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Clinical Research Article

Temperature Differences Between Controlled Primary Hypothyroidism and Healthy Patients: An Exploratory Study

Maria Elena Romero-Ibarguengoitia,[1,2] Arnulfo Garza-Silva,[1,2] Andrea Rivera-Cavazos,[1,2] Devany Paola Morales-Rodriguez,[1,2] Omar Israel González-Peña,[2] Irene Antonieta Barco-Flores,[2] Edgar Manilla-Muñoz,[1] Enrique Villarreal-Leal,[1] and Arnulfo González-Cantú[2,3]

[1]Escuela de Medicina, Vicerrectoría de Ciencias de la Salud, Universidad de Monterrey, 66238 San Pedro Garza García, Nuevo León, Mexico
[2]Research Department, Hospital Clínica Nova de Monterrey, 66450 San Nicolás de los Garza, Nuevo León, Mexico
[3]Endocrinology Department, Hospital Clínica Nova de Monterrey, 66450 San Nicolás de los Garza, Nuevo León, Mexico

Correspondence: Maria Elena Romero-Ibarguengoitia, MD, MSc, PHD, Research Department, Hospital Clínica Nova de Monterrey, Av. del Bosque 139, Cuauhtemoc, Cuauhtemoc, 66450 San Nicolás de los Garza, Nuevo León, Mexico. Email: mromeroi@novaservicios.com.mx; elenaromero83@gmail.com.

Abstract

Introduction: Hypothyroidism is conventionally treated with replacement therapy through levothyroxine (LT4). Despite the improvement in symptoms, cold intolerance persists in some patients. The present study aims to determine whether there is a difference in temperature perception and skin temperature between patients with primary controlled hypothyroidism (PCH) and a group of healthy controls matched for body mass index and age. Secondarily we aimed to determine difference in quality of life.

Methodology: Skin temperature measurements were performed in both groups, both in the central and peripheral regions of the body. In addition, subjects were asked about their perception of temperature in a temperature-controlled room; anthropometric measurements were taken, their quality of life was assessed using the ThyPRO-39, and a thyroid hormone profile was performed.

Results: Eleven patients in the PCH group and 30 patients in the control group were studied. It was found that the group with PCH presented a significantly lower palmar temperature than the control group [mean (SD) of 32.05 (1.79) vs 33.10 (1.30) oC, $P = .046$]. A mediation model showed a direct effect. Temperature perception was equal between groups. The median (interquartile range) of ThyPRO was 8 (5.2) points in the control group vs 21.8 (13.5) in the group of controlled hypothyroidism, $P < .001$.

Discussion: These results suggest that, despite LT4 treatment, patients continue to present abnormalities in thermogenesis-related thermogenesis, and this may be due to a lack of hormonal adaptation to environmental changes and physiological demands, leading to lower body temperatures and increased sensitivity to cold.

Key Words: hypothyroidism, thermogenesis, quality of life

Primary hypothyroidism is a thyroid gland disorder that results in insufficient thyroid hormone production [1]. It is more prevalent in women, and the most frequent cause is Hashimoto's thyroiditis [2, 3]. Patients with hypothyroidism become affected by deficient energy metabolism and impaired thermogenesis, which are seen through the symptoms of weight gain and cold intolerance [4]. Hypothyroidism symptoms tend to be diminished by hormone therapy replacement with levothyroxine (LT4), and it has been previously studied that, with this treatment, energy expenditure can lead to improved metabolism and, as a result, enhanced thermogenesis [5].

Thyroid hormones play a crucial role in regulating various metabolic pathways, which have to do with energy expenditure and thermogenesis, as well as controlling lipid and glucose metabolism [6]. Temperature regulation is a complex physiological process involving heat generation and dissipation to maintain body temperature homeostasis. Its main components are the basal metabolic rate (basal thermogenesis) and facultative thermogenesis. In the thermoneutral zone (approximately 23-33 °C in humans), temperature is maintained by basal metabolism's obligatory thermogenesis, and it should be sufficient to regulate body temperature [7-9]. When ambient temperatures drop below the thermoneutral zone, facultative thermogenesis, involving shivering and nonshivering thermogenesis, comes into play [10].

The main actors of facultative thermogenesis are brown adipose tissue and muscles [11], the first through fatty acid oxidation and the production of the uncoupling protein-1, which allows the uncoupling of oxidative phosphorylation and the generation of heat by operating as a proton carrier, and the latter through an increase of energy expenditure induced by sarcoplasmic and endoplasmic calcium-dependent ATPase (SERCA) that breaks down adenosine triphosphate for calcium cycling and contraction [12-14]. Studies on rat models have demonstrated that thyroid hormones, particularly free

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T3 (FT3), play a crucial role in modulating the hypothalamic-pituitary-thyroid axis setpoint, specifically in the paraventricular and arcuate nuclei, affecting thyroid hormone production [15, 16].

Patients with primary hypothyroidism often report persistent symptoms, including cold intolerance, even after receiving replacement treatment with LT4 [17]. It is important to ascertain whether this perception of cold intolerance is subjective or if there is an actual difference in temperature sensitivity between controlled primary hypothyroidism patients and healthy individuals.

The objective of this study was to examine temperature perception and discern disparities in body temperature between a control group and a group with effectively managed primary hypothyroidism. Our hypothesis is based on the observation that, despite improvements in thermogenesis among controlled hypothyroid patients, a complete return to baseline may not be achieved even with effective patient management.

Materials and Methods

Study Design

This is a cross-sectional exploratory study comprising 2 groups: patients with controlled primary hypothyroidism and a group of healthy subjects matched by age and body mass index (BMI). The study was conducted at Hospital Clinica Nova, a hospital located in northern Mexico. The research adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [18]. Approval for the study was obtained from the local institutional review board (IRB number: 04062019-E-UTIM-CM-CI), and it was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) regarding human experimentation. Informed consent was obtained from each participant, as it was a requirement from local institutional review board.

Setting

Considering that the objective of this study was to investigate the changes in temperature of patients, rigorous measures with a systematic method were followed. This study aimed to ensure protocol uniformity by controlling various variables; for instance, temperature homogeneity was achieved by conducting the study between August and October of both 2022 and 2023 with an outdoor median temperature of 32 °C [interquartile range (IQR) = 8]. All patients were examined in the same designated room, maintained at an ambient temperature with a median of 22.6 °C (IQR = 1) measured with the STEREN brand digital thermometer for indoor/outdoor use (coefficient of variation ± 1,5 °C) (STEREN, Mexico). Patients diagnosed with primary hypothyroidism, who had been under control for their disease at any point over the past 6 months, were invited to participate in the study via the internal medicine and endocrinology consult of the hospital. The control group included family members of outpatients who were randomly invited to participate after applying inclusion criteria.

Selection criteria on patients

The selection criteria included patients from both sexes, ages 18 to 50 years, who had provided a signed informed consent form. Participants were required to have access to medical services at Hospital Clínica Nova or be hospital employees. Additionally, individuals with a BMI ranging from 18.5 to 30 kg/m^2 were eligible. For those within the group with hypothyroidism, regular medication use and controlled TSH levels between 0.4 and 2.5 micro/U/mL were required. Controlled participants were also expected to have had a normal thyroid profile. Exclusion criteria involved individuals who had consumed coffee within 1 hour before the study, those with uncontrolled diabetes mellitus, pregnant individuals, and those with excessive hand sweating, recent infections of any kind, hypothyroidism due to thyroid gland removal, use of T3 thyroid hormone (liothyronine), established conditions affecting hand sensitivity or temperature (neuropathy, Raynaud's phenomenon), heart failure, chronic kidney disease, or cirrhosis. Menopausal individuals, those menstruating at the time of participation, and individuals using medications such as lithium, amiodarone, iodine, interferon-alpha, interleukin-2, thioamides (eg, methimazole), perchlorate, cholestyramine, colestipol, aluminum hydroxide, sucralfate, iron sulfate, carbamazepine, rifampicin, or phenobarbital were also excluded. The exclusion criteria included patients who exhibited alterations in thyroid function tests, specifically with TSH levels falling outside the previously mentioned interval range.

Study Development

The study consists of 4 distinct parts, each with specific procedures as displayed in Fig. 1. Step 1 of the study involved patients entering the examination room, where their medical history was recorded. Patients with a history of numbness, tingling, or pain in their feet or hands were then administered the Leeds assessment of neuropathic symptoms and signs test in Spanish [19]. Those who scored above 12 points in the Leeds test were excluded from the study. Subsequently, the ThyPRO-39 test, validated in Spanish, was applied under the guidance of the research team [20]; the latter was used for measuring the quality of life in the individuals through 39 different items, with higher scores indicating a greater reduction in quality of life. This process required approximately 12 minutes of the patient's time. Step 2 of the assessment consisted of asking the patients to rate their perception of room temperature on a scale from 1 to 7, with 1 representing "cold," 5 "neutral," and 7 "hot." Additionally, anthropometric measurements related to body composition were obtained using the OMRON HBF-514c body composition monitor, and waist circumference was also measured (OMRON, United States). This step took around 3 minutes to complete. After step 2, the patients were in the room for 15 minutes, during which the room had been uninterruptedly closed. The purpose of maintaining the examination room closed and uninterrupted for 15 minutes was to ensure consistent measurements by allowing the system to reach a steady state. In technical terms, this means that the temperature response, referred to as the "reference signal," had reached a relaxed state, as recommended by control theory in dynamic systems [21]. In step 3, temperature readings were taken from various sites on the body at a 10-centimeter distance using the Fluke 62 MAX Infrared thermometer (coefficient of variation ± 1,5 °C) (FLUKE, United States). The areas included the forehead, upper third of the sternum, axillae, and palms of both hands. Three measurements were taken at each site, and the average temperature was recorded. Patients used cotton cloth uniform. Following these assessments, in step 4, a blood sample was collected from each patient for thyroid function tests

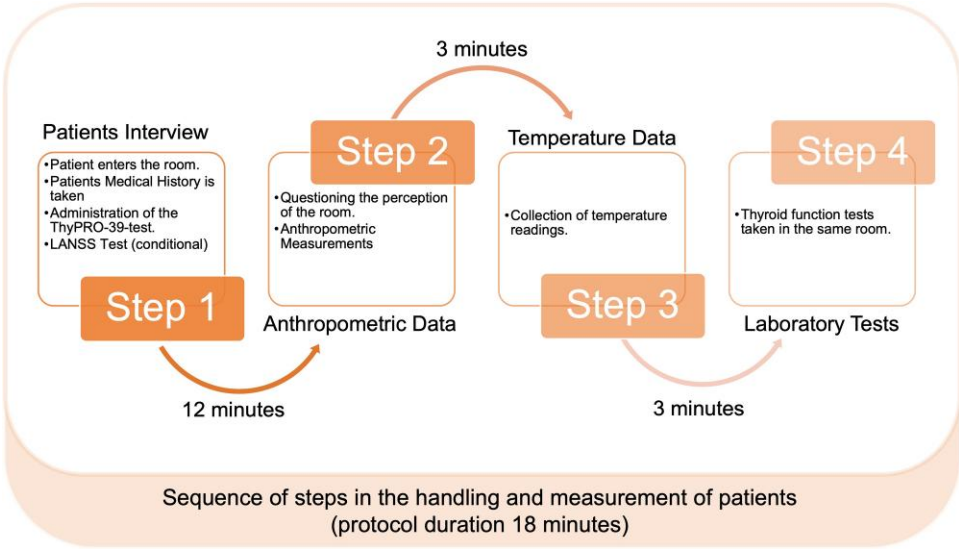

Figure 1. Methodology workflow. Methodology's workflow on the handling and measurement of patients (total length of protocol per patient).

to accurately determine which patients were under control. The atmosphere and room temperature were the same for case and control groups.

Set-up conditions and assumptions on the temperature measurements

In this study, the clinical office was treated as a closed system, characterized by the absence of windows and having only 1 door. The dimensions of the clinical office are 2.69 meters in height, 2.68 meters in length, and 5.43 meters in width. The equilibrium temperature exchange upon the patient's entry into the system is governed by the convection heat transfer equation [22]. Additionally, following Newton's law of cooling or heating, it can be estimated that the relaxation time for temperature measurements does not exceed 10 minutes [23]. Consequently, the temperature measurements obtained are reliable and can be considered causal [21].

Variables

The study analyzed various variables, including age (years), sex, weight (kilograms), height (centimeters), BMI, percentage of total body fat, visceral body fat, muscle mass, and waist circumference (centimeters). Additionally, the results from the ThyPRO-39 questionnaire were considered. Temperature-related data included the perception of room temperature and the average of 3 temperature measurements taken from the forehead, sternum, axilla, and palm. In terms of thyroid function, the study also took into consideration TSH (mLU/L), total T3 (ng/dL], FT3 (pg/mL), T4 (µg/dL), free T4 (FT4; ng/dL), and FT3/FT4 ratio levels with LIAISON XL (DiaSorin, Italy) with a chemiluminescence method.

Statistical analysis

Data was collected on an Excel sheet. Distribution of variables was explored and goodness of fit for normal distribution was assessed through Shapiro–Wilk analysis and histograms. Frequencies and percentages were used for categorical data and mean and standard deviation and median so as interquartile ranges were used for normalized and nonnormalized data, respectively. Independent T-tests were used to compare the 2 groups for the quantitative variables with a normal distribution and for those without normal distribution Mann–Whitney *U* test was utilized. A linear regression where the mean of both hands' palmar temperature was considered as the dependent variable and independent variables included sex, total body fat percentage, and diagnosis of hypothyroidism was also made. A value of $P \leq .05$ was considered significant. Data was analyzed through SPSS version 25.

Results

This study initially involved a total of 64 patients. After applying the selection criteria previously mentioned, the analysis was conducted on 41 patients: 30 from the control group and 11 with controlled primary hypothyroidism. The age distribution was similar between the 2 groups, with the control group having a mean (SD) age of 32.62 (6.16) years and the group with hypothyroidism having an age of 35.36 (6.26) years, $P = .218$. Regarding sex, the control group consisted of 15 (50%) female subjects, while the hypothyroidism group had 10 (90.9%) female subjects, $P = .017$.

Regarding the analyzed anthropometric measurements, there was no difference in BMI between groups, $P = .911$. However, the mean (SD) of total body fat percentage was significantly higher in the hypothyroidism group, 37.1 (4.7%), than in the control group, 32.4 (6.24%), $P = .037$. The visceral fat percentage was significantly higher in the control group, 7.4 (2.36%) vs 5.5 (1.35%), $P = .021$; however, these values are considered normal since they are less than 10%. The mean skeletal muscle percentage was also significantly higher in the control group, 29.86 (5.32%) vs 26.01 (2.34%), $P = .003$. Anthropometric measures and their respective differences between groups are shown in Table 1.

The perceived temperature of patients from the control group and the group with hypothyroidism was not significantly different, $P = .836$. However, when considering the body temperature data of the patients, the palmar temperature was found to be statistically significantly lower in patients

with controlled hypothyroidism with a mean (SD) of 32.05 (1.79) vs 33.10 (1.30) °C, $P = .046$. Additional body temperature measurements can be seen in Fig. 2.

A linear regression model was computed, where the dependent variable was the mean palmar temperature of both hands, and the independent variables involved the percentage of total body fat, sex, and hypothyroidism. Sex did not show a significant influence on palmar temperature. In contrast, the diagnosis of hypothyroidism showed a negative relation ($\beta = -2.061$, $P = .05$), meaning that patients with hypothyroidism had lower palmar temperature in comparison with healthy controls; and the percentage of total body fat a positive relation ($\beta = .259$, $P = .01$); meaning that a higher percentage of total fat was related with higher palmar temperature. The model had an R-squared of 0.206. Visceral fat and muscle percentages, FT4, total T4, and T3/T4 ratio were considered in the initial models but removed for the lack of association.

To test if the effect of hypothyroidism in palmar temperature is mediated by total body fat, we computed a mediation model, showing that that the indirect effect was 0.71 ($P = .12$) and the total effect was −1.6 ($P = .1$), concluding that the effect of hypothyroidism in palmar temperature is not mediated by total fat.

In terms of thyroid hormones, T4 levels were found to be in range in all subjects but significantly higher in patients with controlled hypothyroidism with a mean (SD) of 8.02 (1.66) µg/dL vs 6.84 (1.32) µg/dL, $P = .031$. Similarly, median (IQR) FT4 levels were significantly higher in patients with controlled hypothyroidism 1.20 (0.23) ng/dL vs 0.96 (0.17) ng/dL, $P < .001$, but all in range. The FT3/FT4 ratio values median was significantly lower in patients with controlled hypothyroidism 2.10 (0.39) vs 2.70 (0.65), $P < .001$. The remaining data from the thyroid hormone test can be found in Table 2.

Acknowledging that, with the ThyPRO-39, more points mean poorer quality of life, there was significant differences between the control group, with a median IQR of 8 (5.2) points and the controlled hypothyroidism group with 21.8 (13.5), $P < .001$.

Table 1. Anthropometric measurements

Variable	Group with controlled hypothyroidism (n = 11) Mean (SD)	Control group (n = 30) Mean (SD)	*P*-value
Weight (kg)	68.11 (9.84)	70.12 (11.93)	.621[a]
Height (cm)	165.3 (6.91)	167 (9.25)	.577[a]
BMI	24.9 (2.59)	24.9 (2.22)	.911[a]
Total body fat %	37.1 (4.70)	32.4 (6.24)	.037[a]
Waist circumference (cm)	85.2 (8.96)	84.4 (8.33)	.800[a]
Percentage of visceral fat	5.5 (1.35)	7.4 (2.36)	.021[a]
Percentage of skeletal muscle	26.01 (2.34)	29.86 (5.32)	.003[a]

Abbreviations: BMI, body mass index.
[a]Use of unpaired *t*-test.

Discussion

This study showed significant differences in palmar temperature readings between BMI and age-matched control patients and patients with controlled primary hypothyroidism. The 2 groups had no notable differences in the perceived room temperature. Regarding thyroid hormones, patients with controlled hypothyroidism displayed significantly higher levels of T4 and FT4 and a lower ratio of FT3/FT4. Also, patients with controlled hypothyroidisms presented worse quality of life.

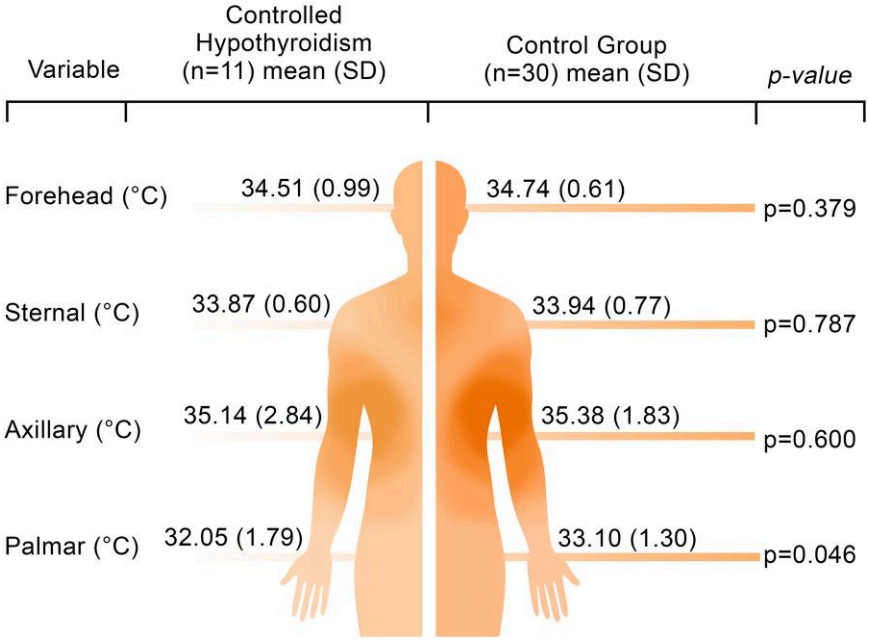

Figure 2. Temperature measurements between patients with controlled hypothyroid vs healthy controls. The figure shows the differences in dermal temperatures of the 2 groups regarding different areas of the body; the *p*-values were obtained through unpaired *t*-test analysis.

Table 2. Thyroid hormone tests

Variable	Group with controlled hypothyroidism (n = 11) Median (IQR)	Control group (n = 30) Median (IQR)	*P*-value
TSH (0.4-4.0)** mlU/L	1.35 (1.78)	1.60 (0.81)	.334[a]
T3 (50.30-123.62)* ng/dL	75.19 (22.21)[b]	82.88 (26.63)[b]	.420[c]
Free T3 (1.68-4.02)* pg/mL	2.47 (0.34)	2.66 (0.48)	.109[a]
T4 (5.37-13.16)* µg/dL	8.02 (1.66)[b]	6.84 (1.32)[b]	*.031*[c]
Free T4 (0.70-1.55)* ng/dL	1.2 (0.23)	0.96 (0.17)	*<.001*[a]
FT3/FT4 ratio (1.52-4.17)*	2.10 (0.39)	2.70 (0.65)	*<.001*[a]

[a]Use of Mann–Whitney *U* test.
[b]Reported in mean (SD).
[c]Use of unpaired *t*-test.
*Normal range values adjusted to Hospital Clínica Nova's local population.
**Normal range value from laboratory reference.

Previous studies analyzing energy expenditure have consistently shown differences in metabolic rates between patients with hypothyroidism and control groups. Most of these studies imply that cold-induced thermogenesis is impaired in patients with primary hypothyroidism, but thermogenesis improves significantly with the restoration of thyroid hormones with LT4 replacement therapy [5, 24, 25]. In this study, the results from the subjects with controlled hypothyroidism revealed no overall significant differences in central body temperature compared to the control group under controlled ambient temperature conditions. However, the patients with controlled hypothyroidism did exhibit a statistically significant lower palmar temperature. In a study by Law et al, where 2 groups of young women were compared—1 group with autoimmune primary hypothyroidism and a control group—it was demonstrated that patients exhibited differences in temperature in a resting state as well as in a cold-induced thermogenesis state [26]. Another study in healthy euthyroid patients indicated a correlation between cold-induced thermogenesis control and FT4 levels, suggesting that variations in thyroid hormone levels within the euthyroid range are related to the capability to adapt to cool temperatures and affect energy balance [27]. These findings imply that, even with controlled hypothyroidism, thermoregulation alterations may occur.

Furthermore, the data from the subjects under study demonstrated no significant difference in temperature perception in a room between the groups of hypothyroidism and control patients. However, 5% to 10% of patients with pharmacologically compensated hypothyroidism are estimated to complain of residual symptoms, including persistent cold intolerance [28]. This study's lack of difference in temperature perception could be attributed to the small sample size.

It must be noticed that humans have a favorable ratio of body surface area to body volume, which makes them less sensitive to changes in ambient temperature by maintaining a more stable internal temperature [29]. The latter suggests there is less temperature loss in central body parts compared to palms, which may explain that though there were lower temperatures overall in patients with hypothyroidism, the palmar temperature was the only one showing statistically significant differences.

It is essential to consider thyroid hormones' physiology and role in central thermoregulation to understand the concept of impaired thermogenesis. Studies on animal models demonstrated that FT3 plays a crucial role in modulating the hypothalamic-pituitary-thyroid axis setpoint, affecting thyroid hormone production and blood levels [15, 16]. Exogenous application of T3 has been shown to activate the sympathetic nervous system outflow and induce hyperthermia at thermoneutrality through thermogenesis from brown adipose tissue (BAT), lipolysis, gluconeogenesis from the liver, and glucose uptake from muscles, contributing to maintaining euthermia [12, 30]. In our study, despite high levels of T4 and FT4, patients displayed a lower FT3/FT4 conversion ratio than the control group, indicating a potential impairment in converting T4 to active T3. This conversion is critical in controlling the hypothalamic-pituitary-thyroid axis setpoint and thermogenesis. A study by Bjerkeim et al also suggested a significant difference in temperature between patients using liothyronine (LT3) therapy compared to LT4, indicating that LT3 might improve cold tolerance in hypothyroid patients [31]. Since hypothyroidism is managed through pharmacological compensation using LT4 replacement therapy and cannot adapt to environmental changes or physiological demands, it is plausible that patients with controlled hypothyroidism may still experience impaired thermogenesis and have difficulties maintaining body temperature. These findings highlight the importance of understanding thyroid hormone regulation in thermoregulation and the potential impact on patient well-being. On the other hand, it is important to recognize that the effects of T3 on vascular smooth muscle cells result in vascular relaxation, which leads to a reduction in systemic vascular resistance [32]. Therefore, if the FT3/FT4 ratio is low, it suggests a limited impact from T3 on these effects. This limited impact could cause an increase in resistance within the arteriole, subsequently reducing blood flow and resulting in a decrease in acral temperature.

Although TSH levels showed no significant differences between the study groups, it is relevant to acknowledge that there remains an area of debate in the literature regarding the connection between TSH and thermogenesis. While some studies conclude that TSH levels improve BAT activation, others suggest no clear link between the 2 [26, 31, 33]. Given that individuals suffering from hypothyroidism have TSH levels within the desired range and receive hormone replacement therapy with a consistent dosage, it is possible that the previously established connection between TSH and thermogenesis may not exert its expected influence.

Regarding body fat percentage, the hypothyroidism group exhibited slightly higher percentage than the control group. Conversely, the control group demonstrated a slightly higher percentage of visceral fat and skeletal muscle. Disturbances in the production of thyroid hormones are known to be responsible for changes in body weight in cases of primary hypothyroidism [34]. After treatment with LT4, patients may experience changes in body composition and weight [35]. However, the specific components of total body weight reduction remain controversial. Previous studies have revealed that the administration of LT4 treatment had no significant impact on total body fat percentage, further adding to the uncertainty

surrounding this issue [35, 36]. Even though our control and case subjects were matched by BMI and had normal values of the thyroid profile range, the case subjects showed higher overall total body fat percentage with lower visceral fat and muscle percentage. This could be explained based on previous studies in patients with pharmacologically compensated hypothyroidism where the standard LT4 therapy did not fully restore the normal metabolic response to carbohydrate ingestion compared to healthy individuals and was shown as a lower resting metabolic rate [37, 38]. Additionally, it is worth noting that the group with controlled hypothyroidism mainly consisted of women, and as has been well established, females generally have a higher proportion of body fat and lower lean mass compared to males; also, the visceral fat percentage is approximately 2 times higher in males [39, 40]. The regression model found that sex did not exhibit statistical significance in predicting palmar temperature, whereas total body fat percentage and hypothyroidism emerged as the primary predictors. These results differ from a prior study that suggested a link between being female, having a higher total body fat percentage, and experiencing elevated temperatures in healthy patients [41]. In this study, it was observed that even though patients with controlled hypothyroidism had a higher percentage of total body fat, which could correlate with higher body temperature, they still had lower palmar temperature. Our mediation analysis supports that there is no effect of percentage of fat in palmar temperature, suggesting that LT4 replacement therapy does not fully restore baseline temperature.

Previous studies have established that patients with treated hypothyroidism experience an improved quality of life compared to the early stages of the disease [42]. However, in the present study, it was observed that patients with controlled hypothyroidism obtained higher scores on the ThyPRO-39 questionnaire than the control group, suggesting that, despite receiving treatment and achieving normal thyroid hormone levels, patients with controlled hypothyroidism may still experience suboptimal quality of life, as indicated in a previous publication [43, 44].

One of the limitations of the present study is that it focused mainly on patients with controlled hypothyroidism under LT4 treatment and healthy individuals, excluding patients with untreated hypothyroidism and hyperthyroidism and those treated for hyperthyroidism. Including the latter groups and patients undergoing dual therapy with LT3/LT4 would provide valuable insights into the impact of thyroid hormone imbalances on thermogenesis. It is also important to acknowledge that multiple mechanisms control facultative nonshivering thermogenesis, such as the sympathetic nervous system and BAT, which should be evaluated from a genetic and molecular perspective. Evidence in humans is still limited. Therefore, it is necessary to conduct additional studies to gain a broader understanding of how thyroid hormones contribute to thermogenesis and whether there are potential factors that influence treatment outcomes in patients with primary hypothyroidism.

Considering control theory as applied to heat transport phenomena [21-23], our calculations indicate that extended exposure of subjects to a constant temperature range (22-24 °C) does not influence mechanisms of adaptive behavior, as the study system achieves a steady-state temperature response. This state facilitates a causal response signal. Nonetheless, future research should consider subjecting individuals to temperatures outside this range (eg, <18 °C or >30 °C) to induce physiological responses such as sweating or shivering.

The importance in the field resides in showing that patients with controlled hypothyroidism do not reach baseline levels of skin temperature readings. Most of previous studies showed that temperature in patients with hypothyroidism improves with LT4 treatment but do not explore comparison to baseline, healthy patients. Further research and exploration of personalized therapeutic approaches may be necessary to optimize the quality of life for individuals living with controlled hypothyroidism, which could contribute to improving patient outcomes.

Conclusion

The results of this study suggest that individuals with controlled primary hypothyroidism displayed a distinct temperature profile compared to the control group, even after accounting for factors such as BMI and age. These findings imply that although LT4 replacement therapy effectively manages hypothyroidism, it might not fully adjust to environmental changes or physiological demands. Consequently, individuals undergoing this treatment might have lower body temperatures and heightened vulnerability to cold exposures.

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Disclosures

The authors have nothing to disclose.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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