± SD)	FT4 (M ± SD)	N (F/M)	Age (M ± SD)	BMI (M ± SD)	TSH (M ± SD)	FT4 (M ± SD)		
Tomov et al. 2023 [21]	Bulgaria	Cross-sectional	OHypo	40 (33/7)	NA	NA	9.66 ± 21.1	10.5 ± 3.4	21 (17/4)	NA	21.6 ± 2.8	NA	NA	NA	ELISA (serum)
			OHyper	5 (2/3)			0.51 ± 0.9	17.1 ± 9.8							
Stoica et al. 2022 [22]	Romania	Cross-sectional	SHypo	11 (11/0)	NA	33.75 ± 4.53	5.99 ± 3.71	1.14 ± 0.1	14 (14/0)	NA	31.91 ± 5.92	2.08 ± 1.32	1.13 ± 0.26	Gender, BMI	IF (serum)
El Amrousy et al. 2022 [23]	Egypt	Cross-sectional	OHypo	30 (19/11)	11 ± 2.17	20.2 ± 4.1	22.4 ± 7.1	8.7 ± 1.1	30 (18/12)	10.8 ± 2.13	19.9 ± 2.2	2. 8 ± 0.67	18 ± 3.5	Age, gender, BMI	ELISA (serum)
Keikhaei et al. 2021 [24]	Iran	Prospective	OHypo	56	35.29 ± 10.65	23.9 ± 3.61	79.65 ± 21.24	0.45 ± 0.16	54	36 ± 8.64	22.79 ± 4.04	1.58 ± 0.82	1.27 ± 0.19	Age, gender, BMI	ELISA (serum)
			OHyper	54	36.22 ± 8.77	22.75 ± 4.14	0.02 ± 0.01	3.12 ± 0.75							
Hammo et al. 2020 [25]	Iraq	Cross-sectional	OHypo	35 (0/35)	NA	NA	26.36 ± 1.712	NA	20 (0/20)	NA	NA	2.230 ± 0.107	NA	Age, gender	ELISA (serum)
			OHyper	35 (0/35)			0.049 ± 0.019	NA							
Stratigou et al. 2018 [26]	Greece	Prospective	SHypo	120 (72/48)	47.2 ± 16.4	25.6 ± 3.6	8.6 ± 1.7	1.3 ± 0.4	120 (72/48)	47.4 ± 15.1	24.4 ± 3.1	2.6 ± 0.6	1.5 ± 0.3	Age, gender	ELISA (serum)
El-Zawawy et al. 2018 [27]	Egypt	Cross-sectional	Hypo	120 (0/120)	41.40 ± 11.91	NA	NA	NA	120 (0/120)	40.15 ± 12.21	NA	NA	NA	Age, gender	ELISA (serum)
Lozanov et al. 2017 [28]	Bulgaria	Cross-sectional	OHypo	59 (40/19)	NA	NA	19.67 ± 23.34	10.72 ± 2.46	59 (35/24)	NA	NA	1.79 ± 0.91	13.26 ± 1.71	NA	ELISA (serum)
Kar et al. 2017 [29]	India	Cross-sectional	Hypo	40 (24/16)	NA	NA	10.37 ± 4.10	NA	40	NA	NA	2.41 ± 2.09	NA	Age, gender	ELISA (serum)
Gómez-Zamudio et al. 2016 [30]	Mexico	Cross-sectional	Hypo	49	44.1 ± 11.6	47.9 ± 7.8	4.78(2.34–7.4)*	1.22(1.09–1.5)*	49	44.4 ± 12.0	46.2 ± 9.1	2.69 (2.05–3.5)*	1.24 (1.17–1.4)*	Age, BMI	ELISA (serum)
Akbaba et al. 2015 [31]	Turkey	Prospective	SHypo	51 (41/10)	36.9 ± 10.6	26.1 ± 5.5	6.2 ± 1.3	0.8 ± 0.1	43 (32/11)	34.9 ± 8.4	25.7 ± 4.2	1.9 ± 0.8	1.02 ± 0.2	Age, gender, BMI	ELISA (serum)
Tohma et al. 2015 [32]	Turkey	Prospective	OHyper	21 (16/5)	39.6 ± 11.6	25 ± 4.4	0.01 (0–0.02)&	1.9 (0.8–4.64)&	33 (25/8)	36.4 ± 14.4	25 ± 4.3	1.24 (0.47–2.46)&	1.16 (0.93–1.45)&	Age, gender, BMI	ELISA (serum)
Yildiz et al. 2013 [33]	Turkey	Cross-sectional	Hypo	27 (23/4)	43.3 ± 12.8	27.2 ± 4.4	33.2 ± 29.2	0.81 ± 0.3	31 (24/7)	40.3 ± 10.6	25.4 ± 5.1	1.94 ± 0.78	1.10 ± 0.92	Age, gender, BMI	ELISA (serum)
			Hyper	27 (18/9)	43.1 ± 14.9	25.8 ± 4.2	0.194 ± 0.2	2.01 ± 1.55							
Yildiz et al. 2013 [34]	Turkey	Prospective	SHypo	43 (43/0)	33.4 ± 10.3	25.3 ± 5.1	9.17 ± 6.44	13.67 ± 1.75	53 (53/0)	34.1 ± 8.2	26.6 ± 5.9	1.91 ± 0.94	15.35 ± 1.85	Age, gender, BMI	RIA (serum)
Guzel et al. 2013 [35]	Turkey	Cross-sectional	OHypo	40 (40/0)	39.83 ± 5.62	26.56 ± 1.36	56.3 ± 27.8	6.1 ± 3.3	25 (25/0)	39.16 ± 5.57	26.11 ± 1.59	2.6 ± 0.9	16.2 ± 2.4	Age, gender, BMI	ELISA (serum)
			SHypo	25 (25/0)	40.56 ± 4.90	26.48 ± 1.29	11.9 ± 3.3	14.6 ± 2.5							
Dutta et al. 2012 [17]	India	Prospective	OHyper	27 (16/11)	31.3 ± 2.2	20.5 ± 0.7	0.1 ± 0.0	NA	28 (14/14)	30.0 ± 1.8	21.6 ± 0.6	NA	NA	Age, BMI	ELISA (plasma)
Teixeira et al. 2009 [36]	Brazil	Prospective	OHypo	20 (20/0)	43.5 ± 15.0	27.1 ± 4.8	57.7 ± 49.4	0.5 ± 0.3	28 (28/0)	45.7 ± 9.9	26.3 ± 6.9	1.5 ± 0.7	1.31 ± 0.2	Age, gender, BMI	RIA (serum)
			SHypo	55 (55/0)	46.1 ± 11.1	27.1 ± 4.8	7.4 ± 2.6	1.0 ± 0.2							
Guldiken et al. 2008 [37]	Turkey	Cross-sectional	OHypo	25 (18/7)	41.4 ± 8.2	28.6 ± 5.8	44.6 ± 25.2	0.63 ± 0.22	25 (20/5)	36.8 ± 5.6	28.1 ± 6.8	1.3 ± 0.6	1.32 ± 0.19	Age, gender, BMI	ELISA (serum)
			SHypo	30 (28/2)	39.7 ± 10.5	27.3 ± 4.8	8.5 ± 1.9	1.21 ± 0.23							
Braclik et al. 2008 [16]	Poland	Prospective	OHypo	11 (11/0)	42.83 ± 10.09	25.55 ± 3.76	151.6 (23.3–913.7) &	4.7 (2.6–10.6) &	19 (19/0)	36.54 ± 10.83	23.56 ± 3.07	1.52 (0.5–11.4) &	14.5 (11.1–18.1) &	Age, gender, BMI	EIA (serum)
			OHyper	17 (17/0)	41.78 ± 12.68	23.95 ± 3.93	0.097 (0.05–0.3) &	52.9 (35.9–126.3) &							
Oge et al. 2005 [14]	Turkey	Prospective	OHypo	26 (14/12)	40.8 ± 10.4	24.35 ± 3.83	22.2 ± 7.6	0.9 ± 0.5	20 (10/10)	35 ± 8.5	23.7 ± 5.7	2.08 ± 2.3	1.4 ± 0.8	Age, gender, BMI	RIA (serum)
			OHyper	22 (12/10)	44 ± 13.6	22.45 ± 4.86	0.01 ± 0.2	6.3 ± 1.5							

Table 1 (continued)

Study	Region	Study type	Case						Control					Case–control match	Measurement type (sample type)
			State	N (F/M)	Age (M ± SD)	BMI (M ± SD)	TSH (M ± SD)	FT4 (M ± SD)	N (F/M)	Age (M ± SD)	BMI (M ± SD)	TSH (M ± SD)	FT4 (M ± SD)		
Santini et al. 2004 [38]	Italy	Cross-sectional	OHypo	15 (11/4)	38.7 ± 11.4	25.6 ± 4.1	53.8 ± 18.1	0.7 ± 0.1	15 (11/4)	40.5 ± 12.2	25.2 ± 4.7	1.42 ± 0.6	13.9 ± 2.6	Age, gender, BMI	RIA (serum)
			OHyper	15 (11/4)	39.5 ± 12.4	25.0 ± 4.4	0.01 ± 0.01	44.8 ± 19.7							
Iglesias et al. 2003 [39]	Spain	Prospective	OHypo	20 (17/3)	51.5 ± 4.1	28.5 ± 1.0	62.6 ± 9.0	5.6 ± 0.5	20 (17/3)	43.1 ± 2.6	25.1 ± 0.9	1.8 ± 0.3	14.8 ± 0.6	Age, gender	RIA (serum)
			OHyper	20 (16/4)	47.2 ± 3.9	22.7 ± 0.5	0.05 ± 0.004	45.8 ± 3.1						Age, gender, BMI	
Wahrenberg et al. 2002 [40]	Sweden	Prospective	Hyper	10 (10/0)	38 ± 4	24.0 ± 1.6	< 0.03	NA	16 (16/0)	34 ± 1	23.7 ± 0.5	2.00 ± 0.25	NA	Age, gender, BMI	RIA (serum)
Hsieh et al. 2002 [41]	China	Prospective	OHypo	33 (26/7)	41.0 ± 10.4	23.7 ± 2.5	46.5 ± 4.6	2.6 ± 1.3	38 (30/8)	40.2 ± 11.3	23.1 ± 2.5	1.6 ± 0.5	19.9 ± 5.1	Age, gender	RIA (serum)
Tagliaferri et al. 2001 [42]	United Kingdom	Cross-sectional	SHypo	108 (92/16)	46.8 ± 15.7	43.4 ± 6.6	6.4 ± 2.7	11.8 ± 2.4	131 (100/31)	47.8 ± 14.0	42.9 ± 6.8	2.1 ± 1.1	12.3 ± 2.2	Age, gender, BMI	RIA (serum)
Obermayer-Pietsch et al. 2001 [43]	Austria	Prospective	OHyper	28 (23/5)	66 ± 8	23.5 ± 3.3	0.02 ± 0.03	36.5 ± 21.8	24 (22/2)	63 ± 12	23.9 ± 2	1.1 ± 0.9	16.5 ± 2	Age, gender, BMI	RIA (plasma)
Nakamura et al. 2000 [44]	Japan	Prospective	OHyper	32 (32/0)	41 ± 3	19.9 ± 0.4	< 0.02	77.3 ± 9.6	30 (30/0)	48 ± 3	20.6 ± 0.5	NA	14.9 ± 0.5	Age, gender, BMI	RIA (serum)
Matsubara et al. 2000 [45]	Japan	Prospective	OHypo	19 (19/0)	54.41 ± 16.89	24.6 ± 3.9	NA	NA	197 (197/0)	52.10 ± 13.05	23.5 ± 4.0	NA	NA	Age, gender	RIA (serum)
			OHyper	27 (27/0)	43.18 ± 12.34	19.7 ± 3.1	NA	NA							
Chen et al. 2000 [46]	China	Cross-sectional	OHypo	20 (20/0)	42.1 ± 3.7	24.2 ± 0.6	23.47 ± 4.50	7.7 ± 1.3	20 (20/0)	41.7 ± 2.4	21.0 ± 0.5	1.06 ± 0.14	14.2 ± 1.3	Age, gender	RIA (plasma)
			OHyper	20 (20/0)	39.6 ± 2.6	20.9 ± 0.6	0.01 ± 0.01	37.4 ± 3.9						Age, gender, BMI	
Al-Shoumer et al. 2000 [47]	Kuwait	Prospective	OHyper	19 (19/0)	34 ± 2	22.8 ± 0.9	< 0.01	85.3 ± 8.4	20 (20/0)	31 ± 2	24.2 ± 0.9	1.30 ± 0.2	15.9 ± 0.6	Age, gender, BMI	RIA (serum)
			OHyper	10 (0/10)	34 ± 2	22.2 ± 1.6	< 0.01	86.8 ± 8.1	12 (0/12)	35 ± 3	25.0 ± 1.0	1.10 ± 0.3	16.2 ± 0.8		
Kautzky-Willer et al. 1999 [48]	Austria	Prospective	OHypo	12 (10/2)	51.1 ± 4.9	22.5 ± 0.7	24.4 ± 4.6	NA	22 (20/2)	42.3 ± 6.8	22.9 ± 1.9	1.36 ± 0.2	NA	Age, gender, BMI	RIA (plasma)
			OHyper	10 (8/2)	44.4 + 6.0	21.8 ± 0.7	< 0.1	NA							
			OHypo	13 (11/2)	56.0 ± 4.1	32.2 ± 1.4	23.7 ± 3.5	NA	22 (20/2)	45.8 ± 7.5	31.5 ± 4.7	2.3 ± 0.5	NA	Age, gender, BMI	
			OHyper	9 (8/1)	52.1 ± 5.2	28.5 ± 1.3	< 0.1	NA							
Zimmermann-Belsing et al. 1998 [49]	Denmark	Prospective	OHyper	10(8/2)	50	24	0.01 ± 1.2	NA	18 (12/6)	39	24	NA	NA	Age, gender, BMI	RIA (serum)
Yoshida et al. 1998 [15]	Japan	Cross-sectional	OHypo	17 (17/0)	44.4 ± 3.4	22.3 ± 0.7	108.3 ± 27.7	4.9 ± 0.5	23 (23/0)	36.8 ± 3.1	21.6 ± 0.5	1.9 ± 0.2	14.9 ± 0.5	Age, gender, BMI	RIA (serum)
			OHyper	19 (19/0)	34.9 ± 2.4	20.7 ± 0.4	< 0.02	77.7 ± 5.7							
Pinkney et al. 1998 [50]	United Kingdom	Prospective	OHypo	22 (20/2)	48.74 ± 17.83	26.10 ± 4.63	43 (31.5–50) [&]	NA	32 (19/13)	42.67 ± 17.05	24.02 ± 3.27	1.2 (0.78–2.53) [*]	NA	Age	RIA (plasma)
			OHyper	18 (17/1)	42.78 ± 14.08	23.0 ± 2.48	< 0.05	NA							
Ozata et al. 1998 [51]	Turkey	Prospective	OHypo	20 (20/0)	24.05 ± 5.2	23.1 ± 1.78	164.6 ± 17.9	0.47 ± 0.25	20 (20/0)	22.9 ± 4.15	22.8 ± 1.32	1.58 ± 0.50	1.43 ± 0.32	Age, gender, BMI	RIA (plasma)
			Hyper	20 (20/0)	25.5 ± 7.2	22.2 ± 3.1	0.024 ± 0.03	5.5 ± 3.7							
Leonhardt et al. 1998 [52]	Germany	Cross-sectional	OHypo	23 (19/4)	51.2 ± 2.8	26.8 ± 1.0	69.35 ± 9.66	0.04 ± 0.03	21 (13/8)	51.7 ± 3.6	23.8 ± 1.1	1.13 ± 0.13	0.12 ± 0.01	NA	RIA (serum)
			OHyper	19 (14/5)	55.8 ± 3.8	23.9 ± 0.9	0.01 ± 0.00	0.49 ± 0.01							

Table 1 (continued)

Study	Region	Study type	Case						Control					Case–control match	Measurement type (sample type)
			State	N (F/M)	Age (M ± SD)	BMI (M ± SD)	TSH (M ± SD)	FT4 (M ± SD)	N (F/M)	Age (M ± SD)	BMI (M ± SD)	TSH (M ± SD)	FT4 (M ± SD)		
Sreenan et al. 1997 [53]	America	Cross-sectional	OHypo	6 (3/3)	62.2 ± 5.3	30.1 ± 0.7	72.8 ± 16.1	NA	11 (8/3)	55.0 ± 5.9	27.2 ± 2.5	1.2 ± 0.2	NA	Age, gender, BMI	RIA (serum)
			OHyper	6 (6/0)	40.3 ± 7.2	28.0 ± 1.2	0.04 ± 0.003	NA							
Corbetta et al. 1997 [54]	Italy	Prospective	OHypo	25 (25/0)	NA	25 ± 6.3	54.6 ± 12.6	4.4 ± 2.8	561 (561/0)	NA	24.4 ± 4	0.3 ± 4.0	10 ± 18	Gender, BMI	RIA (serum)
			OHyper	27 (27/0)	NA	22.6 ± 3.5	< 0.01	36.3 ± 19.8							
			OHypo	11 (0/11)	NA	26 ± 6	22.8 ± 17.8	7.6 ± 3.6	393 (0/393)	NA	24.6 ± 3.3				
			OHyper	13 (0/13)	NA	26.2 ± 5.9	< 0.01	34.2 ± 14.3							

Hypo hypothyroidism, *OHypo* overt hypothyroidism, *SHypo* subclinical hypothyroidism, *Hyper* hyperthyroidism, *OHyper* overt hyperthyroidism, *N* sample size, *F* females, *M* males, *BMI* body mass index, *TSH* thyroid-stimulating hormone, *FT4* free thyroxin, *RIA* radioimmunoassay, *ELISA* enzyme-linked immunosorbent assay, *IF* immunofluorescence, *EIA* immunoenzymatic assays, *NA* unknown. * median (p25-p75); & median (minimum–maximum)

Table 2 Characteristics of studies reporting correlations between leptin levels and TH levels in TD

Study	Region	Study type	Case						Detection method (sample type)
			State	N (F/M)	Age (M ± SD)	BMI (M ± SD)	TSH	FT4	
El Amrousy et al. 2022 [23]	Egypt	Cross-sectional	Hypothyroidism	30 (19/11)	11 ± 2.17	20.2 ± 4.1	22.4 ± 7.1	8. 7 ± 1.1	ELISA (serum)
			Hypothyroidism	30 (20/10)	10.6 ± 2.1	30 ± 4.3	26.2 ± 9.6	8.1 ± 1.7	
Keikhaei et al. 2021 [24]	Iran	Prospective	Hypothyroidism	56	35.29 ± 10.65	23.9 ± 3.61	79.65 ± 21.24	0.45 ± 0.16	ELISA (serum)
Hammo et al. 2020 [25]	Iraq	Cross-sectional	Hypothyroidism	35 (0/35)	NA	NA	26.36 ± 1.712	NA	ELISA (serum)
			Hyperthyroidism	35 (0/35)	NA	NA	0.049 ± 0.019	NA	
Lozanov et al. 2017 [28]	Bulgaria	Cross-sectional	Hypothyroidism	59 (40/19)	NA	NA	19.67 ± 23.34	10.72 ± 2.46	ELISA (serum)
Akbaba et al. 2015 [31]	Turkey	Prospective	Hypothyroidism	51 (41/10)	36.9 ± 10.6	26.1 ± 5.5	6.2 ± 1.3	0.8 ± 0.1	ELISA (serum)
Ağbaht et al. 2014 [55]	Turkey	Prospective	Hyperthyroidism	40 (22/18)	49.5 ± 15.2	26.2 ± 4.5	0.01 (0.005–0.03)*	29.2 (21.0–42.8) *	RIA (plasma)
Guzel et al. 2013 [35]	Turkey	Cross-sectional	Hypothyroidism	40 (40/0)	39.83 ± 5.62	26.56 ± 1.36	56.3 ± 27.8	6.1 ± 3.3	ELISA (serum)
Saraç et al. 2010 [56]	Turkey	Prospective	Hypothyroidism	30 (30/0)	39.9 ± 4.1	23.2 ± 2.5	8.7 ± 2.6	0.75 ± 0.1	ELISA (serum)
Teixeira et al. 2009 [36]	Brazil	Prospective	Hypothyroidism	20 (20/0)	43.5 ± 15.0	27.1 ± 4.8	57.7 ± 49.4	0.5 ± 0.3	RIA (serum)
			Hypothyroidism	55 (55/0)	46.1 ± 11.1	27.1 ± 4.8	7.4 ± 2.6	1.0 ± 0.2	
Braclik et al. 2008 [16]	Poland	Prospective	Hypothyroidism	11 (11/0)	42.83 ± 10.09	25.55 ± 3.76	151.6 (23.3–913.7) &	4.7 (2.6–10.6)&	EIA (serum)
			Hyperthyroidism	17 (17/0)	41.78 ± 12.68	23.95 ± 3.93	0.097 (0.05–0.3) &	52.9 (35.9–126.3)&	
Oge et al. 2005 [14]	Turkey	Prospective	Hypothyroidism	26 (14/12)	40.8 ± 10.4	24.35 ± 3.83	22.2 ± 7.6	0.9 ± 0.5	RIA (serum)
			Hyperthyroidism	22 (12/10)	44 ± 13.6	22.45 ± 4.86	0.01 ± 0.2	6.3 ± 1.5	
Yaturu et al. 2004 [57]	America	Prospective	Hyperthyroidism	35	NA	NA	NA	NA	EIA (serum)
Al-Shoumer et al. 2000 [47]	Kuwait	Prospective	Hyperthyroidism	29 (19/10)	34 ± 2	23.0 ± 0.9	< 0.01	85.6 ± 6 .0	RIA (serum)
Zimmermann-Belsing et al. 1998 [49]	Denmark	Prospective	Hyperthyroidism	10(8/2)	50	24	0.01 ± 1.2	NA	RIA (serum)
Pinkney et al. 1998 [50]	United Kingdom	Prospective	Hypothyroidism	22 (20/2)	48.74 ± 17.83	26.10 ± 4.63	43 (31.5–50)&	NA	RIA (plasma)
			Hyperthyroidism	18 (17/1)	42.78 ± 14.08	23.0 ± 2.48	< 0.05	NA	
Leonhardt et al. 1998 [52]	Germany	Cross-sectional	Hypothyroidism	23 (19/4)	51.2 ± 2.8	26.8 ± 1.0	69.35 ± 9.66	0.04 ± 0.03	RIA (serum)

N sample size, *F* females, *M* males, *BMI* body mass index, *TSH* thyroid-stimulating hormone, *FT4* free thyroxin, *RIA* radioimmunoassay, *ELISA* enzyme-linked immunosorbent assay, *EIA* immunoenzymatic assays, *NA* unknown. * median (p25-p75); & median (minimum–maximum)

Discussion

The present study found that circulating leptin levels were significantly higher in hypothyroidism, and not significantly altered in hyperthyroidism compared to euthyroidism; the above associations remained after adjusting for age, gender, and BMI. What's more, leptin

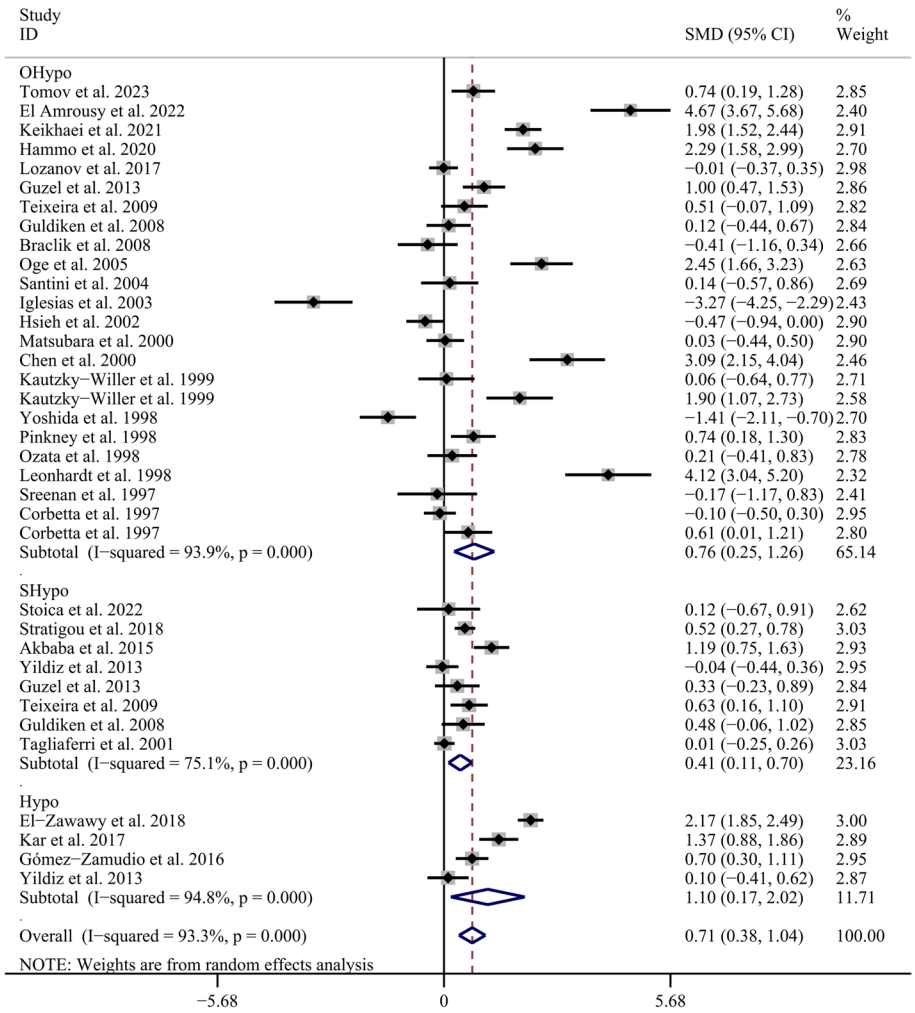

Fig. 2 Forest plot of circulating leptin levels in hypothyroidism and euthyroidism. OHypo, overt hypothyroidism; SHypo, subclinical hypothyroidism; Hypo, hypothyroidism; SMD, standardized mean difference; CI, confidence interval

levels displayed a positive correlation with TSH levels and a negative correlation with T3 levels in TD. Overall, these findings suggested that leptin may be involved in an underlying mechanism of hypothyroidism, but not in hyperthyroidism. Besides, leptin levels in TD may be directly regulated by TSH and T3 levels, independent of BMI.

Our study showed that leptin levels were significantly higher in hypothyroidism, and not significantly altered in hyperthyroidism compared to euthyroidism. Leptin expression and secretion are regulated by a variety of hormones and body fat (BF) content. Leptin levels are higher in females than in males, due to differences in their BF (higher in females) as well as their sex hormones (estrogen and testosterone) [10]. Circulating leptin levels are directly correlated with elevated BMI [58]. Therefore, changes in BMI in TD are an important determinant of its leptin levels. It is known that TH is involved in the regulation of BMI, but whether TH has a direct effect on leptin levels remains controversial. TD provides a good model for exploring the effect of TH on leptin levels. Considering the effect of confounding factors (especially BMI) on leptin levels, we only included those studies that explicitly showed TD and euthyroidism were matched for age, gender, and BMI for sensitivity analysis. Surprisingly, the pooled results were consistent with the original results. Furthermore, our findings displayed a significant correlation between leptin levels and TH levels in TD. Hsieh et al. [41] indicated that TH was involved in regulating leptin metabolism independent of BMI and BF, and similar results were reported by Bettry et al. [59]. Also, Escobar-Morreale et al. [60] pointed out that the effect of TH on serum leptin concentration was higher than the prospected end of organism weight itself. Therefore, BMI is not the only factor affecting leptin levels in TD, which did not support the conclusions of Sreenan et al. [53].

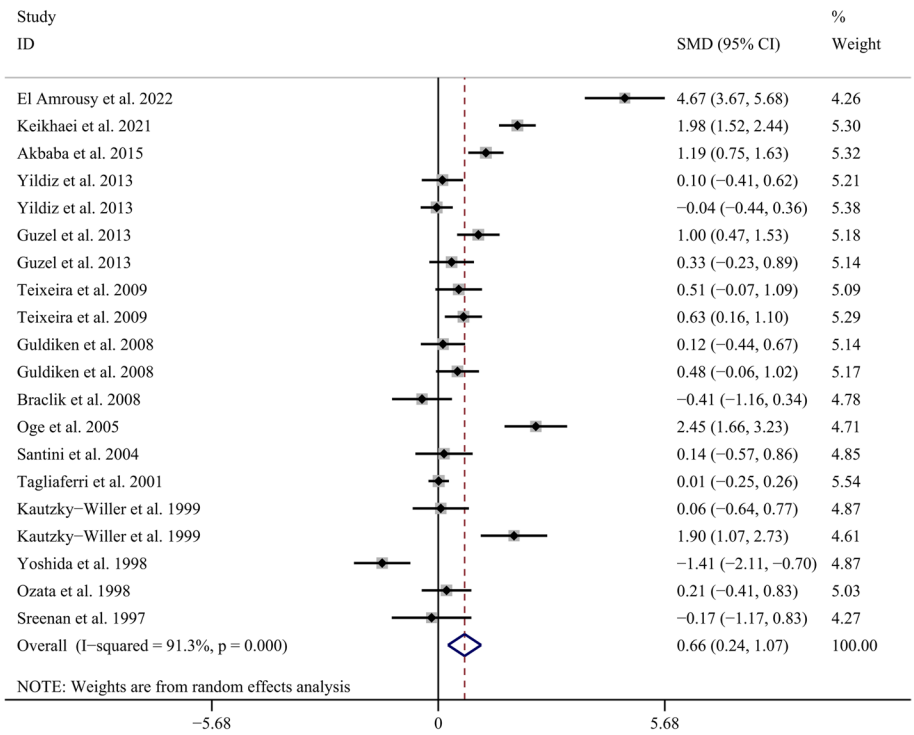

Fig. 3 Forest plot of circulating leptin levels in hypothyroidism and age-, gender-, and BMI-matched euthyroidism. SMD, standardized mean difference; CI, confidence interval

Taken together, leptin levels in TD may be directly influenced by their TH levels, independent of BMI.

Leptin is recognized as a key neuroendocrine regulator of the HPT axis [61]. Thyrotropin-releasing hormone (TRH), a crucial peptide hormone in HPT regulation, functions as a metabolic sensor for thyroid function and energy balance regulation and is sensitive to energy balance regulators like leptin [62]. It has been reported that food deprivation (low circulating leptin concentrations) contributed to reduced TRH synthesis in the hypothalamic paraventricular nucleus (PVN), and exogenous leptin supplementation restored food deprivation-associated TRH gene expression, as well as reversing the inhibitory effect of fasting on spontaneous TSH secretion [63–65]. Specifically, leptin binds to the ObRb in the hypothalamic arcuate nucleus (ARC) or acts directly on the PVN to promote the release of TRH and thereby promote the release of TSH from the pituitary [66]. Therefore, leptin promotes energy expenditure by increasing TH levels. The above also explains why ObRb mutation can lead to central hypothyroidism [67]. However, the role of HPT on leptin remains contentious. Our study showed a positive correlation between leptin levels and TSH levels. The presence of functional TSH receptor (TSHR) in adipocytes has been demonstrated [68, 69]. Menendez et al. [70] demonstrated that TSH can act directly on adipose tissue to promote leptin secretion by employing human omental adipose tissue. Besides, Santini et al. [71] also noted that acute exogenous supplementation of TSH significantly increased serum leptin levels. Notely, Mantzoros et al. [72] pointed out that both leptin and TSH release were highly organized and pulsatile, with similar circadian rhythms and overlapping peaks, and that there was a strong positive correlation between their patterns of 24-h variability. In sum, there may be a complex positive feedback system between leptin and TSH. Moreover, leptin upregulates type 1 and 2 iodothyronine deiodinase activity in adipose tissue [73, 74]. The present study showed a negative correlation between leptin levels and T3 levels. Current evidence suggests a complex role for T3 in regulating leptin. Kristensen et al. [75] demonstrated that T3 directly inhibits leptin expression and release by human subcutaneous adipose tissue. In the periphery, leptin regulation of energy metabolism is dependent on sympathetic nervous system (SNS) activity [10]. Fain et al. [76] observed that T3 injection resulted in an increase in β-adrenergic receptor mRNA expression and a decrease in leptin mRNA expression in adipose tissue of hypothyroid rats. Kosaki et al. [77] found that treatment of 3T3-L1 adipocytes with either norepinephrine or isoprenaline suppressed leptin mRNA levels in a dose-dependent manner,

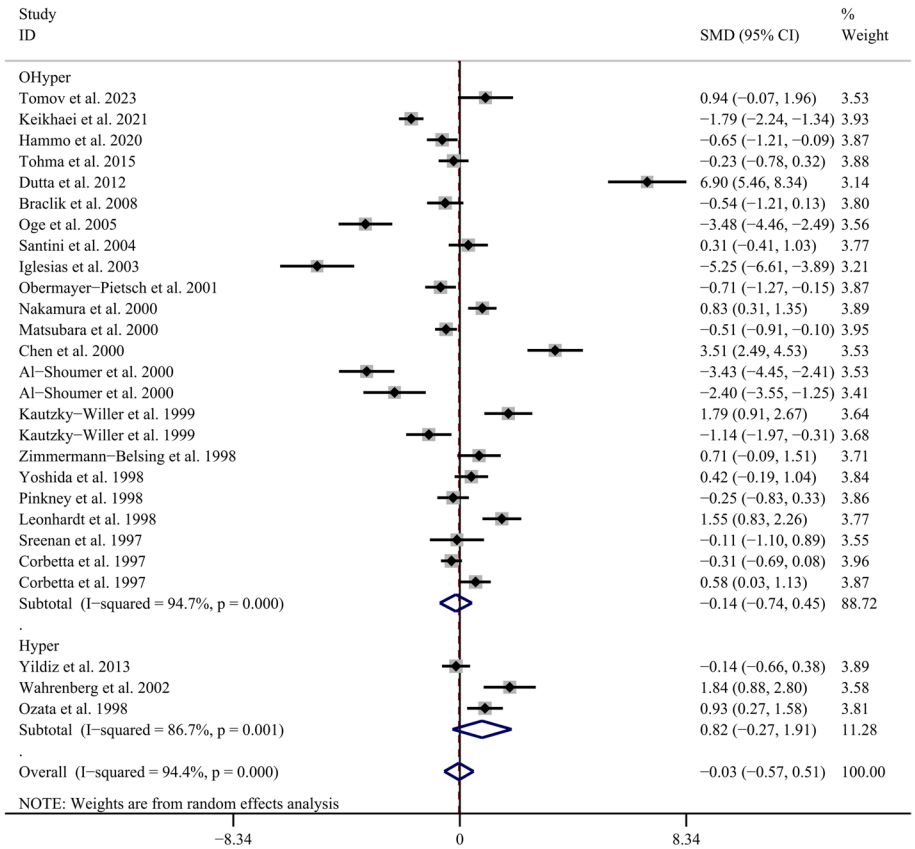

Fig. 4 Forest plot of circulating leptin levels in hyperthyroidism and euthyroidism. OHyper, overt hyperthyroidism; Hyper, hyperthyroidism; SMD, standardized mean difference; CI, confidence interval

which was attenuated by the addition of propranolol (β-adrenergic receptor blocker). In short, stimulation of β-adrenergic receptors decreases leptin expression and release, as evidenced in both humans and rodents [78, 79]. It is well known that T3 makes peripheral tissues hyperresponsive to adrenergic hormones. So, the action of T3 on leptin can be interpreted in the context of adipocyte β-adrenergic receptor sensitivity. Hypothyroidism and hyperthyroidism have functional hypo- and hyperadrenergic states, respectively [80]. However, Fain et al. [81] reported that T3 stimulated or inhibited adipose tissue leptin mRNA expression, which was inhibited by T3 alone but stimulated by T3 in the presence of insulin. The negative feedback loop of insulin and leptin is known to play an essential role in maintaining nutritional homeostasis [82]. The current evidence has shown that insulin promotes the expression and release of leptin in adipose tissue [83, 84]. Notably, T3 can stimulate insulin secretion and induce hyperinsulinemia [85, 86]. Besides, elevated or lowered T3 levels can result in the development of insulin resistance [86, 87]. Peripheral insulin resistance occurs in hypothyroidism, and in hyperthyroidism, hepatic and peripheral insulin resistance are observed [86–88]. Therefore, the increases offsetting the decreases could be a plausible explanation for the lack of significant changes in leptin levels in hyperthyroidism. In sum, leptin secretion or degradation in TD may be directly affected by TSH and T3 levels.

Leptin is not only a peptide hormone that regulates energy homeostasis, but also a signaling molecule that regulates physiological equilibrium, and leptin dysregulation has been associated with a variety of diseases [12, 58]. Elevated leptin levels promote processes such as dyslipidemia, insulin resistance, inflammation, oxidative stress, vascular smooth muscle proliferation, platelet aggregation, and vascular endothelial damage, thereby accelerating the onset of metabolic diseases, cardiovascular diseases, and others [58, 89]. Additionally, chronically high leptin levels lead to the occurrence of leptin resistance, initiating a vicious positive feedback loop, further aggravating obesity and related metabolic disorders [58, 90]. Taken together, high leptin levels may be involved in increasing the risk of hypothyroidism-related complications. Therefore, monitoring leptin levels in hypothyroidism may help predict and prevent serious consequences of the disease in the future.

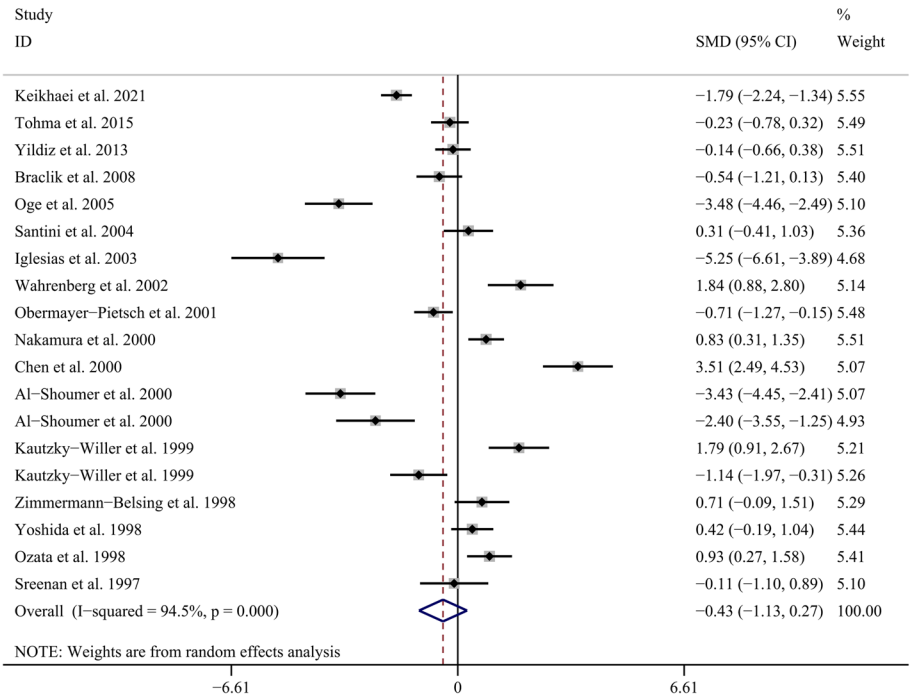

Fig. 5 Forest plot of circulating leptin levels in hyperthyroidism and age-, gender-, and BMI-matched euthyroidism. SMD, standardized mean difference; CI, confidence interval

Table 3 Correlations between leptin levels and TH levels in TD

Parameters	N	*r*	[95%CI]	I^2 (%)	*P*-value
TSH	527	0.19	[0.04, 0.34]	66.70	0.015
T4	70	-0.46	[-0.88, 0.35]	92.00	0.255
T3	144	-0.40	[-0.64, -0.10]	70.00	0.010
FT4	286	-0.08	[-0.26, 0.11]	56.40	0.397
FT3	286	0.05	[-0.17, 0.26]	67.60	0.664

TSH thyroid-stimulating hormone, *T4* thyroxine, *T3* triiodothyronine, *FT4* free thyroxine, *FT3* free triiodothyronine, *N* sample size, *r* correlation coefficient, *CI* confidence interval

To our knowledge, this is the first meta-analysis to explore circulating leptin levels in TD. Additionally, we conducted sensitivity analyses to exclude confounders including age, gender, and BMI as much as possible, as well as pooled the correlations between leptin levels and TH levels to demonstrate the direct effect of thyroid function itself on leptin levels. However, it did have some limitations. Firstly, due to the cross-sectional nature of the included studies, the causal relationship between TD and leptin cannot be well illustrated. Secondly, we were unable to exclude the effect of Body fat percentage (BF%) on the results, as it was not available in most included studies. Dutta et al. [17] showed that leptin levels were significantly higher in hyperthyroidism than in euthyroidism,

Table 4 Meta-regression analysis of studies reporting circulating leptin levels in TD and euthyroidism

Covariates	Hypothyroidism and Euthyroidism			Hyperthyroidism and Euthyroidism		
	Coefficient	[95% CI]	*P*-value	Coefficient	[95% CI]	*P*-value
Age (years)	-0.01	[-0.05, 0.03]	0.666	-0.02	[-0.11, 0.07]	0.653
Gender	0.20	[-0.63, 1.04]	0.619	-0.02	[-1.88, 1.85]	0.986
BMI (kg/m^2)	-0.01	[-0.06, 0.05]	0.856	-0.01	[-0.21, 0.20]	0.956
Detection method	-0.47	[-1.37, 0.43]	0.296	-1.08	[-4.29, 2.13]	0.489
Sample type	1.28	[-0.34, 2.89]	0.117	2.41	[-0.02, 4.84]	0.051
Study region	0.09	[-0.20, 0.37]	0.549	0.10	[-0.30, 0.50]	0.608
Publication date	0.08	[-0.07, 0.23]	0.297	0.01	[-0.31, 0.33]	0.930

BMI body mass index, *CI* confidence interval

which may be related to the significant difference in BF%. Thirdly, the pooled results showed strong heterogeneity, although we performed meta-regression to explore the sources of heterogeneity, the results were unsatisfactory. Additionally, we did not further analyze the etiology of TD due to its diversity. Fourthly, we only included studies published in English, which may have missed suitable studies published in other languages. Given these factors, the results of our study should be interpreted with caution. Future relevant large prospective studies to verify the feasibility of our results are necessary.

Conclusion

In conclusion, circulating leptin levels were significantly higher in hypothyroidism, and not significantly altered in hyperthyroidism compared to euthyroidism. Besides, leptin levels in TD may be directly regulated by TSH and T3 levels, independent of BMI. Leptin may be a potential marker and effective therapeutic target for hypothyroidism. Future large-scale experimental studies and clinical trials to explore the potential mechanisms and clinical value of leptin in hypothyroidism are necessary.

Abbreviations

TD	Thyroid dysfunction
HPT	Hypothalamic-pituitary-thyroid
TRH	Thyrotropin-releasing hormone
TH	Thyroid hormone
TSH	Thyroid-stimulating hormone
T4	Thyroxine
T3	Triiodothyronine
FT4	Free thyroxine
FT3	Free triiodothyronine
TSHR	Thyroid-stimulating hormone receptor
BMR	Basal metabolic rate
BMI	Body mass index
BF	Body fat
BF%	Body fat percentage
Ob	Obesity
ObRb	Leptin receptor
RIA	Radioimmunoassay
ELISA	Enzyme-linked immunosorbent assay
PVN	Paraventricular nucleus
ARC	Arcuate nucleus
SNS	Sympathetic nervous system
SMD	Standardized mean difference
CI	Confidence interval
ES	Effect size
R	Correlation coefficient
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
NOS	Newcastle Ottawa Scale
AHRQ	Healthcare Research and Quality Scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01943-y.

Supplementary Material 1.

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Clinical trial number

Not applicable.

Authors' contributions

All authors were involved in the conception and design of the study. SL, JM, LZ, and YY completed the data preparation, data extraction, and data analysis. SL wrote the first draft. The draft was reviewed and revised by LT and ZH. All authors read and finalized the final version of the manuscript.

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Data availability

All available data analyzed in this study are included in the manuscript and its supplementary materials.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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