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Risk of neurally mediated syncope in hypothyroidism and obesity

Riesgo de síncope neuromediado en hipotiroidismo y obesidad

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SUMMARY

Introduction and rationale: *Thyroid hormones participate in several known mechanisms of cardiac function, being compromised in hypothyroidism (HPT), when uncontrolled, it is associated with weight gain. HPT and Obesity participate in autonomic dysfunction. However, there is no information on syncope risk assessment for this association.* **Objective**: *to analyze HPT and euthyroid patients undergoing Tilt test evaluating their relationship with other cardiovascular risk factors on neurally mediated syncope.* **Methodology**: *From a hospital database with 623 patients, selecting 509 cases, evaluated consecutively. The factors include a body mass index (BMI) above 25, HPT, age, sex, diabetes (DM), and hypertension (HT). The type of response was based on the current guidelines. Patients under 18 years, with extreme obesity or BMI <18 were excluded. Chi-square test, T-test, and logistic regression analysis were used, as appropriate.* **Results**: *The mean age was 53.1 ± 20 years, 70 HPT, and 455 euthyroid patients. The presence of positivity of the Tilt test was similar in both groups (60 % vs. 53 %, P= 0.27). As well as the type of response, the mixed response prevailing in both (50 % vs. 46.5 %, P= 0.673). Age, BMI> 25, DM, and HT had no isolated influence on the test positivity. However, there was an influence on the HPT-BMI> 25 association; odds ratio: 2.328 (CI95: 1.107- 4.898, P= 0.026).* **Conclusion**: *The HPT patient presents similar characteristics to the control population in the Tilt test. However, the association of HPT-BMI >25 carries a high risk of neurally mediated syncope.*

Keywords: *Neurally mediated syncope, obesity, hypothyroidism, autonomic function test.*

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RESUMEN

Introducción y fundamento*: Las hormonas tiroideas participan en varios mecanismos conocidos de la función cardíaca, viéndose comprometidos en el hipotiroidismo (HPT), cuando no controlado, se asocia con aumento de peso. HPT y obesidad participan en la disfunción del sistema autónomo. Sin embargo, no existe información sobre el riesgo de síncope para esta asociación.* **Objetivo***: analizar pacientes HPT y eutiroideos evaluando su relación con factores de riesgo cardiovascular en el síncope neuromediado.* **Metodología***: De una base de datos hospitalaria con 623 pacientes, seleccionando 509 casos, evaluados de forma consecutiva. Los factores considerados fueron: índice de masa corporal (IMC) mayor de 25, edad, sexo, diabetes (DM) e hipertensión (HT). El tipo de respuesta fue basado en las guías actuales. Los pacientes menores de 18 años, con obesidad extrema o IMC<18 fueron excluidos.* **Resultados***: la edad media fue 53,1 ±20 años, 70 hipotiroideos y 455 eutiroideos. La presencia de positividad de la prueba fue similar en ambos grupos (60 % vs. 53 %, P= 0,27). Así como el tipo de respuesta, predominando en ambos la respuesta mixta (50 % vs. 46,5 %, P= 0,673). Edad, IMC >25, DM e HT no tuvieron influencia en la positividad de la prueba. Sin embargo, sí hubo influencia en la asociación HPT-IMC >25; odds ratio: 2,328 (CI95: 1,107- 4,898, P= 0,026).* **Conclusión***: El paciente HPT presenta características similares a la población control en el Tilt test. No obstante, la asociación de pacientes HPT-IMC >25 acarrea un alto riesgo de síncope neuromediado.*

Palabras clave: *Síncope mediado neuralmente, obesidad, hipotiroidismo, prueba de función autonómica.*

INTRODUCTION

The thyroid gland through its two hormones exerts many effects on the heart and the cardiovascular system. A gland dysfunction is manifested clinically with weight gain, a consequence of an underactive thyroid and a low basal metabolic rate (1). Otherwise, obesity and thyroid insufficiency are common diseases and can coexist. Studies have shown a higher prevalence of obesity and evident hypothyroidism concerning the subclinical (2), and in some cases, when treated with hormonal therapy, regression of weight gain is observed (3).

The incidence of this disorder has a 3:1 ratio in women when compared to men. This explanation may be related to the direct effects of estrogens on thyroid function. It is known that the presence of estrogen receptors in the thyroid gland acts in two ways; either by genomic transcription or by kinase and phosphatase signaling, with subsequently increased ion flux through the cell membrane (4).

Clinically, the repercussions of hypothyroidism on cardiovascular structure and function include diastolic dysfunction (5), increased arterial stiffness (6), endothelial dysfunction (7), and increased systemic vascular resistance (8). In the conduction system, patients with hypothyroidism manifest autonomic neuropathies with increased vagal tone (9). In addition, we know that hypothyroidism manifests itself with weight gain and this increase may reflect other factors involved in the adequate control of autonomic functions (10), with leptin being one of the most studied molecules, altered in obesity (11) and acts related to the body's energy balance including hypothalamic pathways, which modulate the autonomic response, both sympathetic and parasympathetic.

In this scenario, we study the behavior of autonomic dysfunction in patients submitted to the TILT Test, with emphasis on hypothyroid patients with BMI >25 association.

MATERIAL AND METHOD

This is a cross-sectional, observational, retrospective, single-center study. We evaluated tests referred from patients to perform the tilt table test searching neurally mediated syncope at the San Joaquín Hospital, part of the Beneficencia Portuguesa Hospital of Sao Paulo consecutively in two years and a half coming from a database. A simple questionnaire before the test, to fulfill the database included the following variables for analysis: age, sex, HPT, HT, and DM was collected. The diagnosis of DM was by laboratory examination (fasting glucose levels >126 mg/dL and/or A1C levels above 6.5 %) and/or use of hypoglycemic agents. For HPT diagnosis if TSH levels were above 5mU/L accompany by T4 free levels below five micrograms per deciliter. For

HPT could also count for a confirmed diagnosis if the patient was in the use of thyroid hormone replacement therapy. Unfortunately, we were unable to establish by recent lab result data if the patient had disease control or during how long the diagnosis was made. HT was defined if the patient had blood pressure above 140/90 mmHg or was using antihypertensive drugs. Patients with extreme BMI (<18 or >40) and those with missing data in the questionnaire were excluded. Considered as confounding factors; causes of syncope other than neurally mediated were removed, such as those derived from the cardiac output fall observed in arrhythmias, or patients with syncope due to hypoglycemic episode (metabolic syncope), epilepsy, or psychiatric pseudosyncope. In this way, a final sample of 509 patients was obtained (Figure 1). The test was considered positive following the modified criteria of the VASIS study (12).

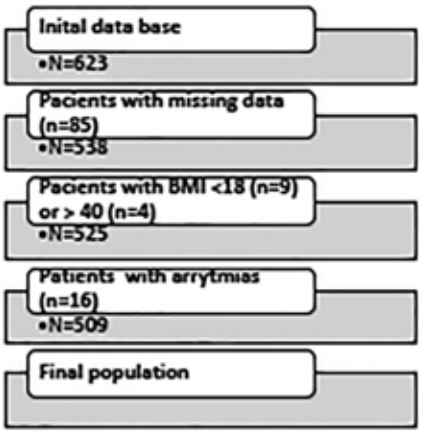

Figure 1. Working flowchart.

Statistical analysis

The a priori sample size calculation was performed using the G * Power program version 3.1.9.7 (Heinrich Heine University, Düsseldorf, Germany) for logistic regression, considering a statistical power of 90 % and an error α= 0.05. The variables were expressed as mean and standard deviation for continuous variables and accounted for as percentages if they were categorical variables. We analyzed categorical variables by the Chi square method and if necessary, using Fisher's correction. The evaluation of the presence of a positive tilt test and the influence of other variables were analyzed using logistic regressions. Data were analyzed using SPSS version 23 (SPSS, Chicago Illinois). All tests were two-tailed.

RESULTS

The final 509 patients had a mean age of 53.1 ± 20 years, 199 (39.1 %) men and 310 (60.9 %) women. Two hundred and seventy-nine patients presented positive test criteria (54.8 %). The most frequent response observed at the tilt test was mixed or type-I (47.7 %), and exception II (asymptomatic postural hypotension) in 20.8 %. The mixed or type I response was similar in hypothyroid and euthyroid (50 vs. 46.5 %, P= 0.673). The prevalence of hypothyroidism in the population was 13.6 % (n = 69) with an average BMI= 26 ± 4. The percentage of positive tests between gender was similar. There was no relationship between the presence of DM or HT, in an isolated manner, with test positivity. However, there was an association with older age in those with a positive test in the univariate analyzes (Table 1).

Table 1

Risk factors and positive Tilt test

	Negative test	Positive test	P
Age (years)	51+19	55+21	0.03
HT	82 (44.1 %)	104 (55.9 %)	0.70
DM	27 (47.4 %)	30 (52.6 %)	0.72
IMC > 25	131 (48.0 %)	142 (58.1 %)	0.17
Gender			
Male	94 (47.2 %)	105 (52.8 %)	0.46
Female	136 (43.9 %)	174 (56.1 %)	

Sixty-nine patients presented hypothyroidism, mostly women, n = 54 (79.3 %) and 15 (21.7 %) were men, P= 0.001. We subsequently evaluated the influence of BMI >25 in hypothyroid patients in the Tilt test (n = 41). In the general population, we found an important association of hypothyroidism and BMI >25 influencing the

presence of neurally mediated syncope (Table 2), deriving an odds ratio: 4.22 (CI95: 1.51-11.75). When analyzed by gender, in univariate analysis, we found a high prevalence of positive tests in hypothyroid women and BM I >25 (22/31 patients in the BMI >25 groups vs. 14/23 in the group with BMI <25, P= 0.019). In the case of males, the small number of cases limited their value; HPT-BMI >25 (8/105) versus (2/92) in the HPT-BMI <25 groups, P= 0.106.

At first, we did not find any association between the selected variables and a positive test in the multivariate analysis (Table 3). However, when joining HPT and BMI> 25, the relationship becomes evident (Table 4), with a risk greater than two times concerning those without the present association of factors.

Table 2

Hypothyroid patients, BMI and Tilt test results

N=69	Negative test	Positive test	P
IMC <25	11 (26.8 %)	17 (73.2 %)	0.005
IMC >25	17 (60.7 %)	11 (39.3 %)	

Table 3

Neurally mediated syncope risk according to multiple factors

	B	Wald	P	Exp(B)	CI95 %	
					Inferior	Superior
Age	-0.015	6.467	0.011	0.986	0.975	0.997
Gender (fem)	0.173	0.843	0.359	1.189	0.822	1.719
HT	-0.168	0.513	0.474	0.845	0.533	1.340
DM	-0.211	0.481	0.488	0.810	0.446	1.470
HPT	0.126	0.213	0.645	1.135	0.663	1.940
BMI >25	-0.279	2.173	0.140	0.757	0.522	1.096
Constant	1.100	3.419	0.064	3.003		

Legend: Exp(B): Beta exponential, CI95 %: confidence interval 95 %. Regarding gender, the female patients (fem) were taken as a reference, for the other variables if they were present. HT: Hypertension, DM: Diabetes, HPT: Hypothyroidism.

Table 4

Syncope risk in patients with hypothyroidism and IMC>25 in relation to other risk factors

	B	Wald	P	Exp(B)	CI95 %	
					Inferior	Superior
Age	-0.014	5.756	0.016	0.986	0.975	0.998
Gender (fem)	0.153	0.665	0.415	1.165	0.807	1.680
HT	-0.277	1.412	0.235	0.758	0.479	1.197
DM	-0.346	1.276	0.259	0.708	0.389	1.289
HPT-BMI >25	0.845	4.963	0.026	2.328	1.107	4.898
Constant	0.170	0.082	0.775	1.186		

Legend: Exp(B): Beta exponential, CI95 %: confidence interval 95 %. Regarding gender, the female patients (fem) were taken as a reference, for the other variables if they were present. HPT-BMI: The presence of hypothyroidism associated with BMI >25, HT: Hypertension, DM: Diabetes.

DISCUSSION

In this work, we found an association between neurally mediated syncope in people with hyperthyroidism and weight gain determined by the cut-off value of the BMI >25. Through the evidence found in the literature, we know how thyroid status influences blood pressure and heart rate, this is through its effect on the cells of the autonomic system responsible for the baroreflex (13).

We observed that between risk factors and tilt test positivity was lack of association with DM or HT. Such phenomenon can be explained by the absence of expressive and detailed information of the patient about their glycemic control or in factors which may influence alteration of the autonomic system, both in diabetic or long-term hypertensive patients where diabetic neuropathy may exist (14,15) or exacerbation of the sympathetic tone in hypertensive patients (16). However, in the latter situation (HT), the causes of syncope are generally attributed to antihypertensive medications (17,18).

Concerning age; It is known that aging alters the function of the vagus nerve (due to several factors which include the variability of blood pressure derived from the increase in oxidative stress and vascular hardening) with subsequent involvement of the baroreceptors, and a decrease in the cholinergic receptor's response (19). In our results, the hypothesis contrast was significant (P-value). However, the magnitude of such difference (confidence interval) was different thus, manifesting a type II or β error (20). We believe that it is a problem related to the sample size and the distribution of the percentiles.

On the other hand, following epidemiological studies, we found a higher prevalence of hypothyroidism in women than in men (21-23). Worth noting, our sample is limited for analysis in the latter group due to its low representation number.

Furthermore, hypothyroidism in women can be explained by several approaches. First, the most potent estrogen produced by the body, 17β-estradiol (E2) has recently been described to affect thyroid function directly, through the alpha and beta estrogen receptors responsible for the transcription of target genes (24), second; by the non-genomic pathways involved in the proliferation of the gland cells by the kinase pathway in the prevention of apoptosis and inducing the cell cycle (25).

In obesity, an alteration of the sensitivity of the baroreceptors was demonstrated in women by up to 50 % (26). Additionally, the authors found an association between hyperinsulinemia (frequent in obesity) and alteration of the receptors in the univariate analysis. This association was also described in another study, where hyperinsulinemia acts on nerve pathways in the hypothalamus that modulate autonomic functions (27). In most cases, leptin levels (altered in obesity) are also involved as an independent predictor of sympathetic activity and parasympathetic decrease, being accused as the mediating mechanisms of cardiovascular health in women and the adverse effects of obesity and stress (28). Thus, there is evidence that favors the presence of this association in higher positive tilt test incidence.

Within the study limitations, we point out that we do not have information on the patients who controlled hypothyroidism with medication, and we only analyzed the presence of it by the previous diagnosis before the test. Therefore, we do not know its influence, although there are recent data on the reversal of arterial stiffness in patients with hormonal dysfunction after treatment with levothyroxine (29) and that such hormone replacement could also modulate the pathways in the hypothalamus responsible for autonomic control if evaluated in future studies.

Other authors mention the autonomic dysfunction reversal by achieving a stable euthyroid state with medications (31,31). Weight gain can be considered a reflection of the state of the thyroid gland and denote a factor in response to the tilt test.

CONCLUSION

The HPT patient presents characteristics similar to the control population in the Tilt test. However, the association of HPT-BMI >25 patients carry a high risk of neurally mediated syncope.

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