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MINIREVIEWS

Type 2 diabetes and thyroid cancer: Synergized risk with rising air pollution

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Abstract

Diabetes is a complex condition, and the causes are still not fully understood. However, a growing body of evidence suggests that exposure to air pollution could be linked to an increased risk of diabetes. Specifically, exposure to certain pollutants, such as particulate Matter and Ozone, has been associated with higher rates of diabetes. At the same time, air pollution has also been linked to an increased risk of thyroid cancer. While there is less evidence linking air pollution to thyroid cancer than to diabetes, it is clear that air pollution could have severe implications for thyroid health. Air pollution could increase the risk of diabetes and thyroid cancer through several mechanisms. For example, air pollution could increase inflammation in the body, which is linked to an increased risk of diabetes and thyroid cancer. Air pollution could also increase oxidative stress, which is linked to an increased risk of diabetes and thyroid cancer. Additionally, air pollution could increase the risk of diabetes and thyroid cancer by affecting the endocrine system. This review explores the link between diabetes and air pollution on thyroid cancer. We will discuss the evidence for an association between air pollution exposure and diabetes and thyroid cancer, as well as the potential implications of air pollution for thyroid health. Given the connections between diabetes, air pollution, and thyroid cancer, it is essential to take preventive measures to reduce the risk of developing the condition.

Key Words: Air pollution; Diabetes mellitus; Health risk; Thyroid cancer; Thyroid disorders

Core Tip: Although the direct link between diabetes and air pollution on thyroid cancer is not yet established, recent research has suggested a strong correlation between air pollution exposure and the risk of endocrinopathies and developing certain types of cancer, including thyroid cancer. This suggests that people with diabetes may be at an increased risk of developing thyroid cancer if exposed to high levels of air pollution. It is essential for people with diabetes to be aware of the potential health risks associated with air pollution and to take steps to reduce their exposure to air pollution and to control their blood glucose levels as well as eat healthy food.

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INTRODUCTION

Diabetes mellitus (DM) and thyroid dysfunction are the most common endocrinopathies[1]. There is accumulating evidence indicating a contribution of thyroid hormone dysfunction to type 2 DM (T2DM) and vice versa[1,2]. Thyroid hormones have a direct effect on insulin production and clearance. Fluctuations in thyroid hormones raise the risk of developing T2DM and can worsen diabetic symptoms and complications[1,3]. In 2017, patients with DM reached 476 million affected people worldwide, with an expected projection of 570.9 and 783.2 million in 2025 and 2045, respectively [4,5]. Patients with DM are at higher risk of vascular disease and poor lung function, rendering them vulnerable to declining air quality[6]. A growing body of evidence suggests that exposure to air pollution could be linked to an increased risk of diabetes[7]. Specifically, exposure to certain pollutants, such as particulate matter (PM) – the primary carbon-based component of air pollution – and ozone, has been associated with higher rates of diabetes[7]. At the same time, air pollution has also been linked to an increased risk of thyroid disorders, including thyroid cancer (TC)[8]. The latter is an endocrine tumor with the highest occurrence, and its incidence has increased in recent decades[9]. By 2030, this type of cancer is anticipated to rank as the fourth-most frequent cancer in the United States[10]. While there is less evidence linking air pollution to TC than to diabetes, it is clear that air pollution could have severe implications for thyroid health[11].

This narrative review aims to explore the link between diabetes and air pollution on thyroid cancer. The evidence for an association between air pollution exposure and both diabetes and thyroid cancer, as well as the potential mechanisms underlying this type of synergism, will be discussed.

LITERATURE SEARCH

Literature was screened *via* several electronic databases such as PubMed, Google Scholar, and Web of Science. The compiled literature included peer-reviewed articles published from 1991 to 2022 written in English. Authors utilized the phrases "Diabetes mellitus, type 1 diabetes, type 2 diabetes, particulate matter, air pollution, hyperthyroidism, hypothyroidism, thyroid carcinoma, insulin resistance" in the screening process. Organizational reports, literature reviews, cross-sectional studies, cohort studies, clinical studies, animal studies, and time series categories of literature were retained, and letters of opinion were excluded. Literature deemed acceptable was screened with a focus on: (1) The prevalence and incidence of DM and thyroid pathology and their respective etiologies; (2) Air pollution and particulate matter trends globally stemming from anthropogenic PM production; and (3) Non-duplicate studies, in which examples of comparative literature were decided upon by more recent publication. Additionally, data mining in the publicly available "comparative toxicogenomic database; CTD" (http://ctdbase.org/) (last accessed 25 March, 2023) was done to unravel how environmental exposures to the specified pollutant of the current review could impact human health[12].

PATHOGENESIS

An overview of the problem

Many factors play significant roles in the development of DM and thyroid diseases, such as genetic liability, environmental factors, lifestyle, family history, and comorbidities[13-15]. Exposures to specific environmental toxicants, such as air pollution, have been reported to have a negative impact on the thyroid gland and pancreas[7]. Global populations are growing annually, and an expanding populace comes with an increased demand for industrialization[16]. The World Health Organization (WHO) has identified industrial development as a significant driver of air pollution, with fossil fuel consumption, large-scale agriculture, and the accelerating need to meet comfortable lifestyle parameters as significant contributors[17]. The WHO defines air pollution as "contamination of the indoor or outdoor environment by any chemical, physical or biological agent that modifies the natural characteristics of the atmosphere"[17]. The air pollutants with the most significant negative impact on public health are sulfur dioxide, carbon monoxide, nitrogen dioxide (NO_2), ozone, and fine PM[18] (Tables 1-5), respectively. According to the International Agency for Research on Cancer Working Group, air pollution was categorized as carcinogenic in 2013[19]. The damaging effect of these pollutants substantially depends on the pollutants' type, the dose and time of exposure, and the body's accumulation of pollutants over time[20]. PM, also known as atmospheric aerosol, comprises the deleterious component of air pollution established to be harmful to human health[21] and has been associated with numerous cancers, endocrine disorders, cardiovascular diseases, and other forms of significant inflammation[22]. Patients with high-risk pulmonary conditions such as asthma, chronic obstructive pulmonary disease, lung cancer, and so forth are of frequent consideration with rising PM levels globally, yet impacts on the endocrine system are substantial[23]. Increasing DM cases globally pose a point of concern, as complications of the disease may manifest in acute and chronic settings, with consequences including declining patient quality of life, healthcare costs, and economic burden[5]. Coronary artery disease, stroke, peripheral vascular disease, end-stage renal disease, neuropathy, and lower-extremity amputation comprise the most burdensome complications. Notably, excluding confounding factors such as environmental conditions, physical activity, family history of TC, genetic sustainability, dietary habits, and history of radiation exposure should be done to link air pollution to DM and thyroid diseases [24].

Diabetes is multifactorial in origin, with T2DM being more so reliant on lifestyle and environmental risk factors[25], as opposed to its more genetic-reliant counterpart type 1 DM (T1DM) (still influenced by environment and lifestyle, although a lesser degree). Recently, T2DM was also occurring increasingly frequently in children[26]. A recent meta-analysis from Yang *et al*[27] has highlighted the substantial role PM exposure plays in the development of T2DM, with proposed mechanisms predominantly pertaining to increased systemic inflammation, mitochondrial dysfunction, and cardiovascular stress, with the contribution of some epigenetic changes. When controlling for genetic risk factors, air pollution was still found to impact T2DM development significantly[23]. While the weight of these findings alone is undoubtedly essential, with air pollution rates rising globally and a curbing solution yet to be implemented, it is of utmost importance to examine the intricate web of PM's impact on the endocrine system and alternate routes of exacerbation in the diabetes crisis. Diabetes may be the most common endocrine disease, but thyroid disease follows closely as one of the most prevalent endocrine organ diseases[28].

Patients diagnosed with DM, interestingly, exhibit a higher rate of hyperthyroidism than the non-diabetic remainder [29]. About 4.4% of T2DM patients over eighteen exhibit overt hyperthyroidism, and 2%-4% exhibit subclinical hyperthyroidism[30]. Glycemic control deteriorates in hyperthyroid diabetic individuals. Excess TH in the blood is linked to hyperglycemia, low circulating insulin levels, and poor glycemic control in hyperthyroidism. Nearly 2%-3% of patients having hyperthyroidism progress into developing overt diabetes[31]. In Grave's disease, a hyperthyroid condition of autoimmune origin, modest glucose intolerance is seen in over 50% of patients[31]. Thyrotoxicosis has been found to lead to endothelial dysfunction[32] and diabetic ketoacidosis[33], among other consequences. As a result, cardiovascular comorbidities are at a higher rate due to endothelial dysfunction, potentially contributing to the worsening of vascular integrity in patients diagnosed with existing T2DM or progression toward it. With accumulating data establishing connections between the two endocrine disease groups, it is crucial to assess possible physiologic links further to bolster clinical intervention methods, identify prevention strategies, and, in time, mitigate risk of T2DM development.

Air pollution role in thyroid disease and type 2 diabetes

Air pollution is a significant issue that affects human health on a global scale, mainly in crowded industrial cities where the daily emission of PM and other pollutants continuously exceeds permitted levels[34]. More people are affected by PM than by any other pollution[35]. Sulfate, nitrates, ammonia, sodium chloride, black carbon, mineral particles, and water are the main components of PM, which comprises a complex mixture of solid and liquid particles of organic and inorganic materials suspended in the air. The Environmental Protection Agency classified PM based on aerodynamic diameter into ($PM_{2.5}$: ≤ 2.5 mm) and (PM_{10}: ≤ 10 mm)[36]. $PM_{2.5}$ comprises "secondary" particles formed in the atmosphere by the chemical reactions of gaseous emissions, whereas PM_{10} is composed of coarse or "primary" particles, such as dust and carbon dioxide combustion[36]. These particles can be inhaled and enter the bloodstream[37].

According to the WHO, $PM_{2.5}$ is frequently used to indicate air pollution, and the upper limit concentration of $PM_{2.5}$ is set at 10 mg/m^3[38]. Globally, PM pollution in the atmosphere is increasing. $PM_{2.5}$ levels in India and China increased by 69.8% and 52.7%, respectively. These raise alarming signs in areas where the health burden of air pollution is high[39]. However, a few studies have evaluated the impact of $PM_{2.5}$ on human health[39]. High levels of $PM_{2.5}$ are linked with negative impacts on cardiovascular diseases, cognitive deterioration, and mortality, among others[40] (Table 5). Even though there have been a few studies regarding the relationship between air pollution and TC, it has been suggested that air pollution is a potential risk factor for rising TC risks[24]. Remarkably, In the Chinese population, industrial waste gas air pollution was significantly linked to an increased risk of TC[9,41]. A recent study reported that the incidence of

Table 1 Summary of the impact of sulfur dioxide on human health

Type of interaction	Ref. (PMID)
Sulfur Dioxide results in increased interleukin-6 production	20056584
Sulfur Dioxide affects the glucose metabolic process	26166095
[Air Pollutants results in increased abundance of Sulfur Dioxide] which affects the regulation of heart rate	28129768
[Air Pollutants results in increased abundance of Sulfur Dioxide] which affects the regulation of systemic arterial blood pressure	27015811
[Air Pollutants results in increased abundance of Sulfur Dioxide] which results in increased response to oxidative stress	27015811
Sulfur Dioxide results in decreased leukocyte homeostasis	30826618
Sulfur Dioxide decreases the respiratory system process	32000783
Sulfur Dioxide affects cytokine production involved in the immune response	32000783
[[*TNF* gene SNP affects the susceptibility to [[Air Pollutants results in increased abundance of Fuel Oils] which results in increased abundance of Sulfur Dioxide]] which results in increased tumor necrosis factor production] which results in increased secretion of TNF protein	24056475

Data source: The comparative toxicogenomic database (http://ctdbase.org/)[12].

Table 2 Summary of the impact of carbon monoxide on human health

Type of interaction	Ref. (PMID)
Carbon Monoxide inhibits the reaction [Rotenone results in increased apoptotic process]	23593279
Carbon Monoxide results in the decreased xenobiotic catabolic process	7908050
Carbon Monoxide inhibits the reaction [NADP results in increased oxidative demethylation]	8498088
[*IL6* gene SNP results in increased susceptibility to Carbon Monoxide] which results in increased positive regulation of interleukin-6 production	19750100
[Air Pollutants results in increased abundance of Carbon Monoxide] which results in decreased response to bronchodilator	26187234
Carbon Monoxide results in an increased inflammatory response	23717615
[Air Pollutants result in an increased abundance of Carbon Monoxide] which affects the regulation of blood pressure	28732501
[Air Pollutants results in increased abundance of Carbon Monoxide] which affects the regulation of heart rate	28129768
Carbon Monoxide inhibits the reaction [HMOX1 protein affects the reaction [Ammonium Chloride inhibits the reaction [[TNF protein co-treated with Cycloheximide] results in decreased cell growth]]]	27867098
Carbon Monoxide inhibits the reaction [[TNF protein co-treated with Cycloheximide] results in decreased cell growth]	27867098
Carbon Monoxide results in decreased leukocyte homeostasis	30826618
Carbon Monoxide results in the decreased respiratory system process	31861594 | 32000783
Carbon Monoxide affects cytokine production involved in the immune response	32000783
[Air Pollutants results in increased abundance of Carbon Monoxide] which affects T cell homeostasis	33603036
[Air Pollutants result in an increased abundance of Carbon Monoxide] which affects the regulation of blood pressure	33603036
[[[Vehicle Emissions results in increased abundance of Air Pollutants] which results in increased abundance of Carbon Monoxide] which results in increased membrane lipid catabolic process] which results in increased abundance of 8-epi-prostaglandin F2alpha	34417545

Data source: The comparative toxicogenomic database (http://ctdbase.org/)[12].

papillary thyroid carcinoma with 2 and 3 years of $PM_{2.5}$ exposure is directly linked to the dose and duration of exposure to $PM_{2.5}$[42]. Although Yanagi *et al*[43] stated that the statistical correlation between overall exposure to urban PM_{10} and TC incidence was high and significant, Park *et al*[24] reported a negative correlation between PM_{10} and TC.

A retrospective population-based study conducted in Shanghai, China, by Cong *et al*[41] recruited 550000 new cancer patients for assessment, and the investigators found that TC incidence was positively correlated with ambient air pollution from waste gas emissions, linking thyroid pathology and PM. Air pollution and its insidious hazards garnered attention in the American public's concerns following the aftermath of 9/11, in which first responders and other persons exposed to the explosion's remains began reporting alarmingly high rates of TC[44]. The Solan *et al*[45] study of 9/11 first responders, including 20984 participants, found that those assisting on-site exhibited an increased TC standardized

Table 3 Summary of the impact of nitrogen dioxide on human health

Type of interaction	Ref. (PMID)
Regulation of inflammatory response	18560490
Regulation of gene expression	22306530
Glucose metabolic process	26166095
[Air Pollutants result in an increased abundance of NO_2] which affects the regulation of blood pressure	27219456
[Nitrogen Dioxide results in decreased mitochondrial DNA metabolic process] which affects the expression of ND1 mRNA	26317635
[Air Pollutants results in increased abundance of Nitrogen Dioxide] which affects DNA methylation on cytosine within a CG sequence	27448387
[Air Pollutants results in increased abundance of NO_2] which results in decreased hemoglobin biosynthesis	28153527
[[Vehicle Emissions results in increased abundance of Air Pollutants] which results in increased abundance of Nitrogen Dioxide] which results in increased positive regulation of interleukin-6/10/13/ tumor necrosis factor (TNF) production	28669936
[Air Pollutants results in increased abundance of NO_2] which results in increased response to oxidative stress	27015811
Nitrogen Dioxide affects musculoskeletal movement	29364820
[Air Pollutants results in increased abundance of NO_2] which results in decreased cognition	28921105
[Air Pollutants results in increased abundance of NO_2] which results in decreased motor behavior	28921105
Decreased leukocyte homeostasis	30826618
cytokine-mediated signaling pathway	29114965
[Air Pollutants results in increased abundance of NO_2] which results in increased negative regulation of telomere maintenance	31393792
Cytokine production is involved in the immune response	32000783
[[Air Pollutants results in increased abundance of NO_2] which affects glucose homeostasis] which affects the abundance of Blood Glucose	32552747
[[Air Pollutants results in increased abundance of NO_2] which affects the regulation of cholesterol metabolic process] which affects the abundance of Cholesterol	31622905
[Air Pollutants results in increased abundance of NO_2] which affects T cell homeostasis	33603036
[Air Pollutants results in increased abundance of NO_2] which affects B cell homeostasis	33603036
[[[Vehicle Emissions results in increased abundance of Air Pollutants] which results in increased abundance of NO_2] which results in increased negative regulation of cholesterol metabolic process] which results in decreased abundance of cholesterol, HDL, and membrane lipid catabolic process	34417545

Data source: The comparative toxicogenomic database (http://ctdbase.org/)[12].

incidence rate of 2.39, seven years post-exposure. While it is not incorrect to assert that TC rates have increased globally due in part to enhanced detection capability, data from the Solan *et al*[45] study suggests a robust correlative effect. Should the higher incidence be a product of screening opportunity, one would expect increased detection of small, localized, early-stage cancer; yet, 40% of patients exposed to Ground Zero diagnosed with TC presented with more advanced disease, including lymph node metastasis[44], suggesting PM exposure to be of significance in thyroid disease etiology and progression. Ghassabian *et al*[46] reported that only high exposure to $PM_{2.5}$ was linked to hypothyroxinemia. It is firmly established that hyperthyroidism is associated with a high incidence of TC[47]; however, hyperthyroidism may be the pathological link between PM exposure and TC development and progression, and further investigation is necessary to confirm or deny the actual mechanism.

NO_2 is a reactive compound and a potential endocrine-disrupting chemical in polluted air with several health impacts [24] (Table 3). A significant association between chronic exposure to NO_2 and TC (1.33, 95%CI: 1.24-1.43, $P < 0.001$) has been documented[24]. Zaccarelli-Marino *et al*[48] found that a raised NO_2 concentration in air pollutants revealed a strong correlation with elevated odds of primary hypothyroidism (spearman correlation coefficients; adolescent female = 0.94, adolescent male = 0.94). Exposure to NO_2 was linked to TC in a study conducted in cohort data of 4632 patients with TC from 2002 to 2015[24]. Additionally, exposure to ambient NO_2 was significantly associated with reduced free thyroxine (FT4) concentration and a rise in thyroid-stimulating hormone (TSH)[49]. Interestingly, the increased circulating TSH level due to NO_2 exposure was followed by increased TSH receptor signaling and, consequently, a rise in thyroid cancer [24,50].

Furthermore, Zeng *et al*[51] performed a retrospective cross-sectional study and found that a 10 μg/m^3 increase in $PM_{2.5}$ was linked with a decrease in FT4 and an increase in FT3, and the FT4/FT3 ratio was inversely associated with $PM_{2.5}$ (coefficient: −0.06, $P < 0.01$). Dong *et al*[52] stated that $PM_{2.5}$ exposure could perturb TH homeostasis by affecting TH biosynthesis, biotransformation, and transport, affecting TH receptor levels, and inducing oxidative stress and inflammatory responses in female rats. $PM_{2.5}$ induced oxidative stress accompanied by pathologic changes in rat thyroid and

Table 4 Summary of the impact of ozone on human health

Type of interaction	Ref. (PMID)
Ozone results in increased gene expression	18332784
Ozone affects heart contraction	18091001
Ozone affects the regulation of inflammatory response	18560490
Ozone results in increased interleukin-6 production	20056584
[Vehicle Emissions co-treated with Ozone] affects neutrophil, lymphocyte, and monocyte homeostasis	27058360
[Air Pollutants results in increased abundance of Ozone] which results in increased DNA methylation	27219456
DNMT1 gene polymorphism affects the reaction [[Air Pollutants results in increased abundance of Ozone] which affects the regulation of blood pressure]	27219456
Ozone results in increased cholesterol metabolic process	27703007
[Cholesterol co-treated with Ozone] results in increased protein lipidation	27703007
Ozone results in increased mRNA and rRNA transcription	28652203
[Dust co-treated with Ozone] results in increased negative regulation of lymphoid progenitor cell differentiation	29767793
[Dust co-treated with Ozone] results in increased positive regulation of reactive oxygen species biosynthetic process	29767793
Ozone results in increased positive regulation of glycolytic process and cellular response to oxidative stress	29471466
Ozone results in increased positive regulation of proteolysis and amino acid metabolic process	29471466
Ozone affects the regulation of the membrane lipid metabolic process	29471466
Ozone results in increased tissue regeneration	29471466
[Air Pollutants results in increased abundance of Ozone] which affects the regulation of heart rate	28129768
Ozone results in increased positive regulation of ERK1, ERK2, and p38MAPK cascade	29925859
Ozone results in increased iron ion transport, homeostasis	24862973
Ozone results in increased viral entry into the host cell and the viral life cycle	22496898
Ozone results in increased chloride transmembrane transport	27886375
Ozone affects cytokine production involved in the immune response	32000783
[Air Pollutants results in increased abundance of Ozone] which results in increased positive regulation of heart rate	31349208
[Ozone results in increased oxidation of dimethylselenide] which results in increased ncRNA transcription	33656867
Ozone affects the aspartate/glutamate/ornithine/taurine metabolic process	33993003
[Oxygen co-treated with Ozone] results in the decreased cellular metabolic process	32992648
[Oxygen co-treated with Ozone] results in increased necrotic cell death	32992648
[Air Pollutants results in increased abundance of Ozone] which affects T cell homeostasis	33603036

Data source: The comparative toxicogenomic database (http://ctdbase.org/)[12].

liver characterized by increased follicular cavity size and decreased amounts of follicular epithelial cells and fat vacuoles [52]. Activation of the hypothalamic-pituitary-thyroid axis and altered hepatic transthyretin levels, therefore, play a crucial role in $PM_{2.5}$-induced thyroid dysfunction[52]. In addition, NO and PM with a diameter of fewer than 10 μm are the air pollutants most influential on diabetes[20].

CO exposure has been shown to have a negative impact on thyroid function and the pancreas, particularly in cigarette smoking[53,54]. A national cohort study from Taiwan confirmed that exposure to CO increases the risk of developing hypothyroidism[55]. A study of adult Koreans shows that a significantly high serum concentration of TSH and low FT4 could be attributed to CO exposure, especially in overweight or obese older people than younger adults[49].

Air pollution could play a role in genomic instability, driving the tumorigenesis process[34]. PM and NO_2 have been reported to be endocrine-disruptive compounds and carcinogenic in humans[24,42]. Exposure to PM_{10}, $PM_{2.5}$, and NO_2 was closely associated with thyroid cancer occurrence[24,42]. At the cellular level, PM and NO_2 can have several impacts, including inflammation, DNA damage, and genomic instability[34,56]. NO_2 exposure mediates oxidative stress and inflammation pathways; thus, it has been classified as a carcinogen[56]. NO_2 induces oxidative stress, interacts with unsaturated fatty acids, and causes organic molecules to undergo autooxidation, which can start free radical processes

Table 5 Some examples of the impact of particulate matter on human health

Type of interaction	Ref. (PMID)
[Air Pollutants results in increased abundance of Particulate Matter] which affects glucose homeostasis	27219535
Affects the glucose metabolic process	29616776 | 31851346
[Particulate Matter results in increased lipid oxidation] which results in an increased abundance of 4-hydroxy-2-nonenal	30716388
Affects the thyroid hormone metabolic process	27623605
[Vehicle Emissions results in increased abundance of Particulate Matter] which results in increased positive regulation of superoxide anion generation	28013216
Results in increased cell death	26856867
Results in increased reactive oxygen species metabolic process	21384498
Affects the positive regulation of cellular response to oxidative stress	23542817
[Particulate Matter co-treated with Biological Products] affects positive regulation of the apoptotic process	23454527
Particulate Matter affects the positive regulation of interleukin-6/8 production and NF-kB transcription factor activity	23201440
Results in decreased cell population proliferation	23722391
Results in increased T-helper 2 cell chemotaxis	16890758
Results in increased cell population proliferation	16455839
Results in increased negative regulation of mitotic cell cycle	25336953
Results in increased lipid catabolic process	21233593
Results in increased positive regulation of p38MAPK cascade	23900936
Results in increased positive regulation of apoptotic DNA fragmentation	26507108
Affects the vascular process in the circulatory system	25233101
Affects inflammatory response	25233101
Affects the insulin metabolic process	25233101
Results in increased inflammatory response	25479755
Results in decreased cognition	27128166
Affects the cholesterol biosynthetic process	26967543
Affects the positive regulation of telomere maintenance *via* telomere lengthening	21169126
Results in increased positive regulation of autophagosome assembly	27125970
[Air Pollutants result in an increased abundance of Particulate Matter] which affects the regulation of endothelial cell differentiation	27311922
[Vehicle Emissions results in increased abundance of Particulate Matter] which results in increased respiratory burst after phagocytosis	28013216
Affects the electron transport chain, mitochondrial translation, and tricarboxylic acid cycle	28821289
Affects the regulation of mitochondrial membrane potential	26989813
Results in decreased superoxide dismutase activity	26989813
Results in increased positive regulation of endothelial cell activation	29244817
Affects histone modification	27918982
Affects gene expression	25564368 | 28821289 | 29114965 | 29342453
Affects T and B cell homeostasis	20678227
[Vehicle Emissions results in increased abundance of Particulate Matter] which results in increased cellular senescence	31551408
[[Vehicle Emissions results in increased abundance of Particulate Matter] which co-treated with Oleic Acid] results in increased triglyceride biosynthetic process	31340670
[Air Pollutants results in increased abundance of Particulate Matter] which affects negative regulation of DNA-	26298100

templated transcription	
Results in increased cell migration and cell chemotaxis	29913439
Results in decreased learning or memory	31881430
Results in increased activation of protein kinase B activity and p38MAPK cascade	32687961
Results in decreased endothelial cell-cell adhesion	33159583
[Air Pollutants result in an increased abundance of Particulate Matter] which affects ATP metabolic process	32487172

Data source: The comparative toxicogenomic database (http://ctdbase.org/)[12].

[57]. The induced systemic inflammation and the immune response to autoantigens resulting in the production of reactive oxygen species have been proposed as mechanisms of PM carcinogenesis in thyroid cancer patients[56]. Oziol *et al*[58] reported that ambient air in French urban areas had thyroid receptor alpha-1 agonistic effects without competitive effects concerning T3-dependent transcriptional activity. Similarly, Nováková *et al*[59] conducted an *in vitro* experiment and found that exposure to PM_{10} in ambient air significantly increased thyroid receptor-mediated activity.

Numerous air pollutants have also been linked to other diseases of systemic inflammation[60]. Air pollution modifies T-cell-dependent immunity, predisposing to autoimmune illnesses and inflammation[61]. It may also cause oxidative stress and lung formation of reactive oxygen species to harm the beta cells in the pancreas, which would limit insulin release and contribute to T2DM risk[62,63]. According to research by Chuang *et al*[64], exposure to PM_{10} alters blood pressure, blood lipids, and hemoglobin A1c. Chronic exposure to such particles increases the risk of lung cancer, as well as respiratory and cardiovascular problems, further fueling T2DM morbidity. In an Iranian study by Kelishadi *et al*[63], the investigators found that PM_{10} was positively correlated with insulin resistance in children. The risk of developing insulin resistance was later discovered to be positively correlated with residential proximity to high levels of automotive traffic – and subsequently a high degree of PM – among a German cohort of children[65]. Impaired glucose tolerance in pregnancy is also linked to exposure to traffic-related air pollution[66]. The possible inhibition of T suppressor cells is also one of the main links in the genetic predisposition for autoimmune TD. In this situation, T helper cells have a great deal to do, both in the activation of B lymphocytes, which create enhanced thyroid antibodies, and so also interferon[18]. High exposure to $PM_{2.5}$ and NO_2 in the first trimester of pregnancy is associated with mild thyroid dysfunction with positive thyroid peroxidase antibodies[46]. Figure 1 summarizes the synergetic impact of air pollution and diabetes on thyroid tumorigenesis risk.

Thyroid dysregulation as a diabetes risk factor

The lab of Brandt *et al*[30] found, in a Danish study conducted on a national level, that patients exhibiting hyperthyroidism – clinical or subclinical – had a greater risk of developing T2DM. TSH levels in patients with subclinical hyperthyroidism and pre-existing diabetes can be returned to normal function as diabetes control improves, indicating that T2DM therapies may help restore normal thyroid function prior to progression to overt hyperthyroidism for these patients[67]. However, a recent study found that hyperthyroidism patients who did not have diabetes had a higher chance of progressing to T2DM later in life than euthyroid cohorts. Thus, it is likely that thyroid dysfunction may occur before diabetogenic processes as a primary catalyst[68].

Insulin resistance in hyperthyroidism

Hyperthyroidism can often be detected clinically by characteristic symptoms, including palpitations, fatigue, tremor, weight loss, anxiety, and excessive sweating. However, subclinical hyperthyroidism may exist with few, if any, symptoms and is characterized by low TSH levels despite adequate TH levels. A study assessing individuals with either overt or subclinical hyperthyroidism who underwent a glucose tolerance test found that higher blood levels of both glucose and insulin may be found in either form[69]. Increased Cory cycle activity, which suggests that muscle tissue serves as a source of substrates for hepatic gluconeogenesis, supports higher rates of gluconeogenesis (lactate and certain amino acids such as alanine and glutamine). This process entails a dynamic glucose buffer that enables other tissues to utilize it as necessary when they have a glucose demand. Phosphoenolpyruvate carboxykinase is the rate-limiting step in gluconeogenesis, and it is known that TH – specifically triiodothyronine (T3) – increases its expression in the liver, indicating a direct involvement for THs in the control of endogenous glucose production[69]. High THs also increase gluconeogenesis through accelerated lipid mobilization as well[69]. Inducing Sterol response element-binding protein 2 expression and enhancing LDL receptor expression, TH lowers blood levels of TGs and cholesterol-containing lipoproteins. This potentiates hepatic cholesterol absorption. The mechanism is presumed to occur through increasing the expression of acetyl CoA carboxylase and carnitine palmitoyltransferase Iα, which will increase the hepatic uptake of fatty acids[70].

It has been demonstrated that hepatic insulin resistance in hyperthyroid patients increases gluconeogenesis and, subsequently, hepatic glucose production[71,72]. Studies mimicking hyperthyroidism in mice *via* exogenous T4 have shed light on insulin signaling concerning TH; despite fasting conditions, insulin target tissues demonstrate active insulin signaling, presumed to result from deregulated insulin production from the endocrine pancreas[73]. Compared to healthy people, hyperthyroid patients have higher basal hepatic glucose production and fasting insulin levels; however, when treated with methimazole (an antithyroid agent), these levels were dramatically minimized, reducing THs to the levels of

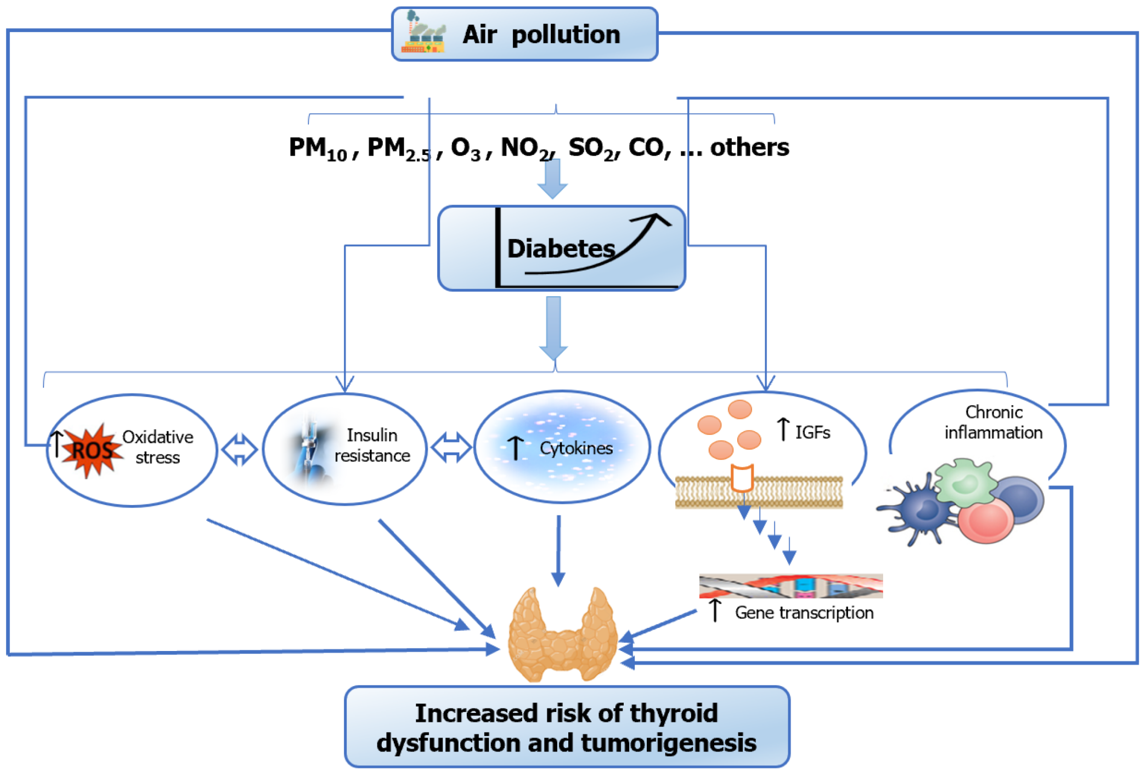

Figure 1 Air pollution could increase the risk of diabetes and thyroid cancer through several mechanisms. For example, it could increase inflammation and oxidative stress in the body and disrupt the production of cytokines and several hormones, such as insulin and thyroid hormones, linked to increased risk of diabetes and thyroid cancer. IGFs: Insulin-like growth factors; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3: Ozone; PM: Particle matter; ROS: Reactive oxygen species; SO_2: Sulfur dioxide.

the healthy control group[74].

Collectively, this review consolidates links between thyroid dysfunction and diabetes development, common pathways of synergy, and the catalytic role PM plays in the emergence of diabetes and thyroid cancer. However, while the connections between PM and thyroid cancer, and between hyperthyroidism and PM, have been established, further exploration is needed to support or reject the presumption that PM contributes to thyroid cancer with hyperthyroidism as the pathogenic liaison. Future focus areas should prioritize longitudinal assessment of thyroid pathology following significant PM exposure to identify possible cancer development courses and mechanisms.

CONCLUSION

Air pollution, specifically PM, contributes significantly to developing thyroid disease and T2DM, both independently and synergistically. Identifying these interconnections within the unique endocrine system is essential to mitigate the exacerbation of insulin resistance, reduce T2DM development and progression, and identify PM-exacerbated specific risk factors for diabetic patients in the face of ever-accumulating air pollution.

FOOTNOTES

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