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RESEARCH ARTICLE

SUBCLINICAL HYPOTHYROIDISM AND ITS ASSOCIATED COMPLICATIONS IN TYPE 2 DIABETES MELLITUS PATIENTS

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Abstract

This study assessed the relationship between subclinical hypothyroidism (SCH) and its associated complications in type 2 diabetic (T2D) patients. We aimed to conduct a systematic review and meta-analysis on published literature extracted from PubMed/Medline, Google scholar, and Cochrane library. A random effect model meta-analysis was used to find the odd ratio (OR) with a 95% confidence interval (CI). The heterogeneity was assessed with I^2. Egger's test and funnel plot was used to assess publication bias. A total of 62 studies were included involving 36500 patients. The patients who suffered from type 2 diabetes mellitus were seen at increased risk of subclinical hypothyroidism (OR= 1.88, 95% CI= 1.33-2.66). Furthermore, SCH was also associated with increased complications in type 2 diabetic patients with an estimated (OR= 3.31, 95% CI= 1.56-7.02) for Diabetic nephropathy (DN). Although, complications like Diabetic peripheral neuropathy (DPN) and Cardiovascular diseases (CVD) were not seen at an increased risk in type 2 diabetic (T2D) patients as their estimate odd ratio with 95% CI came out to be (OR= 1.11, 95% CI= 0.62-2.00) for Diabetic peripheral neuropathy (DPN) and (OR= 1.68, 95% CI= 0.95-2.97) for Cardiovascular diseases (CVD). The study shows that subclinical hypothyroidism (SCH) and some of its associated complications, like Diabetic nephropathy (DN), is more prevalent in type 2 diabetic (T2D) patients.

Introduction:-

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycaemia due to insulin section, insulin action abnormalities, or both [1]. The number of cases of diabetes mellitus is increasing daily because of the increasing population growth, aging, lifestyle changes, obesity, and lack of physical activity. Thyroid disorders are also commonly observed in diabetes mellitus type 2 patients [2, 3]. Both type 2 DM and thyroid disorders are the most common endocrine disorders seen in clinical practice and becoming the primary reason for morbidity and premature mortality. Many alterations in thyroid functions are observed in DM type 2 patients [4-6]. The association between type 2 DM and subclinical hypothyroidism is well known, which could be genetic, biochemical, or hormonal changes (Talwalker et al.) [7].

Subclinical hypothyroidism (SCH) is a condition in which serum free thyroxin (fT4) and triiodothyronine (T3)

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concentrations are standard in the presence of an elevated serum thyrotropin (TSH) concentration [8, 9]. Its prevalence increases with age, higher in females than males and higher in whites than in blacks [10]. Often, SCH is asymptomatic; however, approximately 30% of patients have symptoms similar to hypothyroidism [11].

Globally, the number of people with DM is excepted to rise by 300 million in 2025 [12, 13]. Numerous studies showed that thyroid disorders are more common in type 1 and type 2 diabetes patients than in normal individuals [5]. The most common disorder is subclinical hypothyroidism [14, 15]. SCH is an influential factor in causing atherosclerosis and MI in older women, diabetes, previous smoking, and hypertension [16]. In addition, patients with type 2 DM with SCH have an increased risk of nephropathy, cardiovascular diseases, and sight-threatening diabetic retinopathy. Hence screening of subclinical hypothyroidism in type 2 DM patients will be helpful in early detection and better management of hypothyroidism [17].

Review

Materials & Methods:-

Search Strategy

Full-text articles were obtained for the relevant studies satisfying the inclusion criteria, and their data were extracted independently by authors GP and AB. Extracted data were cross-checked independently by the author (AB). Any disagreement between the authors was resolved by consensus. We searched electronic databases like PubMed/Medline, Google Scholar, and Cochrane library. Most of the data were extracted from PubMed. We used the advance search option on PubMed for our search strategy and follow-ups. We used various filters to filter out and refine our search for publications that fit according to inclusion criteria. The terms used to search for the relevant articles were "Subclinical hypothyroidism," "Type 2 Diabetes", "Diabetic Nephropathy," "Diabetic peripheral neuropathy," "Cardiovascular diseases," and "Thyroid dysfunction." Inclusion criteria were a) Age range 18-75, b) CC, CSS, Cohort studies, RCTs, c) Thyroid dysfunction must include subclinical hypothyroidism, and d) Type 2 diabetic studies. The exclusion criteria were a) Age below 18, b) Type 1 Diabetic studies, c) No Thyroid dysfunction, and d) Meta-analysis, literature reviews, case reports, and articles.

Data Extraction & Collection

A total of 62 complete text studies were included in the analysis. They were put in a citation manager software Zotero using their PMID/DOI to keep the final data separated. The overall selection process is shown in (figure **1**). There was no disagreement or doubt between the authors. The following data were extracted from the studies: author, year of publication, country, sample size, design of the studies, disease status, and outcome OR (95% CI) of each study included. The summary for characterization of the studies included is given in table **1**.

Statistical analysis

For conducting our study and writing a systematic review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. The PRISMA flow diagram is shown in figure **1**. The statistical analyses of the data extracted from the studies were carried out using Review Manager Software (RevMan version 5.3; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) [19]. We used unadjusted estimates for meta-analysis and the Inverse variance method to combine data on dichotomous outcomes, and measures of effect are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The heterogeneity between studies was assessed with I^2 statistics. The presence of substantial heterogeneity was adjudged using the I^2 statistic ($I^2 \geq 50\%$). The prevalence estimates from individual studies were pooled with a random-effects model because of marked heterogeneity among studies. When the value of $p<0.05$, we considered it significant for meta-analysis. Newcastle-Ottawa Scale (NOS) was used to assess the quality of included studies. Sample representativeness, Comparability of the study, and Exposure of the study were included to evaluate the quality of the study. It was done manually through an assessment scale obtained from NCBI and other sources. The Newcastle-Ottawa Scale quality instrument is scored by awarding a point for each answer. Possible total points are 4 points for Selection, 2 points for Comparability, and 3 points for Outcomes. The maximum number of points a study can score is 9 [20]. All the included studies scored an excellent score of a minimum of 5. Therefore, we did not exclude any of the studies included.

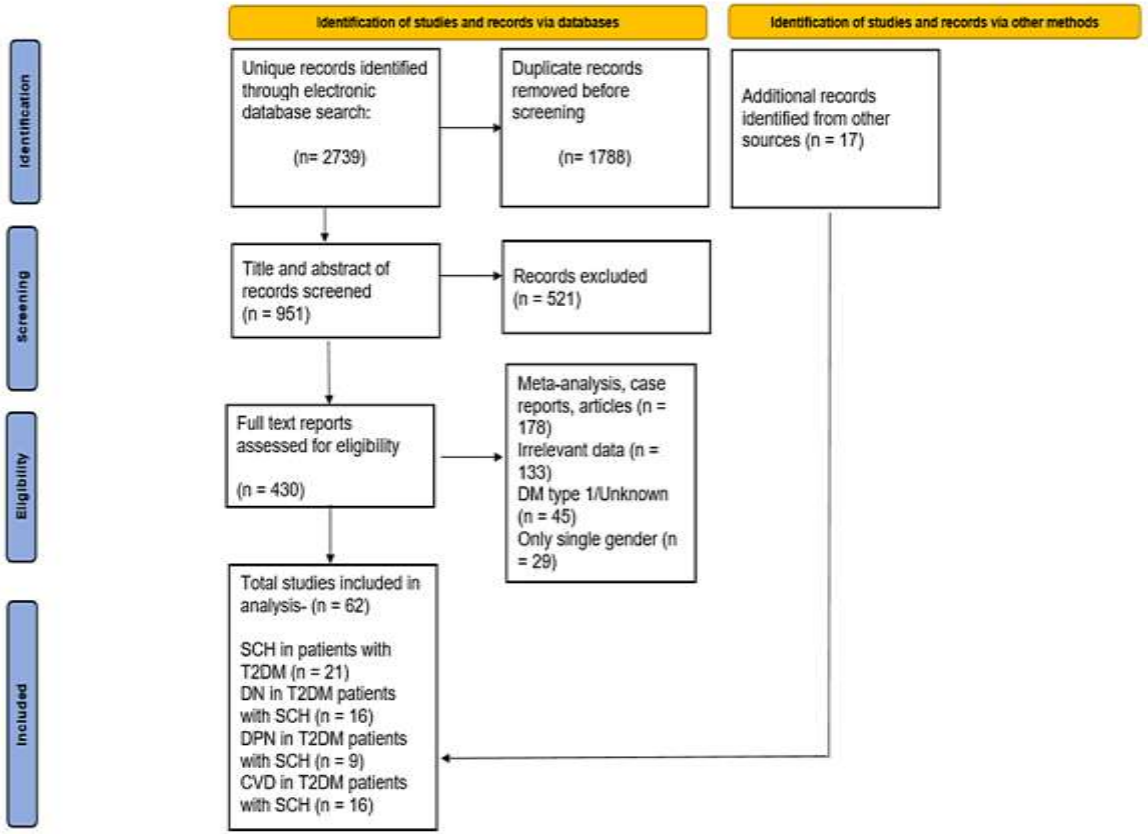

Figure 1:- PRISMA flow diagram of study selection.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
SCH: Subclinical hypothyroidism; T2DM: Type 2 diabetes mellitus; DN: Diabetic nephropathy; DPN: Diabetic peripheral neuropathy; CVD: Cardiovascular diseases; DM: Diabetes mellitus.

Author, year	Country	Sample Size	Disease Status	Study design	OR (95% CI)
Talwalkar et al. 2019 [7]	India	999	T2DM, SCH	CSS	0.61[0.37, 1.02]
H Chen et al. 2014 [15]	Taiwan	556	T2DM, SCH, CVD	CSS	5.04 [2.26, 11.21]
Al-Rubaye et al. 2019 [21]	Iraq	500	T2DM, SCH	CSS	3.41[1.02, 11.46]
Cho et al. 2016 [22]	South Korea	7966	T2DM, SCH	CSS	0.92[0.68, 1.25}
Diez et al. 2012 [23]	Spain	2023	T2DM, SCH	CSS	4.11[2.52, 6.72]
Elgazar et al. 2019 [24]	Egypt	400	T2DM, SCH	CSS	4.93[1.94, 12.01]
Ghazali SM et al. 2010 [25]	Nigeria	100	T2DM, SCH	CC	4.15[0.21, 82.73]
Gopinath B et al. 2008 [26]	Australia	1063	T2DM, SCH	Cohort	2.01[0.67, 6.09]
Xiutung Huang et al. 2020 [27]	China	2918	T2DM, SCH	CSS	1.72[1.01, 2.93]
Jalal et al. 2019 [28]	India	100	T2DM, SCH	CC	5.44[0.61, 48.40]
Jimoh et al. 2022 [29]	Nigeria	78	T2DM, SCH	CSS	2.94[0.15, 59.36]
Khassawneh et al. 2020 [30]	Jordan	1341	T2DM, SCH	CC	1.68[1.08, 2.59]
Yanli Li et al. 2021 [31]	China	460	T2DM, SCH	CC	1.78[0.08, 37.34]
Menon et al. 2018 [32]	India	892	T2DM, SCH	Cohort	0.97[0.59, 1.61]
Radaideh et al. 2004 [33]	Jordan	1212	T2DM, SCH	CC	0.82[0.44, 1.51]
Raghuwanshi et al. 2004 [34]	India	80	T2DM, SCH	CC	2.18[0.50, 9.39]
Reddy et al. 2020 [35]	India	496	T2DM, SCH	CSS	2.38[1.26, 4.51]
Telwani et al. 2017 [36]	India	200	T2DM, SCH	CC	3.62[1.27, 10.30]
Uppal et al. 2013 [37]	India	237	T2DM, SCH	CC	22.33[1.29, 385.62]

Vamshidhar et al. 2020 [38]	India	100	T2DM, SCH	CSS	3.13[0.31, 31.14]
Tiwari et al. 2019 [39]	India	200	T2DM, SCH	CC	6.16[1.73, 21.87]
Kashyap et al. 2020 [40]	India	200	T2DM, SCH	CSS	0.65[0.22, 1.89]
Alsolami et al. 2018 [41]	Saudi Arabia	234	T2DM, SCH, DN	CC	25.10 [1.45, 433.51]
Alsolami et al. 2018 [41]	Saudi Arabia	240	T2DM, SCH, CVD	CC	9.63 [0.51, 180.84]
Furukawa et al. 2014 [42]	Japan	415	T2DM, SCH, DN	Cohort	3.10 [1.17, 8.19]
Furukawa et al. 2014 [42]	Japan	414	T2DM, SCH, CVD	Cohort	0.56 [0.13, 2.42]
Golwalkar et al. 2020 [43]	India	96	T2DM, SCH, DN	CSS	57.40 [9.37, 351.57]
Kim et al. 2011 [44]	South Korea	489	T2DM, SCH, DN	Cohort	1.13 [0.38, 3.37]
Molla et al. 2022 [45]	Ethopia	273	T2DM, SCH, DN	CC	1.00 [0.54, 1.86]
Molla et al. 2022 [45]	Ethiopia	174	T2DM, SCH, CVD	CC	0.63 [0.34, 1.19]
Ogbonna et al. 2019 [46]	Nigeria	308	T2DM, SCH, DN	CSS	30.41 [11.35, 81.47]
Zhao et al. 2018 [47]	China	242	T2DM, SCH, DN	CC	2.99 [0.96, 9.31]
H Chen et al. 2007 [48]	Taiwan	519	T2DM, SCH, DN	CSS	2.76 [1.38, 5.54]
Mansournia et al. 2017 [49]	Iran	255	T2DM, SCH, DN	CSS	2.99 [1.54, 5.79]
Mansournia et al. 2017 [49]	Iran	255	T2DM, SCH, CVD	CSS	1.29 [0.66, 2.54]
Jose et al. 2020 [50]	India	384	T2DM, SCH, DN	CSS	0.13 [0.08, 0.20]
Ozair et al. 2017 [51]	India	194	T2DM, SCH, DN	CSS	35.54 [7.52, 168.04]
Zhang Lin et al. 2016 [52]	China	483	T2DM, SCH, DN	CC	4.58 [2.52, 8.32]
Wang M et al. 2012 [53]	China	121	T2DM, SCH, DN	CC	2.35 [1.08, 5.09]
Tang JD et al. 2012 [54]	China	1136	T2DM, SCH, DN	CC	1.48 [1.05, 2.09]
Abd-Elrahman et al. 2018 [55]	Egypt	72	T2DM, SCH, DN	CSS	74.13 [4.25, 1291.53]
Lv B et al. 2014 [56]	China	253	T2DM, SCH, DN	CSS	0.49 [0.25, 0.98]
Allam et al. 2021 [57]	Egypt	300	T2DM, SCH, DPN	CSS	0.75 [0.34, 1.69]
Anjum et al. 2022 [58]	Pakistan	10	T2DM, SCH, DPN	CC	0.27 [0.01, 8.46]
Gao & Feng et al. 2014 [59]	China	133	T2DM, SCH, DPN	Cohort	0.53 [0.18, 1.56]
Ghada A et al. 2017 [60]	Kuwait	110	T2DM, SCH, DPN	CSS	1.52 [0.55, 4.25]
Nageeb et al. 2021 [61]	Egypt	133	T2DM, SCH, DPN	CSS	3.93 [0.83, 18.50]
Nageeb et al. 2021 [61]	Egypt	133	T2DM, SCH, CVD	CSS	0.11 [0.01, 1.99]
Reshdat et al. 2022 [62]	Iran	154	T2DM, SCH, DPN	Cohort	0.22 [0.10, 0.51]
Shen YJ et al. 2012 [63]	China	448	T2DM, SCH, DPN	CC	1.17 [0.77, 1.78]
Zhang DM et al. 2014 [64]	China	1170	T2DM, SCH, DPN	CC	2.51 [1.86, 3.38]
Shao F et al. 2012 [65]	China	92	T2DM, SCH, DPN	CC	2.33 [0.99, 5.49]
Cappola et al. 2015 [66]	England	435	T2DM, SCH, CVD	Cohort	1.14 [0.61, 2.13]
Imaizumi et al. 2003 [67]	Japan	160	T2DM, SCH, CVD	Cohort	3.63 [0.31, 42.00]
Park et al. 2011 [68]	South Korea	322	T2DM, SCH, CVD	Cohort	2.45 [0.58, 10.45]
Rodondi et al. 2005 [69]	USA	408	T2DM, SCH, CVD	Cohort	0.89 [0.33, 2.36]
Kantanka et al. 2018 [70]	Ghana	742	T2DM, SCH, CVD	CSS	10.64 [6.06, 18.67]
Sathyapalan et al. 2010 [71]	United Kingdom	944	T2DM, SCH, CVD	CC	0.52 [0.39, 0.70]
Walsh et al. 2005 [72]	Australia	59	T2DM, SCH, CVD	CSS	3.33 [0.29, 38.35]
Drechsler et al. 2014 [73]	Germany	797	T2DM, SCH, CVD	Cohort	2.56 [0.88, 7.44]
Jia F et al. 2015 [74]	China	933	T2DM, SCH, CVD	CSS	1.62 [1.02, 2.57]
Hong T et al. 2007 [75]	China	339	T2DM, SCH, CVD	Cohort	2.57 [1.27, 5.21]

Table 1:- Characteristics of the studies included.

SCH: Subclinical hypothyroidism; T2DM: Type 2 diabetes mellitus; DN: Diabetic nephropathy; DPN: Diabetic peripheral neuropathy; CVD: Cardiovascular diseases; CC: Case Control; CSS: Cross Sectional Study; OR: Odd ratio; CI: Confidence interval.

Results:-

Association between Subclinical hypothyroidism and Type 2 Diabetes Mellitus

The analysis included data from 21[7, 21-40]different individual studies, which included 7140 cases of patients who had diabetes, and 14425 controls were the subjects who did not have diabetes. Prevalence rates of subclinical hypothyroidism across these studies were 49.49%. The patients who had type 2 diabetes mellitus were seen at

increased risk of suffering from subclinical hypothyroidism P<0.05 (P=0.0004). The pooled OR with inverse variance random effect model was (OR= 1.88 95% CI 1.33- 2.66; I^2 = 72%; 21 studies). According to Cochrane, the study variation produces significant heterogeneity as it falls between 75%-100%. The forest plot for the pooled OR is shown in figure **2**. A funnel plot was plotted, and Egger's test was done to find the presence of potential publication bias. We found no publication bias. The funnel plot is shown in figure **3**. Egger's test is shown in table **2**.

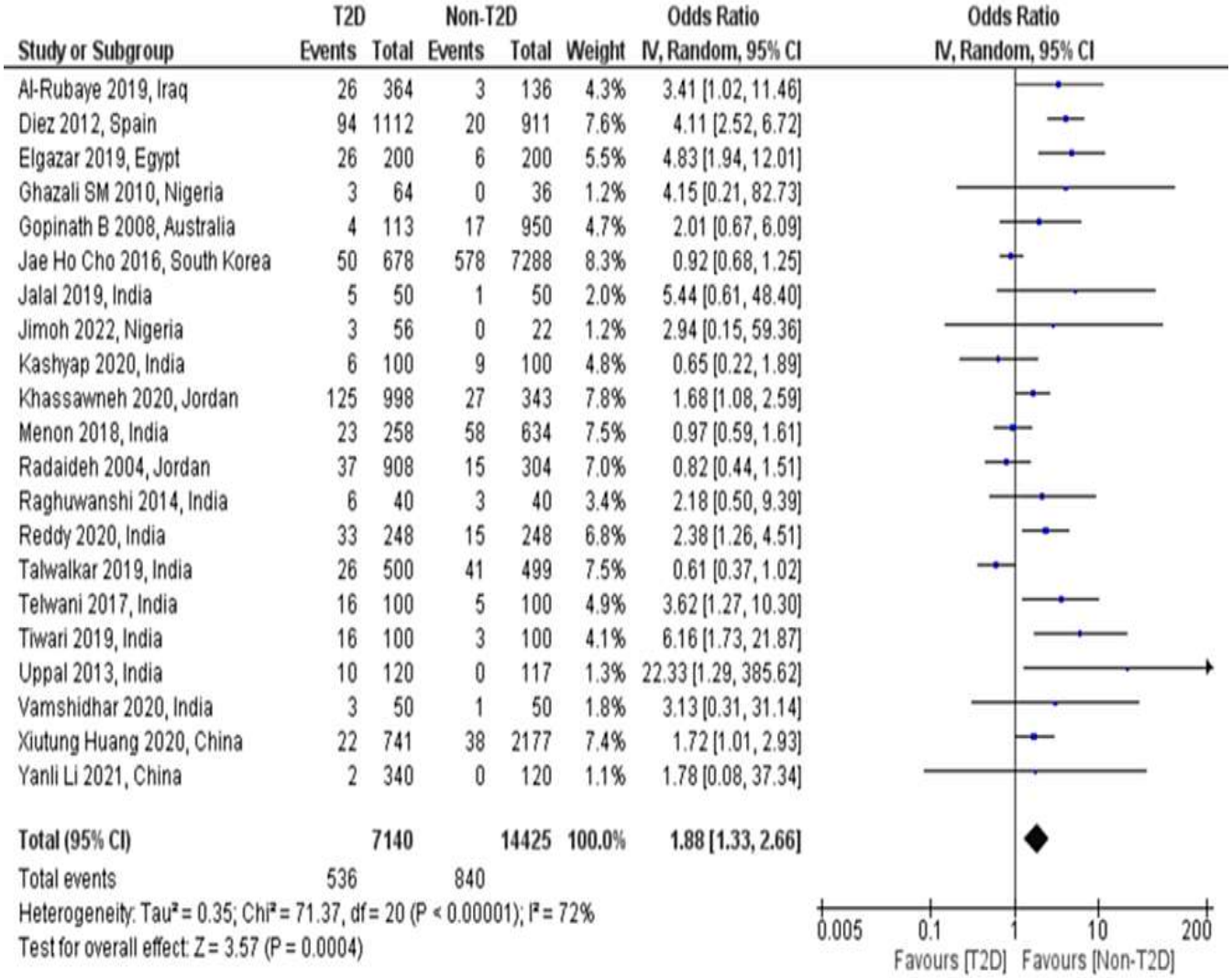

Figure 2:- Forest plot of SCH- T2DM vs Non-T2DM.

T2D: Type 2 diabetes; Non-T2D: Non-Type 2 diabetes; IV: Inverse variance; CI: Confidence interval; df: Degrees of freedom; P: P-value; I^2: Heterogeneity; Z: Z-value.

Egger's test	
Intercept	1.5333
95% CI	0.1171 to 2.9496
Significance level	P = 0.0353

Table 2:- Egger's test for publication bias in SCH- T2DM vs Non-T2DM.

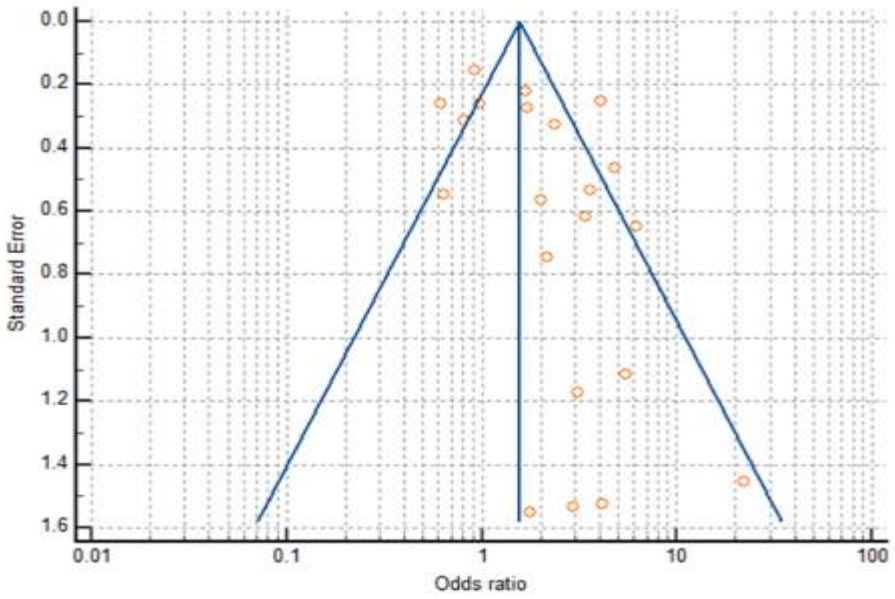

Figure 3:- Funnel plot for publication bias of SCH- T2DM vs Non-T2DM.

Association between Subclinical hypothyroidism and Diabetic nephropathy in T2DM patients

The analysis included data from 16[41-56] individual studies, which included 1343 cases and 4131 controls. Prevalence rates of Diabetic nephropathy across these studies were 32.52%. Type 2 diabetes mellitus patients with subclinical hypothyroidism were also at increased risk of suffering from diabetic nephropathy P<0.05 (P=0.002). The pooled OR with inverse variance random effect model was (OR= 3.31 95% CI 1.56- 7.02; I^2 = 93%; 16 studies). According to Cochrane, the study variation produces significant heterogeneity as it falls between 75%-100%. The forest plot for the pooled OR is shown in figure **4**. The forest plot for the pooled OR is shown in figure **4**. A funnel plot was plotted, and Egger's test was done to find the presence of potential publication bias. We found no publication bias. The funnel plot is shown in figure **5**. Egger's test is shown in table **3**.

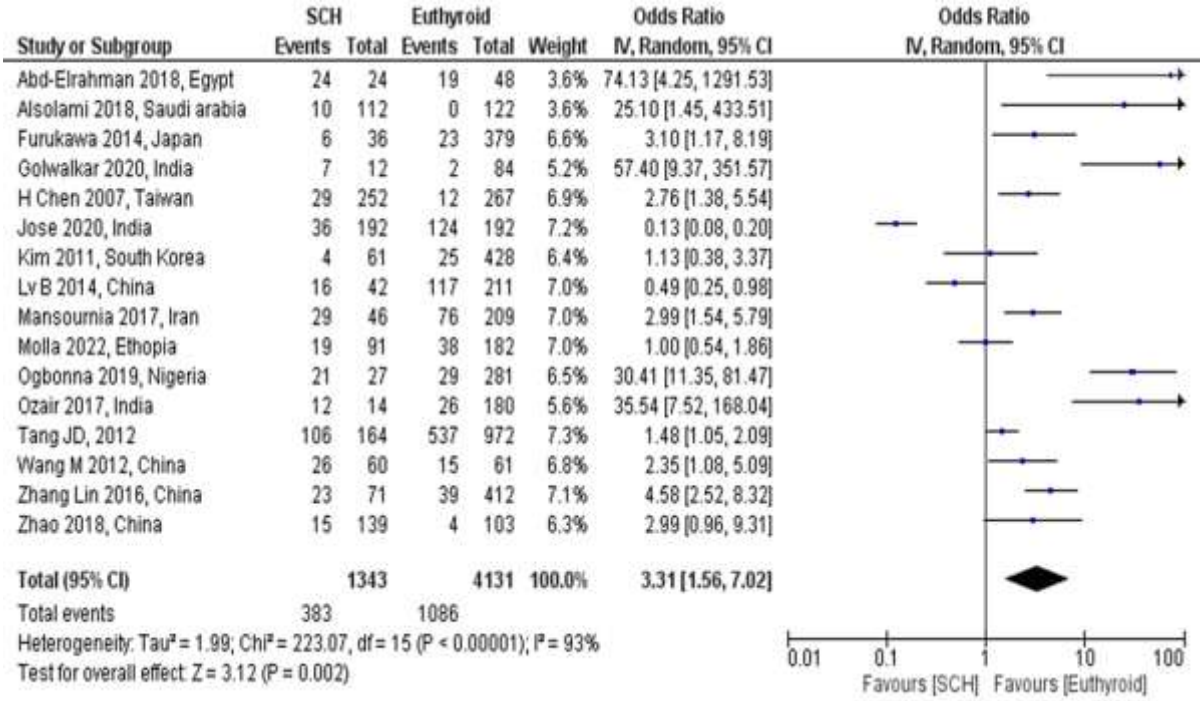

Figure 4:- Forest plot of DN with SCH in T2DM.

SCH: Subclinical hypothyroidism; IV: Inverse variance; CI: Confidence interval; df: Degrees of freedom; P: P-value; I^2: Heterogeneity; Z: Z-value.

Egger's test	
Intercept	4.3701
95% CI	0.5314 to 8.2087
Significance level	P = 0.0285

Table 3:- Egger's test for publication bias in DN with SCH in T2DM.

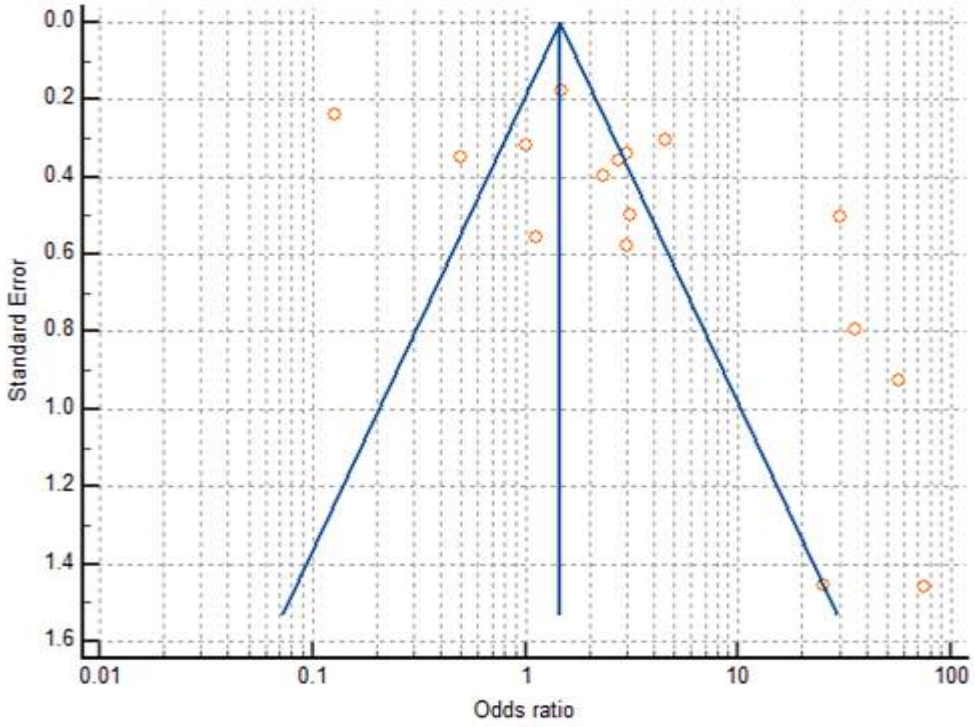

Figure 5:- Funnel plot of DN with SCH in T2DM.

Association between Subclinical hypothyroidism and Diabetic peripheral neuropathy in T2DM patients

The analysis included data from 9[57-65] individual studies, which included 633 cases and 1917 controls. Prevalence rates of Diabetic peripheral neuropathy across these studies were found to be 33%. Type 2 diabetes mellitus patients with subclinical hypothyroidism were not seen at increased risk of suffering from diabetic peripheral neuropathy P<0.05 (P=0.73). The pooled OR with inverse variance random effect model was (OR= 1.11 95% CI 0.62- 2.00; I^2 = 81%; 9 studies). According to Cochrane, the study variation produces significant heterogeneity as it falls between 75%-100%. The forest plot for the pooled OR is shown in figure **6**. A funnel plot was plotted, and Egger's test was done to find the presence of potential publication bias. We found no significant publication bias. The funnel plot is shown in figure **7**. Egger's test is shown in table **4**.

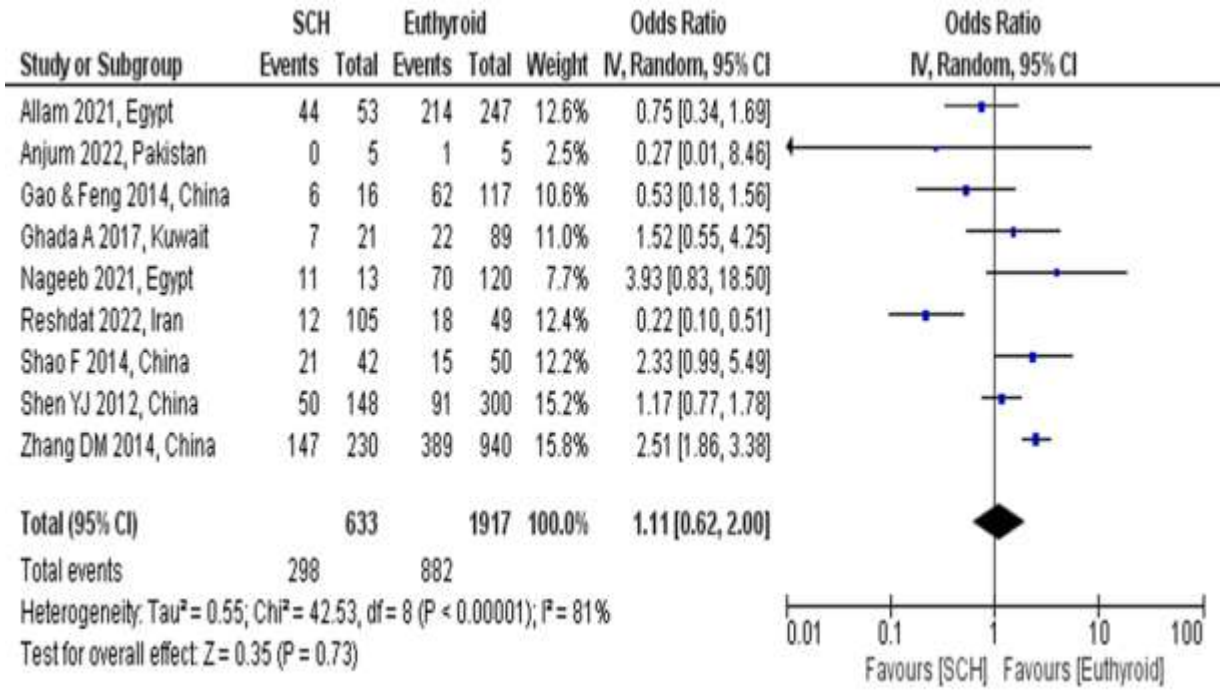

Figure 6:- Forest plot of DPN with SCH in T2DM.

SCH: Subclinical hypothyroidism; IV: Inverse variance; CI: Confidence interval; df: Degrees of freedom; P: P-value; I²: Heterogeneity; Z: Z-value.

Egger's test	
Intercept	-1.8855
95% CI	-5.0078 to 1.2369
Significance level	P = 0.1964

Table 4:- Egger's test for publication bias in DPN with SCH in T2DM.

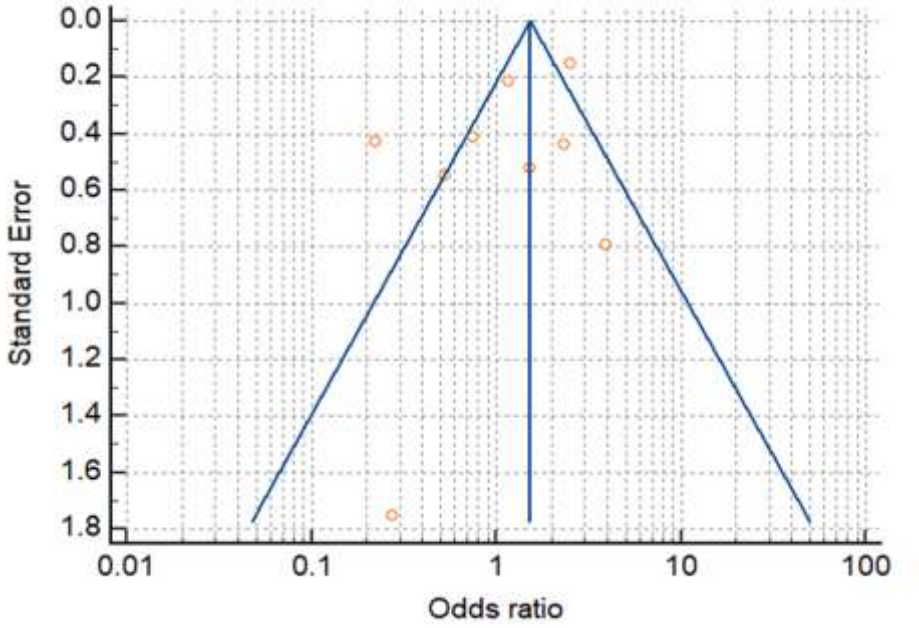

Figure 7:- Funnel plot of DPN with SCH in T2DM.

Association between Subclinical hypothyroidism and cardiovascular diseases in T2DM patients

The analysis included data from 16[41, 42, 45, 48, 49, 61, 66-75] studies, including 1195 cases and 5716 controls. Prevalence rates of cardiovascular diseases across these studies were 20%. Type 2 diabetes mellitus patients with subclinical hypothyroidism were not seen at increased risk of suffering from diabetic peripheral neuropathy P<0.05 (P=0.08). The pooled OR with inverse variance random effect model was (OR= 1.68 95% CI 0.95- 2.97; I^2 = 88%; 16 studies). According to Cochrane, the study variation produces significant heterogeneity as it falls between 75%-100%. The forest plot for the pooled OR is shown in figure **8**. A funnel plot was plotted, and Egger's test was done to find the presence of potential publication bias. We found no significant publication bias. The funnel plot is shown in figure **9**. Egger's test is shown in table **5**.

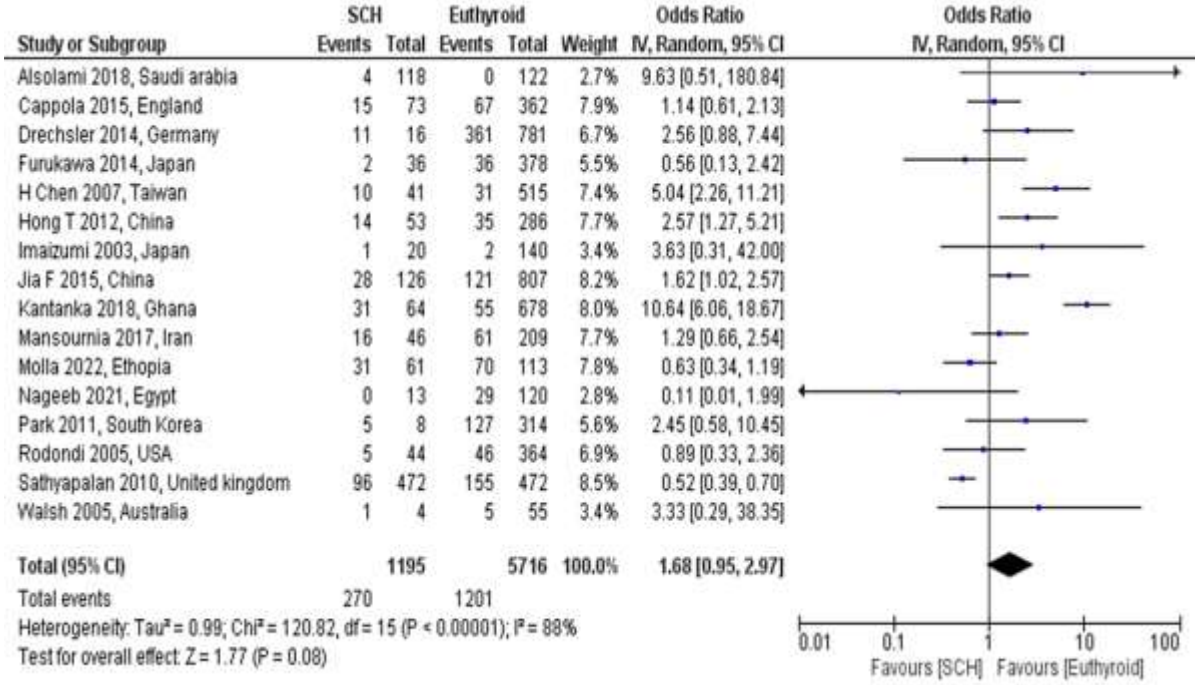

Figure 8:- Forest plot of CVD with SCH in T2DM.

SCH: Subclinical hypothyroidism; IV: Inverse variance; CI: Confidence interval; df: Degrees of freedom; P: P-value; I^2: Heterogeneity; Z: Z-value.

Egger's test	
Intercept	1.5943
95% CI	-1.1715 to 4.3602
Significance level	P = 0.2367

Table 5:- Egger's test for publication bias in CVD with SCH in T2DM.

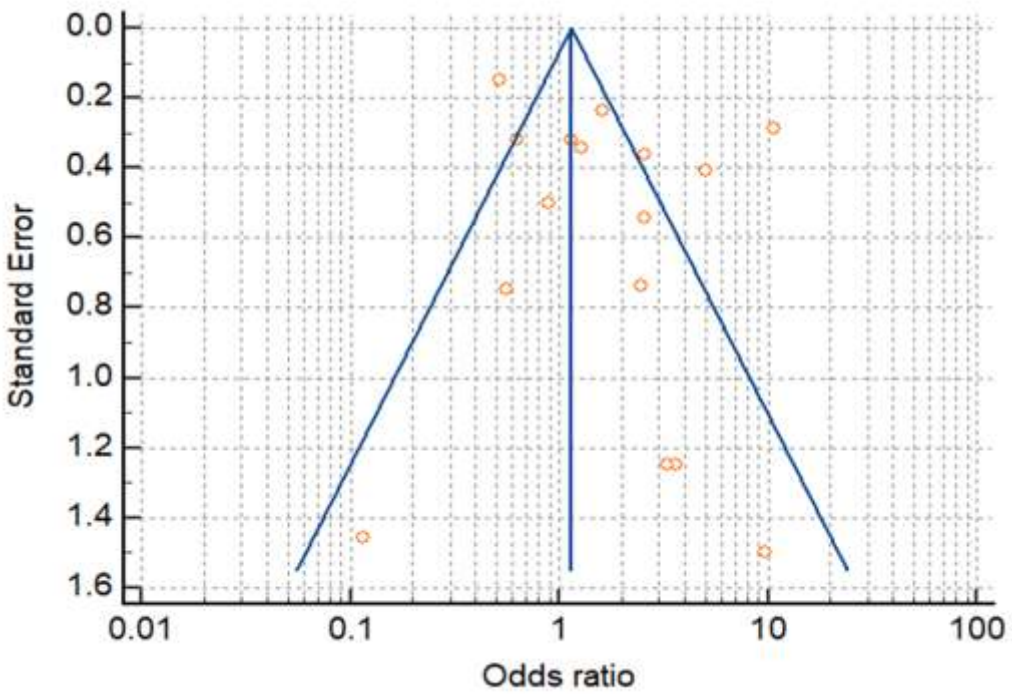

Figure 9:- Funnel plot of CVD with SCH in T2DM.

Discussion:-

The present study and meta-analysis were conducted based on 62 complete text studies that included a wide range of characteristics in terms of study design and patients to evaluate hypothyroidism's prognostic role in type 2 diabetic patients. Meta-analysis of the present study found that high TSH and low FT3/T4 are associated with a higher risk of T2DM, and the risk of dose-dependently T2DM rises as TSH rises and thyroid hormones decrease. In addition, the present study observed that patients with type 2 DM had an increased risk of having sub-clinical hypothyroidism. A meta-analysis conducted by Han et al. found that type-2 DM patients were more likely to have an excess risk of hypothyroidism. Hypothyroidism in diabetic patients results in excess risk of diabetic nephropathy (DN), diabetic retinopathy (DR), peripheral arterial disease, and diabetic peripheral neuropathy complications compared to the general population.

In the present study, type 2 DM with subclinical hypothyroidism did not show any association with diabetic nephropathy, diabetic peripheral neuropathy, or cardiovascular diseases, similar to the findings of Zang et al. [76] which revealed no significant association between hypothyroidism and major cardiovascular events in diabetic patients. However, Han et al., Jia et al., and Wu et al. observed an association between DM type 2 patients with subclinical hypothyroidism with an excess risk of DN, Diabetic neuropathy, and other cardiovascular diseases. In addition, Kim et al. also revealed that hypothyroidism was associated with an increased risk of severe diabetic retinopathy (DR) in type 2 DM patients [17, 77]. This study included the patients who had undergone a comprehensive evaluation for DR based on dilated study eye examination and fluorescein angiography.

A study conducted by Zhou et al. also described the association of patients with hypothyroidism in type 2 DM with an increased risk of CK. This association may be due to thyroid hormone affecting kidney growth and function, correlation of hypothyroidism with endothelial dysfunction, low cardiac output associated with hypothyroidism, and increased peripheral vascular resistance caused by intrarenalvaso-constriction and autoimmune thyroiditis are significantly associated with chronic inflammation [78].

Limitations

Our study had some limitations. Firstly, in our study, some cross-sectional and retrospective studies were included, which had potential uncontrolled biases and caused an overestimation of the effect estimates. Secondly, only a few studies were available to pool results for cardiac death, stroke, and DN; thus, they were calculated from smaller

numbers of included studies, making results unreliable. Hence significant numbers of studies should be included. Thirdly, most of the studies included in our analysis were hospital-based, affecting the significance of the results and the study's quality. Therefore, we need to assess well-designed community or population-based studies. Lastly, publication biases might exist as the analysis was based on published articles.

Conclusions:-

In our study, the prevalence of subclinical hypothyroidism is higher in patients with type 2 DM; thus, type 2 DM patients are associated with an increased risk of subclinical hypothyroidism. Furthermore, subclinical hypothyroidism might also be associated with an increased risk of diabetic nephropathy in type 2 diabetes mellitus patients. On the other hand, there was no significant risk of diabetic peripheral neuropathy and cardiovascular diseases associated with subclinical hypothyroidism in type 2 diabetes mellitus patients. Therefore, type 2 DM patients should be screened for subclinical hypothyroidism and its associated complications to intervene early to prevent complications and progression of hypothyroidism.

Credit Authorship Contribution Statement

GP: concept, data extraction, manuscript writing, and critical revision; AB: concept, data extraction, manuscript writing, and critical revision.

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Ethical Committee Approval

Not needed.

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