

Original Article



The relationship between shift work pattern and thyroid stimulating hormone in female workers

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Abbreviations

BMI: body mass index; CI: confidence interval; GEE: generalized estimation equation; GLM: general linear model; ILO: International Labor

ABSTRACT

Background: Shift work is known to cause changes in the circadian rhythm of the human body and adversely affect not only physical health but also mental health. Some studies have demonstrated the correlation between shift work and thyroid stimulating hormone (TSH), a hormone that changes according to the diurnal rhythm, but few studies have reported the different TSH levels according to the shift work type. This study aimed to investigate changes in TSH according to the shift work type.

Methods: This study included 1,318 female workers who had a medical checkup at a university hospital in Changwon from 2015 to 2019. Shift work types were classified as non-shift work, regular 2 shifts, and irregular three shifts, and a TSH ≥ 4.2 mIU/L was defined as abnormal. A general linear model (GLM) was used to compare the TSH levels and the risk of subclinical hypothyroidism in each year, and a binary logistic analysis was performed using a generalized estimation equation (GEE) to compare the risk of subclinical hypothyroidism over the 5-year period.

Results: Of the 1,318 participants included in this study, 363, 711, and 244 were non-shift, two-shift, and irregular three-shift workers, respectively. In the GEE analysis, after adjusting for age, body mass index, smoking, and alcohol consumption, the odds ratios (ORs) were 1.81 (95% confidence interval [CI]: 1.15–2.86; $p = 0.011$) in 2 shifts and 2.02 (95% CI: 1.23–3.32; $p = 0.006$) in irregular three shifts, compared to non-shift.

Conclusions: Our results showed that shift work had a higher risk of subclinical hypothyroidism than non-shift work and that there was a significant difference in the risk of subclinical hypothyroidism according to the shift work type. These findings suggest that the shift work type can be considered in future thyroid function tests and evaluations.

Keywords: Shift work type; Thyroid-stimulating hormone; Subclinical hypothyroidism

BACKGROUND

According to the International Labor Organization (ILO), shift work is a method of organizing work time in which workers substitute one another at the workplace so that the establishment can operate longer than the work hours of individual workers at different daily and night

Organization; OR: odds ratio; T4: thyroxine; TPO: thyroid peroxidase; TSH: thyroid stimulating hormone.

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Competing interests

The authors declare that they have no competing interests.

Author Contributions

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hours. The National Institute for Occupational Safety and Health defined that the period of 7 a.m. to 6 p.m. is normal standard working hours, and outside of that period is shift work. The sixth Korean Working Conditions Survey applied to 50,538 workers aged at least 15 years showed that 9%–10% of workers were working in shifts.¹ According to the ILO survey, 17% of total workers are working in shifts, but it varies with countries.² As of 2004, approximately 15% of full-time workers in the USA have reported that they perform shift work.²

Shift work adversely impacts workers by changing circadian rhythms in the body, decreasing sleep quality, and disturbing social life.^{2,3} Reportedly, shift work has been known to cause cardiovascular diseases, such as myocardial infarction,^{4,5} and gastrointestinal diseases⁶ or metabolic syndrome,⁴ and increase the risks of breast cancer,⁷ low birth weight babies, and premature deliveries in women.^{8,9} Furthermore, the International Agency for Research on Cancer classified shift work as probably carcinogenic to humans (group 2A).¹⁰ In addition to these physical effects, in terms of mental health, several studies have reported that shift work is associated with increased fatigue and depression due to sleep disturbance.^{11,12} Sleepiness at work due to sleep disturbances can especially be a safety issue for workers.¹³ Sleep disturbances and changed circadian rhythms due to shift work can also affect some hormones. For example, changes in concentrations of prolactin, cortisol, and growth hormone depending on shift work have been reported.^{14,16}

A thyroid stimulating hormone (TSH) test is used to detect thyroid function abnormalities, and TSH levels can change depending on circadian rhythms.^{17,18} Subclinical hypothyroidism, one of the thyroid function diseases, may be associated with an increased risk of cardiovascular diseases¹⁹ and have high risk of progressing to overt hypothyroidism.²⁰ Few studies have investigated the relationship between shift work and thyroid diseases in the past, but more recent studies have been conducted. A study reported that the cycle of circadian variations of the TSH changed in night shift workers.²¹ Furthermore, one study has compared changes in TSH levels by shift work in adult male manufacturing workers.²² Another study has compared the TSH levels and risk of subclinical hypothyroidism over 5 years between nurses working in shifts and staff not working in shifts at a university hospital.²³ However, changes in TSH levels and their association with different types of shift work have not been fully studied. Therefore, our study aimed to investigate the changes in TSH levels by not only comparing shift and non-shift workers but also various types of shift work.

METHODS

Data collection

This study targeted a total of 3,798 female workers under the age of 40 years who started working in a hospital or manufacturing industry company before 2015 and received health checkups at a university hospital in Changwon from 2015 to 2019. A total of 1,318 participants were included in the final analysis. Of 1,318 participants, 547 were received health checkups for 2 years, 392 for 3 years, 213 for 4 years, and 166 for every year. We excluded individuals in whom the test was performed only once, those with a history of thyroid disease, those in whom free thyroxine (T4) level was abnormal, those in whom TSH level was below the lowest value, those who moved to another department of shift work type in 5 years, and those with a missing data. Data on sex, age, height, weight, work type, TSH level, and past diseases were obtained. The normal ranges were defined as 0.80–1.80 ng/dL for the free T4 level and 0.35–4.20 mIU/L for the TSH level. Cobas 8000 e602 (Roche

Diagnostics, Mannheim, Germany) was used for blood test analysis. Age was classified into 2 groups (≤ 29 and 30–39 years), and body mass index (BMI) was classified into 2 groups (normal, $< 25 \text{ kg/m}^2$; obese, $\geq 25 \text{ kg/m}^2$). Smoking, alcohol consumption, exercise, and lifestyle habits were identified. Smoking was classified into 2 categories, smokers and non-smokers (including former smokers), according to current smoking status, and alcohol consumption was defined as ‘non/moderate drinker’ and ‘excessive drinker’ based on twice a week consumption. For exercise, based on the results of the questionnaire, medium- and high-intensity physical activity time was calculated. If < 150 minutes of physical activity during the week were performed, it was defined as ‘lack of physical activity,’ and if strength exercise was performed less than twice a week, it was defined as ‘lack of strength exercise.’ If both were applicable, it was defined as ‘no physical activity.’

Shift work type

Based on the information entered at the time of check-up, the shift work type was classified into three categories: non-shift, regular 2 shifts, and irregular three shifts. The regular 2 shifts were carried out in three groups of 2 shifts, in that the employees work 12 hours daily and take 2 days off after 4 days of work, regardless of weekends. This allows for a 24-hour business operation without a day off. The irregular 3 shifts took the form of changing the working time every day according to the schedule while working 8 hours daily. However, actual working hours are more likely to be higher considering the time required for handover and extra work.

Subclinical hypothyroidism

Subclinical hypothyroidism, one of the thyroid function diseases, is defined when an individual has elevated TSH levels with normal levels of free T4. In the present study, the upper limit of the normal TSH range was set at 4.2 mIU/L, following clinical guidelines for laboratory study.²⁴

Statistical analysis

All statistical analyses were performed using SPSS (version 25.0; IBM Corp., Armonk, NY, USA). A χ^2 test was used to confirm the difference in basic characteristics according to shift work status and type. The general linear model (GLM) was used to analyze annual differences in TSH level according to the type of work by adjusting for age, and annual risk of subclinical hypothyroidism according to the type of work by adjusting for age, BMI, smoking, and alcohol consumption. The generalized estimation equation (GEE) was used to estimate the correlation between work type and TSH level throughout the 5-year period. GEE is an analysis method used when binary data is repeatedly measured. It is not affected by missing values and can be analyzed even when the numbers of observations was different. A binary logistic regression analysis was performed with work type as an independent variable and abnormal TSH level as a dependent variable, adjusting for age, BMI, smoking, and alcohol consumption. TSH level was reported as a categorical variable for the odds ratio (OR) analysis (upper limit of normal: 4.2 mIU/L). The statistical significance level was defined as $p < 0.05$.

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of Samsung Changwon Hospital before implementation (approval No. SCMC 2022-11-015) and waived the requirement for informed consent. This was due to the use of anonymized data that were routinely collected as part of a health checkup program.

RESULTS

We identified the characteristics of 1,318 participants, including 363 non-shift (27.5%), 711 two-shift (53.9%), and 244 irregular three-shift (18.5%) workers (**Table 1**). Among non-shift workers, 57 workers (15.7%) were under the age of 30 years, and 306 workers (84.3%) were in the 30–39 years age group, which showed a very high proportion of participants in the 30–39 years age group. Similarly, the proportion of those in their 30s was higher than those under 30 years of age among shift workers, but the difference was not large compared to non-shift workers. The proportion of obesity, smoking, and excessive alcohol consumption was higher among shift workers than non-shift workers, but in detail, irregular three-shifts workers had lower rates than non-shift workers, and two-shift workers had the highest rates. Physical activity was higher among shift workers, but it was not statistically significant ($p = 0.178$).

The GLM was used to compare average TSH levels every year according to shift work type (**Table 2**). Compared to non-shift work, the average TSH levels were higher in 2 and irregular three shifts. In comparison between shift workers, the average TSH levels were higher in 2 shifts, except for 2018. However, it was not statistically significant.

We also used the GLM to compare risk of subclinical hypothyroidism every year according to shift work type (**Table 3**). Proportion of subclinical hypothyroidism was about 5%–7% and risk of subclinical hypothyroidism was higher in shift work compared to non-shift work

Table 1. Characteristics of study populations according to shift work type

Characteristics	Total	Non-shift group	Shift work		<i>p</i> -value ^a
			Two-shift group	Irregular three-shift group	
Total	1,318 (100.0)	363 (27.5)	711 (53.9)	244 (18.5)	
Age (years)					< 0.001***
≤ 29	495 (37.6)	57 (15.7)	332 (46.7)	106 (43.4)	
30–39	823 (62.4)	306 (84.3)	379 (53.3)	138 (56.6)	
BMI (kg/m ²)					< 0.001***
< 25	1,009 (76.6)	298 (82.1)	494 (69.5)	217 (88.9)	
≥ 25	309 (23.4)	65 (17.9)	217 (30.5)	27 (11.1)	
Smoking					< 0.001***
Non/Former	1,171 (88.8)	356 (98.1)	571 (80.3)	244 (100.0)	
Current	147 (11.2)	7 (1.9)	140 (19.7)	0 (0.0)	
Alcohol consumption					< 0.001***
Non/moderate	1,083 (82.2)	310 (85.4)	546 (76.8)	227 (93.0)	
Excessive	235 (17.8)	53 (14.6)	165 (23.2)	17 (7.0)	
Physical activity					0.178
No	976 (74.1)	280 (77.1)	524 (73.7)	172 (70.5)	
Yes	342 (25.9)	83 (22.9)	187 (26.3)	72 (29.5)	

BMI: body mass index.

^aCalculated using the χ^2 test.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 2. Annual average thyroid stimulating hormone levels according to shift work type in 5 years

Year	Total No.	Non-shift group			Two-shift group			Irregular three-shift group			<i>p</i> -value
		n	Mean	SD	n	Mean	SD	n	Mean	SD	
2015	801	254	1.89	1.01	319	2.16	2.19	228	2.02	1.29	0.199
2016	984	249	1.98	1.30	516	2.32	2.21	219	2.13	1.56	0.167
2017	809	218	1.91	1.10	407	2.14	1.47	184	2.08	1.45	0.105
2018	749	193	2.14	1.32	419	2.26	1.58	137	2.37	1.37	0.275
2019	609	183	2.02	1.25	303	2.43	5.36	123	2.34	1.47	0.339

Analyzed using analysis of covariance (adjusted for age).

SD: standard deviation.

Table 3. Annual risk of subclinical hypothyroidism according to shift work type in 5 years^a

Year	Total No.	SH	Shift work		
			Non-shift group	Two-shift group	Irregular three-shift group
			OR (95% CI) ^b	OR (95% CI) ^b	OR (95% CI) ^b
2015	801	41 (5.1)	2.76 (1.11–6.89)*	2.15 (0.78–5.97)	3.55 (1.36–9.59)*
2016	984	71 (7.2)	2.63 (1.24–5.60)*	2.94 (1.38–6.26)*	2.20 (0.97–5.00)
2017	809	54 (6.7)	1.36 (0.67–2.75)	1.31 (0.63–2.76)	1.41 (0.67–3.00)
2018	749	58 (7.7)	1.69 (0.80–3.60)	1.75 (0.80–3.80)	1.58 (0.66–3.82)
2019	609	45 (7.4)	1.35 (0.62–2.93)	0.94 (0.41–2.18)	2.33 (0.96–5.64)

SH: subclinical hypothyroidism, OR: odds ratio, CI: confidence interval.

^aAdjusted for age, body mass index, smoking, and alcohol consumption.

^bNon-shift was reference in this analysis.

* $p < 0.05$.

Table 4. The relationship between shift work type and subclinical hypothyroidism

Group	Crude		Adjusted model ^a	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Non-shift group	1.00 (reference)		1.00 (reference)	
Two-shift group	1.73 (1.11–2.69)	0.015*	1.81 (1.15–2.86)	0.011*
Irregular three-shift group	1.91 (1.16–3.15)	0.011*	2.02 (1.23–3.32)	0.006**

OR: odds ratio, CI: confidence interval.

^aAdjusted for age, body mass index, smoking, and alcohol consumption.

* $p < 0.05$, ** $p < 0.01$.

except for 2 shifts in 2019. However, it was not statistically significant except for total shift work and irregular three shifts in 2015 and total shift work and two shifts in 2016.

We used the GEE to confirm the relationship between the work type of female workers for 5 years and subclinical hypothyroidism (Table 4). Regardless of whether adjustment was made, subclinical hypothyroidism risk was significantly higher in shift work compared to non-shift work. In the model that adjusted for age, BMI, smoking, and alcohol consumption, the ORs were 1.81 (95% confidence interval [CI]: 1.15–2.86; $p = 0.011$) in the two shifts and 2.02 (95% CI: 1.23–3.32; $p = 0.006$) in the irregular three shifts. Wald test was used as a statistical test ($p = 0.014$).

DISCUSSION

This study retrospectively analyzed data on TSH levels for 5 years. The mean TSH level for 5 years was higher in the shift group compared to the non-shift group. Except for 2018, the two-shift group showed higher TSH levels than the irregular three-shift group, but it was not statistically significant. In that analysis, we adjusted for age because TSH levels are known to increase with age.²⁵ ORs for subclinical hypothyroidism for 5 years with adjusted age, BMI, smoking, and alcohol consumption were significantly higher in the shift group than in the non-shift group. In detail, the two-shift and irregular three-shift groups had 1.81- and 2.02-fold higher risk of subclinical hypothyroidism, respectively.

According to a US report in 2015, irregular shift workers were more likely to experience work-home conflict and work-related stress than regular shift workers.²⁶ Work-related stress is known to be one of the factors causing physical and mental impairment.²⁷ Therefore, we deduced that there are differences in physical and mental impairment according to types of shift work, and classified shift work type into three categories in this study.

TSH is the most widely used indicators to test thyroid function and its levels increase with age.²⁵ The incidence of thyroid diseases has steadily increased in Korea. As of 2018, the

proportion of women who had been treated for hypo- and hyperthyroidism was 5.3- and 2.5-fold higher than that of men, respectively.²⁸ Abnormal TSH levels in women can be caused by an abnormal immune system due to female hormones.²⁹ In a study, a genetic impact on the TSH levels was prominent in women, which can be an influencing factor on the thyroid gland function in women.³⁰

TSH is generally higher during nighttime than daytime.¹⁷ Levels are highest at dawn, but usually lowest in the afternoon.¹⁷ Thyrotropin-releasing hormone, which stimulates TSH secretion, is released by the hypothalamus, and the hypothalamic-pituitary-adrenal axis is known to be related to sleep, suggesting that circadian variations of TSH are associated with sleep.^{18,31} Moreover, some studies have demonstrated an association between sleep disturbances and increased TSH levels.³² Several studies have investigated the association between shift work and thyroid function and diseases. In a cross-sectional study conducted on male adults working in a manufacturing unit in Korea, the TSH levels in the shift group were significantly higher than in the non-shift group, and the OR for subclinical hypothyroidism was 2.81.²² A 5-year comparative study of nurses working in shifts versus non-shifts at a university hospital showed results similar to a cross-sectional study of male adults, who had undergone health screening at a health examination center, and their ORs (1.40 and 1.99, respectively) were statistically significant.^{23,33} Meta-analyses conducted in Italy and China also showed similar results.^{34,35} However, a 9-year retrospective cohort study of individuals, who had undergone health screening at a Taiwanese hospital, did not demonstrate a significant association between work shift and subclinical hypothyroidism (hazard ratio: 0.52).³⁶

The prevalence of subclinical hypothyroidism was 4%–15% in the entire population and 20% in older adults (aged at least 60 years) and women, but its prevalence varied with studies.³⁷⁻³⁹ Subclinical hypothyroidism progresses to overt hypothyroidism in approximately 2%–5% of cases annually and 25%–50% of cases within 20 years in the presence of anti-thyroid peroxidase (TPO) antibodies, and patients with TSH levels between 3.0 and 4.5 mIU/L should be monitored regularly because they are considered at risk even in the absence of anti-TPO antibodies.^{20,40} Clinical guidelines recommend initiation of medication in patients with TSH levels > 10 mIU/L, and management of patients with a TSH level of 4.5–10 mIU/L is still controversial.⁴¹⁻⁴³

Based on results, shift workers are at higher risk of developing subclinical hypothyroidism compared to non-shift workers due to several reasons. First, a circadian variation of the TSH level is more likely to be influenced by the types of shift work. TSH levels peak between 2 and 4 a.m. and decrease to their lowest levels between 4 and 8 p.m.¹⁷ This result may arise from an assumption that workers get normal sleep at night. Some studies reported that sleep affects a circadian variation of the TSH level, and sleep deprivation of night shift workers increases the chances of elevating the TSH level.⁴⁴ Accordingly, circadian variation of sleep, insufficient sleep, and poor sleep quality due to shift work can cause abnormal circadian variations of TSH levels.

Second, a study reported that shift work affects women's circadian rhythm resulting in changes in female hormones, reproductive organs, and menstruation cycle.⁴⁵⁻⁴⁷ Estrogen is a well-known hormone that affects thyroid function²⁹ and can be more sensitive to hormone changes related to night shift work affecting the TSH levels in women.

Third, shift workers are more likely to eat during the night and have irregular eating habits. These habits can affect hormone levels, including TSH levels.⁴⁸

Fourth, changes in circadian rhythm due to shift work affect not only hormones but also the immune system, resulting in an increased risk for autoimmune disease.^{49,50} In other words, shift work can increase the chances of developing autoimmune hypothyroidism. Since we did not perform a test that identifies auto-antibodies, we were unable to verify whether changes in TSH levels were induced by a disorder of the immune system. However, we hypothesized that it can be one of the factors that significantly increase TSH levels.

Additionally, in cases of regular shift work, employees experienced physical and mental difficulties due to changes in lifestyle, including circadian rhythm and sleep, initially after their work shifts changed. However, once their working hours became consistent and their circadian rhythm and lifestyle became regular, their hormone variations, including TSH, became steady. Contrastingly, in cases of irregular shift work, employees are more likely to experience persistent physical and mental difficulties due to continuous changes in circadian rhythm and lifestyle. Moreover, when considering that irregular shift workers experience more stress that affects the immune system,^{26,50} they have an increasingly higher chance of developing autoimmune hypothyroidism.

Although this study was not designed to identify the causal factors that lead to the increased risk of subclinical hypothyroidism among shift workers, we assume that the risk of subclinical hypothyroidism can increase in shift work, especially in irregular shift work, compared to non-shift work.

This study had several limitations. First, data on workers' employment history, the number of workers in each team, rotation days of one cycle in each team, exact working hours, and differences in work intensity by the working department were not obtained. Second, in addition to occupational history, data on workers' eating habit and immune status that may affect workers' TSH were not obtained. Future research should be conducted to investigate the occupational history, eating habit and immune status of workers to complement them. Third, extrapolating the results to the larger population is difficult because this study only included 2 types of shifts. Fourth, since blood samples were collected at different times, the impacts of circadian rhythm on TSH were not controlled for. However, this study has advantages in that this is the first large-scale study in Korea comparing the association between subclinical hypothyroidism and shift work types, not only overall non-shift and shift works.

CONCLUSIONS

In this study, we found that the annual mean TSH levels and the annual risk of subclinical hypothyroidism were not significantly different between each type of shift work, but the risk level of subclinical hypothyroidism was significantly higher in the shift group than in the non-shift group for 5 years. Among workers in the shift group, the risk level was higher in the irregular three-shift group than in the regular two-shift group. This supports the results of previous studies, and each shift type showed different risk levels. At this point, we expect that shift types can be fully considered when testing and evaluating thyroid function in shift workers. However, since the study had limitations for generalizing the results, additional studies should be conducted to overcome these limitations.

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