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Circadian Rhythm of Oral Temperature in Adult Hyperthyroids, Sudan

Ishag Ibrahim Gumma Sheriff[1,2*] and Hamid Gad Elmoula Mohamed Salim[3]

[1]Physiology Unit, Department of Laboratories, Faculty of Medical Technology, Aljufra University, Houn, Libya.
[2]Department of Physiology, Faculty of Medicine, Alfashir University, Alfashir, Sudan.
[3]Department of Physiology, Faculty of Medicine, Khartoum University, Khartoum, Sudan.

Authors' contributions

This work was carried out in collaboration between both authors. Author IIGS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author HGEMS instructed & supervised the entire work. Both authors read and approved the final paper.

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ABSTRACT

Introduction: A 24 hours long cyclic change in body temperature, ie. body temperature circadian rhythm is used as a marker of other body circadian rhythms.
Objectives: To determine circadian rhythm in oral temperature of adult hyperthyroids at Nyala and Alfashir- western cities, Sudan.
Study Design: A descriptive cross-sectional of stratified random sampling.
Place and Duration of Study: Department of Physiology, Faculty of Medicine, Gezira University, Wadmadani, Sudan, from December 2006 to March 2007.
Methodology: A sample of thirty clinically diagnosed thyrotoxic cases (females = 29, and a male) of age ranging from 18 to 50 years, attended to Sudanese atomic energy corporation (SAEC) for receiving positively confirmed laboratory tests were enrolled to conduct this study. Early morning and late evening oral temperatures were recorded by the mercury-in-glass thermometer. A questionnaire was used to exclude any other fever conditions. Thyroid hormones, ie. T_3, T_4, and TSH levels were measured by radioimmunoassay (RIA) at SAEC of Nyala with reference ranges

*Corresponding author: E-mail: ishagalsheriff@gmail.com;

0.4 - 4.4 mIU/L, 0.69 - 2.02 nmol/L, and 50 - 150 nmol/L for TSH, T_3, and T_4 respectively. Subjects of T_3 and T_4 values above reference ranges with TSH below reference were considered hyperthyroid. The obtained data were analyzed statistically by the statistical package for the social science programme (SPSS), ie. T-test.

Results: Mean oral temperature and circadian rhythm were found to be 37.25 ± 0.34ºC and 0.43 ± 0.30ºC respectively. The effect of sex on mean oral temperature was statistically significant ($p = 0.01$), whereas age did not show any statistical effect ($p = 0.36$).

Conclusion: The decreased oral temperature circadian rhythm of thyrotoxic patients, confirms that other body functions also abnormally affected when body temperature circadian rhythm is abnormal.

Keywords: Circadian rhythm; oral temperature; hyperthyroid patients; adult Sudanese.

1. INTRODUCTION

Almost all plants and animals show cyclic variations in many of their functions. There are cycles of many different durations, but the most prominent are those about 24 hours long, the circadian or diurnal rhythms. In animals and humans, the circadian fluctuations in body temperature, adrenocortical functions, Na^+ and K^+ excretion, and urine volume are among the best known, there are many others. Although a detailed discussion of these rhythms except body temperature is out the scope of this study, it is pertinent that the "biologic clocks" controlling some of them are located in the limbic system. Abnormalities of sleep-wakefulness cycles and body temperature cycles without hypothermia (below 35ºC) or hyperthermia (above 37ºC) have been reported after limbic lesions [1].

There are only minor circadian rhythms among thyroid hormones [2]. Immunoassays for total thyroxine (TT_4), free T_4 (FT_4), total triiodothyronine (TT_3), free T_3 (FT_3) and thyroid-stimulating hormone (TSH) are widely available, and measurements may be made at any time [3].

In this study, the investigator aims to establish the value of circadian rhythm in body temperature orally by using mercury-in-glass thermometers on hyperthyroid subjects of ages from 18 to 50 years at Al-Fashir & Nyala cities, Sudan. A descriptive cross-sectional study is designed for data collection.

Mean morning, mean evening, and the general mean oral temperatures are measured before estimating diurnal variation in body temperature for all subjects under the study. A questionnaire is used to exclude individuals having febrile diseases or any fever-inducing causes. Diurnal variation in oral temperature is expected to be lower in hyperthyroid patients, because of the sustained increase in their body temperatures due to continual increase in basal metabolic rate (BMR). But its magnitude depends on physiological (e.g. age, gender, time of day and season of the year) and pathological (e.g. fever) factors [4].

1.1 Body Temperature

The measurement of body heat is a measure of the body's ability to generate and get rid of heat. The body is very accurate in keeping its temperature within a narrow and safe range in spite of large variations in environmental temperatures. When body temperature increases, the blood vessels in the skin expand (dilate) to carry the excess heat to the skin's surface. A person may begin to sweat, and the sweat evaporates to cool the body. When the person is exposed to cold temperature, his blood vessels narrow (constrict) so that blood flow to his skin is reduced to conserve body heat. He may start shivering, which is an involuntary and rapid contraction of muscles. This extra muscle activity helps generate more heat. Under normal conditions, this keeps the temperature within a narrow and safe range [5].

1.1.1 Some normal values of oral temperature

In the late 19th century Wunderlich et al measured axillary temperature in healthy adults between 36.2 and 37.5ºC, with 37ºC as the mean temperature and people accepted this as" normal" body temperature [6]. But now people found that Wunderlich's thermometers were 1.4 to 2.2ºC higher than today's thermometers [7]. More recent studies measured mean body temperature in healthy subjects aged 18 - 40 years around 36.8ºC [8] and 36.86ºC in subjects aged 64 years and older [9]. No single core temperature level can be considered to be normal, because measurements in many normal people have shown a range of normal temperatures measured orally, from less than 97ºF (36ºC) to over 99.5ºF (37.5ºC). The average normal core temperature is generally considered to be between 98.0ºF and 98.6ºF when measured orally. It remains almost exactly constant, with ±1°F (± 0.6ºC), day in and day out except when a person develops a febrile illness [10]. Body temperature rises about half an hour after meals and reaches is peak after about 1.5 hours; whereas a slight rise (0.2 – 0.3ºC) occurs at the time of ovulation. In homoeothermic animals, the actual temperature at which the body is maintained varies from species to species and a lesser degree from individual to individual. In humans, the traditional normal value for oral temperature is 37ºC, with a standard deviation of 0.2ºC. Therefore, 95% of all young adults would be expected to have a morning oral temperature of 36.3 – 37.1ºC (97.8 – 98.8ºF); mean ± 1.96 standard deviation, some normal adults chronically have a temperature above the normal range (constitutional hyperthermia) [11]. Elderly people (61-71 years) have temperature distribution with peaks close to 36.5ºC and 35.8ºC [12]. Measurement of body temperature is used in the following situations [5]:

- Detecting abnormally low body temperature (hypothermia) in people who have been exposed to cold.
- Detecting abnormally high body temperature (hyperthermia) in people who have been exposed to heat or having a fever.
- Monitoring the effectiveness of fever-reducing medications.
- Planning pregnancy by determining if a woman is ovulating.
- Making a differential diagnosis in a doubtful case of thyrotoxicosis, it is significant if the patient is not losing weight, and does not suffer from increased appetite.

1.2 Regulation of Human Body Temperature

Heat is produced and lost by the following processes [13]:

1.2.1 Heat production

Heat is produced by:

- Ingestion of food.
- Contraction of skeletal muscles.
- Hormonal secretion, epinephrine and thyroid hormones.
- Brown fat, in infants.

1.2.2 Heat loss

The processes of heat loss are:

- Conduction: heat exchange between objects or subjects.
- Convection: the movement of molecules away from the area of contact.
- Radiation: transfer of heat by infrared radiation from one object to another at different temperatures, with which is not in contact.
- Vaporization of water in sweat and through respiration.
- Small amounts of heat are lost in the urine and faeces.

1.3 Altered Temperature

Disturbances in heat-regulating mechanisms will cause a low body temperature or a high body temperature.

1.3.1 Fever

In most adults, oral temperature above 100ºF (37ºC) is considered a fever, which is almost universally known as a hallmark of disease [11] or a characteristic increase in core body temperature by 1 – 4ºC due to infection [14]. Fever may occur as a reaction to:

- Infection. This is the most common cause of fever, infections may affect the whole body or a specific body part (localized infection).
- Medications, such as antibiotics, narcotics, barbiturates, antihistamines, and many others. These are called drug fevers. Some medications such as antibiotics raise the body temperature directly; others interfere with the body's ability to readjust its temperature when other factors cause it to rise.
- Severe trauma or injury, such as a heart attack and stroke, heat exhaustion or heat stroke, or burns.
- Other medical conditions such as hyperthyroidism.

1.4 Some of the Factors Affecting Normal Body Temperature

Most people think of "normal" body temperature as an oral temperature of 98.6ºF (37ºC). This is not always so, but depends on several variables as [5]:

1.4.1 Diurnal variation

The normal body temperature undergoes a regular circadian fluctuation of 0.5 – 0.7ºC. In individuals who sleep at night and are awake during the day (even when hospitalized at bed rest), it is lowest at about 6:00 AM and highest in the evenings. It is lowest during sleep, is slightly higher in the awake but relaxed state, and rises with activity [11]. The circadian pattern of oral temperature rises by 0.3ºC from 09h00 to 23h00 in both young and elderly subjects, and significantly falls to about 0.4ºC (elderly) and about 0.8ºC (young) during the night and 03h00. The stability of the circadian body temperature rhythm comes about because of the large endogenous components it possesses [12].

1.4.2 Age

Elderly nursing home patients have lower mean temperatures than healthy young adults (0.2ºC). There is a decrement in normal resting body temperature with age, it might imply that ability temperature control in elderly subjects could involve a resetting, or change of gain of the central nervous control of thermoregulation [12]. Old aged women (61 – 105 years) have a mean oral temperature of 36ºC, which is significantly lower than what would be expected in a younger population [15]. Whereas oral temperature in 65 – 80 years old women ranges from 35.9 – 36.8ºC with the group mean amplitude of 0.3ºC, resulting in an average peak difference of 0.58ºC [16]. Young adults have a higher mesor (36 – 38ºC) than in older subjects (36.17ºC), with decrease amplitude in elderly subjects. The mean circadian rhythm is similar in both age groups [17].

1.4.3 Gender

Thermoregulation of core body temperature is influenced by gender in addition to other physiological factors [4]. For example, after heat stress a woman will have higher skin temperatures and lower sweat rates than men, but when subjects were matched for body fatness, heat storage and tolerance time, there was no difference between genders [18]. Some gender-related differences caused by hormonal differences, body water regulation, exercise capacity [19]. Some studies found no significant gender-related differences among elderly white men and women [9].

1.5 Thermometers

Thermometers, which are instruments for measuring body temperature calibrated in either degrees Fahrenheit (ºF) or degrees Celsius (ºC), depending on the custom of the region. Thermometers in the USA are often measured in degrees Fahrenheit, but the standard in most other countries in degrees Centigrade (ºC). The equations of converting Centigrade and Fahrenheit scales and corresponding Centigrade measurements for common reported Fahrenheit temperatures are as follows [5]:

> C = 5/9 (ºF – 32); F = (9/5×ºC) + 32; e.g. 40ºC = 104ºF, 37ºC = 98.6ºF, and 35ºC = 95ºF.

1.6 Overview of Thyroid Anatomy

The two lobes of the human thyroid gland are connected by a bridge of tissue, the thyroid isthmus, and there is sometimes a pyramidal lobe arising from the isthmus in front of the larynx. The gland has one of the highest blood flow per gram of any organ in the body. Peripheral hormones secreted by the thyroid gland are T_4 and T_3 [11].

1.6.1 Synthesis, normal levels, functions of thyroid hormones

In study carried by [20], showed synthesis and utilization of the thyroid hormones as follows:

- Iodides in the blood-derived from the dietary intake are absorbed by the thyroid gland.
- The iodide in the gland is oxidized and combined with tyrosine derivatives to form T_3 and T_4.
- The T_3 and T_4 are combined with protein and stored in the gland as thyroglobulin.
- Under the influence of the pituitary hormones, T_3 and T_4 are released in the free form and secreted into the bloodstream.
- In the plasma, the hormones combine with certain proteins and are carried to the various organs and tissues of the body where they are released from the binding proteins and perform their metabolic effects. [11], stated the normal total T_4 in the adults is approximately 8 µg/dL (103 nmol/L) and the plasma T_3 level is approximately 0.15 µg/dL (2.3 nmol/L). Large amounts of both bound to plasma proteins, and they are measured by

radioimmunoassay. The free thyroid hormones in the plasma are in equilibrium with the protein-bound thyroid hormones in the plasma and tissues. Free thyroid hormones are added to the circulating pool by the thyroid. It is the free hormones in plasma that are physiologically active and that inhibit TSH. The function of protein binding appears to be the maintenance of a large pool of readily available free hormones. Also, at least for T_3, hormone-binding protein prevents excess uptake by the first cells encountered and promotes uniform tissue distribution.

The following is a list of some physiological effects of thyroid hormones in different target tissues:

• **Heart:** Thyroid hormones increase the number of β-adrenergic receptors, enhance response to circulatory catecholamines, and increasing proportion of a myosin heavy chain (with higher ATPase activity) resulting in chronotropic and inotropic effects.

• **Adipose tissue and Muscle:** the hormones have a catabolic effect by stimulating lipolysis and increasing protein breakdown respectively.

• **Bone and Nervous system:** the hormones have a developmental effect by promoting normal growth and skeletal development, and promoting normal brain development.

• **Gut and Lipoprotein:** the hormones have a metabolic effect by increasing the rate of carbohydrate absorption and formation of low-density lipoprotein (LDL) (this lowers plasma cholesterol level) receptors.

• **Others:** thyroid hormones have a calorigenic effect by stimulating O_2 consumption and by increasing metabolic rate.

• **Cellular effects of T_3** [21]**:** T_3 affects practically every cell in the body and therefore is a powerful orchestrator of metabolism in the whole organism. The hormone has a potent overall effect on metabolism, although the mechanism of this effect is far from clear. Recent evidence suggests that T_3 affects mitochondrial protein called uncoupling protein-3, increasing metabolic rate by decreasing the efficiency of metabolism. After being actively transported into the cell, T_3 binds to nuclear receptors and alters gene transcription.

Different receptors for T_3 occur in different tissues – this all lurks perpetually in the nucleus, waiting for T_3 to come along and bind. T_4 can bind these receptors, but only has one-tenth of the affinity. There are two distinct thyroid hormone receptor genes TR alpha, and TR beta. Alternative splicing results in four products (TR alpha 1 and 2, TR beta 1 and 2; the alpha 2 form is inactive). Mutations in the ligand-binding pocket of the receptor account for most cases of the rare syndromes of resistance to the actions of thyroid hormones.

The nuclear effects of T_3 are now fairly well characterized. The combination of receptor and T_3 binds to a thyroxine response element (TRE) on DNA, and gene transcription is then altered (decreased or increased). Genes with TREs include:

- Growth hormone.
- Osteocalcin.
- Myosin alpha chains.
- Malic enzyme.
- TSH.
- T_3 receptor gene (!).
- … and many more.

In the absence of T_3, the T_3 receptor may still bind DNA, but have opposite (inhibitory) effects! There may be a 270 KDa 'coreceptor' protein that mediates these inhibitory effects. Things become even more complex, because T_3 receptors may complex with other nuclear receptors (to form heterodimers), for example with retinoic acid receptors! T_3 also has extranuclear ("non-genomic") effects. Extranuclear T_3 receptors occur in:

1. Mitochondria – increased activity of mitochondrial adenine nucleotide translocase, apparently unrelated to gene transcription effects;
2. Ribosomes; and the
3. Plasmalemma.

1.6.2 General guidelines for laboratories and physicians

- Laboratories should store (at 4 – 8ºC) all serum specimens used for thyroid testing for at least one week after the results have been reported to allow physicians time to order additional tests.
- Specimens from differentiated thyroid cancer patients (DTC) sent for serum thyroglobulin measurement should be

achieved (at -20ºC) for a minimum of six months.

1.6.3 Hyperthyroidism and its symptoms

In most patients with hyperthyroidism (Toxic goitre, thyrotoxicosis, and Graves' disease), the thyroid gland is increased to two to three times normal size, with tremendous hyperplasia and infolding of the follicular cell lining into the follicles, so the number of cells is increased greatly. Also, each cell increases its rate of secretion several folds; radioactive iodine uptake studies indicated that some of these hyperplastic glands secrete thyroid hormone at rates 5 to 15 times normal. The changes in the thyroid gland in most instances are similar to those caused by excessive TSH. However, plasma TSH concentrations are less than normal rather than enhanced in all patients and often are essentially zero. However, other substances that have actions similar to those of TSH are found in the blood of most patients. These substances are immunoglobulin antibodies that bind with the same membrane receptors that bind TSH. They include continual activation of cAMP system of the cells, with resultant development of hyperthyroidism. These antibodies are called thyroid-stimulating immunoglobulins (TSI) and occur as a result of autoimmunity that develops against thyroid tissue. From the preceding discussion of thyroid physiology, the symptoms of hyperthyroidism are:

- A high state of excitability.
- Intolerance to heat.
- Increased sweating.
- Mild to extreme weight loss (sometimes as much as 100 pounds).
- Varying degrees of diarrhoea.
- Muscle weakness.
- Nervous or other psychic disorders.
- Extreme fatigue but the inability to sleep.
- Tremor of the hands.
- Rapid heart rate.
- Decreased concentration.
- Pretibial myxedema (lumpy, reddish-coloured thickening of the skin, usually on the chins).
- Shortness of breath [22].

1.6.4 Physiology of hyperthyroidism treatment

The most direct treatment for hyperthyroidism is surgical removal of most of the thyroid gland. In general, it is desirable to prepare the patient for surgical operation by administering propylthiouracil for several weeks, until his basal metabolic rate returns normally. Then, the administration of high concentrations of iodides for 1 to 2 weeks to recede gland's size and to diminish its blood supply. Using these preoperative procedures decreased operative mortality from 1 in 1000 in better hospitals to 1 in 25 patients [10].

2. MATERIALS AND METHODS

2.1 Materials

Ethical clearance & informed consent of national and respondents were obtained. The study design was a descriptive cross-sectional with stratified randomized sampling. Thirty hyperthyroid Sudanese of both sexes and age ranging from 18 – 50 years were enrolled. The patients were classified as hyperthyroid immediately after being diagnosed clinically, which was confirmed by laboratory tests obtained from Sudanese atomic energy corporation (SAEC) for serum T_3, T_4, and thyroid-stimulating hormone (TSH) levels before taking any treatment. The laboratory normally considers physiological levels of the three hormones as 0.4 – 4.4 mu/L, 0.69 – 2.02 nmol/L, and 50 – 150 nmol/L for TSH, T_3, and T_4 respectively. Thus, patients of high values of T_3 and T_4 above their maximal borders with TSH values less than minimal levels were considered hyperthyroid. In some cases, T_4 is in its normal range, but T_3 level is abnormally high, i.e., T_3 thyrotoxicosis [1]. Glass thermometer used for its safety and easy use; cotton and disinfectants were used; a technician and a volunteer helped in data collection and analysis.

2.2 Methodology

Because of study nature that focusing on diurnal variation in body temperature, two temperature readings (07:00 – 09:00 AM & 7:00 – 9:00 PM) were taken from the hyperthyroid patients who were examined individually and oral temperature measured randomly based on a questionnaire. The questionnaire included personal data (name, sex, age, serial number, and address), a question whether subjects contracted one of the febrile diseases (malaria, tonsillitis, stomatitis, chest and wound infections, food poisoning, urinary tract and diarrheal diseases as well as any acute state that tends to raise body temperature) within the last week. Also, people were asked whether smoked, chewed gum, ingested hot or cold liquid within the previous 30 minutes. The questionnaire questioned whether the case was a hyperthyroid or not, and this point was confirmed by the laboratory tests obtained. Finally, the researcher asked female respondents about the onset of their menstrual cycles to exclude those who were at the ovulating time. Oral method which is the most common way of taking a temperature [5]; advised at least 20 – 30 minutes waiting after smoking, eating, or drinking a hot or cold liquid before taking a temperature; if vigorous exercise or a hot bath were performed, the temperature measurements should be taken after an hour. The sequential procedures were made as follows: taking the thermometer out of its holder and held by the end opposite the colored (red, blue) tip; cleaning the thermometer with powder soap and warm water; thermometer was turned in a hand and checked well until it read less than 96°F; with opened mouth, the end with red & blue put under the tongue and lips were closed gently around the thermometer without biting the glass; the thermometer then removed without touching its tip & held at eye level with slowly turning it until silver-coated long mark on the thermometer seen; finally, again the thermometer washed with soap and warm water.

2.3 Data Analysis Method

The obtained data were statistically analyzed by using statistical package for social science programme (SPSS). Software statistical analysis (T-test) was performed considering mean body temperature and its diurnal variation as dependent variables; whereas sex, age, and time of temperature measurement were considered independent variables. The data were represented as mean ±1 SD. The relation between mean body temperature and variables was considered significant only when probability equals or less than 0.05 ($P \leq 0.05$).

3. RESULTS AND DISCUSSION

3.1 The Mean Oral Temperature and Circadian Rhythm among Hyperthyroid Patients

The mean oral temperature and circadian rhythm among the hyperthyroids was 37.25 ± 0.34°C, and 0.43 ± 0.30°C respectively as well as their standard deviations (SD) (Table 1).

3.2 The Relation between Mean Oral Temperature and Circadian Rhythm in Different Hyperthyroid Groups

The hyperthyroid patients grouped and then the relationship between a magnitude of circadian and mean oral temperatures was as in (Table 2).

3.3 Effect of Age on Mean Oral Temperature of Hyperthyroid Patients

The patients more than 30 to 40 years showed the highest mean oral temperature of 37.40ºC as in (Fig. 1). The probability of correlation was found to be 0.36 with a correlation coefficient of 0.18, so no relation recorded between the two variables ($P>0.05$).

The experiment showed mean oral temperature and circadian values among hyperthyroid individuals as 37.25 ± 0.34ºC; and 0.43 ± 0.30ºC respectively. The obtained mean oral temperature among the hyperthyroid patients is higher than values of healthy subjects studied by [8, 9, 10, 11, 12 ,5] as 36.8ºC; 36.86ºC; 36.7 – 37ºC; 37 ± 0.2ºC; 36.5ºC; & 35.8ºC respectively. Thus, results reflect a febrile condition that normally exceeds 37ºC as stated by both

Table 1. Relation of mean oral temperature to circadian rhythm among the hyperthyroid patients

Mean (X)			Circadian rhythm
Morning	**Evening**	**Whole day**	
37.04 ± 0.42ºC	37.46 ± 0.31ºC	37.25 ± 0.34ºC	0.43 ± 0.30ºC

**Mean circadian value in hyperthyroids ranges from 0.13 – 0.73ºC*

Table 2. A comparison between the mean oral temperature and circadian rhythm among three hyperthyroid groups

Group	Mean (X)	Diurnal variation
T_3 hyperthyroid	37.13ºC	0.54ºC
Total hyperthyroid	37.25ºC	0.43ºC
Non-T_3 hyperthyroid	37.28ºC	0.40ºC

**The highest body temperature group (ie. 37.28ºC) records the lowest circadian difference (ie. 0.40ºC) and the vice is versa*

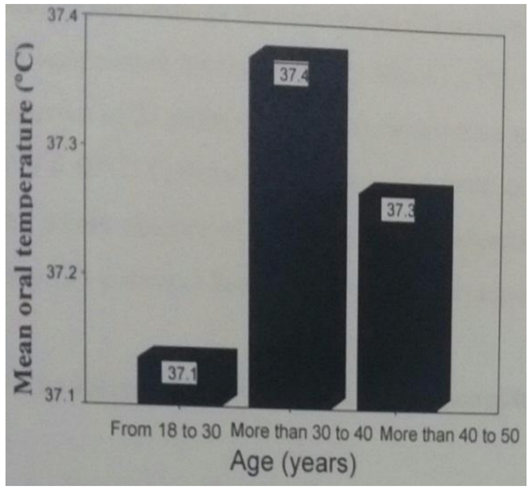

Fig. 1. Effect of age on the mean oral temperature of hyperthyroid patients
**Middle age patients (more than 30 to 40 years) highly affected; therefore, record higher temperatures (ie. 37.40°C) and then inversely low circadian rhythms (Table 2)*

[11] and [10]. This fever is one of the persisting signs of the hyperthyroidism and it is due to increased BMR caused by high levels of thyroid hormones. On the other hand, a lower circadian rhythm in hyperthyroids when compared to some normal subjects in the study foundation noted by [11 &12] as 0.5 – 0.7ºC; & 0.3 – 0.8ºC in respect. We believe that this is due to the continual elevation of temperature in hyperthyroids that minimizes the differences (i.e. circadian rhythms). The study neglected gender effect on oral temperature circadian rhythm for its invalidity due to unmatched categorization of the study population (30 patients), i.e. only one man toward the majority of 29 females. Age showed no statistical effect on hyperthyroid in spite of high record among patients of 30 to 40 years as in (Fig. 1) indicating the fact that the disease affects this period of age.

4. CONCLUSION

In the context of circadian rhythm screening among hyperthyroid patients in Sudan, this study has provided empirical data on circadian change cut-point which can support the decisions on further medical understanding and evaluation of the disease. In our research work, the obtained mean oral and diurnal temperatures among the hyperthyroid patients were 37.25 ± 0.34ºC; and 0.43 ± 0.30ºC respectively. A magnitude of body temperature reversely related to circadian rhythm magnitude, which is seen in hyperthyroids who have low diurnal change with high body temperature (Table 2). It is worth noting that usually, the disease has higher incidence rate in females, but age did not show the statistical effect on temperature circadian rhythm in spite of higher values in the age of 30 to 40 years. Alterations in body temperature circadian rhythm indicate deviations in normal body functions, e.g., limbic system and thyroid gland, so worth noting to raise the awareness of medical professionals and publics about the necessity of measuring this parameter.

CONSENT

All authors declare that informed consent was obtained from the volunteer patients orally after obtaining ethical clearance from the local health department, Northern Darfur, Sudan.

ETHICAL APPROVAL

All procedures performed in the study were following the obtained national ethical clearance standards.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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