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Association between Insulin Resistance and Metabolic Syndrome with Thyroid Status in Normal and Overweight/Obese Population: A Review

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Abstract

Background: Hypothyroidism has multiple etiologies and manifestation where accurate diagnosis and appropriate treatment is required and is influenced by coexisting medical conditions. This paper describes evidence-based clinical causes and indications. **Objective:** The objective is to review the clinical effect of hypothyroidism in different selected aspects and summarize the potential evidence about relationship between subclinical hypothyroidism with cardiovascular disease, diabetes mellitus, insulin resistance and mortality. **Data Sources:** A systematic review was conducted by searching English-language articles identified from 23 databases and search engines, yielding over 1000 documents. **Study Selection:** They are reports on the effects of hypothyroidism versus euthyroidism on obesity, insulin resistance, cardiovascular disease, coronary heart disease and mortality. **Data Extraction:** Data from research articles on hypothyroidism including subclinical hypothyroidism (SCH) and overt hypothyroidism, insulin resistance including diabetes mellitus and risk for coronary heart disease (CHD) including metabolic syndrome were independently assessed and summarized. **Data Synthesis:** Twelve of twenty-nine identified studies involved population-based cohorts, case controls and retrospective studies that included 4306 subjects. All 13 studies examined risks associated with subclinical hypothyroidism with type 2 diabetes mellitus (T2DM) and prevalence rates of SCH in T2DM patients ranged from 4.69% to 64.28% in the 12 included studies. Moreover, 4 studies out of the above 12 studies have revealed insulin resistance in the participants. Another population-based

12 studies have been carried out to assess hypothyroidism-related cardiac manifestation and according to the given data, average prevalence of CHD in hypothyroid participants is 25.20 (vary from 3.73 to 47.14) and it is 13.90 in euthyroid participants (vary from 1.17 to 38.49). **Conclusions:** Type 2 diabetes mellitus people are more likely to get subclinical hypothyroidism and subclinical hypothyroid population also shows several complications associated with type 2 diabetes mellitus. Besides, subclinical thyroid dysfunction might represent a risk factor for coronary artery disease and mortality.

Keywords

Subclinical Hypothyroidism, Euthyroidism, Diabetes Mellitus, Insulin Resistance, Coronary Heart Disease

1. Introduction

The circumstance where thyroid gland does not produce enough thyroid hormone is known as hypothyroidism. It is a common endocrine disorder and can be divided into 3 groups based on the cause of the disease as: 1) Primary hypothyroidism—caused commonly by iodine deficiency and autoimmune thyroiditis; 2) Central hypothyroidism—caused by conditions affecting the pituitary gland; 3) Congenital hypothyroidism (can be transient or central)—caused by maternal iodine deficiency, anti-TSH receptor antibodies or pituitary dysfunction [1] [2] [3]. Serum TSH, free T_3 and free T_4 levels are being measured to assess thyroid function. Based on the TSH and T_4 levels, hypothyroidism is classified into 2 different classes as: 1) Subclinical hypothyroidism—Elevated TSH and normal T_4 (TSH 4.6 to 10 mIU/L); 2) Overt hypothyroidism—Elevated TSH and low T_4 (TSH > 10 mIU/L) [3] [4].

Subclinical hypothyroidism, may be exogenous ((L-thyroxine [5] under-replacement in hypothyroid patients; medication with lithium, cytokines, iodine, or anti-thyroid drugs, and iodine 131 therapy or thyroidectomy) or endogenous (Hashimoto thyroiditis [6] [7] and previous sub-acute or silent thyroiditis [8]) [9]. Its prevalence ranges from 1.3% to 17.5%, depending on age, sex, and iodine intake [10] [11]. People with thyroid antibodies caused by Hashimoto thyroiditis are more likely to get subclinical hypothyroidism [9]. Over time, untreated hypothyroidism can cause multiple clinical manifestations and complications. According to research data, subclinical hypothyroidism increases the risk of coronary heart disease, infertility, diabetes mellitus and obesity and it has been found that iodine deficiency is one of the main causes of hypothyroidism [12] [13] [14] [15].

According to a survey conducted by National Health and Nutrition Examination Survey (NHANES III) in an unselected U.S. population over the age of 12 years, the prevalence of subclinical disease was 4.3% and overt disease was 0.3%

[16] and in another study carried out in Framingham, 5.9% of women and 2.3% of men over the age of 60 years had TSH values over 10 mIU/L and 39% of whom had subnormal T_4 levels [17]. Moreover, a research conducted in Whickham, United Kingdom had come up with results that indicate that 9.3% of women and 1.2% of men had serum TSH values over 10 mIU/L [18] and the incidence of hypothyroidism in women was 3.5 per 1000 survivors per year and in men it was 0.6 per 1000 survivors per year [19]. Further results show that the risk of developing hypothyroidism in women with positive antibodies and elevated TSH was 4% per year versus 2% - 3% per year in those with either alone [19]. But in men, the relative risk rose even more in each category, but the rates remained well below those of women. **Table 1** represents the summary of the above-mentioned research with the prevalence of SCH and OHT in males and females with the TSH values.

The objectives of this review were to answer the following questions on hypothyroidism related clinical manifestations (**Table 2**): They are: "To determine the association between thyroid status and insulin resistance", "To determine the association between thyroid status and presence of metabolic syndrome" and

Table 1. Prevalence of hypothyroidism.

Study	Subclinical	Overt	TSH	Comment
NHANES III	4.3%	0.3%	4.5	
Colorado Thyroid Disease Prevalence	8.5%	0.4%	5.0	Abnormal thyroid function has multiple implications on public health
Framingham			10	Over age 60 years: 5.9% women; 2.3% men; 39% of whom had subnormal T_4
Whickham (UK)			10	9.3% women; 1.2% men

Sources: Hollowell *et al.*, 2002 [16]; Canaris *et al.*, 2000 [20]; Sawin *et al.*, 1985 [17]; Vanderpump *et al.*, 1995 [18]; Vanderpump and Tunbridge, 2002 [19]. NHANES, National Health and Nutrition Examination Survey.

Table 2. Overview of the review article.

Participants	**General population (especially women) including pregnant females from any country**
Key factors	Hypothyroidism, Insulin resistance, Diabetes Mellitus, Coronary Heart disease, Metabolic Syndrome,
Data Source	Databases and search engines
Study Design	Community based, Observational, Cross Sectional, Longitudinal surveys

"To determine the association between thyroid status and anthropometric parameters among normal (controls) and overweight or obese (cases) study participants".

2. Methods

Data sources were journal articles about the effects of thyroid dysfunction in insulin resistance, metabolic syndrome, iodine deficiency, infertility and obesity in humans published between 1990 and September 2020. The following types of studies were included: nonrandomized controlled trials; prospective observational studies that had a control group, such as cohort studies (prospective and retrospective) and controlled before-and-after studies; and prospective observational studies that did not have a control group, including before-and-after studies, in addition, the following documents were excluded: conference abstracts, letters to the editor, and presentations. If there were multiple documents from the same country's practice, only the most recent and comprehensive paper was included. The participants included in the review consisted of the general population older than 5 years (including pregnant women) from any country.

The literature for the review was based on electronic databases and the following databases were searched in May, 2020 and, only articles published in English from the following were perused: PubMed, MEDLINE, Embase, Web of Science, CINAHL (Cumulative Index to Nursing and Allied Health Literature) POPLINE, BIOSIS Previews, OpenGrey, Bibliomap, TRoPHI (Trials Register of Promoting Health Interventions), IBECS, Global Health Library, Indian Medical Journals, Native Health Research Database, and ProQuest Dissertation and Theses.

The full text of each relevant document was read independently by the reviewers and, from relevant documents, the information related to study location, study design, results and outcomes assessed were extracted. Finally, the extracted information was analyzed qualitatively; furthermore, the statistical significance of changes in outcomes of interest as reported in the studies was noted.

3. Results

The database search yielded 1367 English documents; when duplicates were eliminated, 756 documents remained (**Figure 1**). Titles were reviewed independently, and 602 documents were selected for abstract review. Of these, 48 full-text documents were retrieved and reviewed and based on the relevance 29 were included in the analysis.

3.1. Description of Documents

The documents selected for in-depth review presented evaluations of thyroid dysfunction, type 2 diabetes mellitus, insulin resistance and metabolic syndrome in 9 countries: India, The USA, The UK, China, Mongolia, Nigeria, Saudi Arabia, Italy, Spain.

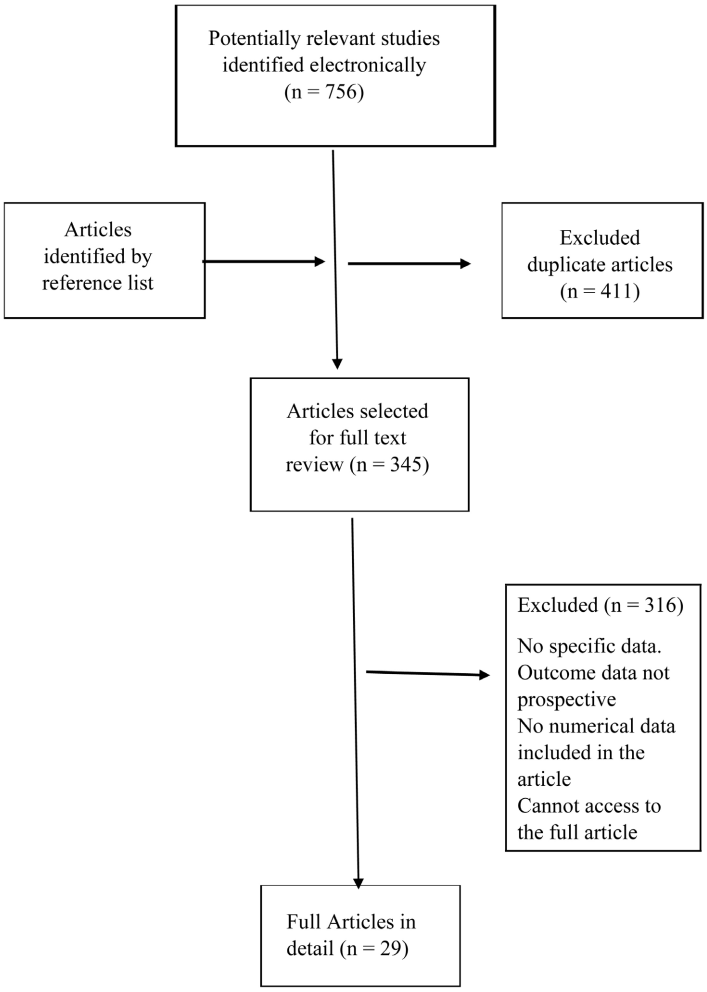

Figure 1. Flow chart of the search and selection process.

3.2. Concurrent Conditions of Special Significance in Hypothyroid Patients

3.2.1. Prevalence of Subclinical Hypothyroidism (SCH) in Type 2 Diabetes Mellitus Patients

The data under review for this section contains data from 13 individual studies which included 863 cases and 4306 subjects (**Table 3** and **Table 4**). Prevalence rates of SCH in T2DM patients ranged from 4.69% to 64.28% in the 13 included studies. It is known that gender and age may influence the observed prevalence of SCH in non-diabetic populations [16]. Several studies have found that non-diabetic adult females are more prone to get SCH compared to males [10] [21] [22]. Thus, a subgroup analysis was conducted to compute the prevalence rates according to gender, age, and location, trying to explain the heterogeneity. As shown in **Table 3** and **Table 4**, sub-group analysis revealed that female T2DM participants had more SCH than male T2DM patients, and elderly T2DM patients (>60 years old) were more frequently suffering from SCH.

Among the total number of 4306, 863 had suffered either subclinical hypothyroidism or overt hypothyroidism associated T2DM. Studies have also revealed

Table 3. Description of the studies included in the review on the summarization of prevalence of SCH in T2DM patients.

Author	Published Year	Country and area	Mean Age	Cases (n)	Total (n)	Prevalence (%)	Research Type
Vanderpump M *et al.* [23]	1995	UK	50 ± 20	178	1051	16.9	Cohort
Ganie M *et al.* [24]	2011	India	30 ± 5	62	291	21.30	CC
Mohn A *et al.* [25]	2002	Italy	15 ± 5	13	281	4.62	CC
Vondra K *et al.* [26]	2005	USA	26 ± 10	47	90	52.22	CS
Vyakaranam S *et al.* [27]	2014	India	30 ± 10	30	60	50	CS
Demitrost L *et al.* [28]	2012	India	55 ± 10	33	202	16.3	RS
Nada A [29]	2013	Saudi Arabia	32 ± 10	27	42	64.28	CC
Zhang D *et al.* [30]	2014	Changsha, China	50 ± 20	244	1294	18.86	CC
Hansen D *et al.* [31]	1999	Pennsylvania	5 - 17	153	235	65.1	Cohort
Ghazali S *et al.* [32]	2010	Nigeria	50 ± 20	3	64	4.69	CC
Zhang N *et al.* [33]	2009	Jiangsu, China	60	50	416	12.02	CS
Diez J *et al.* [34]	2011	Spain	60 ± 20	34	318	10.69	CS
Han C *et al.* [35]	2013	Anhui, China	45 ± 10	22	164	13.41	CS
Total				**896**	**4508**		

Abbreviation: F-Female; M-Male; CC-Case Control study; CS-Cross Sectional study, RS-Retrospective study.

Table 4. TSH, FT_4, IR and HOMA-IR parameters in SCH participants according to gender, age, and country.

Reference	Meann age	Sex	SCH					
			No.	TSH	FT_4	IR	HOMA-IR	P-value
Mohn A *et al.* [25] (Italy)	11.9	F-11 M-22	33	7.6 (5.5 - 19.9) μU/mL	15.5 (11.5 - 22.8) pmol/L	HPG* 5.5 ± 0.4		0.05
Vyakaranamm S *et al.* [27] (India)	25	NM	30	14.20 ± 5.23 μU/mL	2.96 ± 0.80 pg/mL	9.07 ± 3.41 μU/mL	2.03 ± 0.95	0.0001
Nada A [29] (S. Arabia)	21.8	F	27 (OHT)	22.4 ± 36.2 μU/mL	11.2 ± 4.0 pmol/L	2.5 ± 2.1 μIU/mL		0.001
Hansen D *et al.* [31] (USA)	12.8	F/M	105	1.51 (0.59 - 6.18) U/L	94 (66 - 189) nmol/L	0.9 (0.2 - 1.8) IU/Kg	HbA1C 8.0 (5.6 - 15.1)	0.353

Abbreviations: SCH-Sub clinical hypothyroidism, TSH-Thyroid stimulating hormone, T_4-Thyroxine, IR-Insulin Resistance, HOMA-IR-Homeostatic model assessment Insulin Resistance, OHT-Overt Hypothyroidism, F-Female, M-Male, *HPG-Hypoglycemic episode.

that adolescent age group also has a risk of developing diabetes mellitus along with insulin resistance, with a prevalence of 58% [31].

According to the above scatter plot, when TSH level increases, the IR value also increases gradually as observed in three studies carried out in three countries [25] [27] [31]. But one research carried out in Saudi Arabia [29] revealed a low IR value in participants with high TSH values. Therefore, the relationship

between TSH and IR is still questionable and needs further study.

Table 5 illustrates the behavior of TSH, FT_4, IR and HOMA-IR parameters in euthyroid participants in studies mentioned in Table 4 where the listed research findings highlight significant associations.

3.2.2. Hypothyroidism Related Metabolic Syndrome along with Cardiac Dysfunction

The cardiovascular system is very sensitive to thyroid hormone, and a wide spectrum of cardiac changes has long been recognized in overt thyroid dysfunction [36] [37]. Moreover, cardiovascular impairment in patients with subclinical thyroid dysfunction has also been studied in several countries [9] [38] [39]. Based on the effect of low levels of thyroid hormones, increased risk for atherosclerotic vascular diseases had been reported and major concomitant risk factors include dyslipidemia and diastolic hypertension [40]. Dyslipidemia is characterized by elevated serum levels of low-density lipoprotein (LDL) cholesterol where the clearance of excess serum LDL particles is delayed because of a decreased expression of the LDL receptors on liver cell surfaces, which is under the control of T_3 [41] [42]. People having type 2 diabetes mellitus [43], untreated hypothyroidism [44], obesity [45], chronic renal diseases [46], nephrotic syndrome [47], smoking and alcohol consumption [47] show higher susceptibility for dyslipidemia, which contribute to the rising incidence of cardiovascular disease in the world.

3.2.3. Hypothyroidism and Cardiac Manifestations

Table 6 illustrates the risk for cardiac manifestation due to SCH or overt hypothyroidism in several countries with the percentage of SCH cases recorded, and most of the studies show more than 50% of SCH or OHT cases compared to normal population. Table 7 evaluates the occurrence of Coronary heart disease in subclinical hypothyroidism and euthyroid participants with total mortality rates.

Table 5. TSH, FT_4, IR and HOMA-IR parameters in Euthyroid participants according to gender, age, and country.

Reference	Euthyroid					
	No.	TSH	FT_4	IR	HOMA-IR	p-value
Mohn A *et al.* [25] (Italy)	31	1.6 (0.6 - 3.1) μU/mL	15.4 (12.8 - 18) pmol/L	HPG* 1.6 ± 0.1		0.05
Vyakaranam S *et al.* [27] (India)	30	2.24 ± 1.43 μU/mL	1.15 ± 0.52 pg/mL	5.28 ± 2.18 μU/mL	1.05 ± 0.45	0.0001
Nada A [29] (S. Arabia)	15	2.9 ± 1.5 μU/mL	13.7 ± 2.1 pmol/L	2.6 ± 1.5 μIU/mL		0.001
Hansen D *et al.* [31] (USA)	105	1.48 (0.47 - 3.46) U/L	92 (54 - 140) nmol/L		HbA1C 5.1 (4.4 - 5.6)	

Abbreviations: SCH-Sub clinical hypothyroidism, TSH-Thyroid stimulating hormone, T_4-Thyroxine, IR-Insulin Resistance, HOMA-IR-Homeostatic model assessment Insulin Resistance, OHT-Overt Hypothyroidism, F-Female, M-Male. *HPG-Hypoglycemic episode.

Table 6. Population-based studies of subclinical and overt thyroid dysfunction and risk for CHD.

First Author	Published Year	Country and area	Mean Age	Cases (n)	Total (n)	Percentage of recorded cases	Research Type
Vanderpump M *et al.* [23]	1996	Whickham, UK	46	212	664	32%	Cohort
Althaus B *et al.* [38]	1987	Switzerland	30.9	70	116	60.3%	CC
Dikeman T *et al.* [48]	1998	Netherland	44	10	20	50%	CC
Shapiro L *et al.* [49]	1997	USA	43.2	17	34	50%	CC
Mercuro G *et al.* [50]	2000	Cagliari, Italy	41.3	19	38	50%	CC
Biondi B *et al.* [51]	1999	Naples, Italy	36	26	56	46.4%	CS
Nystrom E *et al.* [52]	1988	Sweden	61.5	20	37	54%	CS
Hak A E *et al.* [53]	2000	Netherland	54.5	124	1055	11.7%	Cohort
Parle J V *et al.* [54]	2001	UK	70	386	1191	32.4%	Cohort
Walsh J P *et al.* [55]	2005	Australia	49.6	158	2064	7.6%	CS
Luboshitzky R *et al.* [56]	2002	Nepal	44.1	57	91	62.6%	CC
Bauer D C *et al.* [57]	2007	USA	64.6	36	480	7.5%	
Total				2152	7591	28.3%	

Abbreviations: CS-Cross Sectional study, CC-Case Control study.

Table 7. Occurrence of coronary heart disease in subclinical hypothyroidism and euthyroid participants.

Study, Year	Subclinical Hypothyroid group			Euthyroid Group		
	CHD Events (n)	Participants (n)	Percentage (%)	CHD Events (n)	Participants (n)	Percentage (%)
Althaus B *et al.* [38] 1987	33	70	47.14	5	46	10.86
Hak A E *et al.* [53] 2000	4	107	3.73	10	850	1.17
Parle J V *et al.* [54] 2001	10	76	13.15	118	1026	11.5
Walsh J P *et al.* [55] 2005	33	101	32.67	229	1752	13.07
Vanderpump M *et al.* [23] 1996	12	26	46.15	174	452	38.49
Bauer D C *et al.* [57] 2007	3	36	8.33	33	398	8.29
Cappola A R *et al.* [59] 2006	98	496	19.75	489	2639	18.52

According to the results of each study, it is clear that the clinical characteristics of patients and normal controls were well matched for age, sex, and body surface area. Both heart rate and blood pressure were comparable in the two groups. As expected, TSH levels were significantly higher in patients than in controls and though FT_3, FT_4 levels are in the normal range, they are significantly lower in the patients than in control subjects before the therapy.

According to the details given in Table 7, most of the time the prevalence of coronary heart disease (CHD) is higher in people with hypothyroidism than in

normal, thus based on the given data, the average prevalence of CHD in hypothyroid participants is 25.20 (vary from 3.73 to 47.14) and it is 13.90 in euthyroid participants (vary from 1.17 to 38.49). Table 8 highlights cardiovascular mortality among hypothyroid and euthyroid people where it shows that the mortality rate is not always higher in hypothyroid participants. The literatures in Table 8 clarifies that the death rate is higher in hypothyroid participants ([54] [55] [58] [59]) in some instances but some other studies show euthyroid cardiovascular death rate can be higher than that of hypothyroid cases ([57] [60] [61]).

The above findings illustrate the occurrence of coronary heart disease in people with both SCH and ones who are euthyroid where all the SCH patients are more likely to suffer from CHD than euthyroid participants. This highlights that SCH is associated with a higher chance of coronary heart disease events.

Although CVD events were always higher in persons with SCH than in euthyroid people (Figure 2), some studies have revealed that the mortality percentage is higher in euthyroid people than in identified SCH people [57] [60] [61]. Therefore, we can assume that other than CVD some other factors may also have influenced the deaths in these participants.

3.2.4. Hypothyroidism Related Metabolic Syndrome Manifestations

The metabolic syndrome (MetS) is a common metabolic disorder that results from the increasing prevalence of obesity. It is a cluster of conditions that occur together, increasing the risk of heart disease, stroke and type 2 diabetes and these conditions include increased blood pressure, high blood glucose, excess body fat around the waist, and abnormal cholesterol or triglyceride levels. Therefore, the pathophysiology seems to be largely attributable to cardiac disorders with excessive flux of fatty acids [62]. Many studies have been carried out to find the association between metabolic syndrome and Table 9 highlights how different metabolic syndrome parameters behave in hypothyroid participants when compared to euthyroid participants.

Table 8. Cardiovascular mortality in subclinical hypothyroid group vs. euthyroid group.

Study, Year	Subclinical Hypothyroid group			Euthyroid Group		
	CV Deaths (n)	Participants (n)	Percentage (%)	CV Deaths (n)	Participants (n)	Percentage (%)
Parle J V *et al.* [54] 2001	10	76	13.15	118	1026	11.5
Walsh J P *et al.* [55] 2005	21	101	20.79	170	1752	9.70
Bauer D C *et al.* [57] 2007	3	36	8.33	43	398	10.80
Imaizumi M *et al.* [58] 2004	2	257	0.77	6	2293	0.26
Cappola A R *et al.* [59] 2006	101	496	20.36	474	2639	17.96
Gussekloo J *et al.* [60] 2004	2	30	6.66	75	472	15.88
Rodondi N *et al.* [61] 2005	10	338	2.95	94	2392	3.92

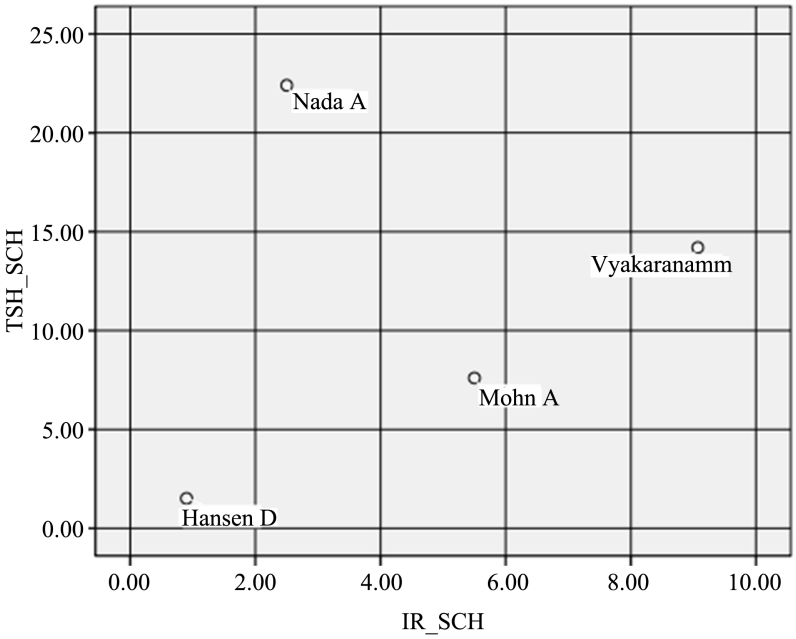

Figure 2. Relationship between TSH vs. insulin resistance in subclinical hypothyroid participants in four studies based on **Table 4**.

Table 9. Literatures of hypothyroidism related metabolic syndrome manifestations with several factors.

	Althaus B [38] 1987		Hak A E [53] 2000		Luboshitzky R [56] 2002		Dikeman T [48] 1998		Walsh J P [55] 2005		Cappola A R [59] 2006		Rodondi N [61] 2005		Biondi B [51] 1999	
	SCH	EUT	SCH	EUT	SCH	EUT	SCH	EUT	SCH	EUT	SCH	EUT	SCH	EUT	SCH	EUT
No. of Participants	52	28	124	931	57	34	10	10	119	1906	496	2639	338	2392	26	30
Age (Mean)	53	47.2	69	68.9	48	45	44	47.2	58.1	49.2	73.2	72.6	74.8	74.7	36	36
BMI	24.4	22.7	27.1	26.7	27.2	27			25.5	25.5	26.2	26.4	26.7	27.3		
M. SBP			137	138	127	120			133	129			132.3	133.9	120	125
M. DBP			73	73	82	75			79	77			69.5	70.5	78	77
TC (mmol/L)	6.02	5.54	6.7	7	1.67	1.29	5.79	4.8	6.3	5.8	5.6	5.5	5.5	5.3		
HDL (mmol/L)	1.6	1.5	1.4	1.5	0.8	0.4	1.46	1.36			1.4	1.3				
LDL (mmol/L)	4.27	3.72			0.8	0.9	3.76	2.89			3.4	3.4				
Tri G (mmol/L)	1.1	0.89			0.3	0.03	1.26	1.32	1.7	1.4						
TSH (mU/L)	8.6	1.3			10	3	75.7	2.7	6.26	1.41	6.67	2.2	15.4	8.5	8.6	1.6
FT_4 (pmol/L)	12	18.5			12	14	5.3	15.1	1.1	1.2	0.99				9.4	15.3
T_3 (nmol/L)	2.1	2.7			2.1	3	1.2	1.7							5.1	6

Abbreviations: SCH-Subclinical hypothyroidism, EUT-Euthyroid, BMI-Body Mass Index, M.SBP-Mean systolic blood pressure, M.DBP-Mean diastolic blood pressure, TC-Total cholesterol, HDL-High density lipoproteins, LDL-Low density lipoproteins, TriG-Triglycerides, TSH-Thyroid stimulating hormone, FT_4-Thyroxine, FT_3-Triiodothryronine, M-Male, F-Female. Reference ranges: TC-3.6 - 5.17 mmol/L, HDL-0.9 - 1.8 mmol/L (M), 0.9 - 2.2 mmol/L (F), LDL- < 3.4 mmol/L, TriG- < 1.7 mmol/L, TSH-0.4 - 4 mU/L, FT_4-12 - 30 pmol/L, FT_3-1.1 - 3 nmol/L. : Data not available in the article.

Further, Table 9 compares different factors affecting metabolic syndrome such as body mass index, mean systolic and diastolic blood pressure, total cholesterol, high density lipoproteins, low density lipoproteins, triglycerides and thyroid hormones in both subclinical hypothyroid and euthyroid participants. According to the data given ([38] [48] [51] [53] [55] [56] [59] [61]), in each study, the participants are having a relatively high body mass index in both subclinical hypothyroid and euthyroid groups. No significant difference can be identified in both mean systolic and diastolic blood pressure values ($P > 0.05$). Moreover, there is no significant difference in the lipid profile, but in contrast, the TSH value of subclinical hypothyroid participants shows a significant difference from euthyroid group as expected, where it has been elevated drastically than normal levels (reference range: 0.4 - 4 mU/L). Therefore, based on the values obtained from the studies, the factors affecting metabolic syndrome have not been changed in a noticeable in relation to the TSH levels (Table 9).

4. Discussion

Analysis of population-based studies, on hypothyroidism related insulin resistance, type 2 diabetes mellitus and metabolic syndrome for this review article, is evident that some studies show a significant relationship among the above factors whereas, some studies show no relationship between them. This review was conducted based on 29 studies conducted in nine countries. According to the data given in Table 3, although some participants in these studies showed a mild hypothyroidism associated with diabetes mellitus there is no statistically significant relationship observed between these two factors [24] [29]. As mentioned by Nada A M [29], his research carried out on twenty-seven overt hypothyroid participants and fifteen euthyroid participants (matching age and BMI; P values 0.444 and 0.607 respectively) to analyze their fasting blood glucose, fasting insulin, insulin resistance total cholesterol and tri glycerides; the results obtained illustrate that there is no significant difference between overt hypothyroid and euthyroid groups (P values; 0.432, 0.621, 0.883, 0.586 and 0.05 respectively for fasting plasma glucose, fasting insulin, insulin resistance, total cholesterol and triglycerides in hypothyroid patients and euthyroid controls).

In contrast, some studies have observed a clear association between subclinical hypothyroidism and insulin-resistant along with type 2 diabetes mellitus [25] [26] [27] [28]. These studies reveal that the prevalence of subclinical hypothyroidism is higher in type 2 diabetes mellitus patients. Such a study conducted by Mohn A *et al.* [25], using 202 type 2 diabetes mellitus participants including 139 euthyroid ones (68.8%) and 33 subclinical hypothyroid ones (16.3%) show that there is a significant increase in prevalence of diabetes mellitus among persons with SCH ($P = 0.016$). In this study, he had identified that people with BMI > 25 are more prone to get type 2 DM and hypothyroidism. Moreover, another study had been carried out among matching subjects of subclinical hypothyroid (SCH) and euthyroid ones to assess thyroid profile, fasting plasma glucose and insulin resistance using Homeostasis Model Assessment (HOMA-IR). Results show that

SCH participants had increased serum TSH levels (14.2 ± 5.23 μU/mL) than euthyroid ones (2.24 ± 1.43 μU/mL); P < 0.0001 and also a higher insulin resistance in SCH participants than that of euthyroid people (9.07 ± 3.41 μU/mL and 5.28 ± 2.18 μU/mL respectively; P < 0.0001 and, the mean HOMA-IR value had also been higher in SCH (2.03 ± 0.95 than in euthyroid people (1.05 ± 0.45); P < 0.0001. Furthermore, this study discovered that increased insulin resistance has more correlations with metabolic syndrome-related disorders such as cardiovascular diseases [27]. Therefore, with the knowledge gained from this analysis we can report that patients with type 2 diabetes mellitus are more likely to gain subclinical hypothyroidism when compared to euthyroid people (prevalence of SCH = 65.1% in type 2 DM people; **Table 3**).

Based on the discovered results of analyzed studies, subclinical hypothyroidism has a clear association with cardiovascular diseases [53] [63] along with elevated cholesterol levels [20] [38]. However, when correlation between subclinical hypothyroidism and cardiovascular disease was analyzed, several studies have come across conflicting results. One such study carried out by Walsh J P *et al.* [55] has discovered a clear association between the above two factors (CI, 1.28 to 2.12) (**Table 7**, **Figure 3**). But contradictory findings have been obtained by two large cohort studies carried out by Cappola A R *et al.* [59] and Rodondi N *et al.* [61] which show no relationship between SCH with CVD in adults (**Table 8**, **Figure 4**). According to the findings of Rodondi N *et al.* [61], the percentage mortality of euthyroid participants is higher than SCH participants during the time period of their study (3.92% and 2.95% respectively). Furthermore, the same pattern can be seen in two other studies [57] [60], where mortality was higher in euthyroid people than SCH people (10.8% and 8.33%, 15.8% and

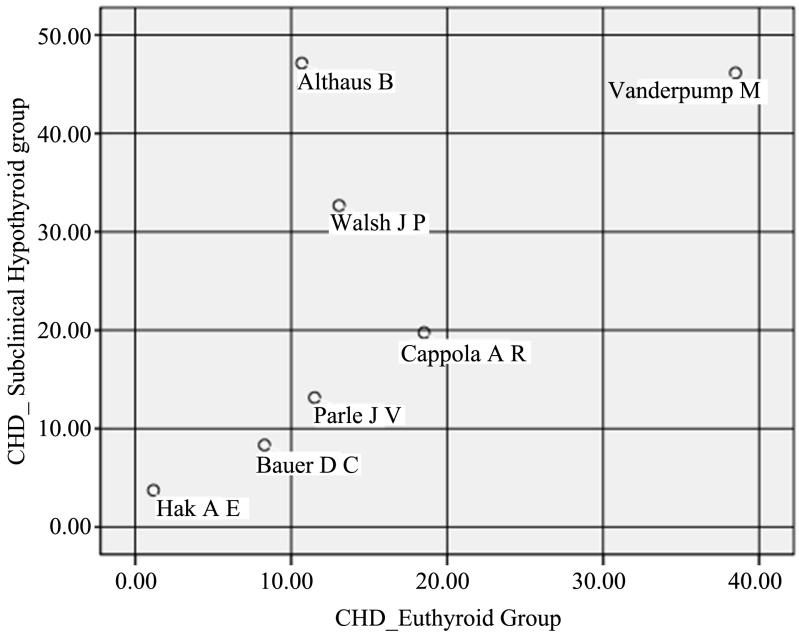

Figure 3. Occurrence of coronary heart disease events in subclinical hypothyroid group vs. euthyroid group in seven studies based on **Table 7**.

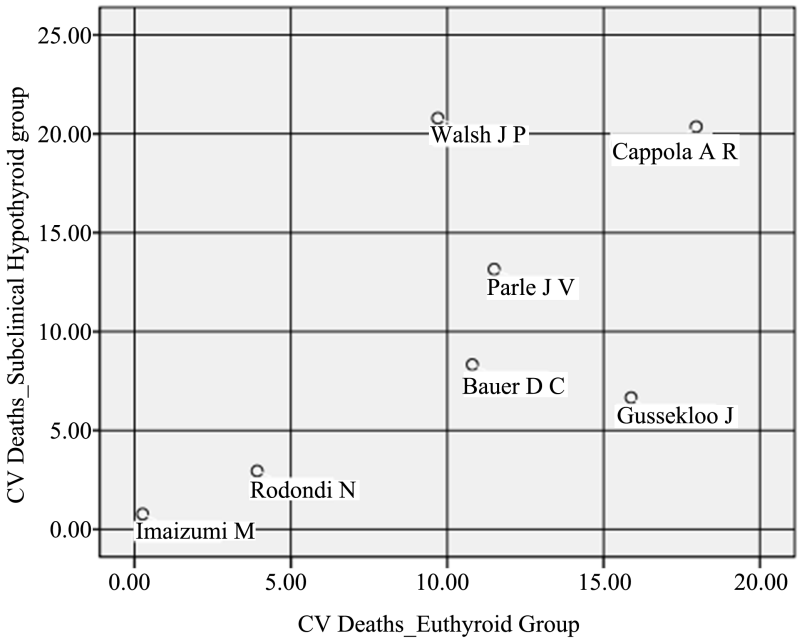

Figure 4. Occurrence of cardiovascular deaths in both subclinical hypothyroid group vs. euthyroid in seven studies based on **Table 8**.

6.66% respectively) (**Table 8**). But our analysis of collected data in this review shows a pattern of higher occurrence of cardiovascular events in subclinical hypothyroid participants than in euthyroid participants [23] [38] [53] [54] [55] [57] (**Table 7**). Therefore, by analyzing the research data, it is clear that there is a higher risk for cardiovascular disease for hypothyroid population when compared to euthyroid persons.

During the analysis data from pre-reviews were not included and research conducted among participants under treatment in comparison-based studies was excluded. Some studies did not give enough data in their original articles, but due to a lack of study articles in the field of association of insulin resistance, type 2 diabetes mellitus and cardiovascular disease with hypothyroidism some of those articles had to be included in this review.

In summary, reviewed data suggest that type 2 diabetes mellitus people are more likely to get subclinical hypothyroidism and subclinical hypothyroid population also show several complications associated with type 2 diabetes mellitus. Besides, subclinical thyroid dysfunction might represent a risk factor for coronary heart disease and mortality. Therefore, we can suggest that it is necessary to conduct screening tests for thyroid function in diabetes mellitus people and for populations with high risk for atherosclerosis with increased blood cholesterol levels.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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