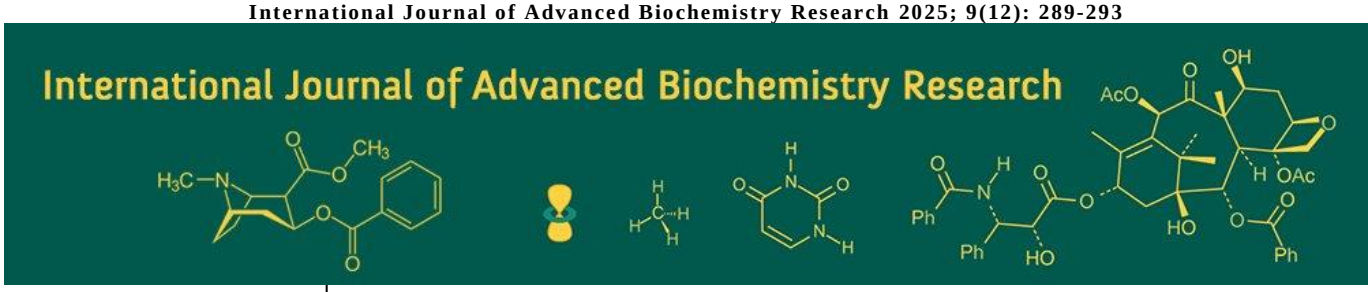

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Evaluating the link between metabolic syndrome components and benign nodular thyroid disease

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Abstract
Background: The clustering of metabolic syndrome (MetS) components is a recognized risk factor for nodular thyroid disease (NTD). A critical gap remains in understanding the individual contribution and relative importance of each MetS component to the development of thyroid nodules.
Objective: To delineate the specific associations between the individual components of metabolic syndrome and the presence of nodular thyroid disease.
Methods: A cross-sectional analytical pilot study was conducted involving 70 participants, divided into two groups: 35 with sonographically confirmed benign NTD and 35 healthy controls. Metabolic syndrome was diagnosed according to standard criteria. All participants underwent detailed clinical evaluation, including anthropometric measurements, blood pressure assessment, and fasting blood analysis for glucose, lipids, and thyroid function. According to the exclusion criteria, cases with malignant thyroid nodules were resected. In this study, as thyroid nodules, only benign thyroid nodules were considered. Statistical analyses, including chi-square tests, t-tests, and multiple logistic regression, were employed to identify independent risk factors.
Results: The prevalence of metabolic syndrome was significantly higher in the nodular thyroid disease (NTD) group (68.57%) versus controls (40.00%, p=0.001). Low HDL-cholesterol was the most prevalent component in the NTD group (82.9% vs. 37.1%, p=0.046), followed by impaired fasting glucose (48.6% vs. 25.7%, p=0.004) and hypertension (51.4% vs. 17.1%, p=0.005). Multiple logistic regression confirmed metabolic syndrome as a strong independent risk factor for NTD (OR=5.00, p=0.001).
Conclusion: Specific metabolic syndrome components, particularly low HDL-cholesterol, show strong associations with nodular thyroid disease. Comprehensive metabolic evaluation should be integrated into the assessment of thyroid nodules, highlighting the link between metabolic health and thyroid pathophysiology. The sample size was very small due to the COVID-19 situation.

Keywords: HDL cholesterol, hypertension, insulin resistance, metabolic syndrome, nodular thyroid disease, risk factors.

Introduction

Nodular thyroid disease (NTD), characterized by the presence of single or multiple thyroid nodules, is a prevalent endocrine disorder whose detected incidence has risen dramatically with the advent of routine neck ultrasonography [1, 2]. While most nodules are benign, their clinical management necessitates the exclusion of malignancy and addresses potential local compressive symptoms or hormonal dysfunction [3]. The pathogenesis of NTD is multifactorial, involving genetic susceptibility, iodine status, and environmental factors, yet a substantial portion of risk appears linked to modifiable metabolic conditions [4]. This has directed research toward understanding the influence of systemic metabolic health on thyroid morphology. Metabolic syndrome (MetS) represents a cluster of interconnected cardiometabolic risk factors, including abdominal obesity, dysglycemia, hypertension, elevated triglycerides, and low high-density lipoprotein cholesterol (HDL-C) [5]. This syndrome is a proxy for insulin resistance and chronic inflammation, constituting a significant risk factor for cardiovascular disease and type 2 diabetes [6]. The collective impact of MetS on various organ systems has been extensively documented, with growing evidence establishing a robust association between MetS and an increased prevalence of thyroid nodules [7, 8].

The prevailing hypothesis suggests that the pro-inflammatory and pro-mitogenic state induced by MetS creates a favorable environment for thyrocyte proliferation [9]. However, treating MetS as a single dichotomous variable may obscure the individual contributions of its components. Each component can independently promote cellular proliferation and oxidative stress through distinct pathways. For instance, insulin resistance, primarily reflected by dysglycemia, can stimulate thyrocyte growth via the mitogenic actions of hyperinsulinemia and increased insulin-like growth factor-1 (IGF-1) signaling [10]. Hypertension, another key component, is associated with endothelial dysfunction and oxidative stress, which may contribute to thyroid tissue remodeling [11]. Notably, dyslipidemia, and specifically low levels of HDL-C, has recently garnered attention. HDL particles possess anti-inflammatory, antioxidant, and anti-apoptotic properties, and their deficiency may permit increased oxidative damage within the thyroid gland, potentially initiating or promoting nodulogenesis [12, 13]. While several studies have confirmed the aggregate risk posed by MetS, a detailed dissection of which specific components such as dyslipidemia (low HDL-C vs. high triglycerides), hypertension, or dysglycemia are the primary drivers of NTD risk within a cohort remains less explored. Understanding this hierarchy is crucial for developing targeted preventive strategies. Therefore, this study aims to move beyond the composite MetS diagnosis and meticulously evaluate the link between each component of metabolic syndrome and the presence of nodular thyroid disease. We hypothesize that specific components, particularly low HDL-C and hypertension, will demonstrate stronger individual associations with NTD than others.

Methodology

Study population: This cross-sectional analytical pilot study was conducted at a tertiary care hospital. The study population consisted of 70 participants, categorized into two groups: 35 patients with sonographically confirmed benign nodular thyroid disease (NTD) and 35 age-matched controls without thyroid nodules.

Inclusion criteria: Participants aged between 18 and 75 years, of both genders, were included. The control group comprised individuals accompanying patients or attending the outpatient clinic for non-thyroid-related issues, who had no evidence of thyroid nodules on ultrasonography.

Exclusion criteria: Exclusion criteria were designed to minimize confounding factors and included malignant thyroid nodules, pregnancy, (renal, hepatic, cardiac), acute or chronic inflammation, malignancy, and the use of medications known to influence thyroid function or metabolic parameters.

Study procedure: All participants underwent a standardized protocol including clinical history, physical examination, anthropometric measurements (weight, height, waist circumference), blood pressure assessment, and thyroid ultrasonography. Fasting venous blood samples were collected for the analysis of glucose, lipid profile, and thyroid function tests (TSH, FT3, FT4).

Data analysis: Data were analyzed using SPSS version 20. Continuous variables were compared using the independent samples t-test, while categorical variables were analyzed with the Chi-square test. A multiple logistic regression model was applied to identify independent associations. A p-value of <0.05 was considered statistically significant.

Results

The study included 70 participants, equally divided into a group with nodular thyroid disease (NTD) and a control group without nodules. The demographic profile revealed that the NTD group was significantly older than the control group (40.90±11.24 years vs. 34.07±7.96 years, p = 0.009). Significant differences were also observed in key metabolic parameters. Participants with NTD had higher mean weight, waist circumference, and both systolic and diastolic blood pressure compared to the control group. The prevalence of metabolic syndrome was significantly higher in the NTD group (68.57%) compared to the control group (40.00%). When analyzing the individual components of MetS, a distinct pattern emerged. The most prevalent component in the NTD group was low HDL-cholesterol, present in 82.9% of patients compared to 37.1% in controls (p = 0.046). This was followed by impaired fasting glucose (48.6% vs. 25.7%, p = 0.004) and high blood pressure (51.4% vs. 17.1%, p = 0.005). In contrast, the prevalence of abdominal obesity and high triglycerides did not differ significantly between the two groups. Analysis of continuous biochemical parameters reinforced these findings. Fasting plasma glucose levels were higher in the NTD group (6.33±1.64 mmol/L vs. 5.96±2.11 mmol/L, p = 0.043). While lipid parameters like triglycerides and HDL-C showed differences in means, they did not reach statistical significance in this analysis. Thyroid function tests indicated that free thyroxine (FT4) was significantly higher in the NTD group (14.10±1.96 pmol/L vs. 12.71±2.40 pmol/L, p = 0.018), whereas free triiodothyronine (FT3) was lower (5.01±0.88 pmol/L vs. 5.42±0.70 pmol/L, p = 0.050). A multiple logistic regression analysis was performed to identify independent factors associated with NTD. After adjusting for all variables, the presence of full metabolic syndrome remained the strongest independent predictor (OR = 5.00, p = 0.001). Among the individual components, systolic blood pressure was a significant independent factor (OR = 0.478, p = 0.019). Thyroid hormones FT3 and FT4 also emerged as significant independent variables in the model.

Table 1: Baseline characteristics of the study participants. (N=70)

Variable	With NTD (n=35) Mean ± SD	Without NTD (n=35) Mean ± SD	p-value
Age (years)	40.90±11.24	34.07±7.96	0.009
Weight (kg)	68.30±9.48	63.20±7.55	0.025
Waist circumference (cm)	90.19±9.52	84.76±8.00	0.020
Systolic BP (mmHg)	124.00±8.65	116.00±6.94	0.020
Diastolic BP (mmHg)	79.00±8.75	73.67±8.50	<0.001

BP: Blood Pressure; Data analyzed using an independent samples t-test

Table 2: Prevalence of metabolic syndrome. (N=70)

Metabolic syndrome	With NTD n (%)	Without NTD n n (%)	p-value
Present	24 (68.57)	14 (40.00)	0.001
Absent	11 (31.43)	21 (60.00)	

Data analyzed using the Chi-square test

Table 3: Prevalence of individual metabolic syndrome components (Categorical). (N=70)

Component	With NTD n (%)	Without NTD n (%)	p-value
Abdominal obesity	24 (68.6)	20 (57.1)	0.458
Impaired fasting glucose	17 (48.6)	9 (25.7)	0.004
High blood pressure	18 (51.4)	6 (17.1)	0.005
High triglycerides	13 (37.1)	13 (37.1)	1.000
Low HDL-C	29 (82.9)	13 (37.1)	0.046

HDL-C: High-Density Lipoprotein Cholesterol; Data analyzed using Chi-square test

Table 4: Comparison of metabolic parameters (Continuous). (N=70)

Parameter	With NTD Mean ± SD	Without NTD Mean ± SD	p-value
Waist circumference (cm)	90.15±9.37	84.76±7.99	0.019
Fasting glucose (mmol/L)	6.33±1.64	5.96±2.11	0.043
Triglycerides (mg/dL)	156.74±100.4	131.73±63.83	0.252
HDL-C (mg/dL)	37.10±6.52	39.07±8.57	0.077

Data analyzed using an independent samples t-test

Table 5: Comparison of thyroid function tests. (N=70)

Hormone	With NTD Mean ± SD	Without NTD Mean ± SD	p-value
TSH (mIU/L)	2.13±1.68	2.30±2.99	0.676
FT3 (pmol/L)	5.01±0.88	5.42±0.70	0.050
FT4 (pmol/L)	14.10±1.96	12.71±2.40	0.018

*TSH: Thyroid-Stimulating Hormone; FT3: Free Triiodothyronine; FT4: Free Thyroxine; Data analyzed using independent samples t-test. *

Table 6: Multiple logistic regression for NTD risk (Anthropometric & Metabolic). (N=70)

Variable	p-value	Odds Ratio (OR)	95% CI for OR
Age (years)	0.037	0.749	0.570 - 0.983
Waist circumference (cm)	0.085	1.188	0.977 - 1.444
Systolic BP (mmHg)	0.019	0.478	0.258 - 0.886
Fasting glucose (mmol/L)	0.965	0.976	0.335 - 2.849
HDL-C (mg/dL)	0.184	1.134	0.942 - 1.364
Metabolic syndrome (Yes)	0.001	5.000	2.475 - 8.600

Dependent variable: Presence of NTD

Table 7: Multiple logistic regression for NTD risk (Including thyroid hormones). (N=70)

Variable	p-value	Odds ratio (OR)	95% CI for OR
FT3 (pmol/L)	0.007	2.150	4.320 - 7.340
FT4 (pmol/L)	0.004	0.385	0.203 - 0.731
Metabolic syndrome (Yes)	0.001	5.000	2.475 - 8.600

Dependent variable: Presence of NTD

Discussion

This study provides a detailed evaluation of the link between individual metabolic syndrome components and nodular thyroid disease, revealing that specific components, particularly low HDL-cholesterol, demonstrate particularly strong associations. Our findings confirm that the prevalence of full metabolic syndrome is significantly higher in patients with NTD compared to controls (68.57% vs. 40.00%), consistent with previous epidemiological studies [7, 14]. However, the novel contribution of this research lies in its dissection of the MetS cluster, which identifies low HDL-C as the most prevalent metabolic abnormality in the NTD group, present in over 82% of patients. The predominance of low HDL-C in our NTD cohort is a noteworthy finding. While often overshadowed by dysglycemia and hypertension in metabolic studies, HDL-C possesses well-documented anti-inflammatory, antioxidant, and anti-apoptotic properties [15, 16]. A deficiency in functional HDL may therefore permit increased oxidative stress within the thyroid gland, creating a microenvironment conducive to cellular proliferation and nodule formation [12, 17]. This finding aligns with emerging research suggesting that low HDL-C is an independent risk factor for benign thyroid nodules, potentially representing a

crucial pathophysiological link [13, 18]. The significant association with hypertension and impaired fasting glucose further supports the involvement of insulin resistance and vascular stress pathways, which can promote growth factor secretion and endothelial dysfunction, contributing to thyroid tissue remodeling [11, 19]. Interestingly, our multivariate analysis presented a nuanced picture. While low HDL-C was highly prevalent in the univariate analysis, its independent effect was attenuated in the regression model when adjusted for other factors, particularly the full MetS diagnosis. This suggests that the risk conveyed by low HDL-C is deeply intertwined with the overall metabolic milieu rather than acting in isolation. In contrast, the presence of full MetS remained the strongest independent predictor of NTD, underscoring the synergistic effect of its components [20]. This synergy likely reflects the amplified state of chronic inflammation and insulin resistance that defines the syndrome. Our analysis of thyroid function revealed subtle alterations, with significantly higher FT4 and lower FT3 levels in the NTD group despite normal TSH. This altered FT3:FT4 ratio may indicate perturbations in peripheral deiodinase activity, possibly influenced by the underlying systemic inflammatory state associated with MetS [21, 22]. Furthermore, both FT3 and FT4 emerged as independent factors in the regression model, suggesting that thyroid hormone homeostasis, even within the euthyroid range, may be intricately linked to nodulogenesis or represent a consequence of the nodular process itself [23]. The limitations of this study include its cross-sectional design, which prevents the establishment of causality. The relatively modest sample size, though sufficient for primary comparisons, may limit the power to detect weaker associations for some components. The single-center recruitment strategy may also affect the generalizability of the findings. This study demonstrates that while metabolic syndrome as a whole is a potent risk factor for nodular thyroid disease, the risk profile is not uniform across its components. Low HDL-C emerged as a particularly prominent abnormality, highlighting the potential role of dyslipidemia-driven oxidative stress in thyroid nodule pathogenesis. These findings suggest that a comprehensive metabolic evaluation, with particular attention to lipid profiles, should be considered in patients presenting with thyroid nodules. Future prospective studies are needed to confirm if low HDL-C is a causal risk factor and to explore the potential benefits of HDL-modifying therapies in the context of NTD prevention.

Limitations

The primary limitations of this study are its cross-sectional design, which precludes causal inference, and the modest sample size from a single center, potentially limiting the generalizability of the findings regarding specific metabolic syndrome components. The sample size was very small due to the COVID-19 situation.

Conclusion

This study demonstrates that specific components of metabolic syndrome, particularly low HDL-cholesterol, exhibit strong individual associations with nodular thyroid disease. While the full syndrome confers the highest risk, dyslipidemia emerges as a prominent factor. These findings underscore the importance of evaluating detailed metabolic profiles, including lipid parameters, in patients with thyroid nodules. Comprehensive management of metabolic health may be crucial for understanding and potentially mitigating the risk of nodular thyroid disease.

Recommendation:

Future large-scale longitudinal studies should investigate the temporal relationship between low HDL-C and nodule development. Clinicians should consider comprehensive metabolic screening, including lipid profiles, in patients with thyroid nodules to enable integrated management of metabolic and thyroid health.

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