The Prevalence of Metabolic Syndrome among Adult Filipinos with Hypothyroidism: A Retrospective Cohort Study

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ABSTRACT

Background and Objectives. Dyslipidemia in hypothyroidism results from the effects of thyroid hormones on lipid metabolism. These, in combination with hypothyroidism-induced hemodynamic changes, are risk factors for cardiometabolic diseases. We determined the prevalence of metabolic syndrome (MS) among adult Filipinos with hypothyroidism and compared clinical and laboratory characteristics of those with versus without MS.

Methods. This is a retrospective study of 105 patients with biochemically confirmed hypothyroidism. A review of records obtained anthropometric measurements, blood pressure, fasting blood glucose, lipid profile, and thyroid hormones. Clinical and laboratory characteristics were then compared between MS and those without. Significant differences were determined by two-way ANOVA, while heterogeneity of categorical variables was determined by chi-square or Fisher exact test. All data analyses were performed using Stata version 17.0 with a significance level of $p<0.05$.

Results. The prevalence of MS is 36.19% (95%CI: 27.04%,46.15%). Body mass index (BMI) peaks at obese class I among those with MS. There is a significantly higher proportion of patients diagnosed to have diabetes (28.95% vs. 7.46%; p=0.003) and hypertension (52.63% vs. 14.93%; $p<0.001$) in the MS group. No significant differences were noted between groups regarding age, sex, etiology of hypothyroidism, blood pressure, fasting glucose, lipid profile, and thyroid hormone levels.

Conclusion. Our study showed that the prevalence of MS in adult Filipinos with hypothyroidism is increased at 36.19%. Only BMI, presence of diabetes, and hypertension were shown to be significantly higher. Emphasis must be placed on early screening among hypothyroid patients at high risk of developing MS. A prospective study using waist circumference and clinical and metabolic parameters is needed to validate these findings.

Keywords: dyslipidemia, hypothyroidism, metabolic syndrome, prevalence

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INTRODUCTION

Thyroid disease is associated with various metabolic abnormalities due to the effects of thyroid hormones on nearly all major metabolic pathways.[1] Thyroid hormones are responsible for regulating basal energy expenditure through their effects on catabolism.[2] Among the common metabolic abnormalities, dyslipidemia in patients with thyroid disease results from the effect of thyroid hormones in almost all aspects of lipid metabolism (synthesis, mobilization, and degradation).[1] This then leads to various lipid alterations, mainly in the total and low-density lipoprotein (LDL) cholesterol levels and less often high-density lipoprotein

(HDL) cholesterol, triglycerides (TG), lipoprotein (a) (LPa), apolipoprotein A1, and apolipoprotein B levels.[3-6]

Overt hypothyroidism affects approximately 3% of the adult female population worldwide.[7] Untreated hypothyroidism results in decreased thyroid hormone action on multiple organs such as the heart, liver, and peripheral vasculature. This state is associated with increased systemic vascular resistance, decreased cardiac contractility, decreased cardiac output, accelerated atherosclerosis, and coronary artery disease resulting from hypercholesterolemia and diastolic hypertension.[7-9] These physiologic changes significantly increase the risk of atherosclerotic cardiovascular disease and stroke.[9] In thyroid disease, dyslipidemia, and the coexisting metabolic abnormalities, in combination with the thyroid hormone-induced hemodynamic alterations, explain the high risk for cardiovascular disease.[7-11] Dyslipidemia is a common finding in patients diagnosed with overt hypothyroidism, consisting mainly of high levels of total and LDL cholesterol.[3-6] A similar trend has also been observed in subclinical hypothyroidism.[4-6] However, data regarding triglycerides, lipoprotein(a) [Lp(a)], HDL, apolipoprotein B (apoB), and apolipoprotein A1 (apoA1) components are scarce, and most studies show either higher or similar levels to euthyroid patients.[3] Of note, the total and LDL cholesterol significantly improves after thyroxine replacement treatment in overt and subclinical hypothyroidism. However, triglycerides, apoB, apoA1, Lp(a) levels, and qualitative abnormalities may normalize or remain unchanged after treatment, suggesting a more complex mechanism of dyslipidemia in hypothyroidism.[5,6] Dyslipidemia seen in hypothyroidism often coexists with other metabolic abnormalities, including hypertension, insulin resistance, and oxidative stress, all risk factors for cardiovascular disease. In addition, dyslipidemia induces insulin resistance and oxidative stress via a vicious cycle.[7-11]

The metabolic syndrome (MS), with a unifying hypothesis and underlying pathophysiology of insulin resistance, has been defined as the presence of at least 3 of the following features: (1) visceral obesity depending on race and sex, (2) raised triglyceride level or specific treatment, (3) reduced HDL cholesterol or specific treatment, (4) raised blood pressure or treatment of previously diagnosed hypertension, and (5) raised fasting plasma glucose, drug treatment or previously diagnosed type 2 diabetes. The threshold criteria vary among definitions suggested by organizations such as the International Diabetes Federation (IDF), the National Cholesterol Education Programme Adult Treatment Panel III (NCEP/ATP III), or the World Health Organization (WHO).[12] The presence of MS increases an individual's risk for atherosclerotic cardiovascular disease (ASCVD), stroke, and diabetes mellitus (DM). In the Philippines, the prevalence of MS ranged from 11.9% by NCEP/ATP III criteria, 14.5% by IDF criteria, and 18.6% by NCEP/ATP III criteria modified by the American Heart Association/National Heart, Lung and Blood Institute (NCEP/ATP III-AHA/NHLBI) criteria.[12]

The overall prevalence of MS in thyroid disease varies depending on the population and type of thyroid disorder. In a study on 112 patients in Nigeria, the overall prevalence of MS was 28%, and the prevalence of hypothyroidism was 40%.[13] Amongst Southeast Asian populations, a study in Nepal on 169 patients with thyroid disease revealed an overall prevalence of 31.9%.[14] A local study in Cebu City, Philippines, in 470 patients with thyroid disease showed that MS had an overall prevalence of 46% in patients with thyroid disease, 40% in hyperthyroidism versus only 6% in hypothyroidism.[15] The prevalence of MS among those with hypothyroidism was even lower than that of the general Filipino population (11.9 – 18.6%).[12] Moreover, our local study only evaluated 31 patients with hypothyroidism which could have led to the underestimation of the true prevalence in this subset of the population.[15] This is in stark contrast with internationally available data as the prevalence of MS ranged from 51.8 (n = 110) – 56.1% (n = 391) in hypothyroid subjects in studies conducted in the United States and Venezuela, respectively.[16,17] Hypothyroidism is characterized as a state of attenuated basal plasma insulin and insulin resistance, which can increase cardiovascular risk, primarily when it is associated with other frequently associated risk factors such as hyperlipidemia and elevated blood pressure.[17,18] Many studies on Asians and research conducted on Asian American populations have shown that the risk of developing diabetes is increased remarkably even at a mean body mass index (BMI) significantly lower than those at defined at-risk BMI levels. There is a gap in the knowledge regarding MS in hypothyroidism in Asians, where we develop diabetes and cardiovascular diseases at much lower BMI.[19,20]

In the Philippines, the Philippine Thyroid Diseases Study (PhilTiDeS 1) showed that thyroid dysfunction was more common among women, with a female to male ratio of 1.6:1.[21] The national prevalence of thyroid function abnormalities is 8.53%, and true hypothyroidism and subclinical hypothyroidism have prevalence rates of 0.41% and 2.18%, respectively. In our thyroid outpatient clinics, most of our patients come from the lower economic spectrum. Most of them have lesser access to necessities and healthcare, which could affect their awareness towards preventive care, cause poorer overall nutritional status, and lower adherence to treatment of hypothyroidism, making them at higher risk of developing MS. However, there is still a lack of data regarding the true prevalence of MS in specific etiologies of hypothyroidism. The generated information from this study will allow us to validate our local analysis, as currently available local data are in stark contrast to international data.[15-17] As hypothyroidism is one of the most common causes of secondary dyslipidemia, international guidelines have recommended screening for hypothyroidism before starting hypolipidemic therapy because increased levels of creatinine kinase in hypothyroidism may substantially increase the risk of developing statin-induced myopathy.[22-23] However, adherence to these guidelines in clinical practice

remains to be investigated.[22-23] There is a lack of explicit local guidance on screening patients for MS among those with hypothyroidism.[24] Data from this study will underscore the need to assess patients for the presence of the MS. Hence, we aimed to determine the prevalence of MS among adult Filipino patients with hypothyroidism seen in our outpatient thyroid clinic. Specifically, we determined and compared the clinical and laboratory characteristics of hypothyroid patients with and without MS stratified by age, sex, BMI, comorbidities, and etiology of hypothyroidism (primary and secondary); we also determined the association between the baseline thyroid function tests (TSH, fT4 or fT3) with the presence of the MS.

MATERIALS AND METHODS

The Research Ethics Board approved the study of the University of the Philippines Manila (UPMREB Code: 2020-605-01) before commencement.

Subjects

A retrospective study of 105 patients diagnosed with hypothyroidism was conducted in our outpatient thyroid clinic at the Philippine General Hospital. A minimum sample size of 86 patients was determined based on the formula

$$n = \frac{Z^2 P (1 - P)}{e^2}$$

where n is the sample size, Z is 1.96, the statistic corresponding to 95% confidence (α of 0.05), P, 6%[15] is the prevalence and e, 0.05 is the assumed error estimate. We reviewed patients who consulted our clinics over ten years, from January 1, 2011, to December 31, 2021. Adult patients who are 19 years old and above were included when they were diagnosed to have any of the following causes of hypothyroidism: (1) autoimmune, (2) post-procedural, (3) subclinical, (4) central, and (5) any of the patients mentioned above from (1) – (4) on glucose-lowering therapy or cholesterol-lowering drugs (i.e., statins, fibrates, nicotinic acid, ezetimibe, fish oil) together with a laboratory result demonstrating biochemically hypothyroid status (high TSH and low fT4 for primary hypothyroidism; normal or low TSH and low fT4 for central or secondary). The bases for the high and low values for both TSH and fT4 were based on values below our institution's reference range of normal values. All patients with the following: patients with active/untreated thyroid malignancies, amiodarone, and drug-induced hyper- or hypothyroidism (except radioactive iodine), and all patients with any of the following comorbidities: chronic liver disease, kidney disease, congestive heart failure, pregnancy, patients on oral contraceptive pills, cancer chemotherapy, and anti-retroviral therapy were excluded from the study. Figure 1 shows a summary of the flowchart.

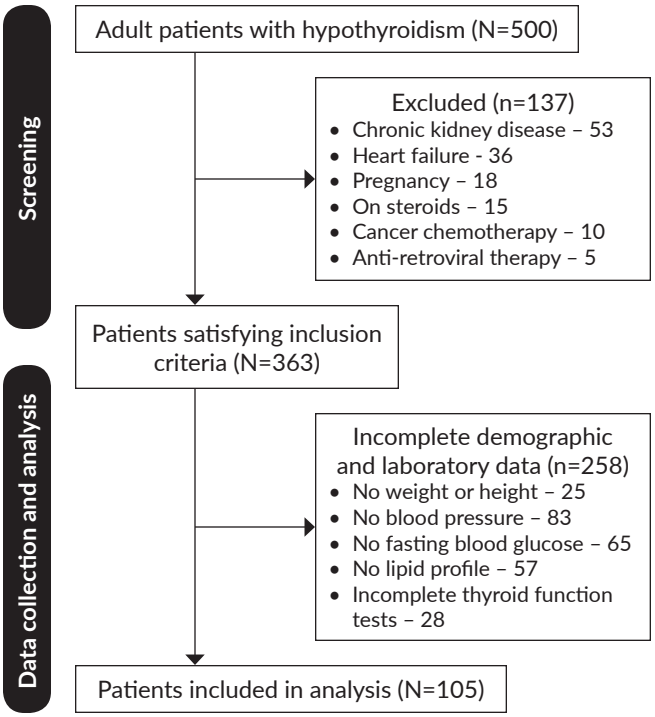

Figure 1. Flowchart of the patient recruitment process.

Data Collection

We obtained demographic data (age, sex, comorbidities – hypertension, DM, myocardial infarction, and stroke), anthropometric measurements (weight, height, and BMI), and blood pressure. We then obtained the following laboratory data from a review of records: A. thyroid stimulating hormone (TSH), B. free thyroxine (fT4) and free triiodothyronine (fT3), D. Fasting blood glucose (FBS), E. Total cholesterol (TC), F. High-density cholesterol (HDL-C), G. Low-density cholesterol (LDL-C), and H. Triglycerides (TG).

Data Analysis

All collected data were encoded, tabulated, and summarized using Microsoft Office Excel 2016. Descriptive statistics summarized clinical and laboratory characteristics of hypothyroid patients. Numerical variables were described as mean and standard deviations (SD) if the data were normally distributed as assessed by the Shapiro-Wilk test for normality and as median and IQR if otherwise. Categorical variables were described as count and proportion. In contrast to the diagnostic criteria for MS using the harmonizing definition, we utilized the WHO Asia-Pacific cut-offs for BMI in place of waist circumference (WC) to identify obesity.[12] In this study, we identified patients to have MS if they satisfy three out of the five criteria below: (a) BMI of more than 25 kg/m^2 in both men and women; (b) triglyceride levels of more than 150 mg/dL or on specific treatment; (c) high-density lipoprotein (HDL-C) levels less than 40 mg/dL (men) or less than 50 mg/dL (women) or on treatment; (d)

systolic blood pressure (SBP) of more than 130 mmHg systolic or diastolic blood pressure (DBP) of more than 85 mmHg, diagnosed to have hypertension or on anti-hypertensive medications; and (e) fasting glucose of more than 100 mg/dL, diagnosed to have type 2 DM or on glucose-lowering therapy. The prevalence estimate of MS among adult patients with hypothyroidism was computed using a 95% confidence interval as the total number of patients satisfying the criteria above for diagnosis divided by the total number of patients enrolled. The different clinical and laboratory characteristics were compared between the two groups: with and without MS. Two-way ANOVA determined significant differences between the two groups to adjust for the variable blocking sex. Heterogeneity of the proportions of the different categorical variables between the two groups was determined by the chi-square test or Fisher exact test. Thyroid function tests were also compared using the same manner. The thyroid function tests and metabolic parameters were also compared among those with MS according to the etiology. All analyses were performed using Stata version 17.0, with a p-value of less than 0.05 considered significant for all tests.

RESULTS

Prevalence of MS in Patients with Hypothyroidism

The baseline characteristics of our patients are summarized in Table 1. There is a male-to-female ratio of 1 to 2 (37:68 patients), and there were no significant differences in age. Patients diagnosed with primary hypothyroidism comprised 85.91% (n = 90) of the population, while the remaining were patients with central or secondary hypothyroidism. Our results showed that the overall prevalence of metabolic among patients with hypothyroidism was 36.19% (95%CI: 27.04%, 46.15%).

Comparison of Clinical and Laboratory Characteristics between Patients with MS versus those without MS

Comparing hypothyroid patients with MS versus those without MS, those with MS have a BMI peak at obese class I (> 25 kg/m^2) while those without MS peak at normal BMI (18 to 22.9 kg/m^2). There is a significantly higher proportion of patients with diabetes (28.95% vs. 7.46%; p = 0.003) and hypertension (52.63% vs. 14.93%; p < 0.001) in the MS group compared to those without (Table 1).

There were no significant differences between those with MS versus those without in terms of age, sex, blood pressure, fasting blood glucose, total cholesterol, high-density lipoprotein levels, low-density lipoprotein levels, non-HDL cholesterol levels, thyroid stimulating hormone levels, free triiodothyronine levels, and free thyroxine levels (Table 2). Further analyses of hypothyroid patients diagnosed with MS did not show any significant differences between thyroid function tests and metabolic parameters versus the etiology of hypothyroidism (Table 3).

DISCUSSION

The prevalence of MS among Filipino adults with hypothyroidism is high at 36.19% (95%CI: 27.04%, 46.15%). Comparing this with available international data, this value falls between data obtained in Nepal at 31.9% (N =169) and

Table 1. Clinical characteristics of patients stratified based on age, sex, waist circumference, BMI, comorbidities, and etiology of hypothyroidism

Characteristics	Overall (n=105)	(+) Metabolic Syndrome (n=38)	(-) Metabolic Syndrome (n=67)	p-value
***Age** (years), n (%)*				0.073
18 - 40	27 (25.71%)	5 (13.16%)	22 (32.84%)	
41 - 60	50 (47.62%)	20 (52.63%)	30 (44.78%)	
≥ 60	28 (26.67%)	13 (34.21%)	15 (22.39%)	
***Sex**, n (%)*				0.554
Female	68 (64.76%)	26 (68.42%)	42 (62.69%)	
Male	37 (35.24%)	12 (31.58%)	25 (37.31%)	
***BMI** (kg/m^2), n (%)*				0.007
< 18.5	5 (4.85%)	1 (2.63%)	4 (6.15%)	
18.5 - 22.9	27 (26.21%)	5 (13.16%)	22 (33.85%)	
23.0 - 24.9	22 (21.36%)	5 (13.16%)	17 (26.15%)	
25.0 - 29.9	40 (38.83%)	21 (55.26%)	19 (29.23%)	
≥ 30.0	9 (8.74%)	6 (15.79%)	3 (4.62%)	
***Comorbidities**, n (%)*				
Diabetes mellitus	16 (15.24%)	11 (28.95%)	5 (7.46%)	0.003
Hypertension	30 (28.57%)	20 (52.63%)	10 (14.93%)	<0.001
Etiology, *n (%)*				0.159
Primary hypothyroidism	90 (85.71%)	35 (92.11%)	55 (82.09%)	
Central hypothyroidism	15 (14.29%)	3 (7.89%)	12 (17.91%)	

Table 2. Comparison of thyroid function tests between hypothyroid patients with and without metabolic syndrome

Thyroid function tests	(+) Metabolic syndrome (n=38)	(-) Metabolic Syndrome (n=67)	p-value
***TSH** (mIU/mL), median (IQR)*	18.08 (45.07)	10.67 (49.06)	0.408
***fT4** (pmol/L), mean (sd)*	9.91 (3.76)	9.88 (4.36)	0.972
***fT3** (pmol), median (IQR)*	2.35 (0.78)	2.30 (0.73)	0.367

Table 3. Clinical and laboratory characteristics of patients with metabolic syndrome and hypothyroidism

	Primary (n=35)	Central (n=3)	p-value
Thyroid Function Tests			
TSH (mIU/mL), *median (IQR)*	22.67 (63.70)	0.47 (0.64)	<0.001
fT4 (pmol/L), *median (IQR)*	9.80 (5.77)	11.12 (4.32)	0.607
fT3 (pmol), *median (IQR)*	2.33 (0.78)	2.79 (1.36)	0.463
Metabolic Parameters			
BMI (kg/m^2), *median (IQR)*	25.86 (4.36)	25.22 (7.90)	0.725
Total cholesterol (mg/dL), *median (IQR)*	198.08 (91.15)	223.45 (137.69)	0.401
LDL_C (mg/dL), *median (IQR)*	117.81 (68.92)	144.23 (113.96)	0.665
Triglycerides (mg/dL), *median (IQR)*	166.36 (117.71)	209.72 (157.52)	0.159
HDL_C (mg/dl), *median (IQR)*	41.70 (14.68)	47.88 (9.83)	0.099
Non-HDL_C (mg/dL), *median (IQR)*	149.40 (67.26)	178.45 (144.64)	0.534
Fasting Blood Glucose (mg/dL), *median (IQR)*	113.99 (35.72)	97.81 (41.07)	0.203
Systolic Blood Pressure (mmHg), *median (IQR)*	130 (40)	110 (10)	0.285
Diastolic Blood Pressure (mmHg), *median (IQR)*	80 (20)	70 (10)	0.574

Nigeria at 40% (N = 112). Still, it is lower than the United States and Venezuela cohorts, where prevalence ranged from 51.8 (N = 110) to 56.1% (N = 391), respectively.[14,16,17] Comparing this to locally available data, our study showed that the prevalence of MS in Filipinos with hypothyroidism is at least 5 to 8 times higher than that obtained from a study conducted locally in Cebu City, where the prevalence was shown to be only 6% in hypothyroid patients (n =31).[15] However, it must be noted that our current locally available data was also retrospective and included other patients with thyroid dysfunction, which may have led to the underestimation of the true prevalence of MS in this subset of patients.

Furthermore, the prevalence of MS is higher than that of the general euthyroid Filipino population at 11.9 to 18.6%.[12] A significantly higher proportion of patients have diabetes and hypertension in the MS group. These findings support studies conducted among Asians and Asian American populations, which have shown that the risk of developing diabetes and metabolic abnormalities is increased remarkably even at a mean BMI significantly lower than those at defined at-risk BMI levels.[19-20]

Most guidelines use WC to measure abdominal obesity, a better predictor of cardiometabolic diseases. In a Polish study, Geirach et al. noted a significant correlation between BMI and WC. The presence of overweight in men (BMI ≥ 25.84 kg/m^2) and normal body weight in women (BMI ≥ 21.62 kg/m^2) corresponds to an increased volume of visceral tissue in the abdomen.[25] In our setting, WC is not routinely measured during consults, and central obesity is mainly based on BMI.[16,25,26] Studies among Asian populations have shown that WC is a better predictor of obesity-related cardiovascular risk factors in both men and women compared to BMI among Filipinos, Malaysians, Cambodians, and Thais.[26-29] Similar findings were reported by Zhu et al. among non-Hispanic blacks, Mexican Americans, and Non-Hispanic whites.[30] Li et al. showed that WC is the essential factor in determining cardiovascular risk compared to BMI.[31] Thus, measuring WC as part of clinic visits and routine care in diagnosing MS is of utmost importance as using BMI may lead to underdiagnosis.

Among hypothyroid patients with MS, there were no significant differences between the etiology of hypothyroidism and associated anthropometric and metabolic parameters. This could be explained by the common final pathway of all types of hypothyroidism. This results in an overall decrease in free thyroxine levels, resulting in similar lipid and metabolic abnormalities.[32-36] Furthermore, we did not identify significant differences between those with MS versus those without in terms of age, sex, blood pressure, fasting blood glucose, total cholesterol, high-density lipoprotein levels, low-density lipoprotein levels, non-HDL cholesterol levels, serum thyroid stimulating hormone levels, free triiodothyronine levels, and free thyroxine levels. This shows that MS is driven mainly by increased BMI, hypertension, and diabetes.[17-20,35,36]

Our study has several limitations. First, the study was retrospective, so the anthropometric measurements and laboratory parameters were not obtained in real-time. Second, only weight, height, and BMI were available since WC is not routinely measured during outpatient clinic visits

and is not adequately documented in the case records. The measurement of WC applying ethnicity and sex-based cut-offs should be performed as part of the diagnostic criteria of MS. Lastly, we were limited in terms of our sample size due to the many patients having incomplete chart records and laboratory results since fasting blood glucose and lipid profile is not part of the standard of care in hypothyroidism. Hence, they were not routinely requested unless the patient had risk factors warranting screening. These limitations above can be new avenues for research by performing a prospective study of patients with hypothyroidism while obtaining real-time anthropometric measurements (weight, height, BMI, and WC) as well as laboratory parameters (fasting blood glucose, lipid profile, and thyroid function tests) in determining the prevalence of MS in this subset of patients. This will also allow us to determine the correlation between WC and BMI in the diagnosis of MS.

CONCLUSION

In summary, our study showed that the prevalence of MS in adult Filipinos with hypothyroidism is consistent with Southeast Asian data, and it is increased at 36% compared to the general population irrespective of the etiology of hypothyroidism age, sex, blood pressure, and metabolic parameters. Only BMI and the presence of diabetes and hypertension were significantly higher among hypothyroid patients with MS. Emphasis must be placed on early screening among hypothyroid patients at high risk of developing MS. A prospective study of patients with hypothyroidism with real-time anthropometric measurements (weight, height, BMI, and WC) and laboratory parameters (fasting blood glucose, lipid profile, and thyroid function tests) is needed to accurately determine the prevalence of MS in this subset of patients.

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Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising, and approved the final version submitted.

Conflict of Interest

All authors have no conflicts of interest to disclose.

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