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INFLUENCE OF OBESITY ON THYROID: A REVIEW

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Abstract

Obesity has increased prevalence globally, and knowledge of its pathophysiology and metabolic effects has significantly improved. The white adipose tissue actively produces many hormones, cytokines, and chemokines that together play significant roles in homeostasis and the control of thyroid hormones. Previously, white adipose tissue was considered to be the body's greatest inactive energy reserve. Obesity is caused by an imbalance between energy intake and energy expenditure. By controlling cellular respiration and thermogenesis as well as modulating resting metabolic rate, thyroid hormones have an impact on energy expenditure. Triiodothyronine stimulates the central nervous system, particularly hypothalamus which regulates appetite and modulates lipid turnover in adipocytes. Additionally, thyroid-stimulating hormones can regulate lipolysis and lipogenesis control, thermogenesis, hunger suppression, and lipid storage regulation. It was established that hypothyroidism leads to obesity, but obesity may also be a risk factor for developing hypothyroidism. The link between thyroid function and obesity has received more attention in recent years due to the considerable interactions that exist between these two conditions. In particular, it's important to pay attention to how adipocytokines and thyroid hormones (THs) interact in obese people. By examining the underlying source of this association, it is needed to check this bidirectional relationship between hypothyroidism and obesity by deep research into the fundamental causes and also to understand how it can be implemented in our clinical practice.

INTRODUCTION

World Health Organisation (WHO) defines obesity as "An abnormal/excessive accumulation of fat that may cause a risk to health". Obesity and being overweight are widely acknowledged as a "global epidemic" and as a severe issue with a high prevalence in both developed and developing countries. There is an accumulation of extra body fat in obesity, caused by high calorie intake and a reduction in utilization of energy (1).

Generalized Obesity (GO) & Abdominal Obesity (AO) are the two main classifications for obesity. Body Mass Index (BMI), an attribute defining GO, is a ratio of weight in kilograms to height in square meters (kg/m^2). BMI is extensively used in clinical settings as a basic indicator of obesity. However, consensus-based recommendations from the Prevention and Management

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of Obesity and Metabolic Syndrome (MetS) group, for Asian Indians about obesity and overweight based on BMI were revised. Asian Indians are classified as overweight (BMI 23.0-24.9 kg/m^2) and obese (BMI 25 kg/m^2) according to these updated recommendations. In comparison to GO, truncal obesity, also known as AO, which gives the body a pear-shaped appearance, is particularly common in Asian Indians. In comparison to GO, truncal obesity, also known as AO, which gives the body a pear-shaped appearance, is particularly common in Asian Indians (2).

The WHO claims that waist circumference (WC) is a more reliable anthropometric index for AO than BMI and can be used to assess AO. According to current guidelines by WHO for South Asians, AO is defined as having a WC≥80 cms in women and ≥90 cms in men (3-5).

Many different physiological processes are known to be affected by obesity and cause a phenotypic change and chronic low-grade inflammation in adipose tissue (6,7). Hypothyroidism and obesity are two prevalent disorders that are linked clsoely. Because thyroid hormones upregulate many metabolic pathways crucial for Resting Energy Expenditure (REE), it is not surprising that people with thyroid issues typically experience changes in body weight, thermogenesis, and adipose tissue lipolysis. Hyperthyroidism has been associated with weight reduction in spite of increased metabolic rate and appetite, hypothyroidism is usually associated with weight gain, decreased thermogenesis, and metabolic rate (8).

With the global prevalence of obesity experiencing a massive surge, the link has gained greater importance. Patients typically believe that thyroid disease is a secondary cause of obesity. According to a novel perspective, alterations in the hormone Thyroid Stimulating Hormone (TSH) may be due to obesity. According to recent researches, obesity and thyroid dysfunction possesses a close interaction, with the adipocyte hormone leptin which appears to serve as a main mediator. We will examine the intriguing connection between obesity and hypothyroidism in this article and also the resulting clinical implications.

Prevalence of AO & GO

Rajat Das Gupta et al. study in 2023, about GO and AO in India, discovered that 13.85% of participants were GO and 57.71% of respondents had AO. Compared to men, females had a higher prevalence of AO. The risk of GO and AO raised with increase in age, being female, educated, residents of Northern India, married and living in urban region. Only AO was considerably elevated in educated and alcoholic individuals leading a less physically demanding lives (9,10). Being married at any time raised the risk of GO and AO in both sexes (11,12).

Alcohol consumption is linked to an increase in adiposity, which makes a person more likely to develop AO (13,14). Recent researches estimated a prevalence between 19% to 71.2% (15-17). A study by Ahirwar et al. from 2019, predicted that 16.9-36.3% of people in India have AO (18). This disparity in prevalence of AO may be the result of various factors, including variations in study populations, study settings, and standard definitions used for defining AO.

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Depots of Adipose Tissue (AT)

Adipose tissue (AT) is considered to be a heterogeneous organ since it is distributed throughout multiple depots and comes in a variety of different types. Due to their extreme variety, these depots have even been compared to "mini-organs" with distinct features and functionality. Aside from heterogeneity, another important trait of AT is plasticity, or the capacity to alter structural, cellular, and molecular characteristics in response to physiological and pathological situations that have an immediate impact on functionality. Depending on how it impacts the functionality of AT, this flexibility may be harmful or advantageous. Additionally, the various fat depots' cellular and structural variations have an impact on the plasticity and remodeling of the AT. White Adipose Tissue (WAT) and Brown Adipose Tissue (BAT), the two primary forms of fat tissue, perform opposing roles in the control of the energy balance. Subcutaneous and visceral deposits are included in WAT, the latter can manifest itself as perivascular, omental, mesenteric, epicardial or retroperitoneal fat (19).

White Adipose Tissue (WAT)

WAT is primarily constituted of white adipocytes and preadipocytes, although additionally includes extracellular matrix (ECM), macrophages, lymphocytes, fibroblasts, and stromal cells. Triglycerides (TG), a type of energy stored in WAT, serve as a source of energy, and also it is a key endocrine producer of adipocytokines. Energy can be used as free fatty acids (FFA) by white adipocytes, which are experts in storage of lipids in response to energy levels, if required. WAT can alter its volume and it can expand or retract. It expands through two processes: hypertrophy (increased adipocyte volume) and hyperplasia (increased fat cell quantity). Adipocyte triglyceride storage, resulting from the balance of lipogenesis and lipolysis, regulates adipocyte size & closely monitored by insulin and catecholamines, although TSH and THs also play a role (19).

Brown Adipose Tissue (BAT)

BAT was once believed to be present only in neonates before disappearing. Recent research has revealed that BAT is present in adults as well and a favorable metabolic profile is related to increased BAT activity (19-21). The primary purpose of a BAT is to generate heat using a process known as thermogenesis. By raising the BMR, THs may promote compulsory thermogenesis and also regulate BAT-mediated adaptive (facultative) thermogenesis. Unlike BAT, which has many smaller droplets of lipids and is densely innervated by sympathetic nerves, WAT is characterized by a single big droplet of lipid storage.

The Mitochondrial uncoupling protein, UCP1 is in charge of dissipating energy as heat, and adrenergic activity, the amount of T_3 in adipocytes are what activate it (19,20). Another compensatory response was documented by Weiner et al. in 2016 and it was noted that WAT had a higher expression of BAT-specific genes and hypothesized that the browning of WAT would serve as compensatory mechanism to prevent additional drop in body temperature in hypothyroidism (22).

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Thyroid stimulating hormone (TSH) & GO

One of the most prevalent endocrine illness in the world is thyroid dysfunction. Around 42 million individuals in India have one or more thyroid diseases (23). Thyroid dysfunction and obesity are two familiar clinical disorders that have a very strong correlation (24). The Basal Metabolic rate (BMR) and thermogenesis are regulated by thyroid hormones. Thyroid hormones may potentially have a role in controlling hunger, according to previous researches (25,26). Thyroid dysfunction is allied with fluctuations in body weight and composition (25). Thyroid Stimulating Hormone (TSH) levels were significantly greater in overweight and obese participants compared to healthy people, according to Makwane H, et al. in 2020. Additionally, it was discovered that among healthy adult Indians, 2% of participants had hyperthyroidism and 10% had hypothyroidism. The study concluded that patients in the obese group had higher rates of hypothyroidism than non-obese. They also suggested a significant positive relationship between BMI and THs, although no correlation between TSH and BMI was found among the study subjects (27). In comparison to lean patients, TSH levels were significantly higher in obese subjects according to Muscogiuri G, et al. in 2013 (28).

Thyroid Stimulating Hormone (TSH) & AO

AO is a form of obesity that is characterized by excessive fat accumulation in the abdominal area with a prevalence of 75% in North Indian females (4). S. Singh, et al. in 2023, reported a prevalence of AO as almost 31% in the Western Uttar Pradesh region in the age group of 18-24 years. They selected this younger age group of 18-24 years, based on the fact that this period is a transition phase to adulthood from the adolescent phase of life and and assumed to be in their active phase of life, physically and metabolically. As per the selection criteria, the subjects did not have a history of pregnancy. There were higher levels of serum TSH in the female subjects and positively correlated with AO. Studies did propose that the aetiopathogenesis of AO is based on the deposition of WAT leading to a low-grade inflammation (29). However, a study by Velluzzi F. et al, in 2022, stated WC as a good marker for metabolic risk, was not significantly correlating with TSH values (30).

Subclinical Hypothyroidism (SCH) & AO

The common pathological condition of thyroid hormone insufficiency is referred to as hypothyroidism. TSH levels above the reference range (0.5-4.49 mIU/L) and free thyroxine (fT_4) level below the reference range (0.8-1.8 ng/dL) are considered signs of overt or clinical primary hypothyroidism (31). A higher thyrotropin (TSH) level of 4.5-12.0 mIU/L, despite normal serum fT_4 levels, characterizes mild or subclinical hypothyroidism (SCH), which is frequently viewed as a marker of early thyroid dysfunction (32,33). It could result in serious health consequences or even death if untreated. Hypothyroidism is mostly defined biochemically due to the vast range of clinical presentations and general lack of symptom specificity (31). Studies done on SCH in Western Uttar Pradesh by Shailza Verma et al. & Thuraya Abdulsalam A.A.Al-Azazi et al. in 2022, in the age group 18 to 60 years, found a mean serum TSH level of 7.0±1.7 & 6.9±1.4 µIU/L respectively (32,33). S. Singh, et al. in 2023, found a mean serum TSH value of 5.4±0.6 mIU/L which may be due to the selection of a

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younger age group population of 18-24 years. A rise in WC in AO females increases the level of serum TSH & Tumor Necrosis Factor-α (TNF-α), presenting a risk of hypothyroidism. They also concluded that, 38% of females were in the SCH state in subjects of 18-24 years age with AO (WC>85 cms), and a thorough biochemical & medical intervention are required in the younger generation (29). TMJ S et al. in 2019, stated that AO defined by WC showed a positive significant association with SCH with a prevalence of 27% (34).

SCH, Obesity & Polycystic Ovarian Syndrome (PCOS)

Polycystic Ovarian Syndrome (PCOS) is the most frequent type of chronic anovulation state linked with androgen excess, affecting around 5-10% of fertile women. It is a diverse illness with multiple etiological factors. Increased risk factors for metabolic and cardiovascular disease, such as obesity, are linked to PCOS. Obesity is a common feature of PCOS, exacerbating numerous of its metabolic and reproductive features. Thyroid conditions, on the other hand, are more frequent in women than in males and have particular effects on menstrual cyclicity and reproduction. Additionally, mucus deposition, salt, and water retention caused by hypothyroidism exacerbate weight gain. Being involved in the control of thermogenesis and basal metabolism, it also possesses a significant impact on lipid and glucose metabolism, thyroid hormones and body composition are thought to be intimately connected. It is generally accepted that PCOS patients are obese and the clinical manifestations of PCOS was caused by obesity (35). Nayak et al. in 2020, discovered that 61% of patients were overweight and 39% of patients were thin and indicated that both overweight and people with normal BMI have PCOS and its clinical symptoms. Patients with PCOS have irregular periods, signs of hyperandrogenism, and a higher blood testosterone level, regardless of their BMI. In PCOS individuals, there was no correlation between obesity and hypothyroidism (35). A study by Saxena et al. in 2012, revealed that 42% of lean women have PCOS (36).

SCH & Metabolic Syndrome (MetS)

The metabolic syndrome (MetS), also called as Syndrome X or insulin resistance syndrome, is a group of metabolic risk factors that includes AO, hypertension, dyslipidemia, and hyperglycemia. All around the world, its prevalence is rising swiftly (37). Even though hypothyroidism and MetS are separate risk factors for cardiovascular disease (CVD) (38-40), data points imply the possibility of MetS elements impacted by thyroid hormone imbalance. Iodine consumption, geographic characteristics, and ethnicity have all been linked to thyroid dysfunction (41). In 2023, a study by Alourfi Z. et al., MetS incidence was greater in SCH (28.5%) compared to euthyroid (27.7%). Additionally, when they looked into the connection between SCH and a MetS component, they found a substantial correlation between AO and SCH. They noted higher levels of leptin, released by adipocytes stimulated TSH levels, maybe the link between obesity and hypothyroidism (42).

Adipocytokines & Thyroid Hormones (TH)

Numerous adipocytokines released by WAT have an impact on target tissues including the pancreas, skeletal muscle, liver, heart, and central nervous system (CNS). Adipokines also have autocrine and paracrine effect on adipocytes in addition to their endocrine function (43). There

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is a relationship between AO and ongoing low-grade inflammation. Adipocytes synthesize cytokines and adipokines, the substances that are impacted by obesity. Inappropriate adipokine and cytokine release leads to impaired metabolism and increased inflammation. Adipocyte growth, altered phenotypes, and inflammation are additional effects of obesity on adipose tissue (44). The hormone leptin, which is created by adipocytes, regulates body weight over the long term by preventing food intake and encouraging energy expenditure and locomotor activity (45). Through the activity of the Janus Activating Kinase-2 (JAK-2) Signal Transducer and Activator of Transcription-3 (STAT-3) proteins, leptin raises serum fT3 and fT4 and promotes the synthesis of TSH Releasing Hormone (TRH) and TSH. Leptin directly mediates the conversion of circulating T4 to T3 in the body. Gaining adipose tissue fat has been associated with lymphocyte activation, which produces thyroid-specific cytokines and autoimmune antibodies that lead to chronic lymphocytic thyroiditis and alter thyroid hormone levels. Body weight, fat mass, thyroid function, circulating fT3 and fT4 levels, and thyroid function may all have an impact on BMR. The drop in fat mass and leptin production from adipocytes, which lowers blood TSH and THs levels and significantly lowers HPT axis activity, also hinders the peripheral conversion of T4 to T3 (46). Leptin and TSH showed a substantial positive connection, as per C Betry et al. in 2015 (47). A study by Van Tienhoven-Wind et al. 2017, suggested the leptin/adiponectin ratio as a reliable indicator of adipose tissue dysfunction which positively correlated with TSH. It was postulated that the Hypothalamus-Pituitary-Thyroid (HPT) axis may be involved in altered adipose tissue function (48). In 2016, Yamamoto M et al. reported that leptin boosted thyroid cell hypertrophy and improved thyroglobulin expression. Thyrocytes were unaffected by low levels of leptin, but hypertrophy was caused by larger levels of leptin up to a certain point, after which they had no impact. The aforementioned phenomena depend on an optimum leptin concentration. Adiponectin, on the other hand, had no impact on thyrocyte morphology or thyroglobulin expression (49).

Therapeutics of Obesity

Lifestyle Modifications

Since there are no specific therapy for treating obesity, "lifestyle modification" remains the cornerstone of its management (50). It is advisable that at least 10% of their body weight should be shredded using a combination of exercise, diet and behavior therapy (lifestyle modification) (51). Significant weight loss can be obtained quickly by dieting (52). High levels of physical activity and ongoing interactions between patients and providers are both necessary for long-term weight control. Changing to a healthier lifestyle result in a substantial reduction of body weight (53).

Anti-Obesity Medications

Pharmacotherapy is advised for people with BMI >25 kg/m2 who are unable to lose weight with lifestyle changes alone. The United States, FDA (Food and Drug Administration) has approved several novel pharmacological medications for the short-term treatment of obesity that include phentermine-topiramate (Qsymia), orlistat (Xenical, Alli), liraglutide (Saxenda) & naltrexone- bupropion (Contrave). (54).

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Clinical Implications of TSH

Since the symptoms and indicators of thyroid dysfunction can vary widely, thyroid function evaluations are frequently performed in clinical settings. Measurements of TSH and thyroid hormones are frequently used to evaluate various illness. A thyroid condition may be categorized as euthyroid, hypothyroid, or hyperthyroid based on the history, physical examination, and lab results.

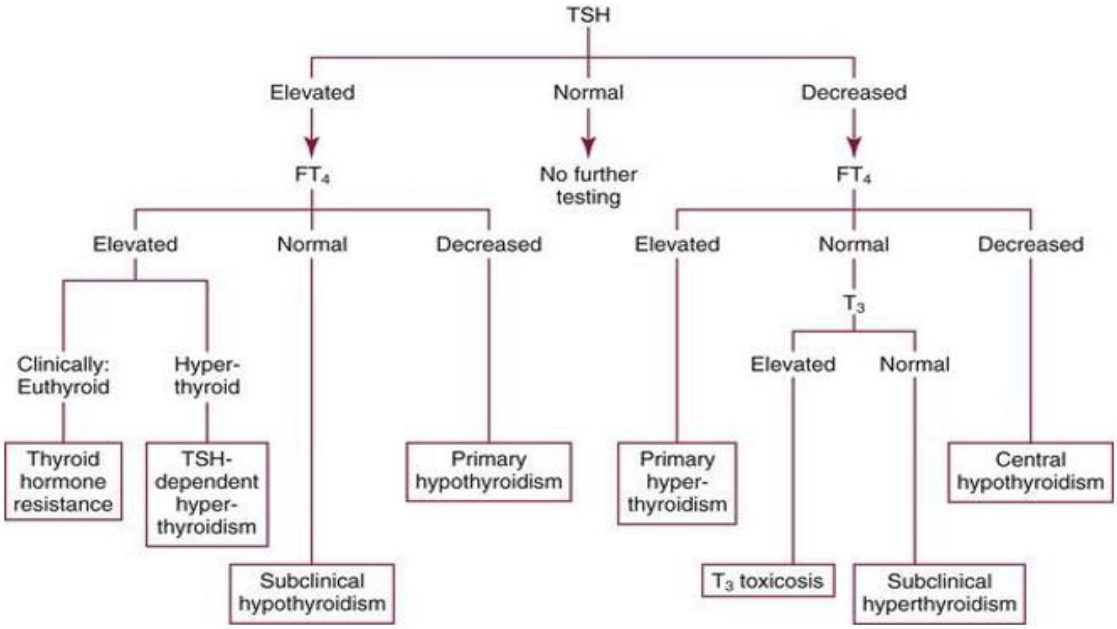

Figure 1: Suggested algorithm for measuring thyroid function in a laboratory (55).

Summary of The Studies

Study	Conclusion
RD Gupta et al., 2023 (9)	According to the findings of this study, 57.17% of the participants had AO, whereas 13.85% had GO. Females have a higher prevalence than their male counterparts. According to this study, abdominal obesity has grown with growing age, being female, having a higher educational position, living in Northern India, being married, and living in an urban location. Alcohol consumption elevated the risk of AO considerably. They also discovered a link between AO and educational attainment.
S. Singh et al., 2023 (29)	Serum TSH & TNF-α levels showed a positive correlation with WC indicating AO, in young females of age 18-24 years. WC may be useful in appropriate interventional measures like healthy lifestyle & diet may lower the risk of thyroid disorder by controlling AO.
AK Jha et al., 2023 (57)	Serum TNF-α & WC were positively correlated in obese individuals. TNF-α levels in obese people may be reduced by adopting lifestyle modifications such weight loss by meal substitution, regular exercise, and avoiding high-calorie diets.

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Alourfi Z et al., 2023 (43)	MetS was higher in SCH (28.5%) compared to euthyroid (27.7%). They also investigated the relationship between SCH and a component of MetS and observed a significant association between AO and SCH.
RD Gupta et al., 2022 (10)	Males were more likely to be underweight, whereas females were more likely to be overweight/obese. Those who were affluent and married had a larger probability of becoming overweight/obese. Increased educational attainment, on the other hand, was inversely related to being underweight.
S. Verma et al., 2022 (33)	This study found significantly low levels of serum Vitamin B12 in cases of subclinical hypothyroidism. Vitamin B12 showed highly significant negative correlation.
T. Abdulsalam A.A.Al-Azazi et al., 2022 (34)	A statistically significant decrease in serum zinc levels in subclinical hypothyroidism patients.
Nayak et al., 2020 (36)	PCOS and its clinical manifestations are seen in both overweight and normal-weight individuals. There was no link found between obesity and hypothyroidism in PCOS individuals.
VK Undavalli et al., 2018(5)	The prevalence of GO and AO was found to be 56% and 71.2%, respectively. Obesity was 45.6% among urban women in the study state of Andhra Pradesh, compared to 27.6% among rural women. The study found that obesity prevention should begin in childhood. Obesity is more difficult to treat in adults than in youngsters. Behavior change communication (BCC) is a technique used to urge people in society to adopt healthy behaviors such as food changes, greater physical activity, or a combination of the two.
Y. Inoue et al., 2018 (13)	The study suggests a positive association between urbanization and obesity. Obesity in children was predominantly observed in more urbanized areas.
Gupta et al., 2017 (17)	Obesity and overweight were high in adults. AO was more prevalent than GO. Women were more obese compared to men.
LJ van Tienhoven-Wind etal., 2017 (49)	This study suggested that the Leptin/Adiponectin ratio can be a predictor of cardiovascular disease and biomarker of adipocyte dysfunction.
N. Ahmad et al., 2016 (6)	AO was observed in 23.8% of males and 66.4% of females. The Asian cut-off for AO resulted in a higher prevalence. The connection between WC and BMI was substantial and positive. The study recommended WC cut-off marks of 92.5 cm in men and 85.5 cm in women for detecting AO. In Malaysian adults, WC is a better predictor of AO than waist hip ratio (WHR).
R Pradeepa et al., 2015 (3)	Generalized Obesity was 24.6, 16.6, 11.8 & 31.3% among residents of Tamilnadu, Maharashtra, Jharkhand, and Chandigarh, while AO was 26.6, 18.7, 16.9 and 36.1%, respectively. Significantly higher GO & AO among urban residents compared to rural residents in all the study regions.
G. Traversy et al., 2015 (15)	Alcohol has most likely contributed to the extra energy intake linked to a weight increase.
C. Bétry et al., 2015 (48)	TSH levels in obese participants increased with BMI. This was linked to leptin, regardless of BMI. The elevation of serum TSH was observed in obese patients which can be due to the result of both fat mass accumulation and a positive energy balance.
M. Mamtani et al., 2014 (56)	WC is an independent predictor of thyroid function. In Mexican American respondents, this association was irrespective of age, gender, and BMI.
G. Muscogiuri et al., 2013(28)	The increase in adipose tissue, particularly visceral adipose tissue, and the resulting insulin resistance may play a critical role in changes in thyroid homeostasis, but the disruption of the HPT axis may worsen the characteristics of obesity. This study also

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	proposed leptin as a possible explanation for increased TSH levels in obese people.
S Bhardwaj et al., 2011 (4)	The prevalence of AO (WC) & GO (BMI) in Asian Indians was 68.9% & 50.1%, respectively. A high prevalence of obesity with 84.5% based on percentage body fat was also observed among the study subjects.

CONCLUSION

The article concludes that there is a link between obesity and thyroid dysfunction. By addressing the interactions between thyroid disease, inflammation, and obesity, there is a hope to enhance patient care and results. An important public health issue related to rising mortality and morbidity rates is abdominal obesity. Each demographic has a different way of categorizing and measuring obesity, as well as choosing the right cut-off points. Contrary to generalized obesity, abdominal obesity has been proven to be strongly associated with thyroid disorders, metabolic syndromes, and PCOS. It is advised to include other anthropometric measurements like WC & Waist-Hip ratio (WHR) to improve the evaluation and prediction of illness risk, including PCOS. To comprehend the pathophysiology of abdominal obesity and its consequences for numerous health disorders, more research is required.

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