ORIGINAL PAPER

The Role of Thermal Camera in the Assessment of Thyroid Eye Disease Activity

Ante Prpic[1], Armin Kasumovic[1], Idoia Goñi Guarro[1], Ines Matoc[1], Gorana Mirosevic[2], Ognjen Zrinscak[1], Renata Ivekovic[1], Ivanka Petric Vickovic[1], Valentina Lacmanovic Loncar[1], Zoran Vatavuk[1], Ivan Sabol[3]

[1]Department of Ophthalmology, University Hospital Center Sestre Milosrdnice, Zagreb, Croatia

[2]Clinic for Thyroid Diseases at the Department of Endocrinology, Diabetes and Metabolic Diseases "Mladen Sekso", University Hospital Center Sestre Milosrdnice, Zagreb, Croatia

[3]Division of Molecular Medicine, Rudjer Bosković Institute, Zagreb, Croatia

Corresponding author: Ante Prpic, MD, Department of Ophthalmology, University Hospital Center Sestre Milosrdnice Address: Vinogradska cesta 29, 10 000, Zagreb, Croatia. Phone: +013787354. E-mail address:ap.prpic@gmail.com. ORCID ID: https://orcid.org/0000-0002-0662-9198.

doi: 10.5455/aim.2023.31.260-264
ACTA INFORM MED. 2023, 31(4): 260-264
Received: NOV 05, 2023
Accepted: DEC 18, 2023

ABSTRACT

Background: Thyroid eye disease (TED; also known as thyroid - associated orbitopathy, Graves ophthalmopathy) is an autoimmune inflammatory disease which presents in typical signs and symptoms such as deep orbital pain, chemosis with or without caruncular edema, unilateral or bilateral proptosis, eyelid retraction, eyelid edema or erythema, restrictive strabismus and compressive optic neuropathy. **Objective:** The aim of this study was to investigate the role of thermal camera in the assessment of thyroid eye disease (TED) activity compared to the Clinical Activity Score (CAS) scale, exophthalmometry values, and thyroid hormone and antibody levels. **Methods:** A total of 50 patients participated in this cross-sectional study of whom 29 were in the active phase of TED according to the sum on CAS scale and 21 patients in the inactive phase. The Flir E8® thermal camera was used to measure the temperature of the orbital area and the values were compared with the CAS scale, exophthalmometry values and thyroid hormone and antibody levels. **Results:** Higher values of temperature (p>0.0001), CAS score (p>0.0001), exophthalmometry (p=0.022), FT4 (p=0.0176) and TRAb (p=0.0091) were found in patients in the active phase of TED. Temperature of orbital area showed statistically significant positive correlation with CAS scale (p=0.0001), exophthalmometry values (p=0.0022) and anti-TPO levels (p=0.019). **Conclusion:** Thermal camera showed higher values of the temperature of the orbital area in patients in the active phase of the disease and positively correlated with the CAS scale, exophthalmometry findings and anti-TPO levels.

Keywords: Clinical Activity Score, exophthalmometry, thermal camera, thyroid eye disease, thyroid hormones and antibodies.

1. BACKGROUND

Thyroid eye disease (TED; also known as thyroid - associated orbitopathy, Graves ophthalmopathy) is an autoimmune inflammatory disease which presents in typical signs and symptoms such as deep orbital pain, chemosis with or without caruncular edema, unilateral or bilateral proptosis, eyelid retraction, eyelid edema or erythema, restrictive strabismus and compressive optic neuropathy. It occurs mostly in patients with Graves hyperthyroidism or Hashimoto thyreoiditis and profoundly affects the patients and their quality of life (1). The disease starts with an active phase plateau which is followed by an inactive ''burn-out'' phase. The active phase usually lasts one year in patients who are not cigarette smokers and two to three years in patients who smoke as they also have about two times greater odds for developing TED (2). Orbital fibroblasts play an active role in the inflammatory process as they express CD40 receptors which are usually found on B cells (3). The treatment of TED usually starts with high-dose corticosteroids or other immuno-suppressive drugs in an active phase of the disease while surgical approach is more suitable in an inactive phase (4,5). Thyroid hormone levels are not sufficient for the diagnosis of TED because the systemic disease is mostly discordant from the eye disease. Most frequently thyroid antibodies such as anti-TPO, TgAt and TRAb are used in the clinical work although some studies have shown that TRAb has no correla-

tion with CAS and degree of severity of clinical-based and CT scan-based TED (6,7,8). Clinical Activity Score (CAS) scale is usually used for the evaluation of clinical features. It consists of 7 signs and symptoms and their sum score of 3 or more defines the active phase of TED. In the follow-up examination after 1 to 3 months 3 more features are added and the active phase of the disease is considered if 4 out of 10 features are found (9,10). CAS scoring is very subjective and it highly depends on the examiner and it also doesn't predict the severity and activity of the disease. For this reason, other methods are needed to objectify TED. In clinical practice MRI is most often used, and ultrasound and scintigraphy are used less often but still as a method of choice (11,12,13). However, not all of these methods are practical in everyday clinical practice because they are expensive, expose patients to radiation, or require a professional to perform and read them. Thermography is increasingly used in medicine to assess the condition of various diseases, most often of inflammatory etiology (14). So far, many studies have been published in which the thermal camera has proven to be a reliable tool in screening various diseases such as rheumatoid arthritis, idiopathic restless legs syndrome, arterio-venous fistulas, etc (15,16,17). Some studies used thermography to assess the response of patients with thyroid eye disease to methylprednisolone pulse therapy with encouraging results (18,19). The thermal camera works on the principle of infrared thermography and it can measure infrared radiation from 1 to 14 μm. It is a non-contact, non-invasive, portable and hygienically and epidemiologically safe tool regardless of the external conditions of the measurement. However, its disadvantages are motion artifacts and uncertainty and accuracy depending on different physiological systems (20,21).

2. OBJECTIVE

The aim of this study was to investigate the role of thermal camera in the assessment of thyroid eye disease (TED) activity compared to the CAS scale, exophthalmometry values, and thyroid hormone and antibody levels and compare the results with the current studies.

3. MATERIAL AND METHODS

This was a prospective cross - sectional study conducted at a tertiary referral center. All patients were treated at the Clinic for Thyroid Diseases at the Department of Endocrinology, Diabetes and Metabolic Diseases "Mladen Sekso" and the Clinic for Ophthalmology at the Clinical Hospital Center "Sestre milosrdnice" in Zagreb between January 2022 and May 2022. A total of 50 patients participated in the study, 7 male and 43 female adults who were in the age range between 19 and 80 years old with the mean age of 55.38 (in inactive TED group mean age was 58.24 and in active TED group was 53.31). Male-female ratio was around 1:5 which is the actual prevalence of this disease found in the current literature. We used 3 on the CAS scale out of 7 to divide patients into two groups, 21 patients were classified in the inactive disease phase and 29 as active. The inclusion criteria for the study were confirmed diagnosis of Graves' disease or thyroid-associated ophthalmopathy, stable disease course determined by a consistent history of symptoms and a stable treatment regimen for at least 6 months prior to the study, no history of previous orbital or eyelid surgery, radiation therapy, orbital infection or inflammation, and orbital tumors or other space-occupying lesions in the orbit. The exclusion criteria were significant comorbidities, such as uncontrolled diabetes or cardiovascular disease, patients who are currently undergoing treatment with corticosteroids or other immunosuppressive medications, and pregnancy or breastfeeding. Two patients had no thyroid treatment, two were treated with selenium (200 mcg), 6 with methimazole (minimum dosage was 10 mg, maximum 25 mg), and 40 with levothyroxine (minimum dosage was 25 mcg, maximum 175 mcg). None of the patients had any current or previous treatment for TED as all of the patients were measured when they were first referred to an ophthalmologist for any TED treatments or when they were referred for a treatment by an ophthalmologist subspecialist. Twenty-two patients were smokers and twenty-eight were non-smokers. All patients were asked to sit in the waiting area after arriving at least 30 minutes and to avoid facial cosmetics, smoking or caffeine. Imaging was performed in the same room with the room temperature of 18°C. This room was designed for optimally controlled and stable room temperature, with minimal differences and all patients were acclimatized in the room for at least 10 minutes before imaging. A Flir E8® thermal camera (Teledyne FLIR, Wilsonville, OR, USA) was used to acquire thermal images of the orbital area. The thermal camera was powered up for at least 1 h prior to imaging. Multiple thermal images were recorded over a period of no longer than 2 minutes as the patient was still, with eyes closed and in the absence of excessive lacrimation. The distance between the camera and patient was 40 centimeters and the same in all imaging. From all the recorded images only the ones with the best quality were selected for the analysis. For each eye on the thermogram, 3 anatomical regions were identified as illustrated in Figure 1: (a) medial part of upper eyelid, (b) middle of upper eyelid, and (c) lateral part of upper eyelid. Figure 1 also shows the difference in temperatures in a patient with inactive TED and a patient with active TED. In addition to thermal imaging, CAS Mourits scale and MW9500 exophthalmometry was obtained on the same day by the same examiner, a third year resident of ophthalmology. Thyroid hormone and antibody levels were obtained in the period of less than a week after thermal imaging and clinical examinations. All patients did thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4), thyroglobulin antibody (TgAt), thyroid peroxidase antibody (anti-TPO), thyrotropin receptor antibody (TRAb). The study was conducted in accordance with the principles of the Helsinki Declaration as revised in 2013 and good research practices and all appropriate processes have been followed. Informed patient/participant consent was obtained during the research and was approved by the Ethics Committee of the institution where the study was conducted (The Ethics Committee of the University Hospital Center Sestre milosrdnice, Zagreb, Croatia). Data was collected in MS Excel tables and analysed in Medcalc software (v20.214, MedCalc Software Ltd, Ostend, Belgium). The statistical analysis was performed by blinded observers. Normality of the data was evaluated by Kolmogorov-Smirnov test. Numerical variables for patients with or without TED were compared by t-test or Mann-Whitney test

	Inactive TED		Active TED			
	mean	SD	mean	SD	diff	Pvalue
MOD /°C	35.1	0.8	36.3	0.7	1.2	<0.0001
MOS /°C	35.1	0.9	36.4	0.8	1.3	<0.0001
MiOD /°C	34.6	1.1	36.1	0.8	1.6	<0.0001
MiOS /°C	34.8	0.9	36.0	0.9	1.2	0.0001
LOD /°C	34.2	0.9	35.7	0.9	1.5	<0.0001
LOS /°C	34.5	0.9	35.6	1.0	1.1	0.0005

Table 1. Measured temperatures of both eyes and groups: MOD (medial part of upper eyelid of the right eye), MiOD (middle of upper eyelid of the right eye), LOD (lateral part of upper eyelid of the right eye), MOS (medial part of upper eyelid of the left eye), MiOS (middle of upper eyelid of the left eye), LOS (lateral part of upper eyelid of the left eye).

depending on the normality of data. Categorical variables were assessed by Chi-square test. Correlations were examined by Spearman rank correlation coefficient. Receiver Operating Characteristic (ROC) curve analysis was performed to find the cut-off for measured temperature which best discriminates patients with active TED.

4. RESULTS

No statistically significant difference between patients with or without active TED was found for age or gender. Patients in the inactive group had mean CAS of 0.38 while patients in the active group had 3.41 and a statistically significant difference was found (t-test, p<0.0001). All clinical signs/ symptoms of CAS between

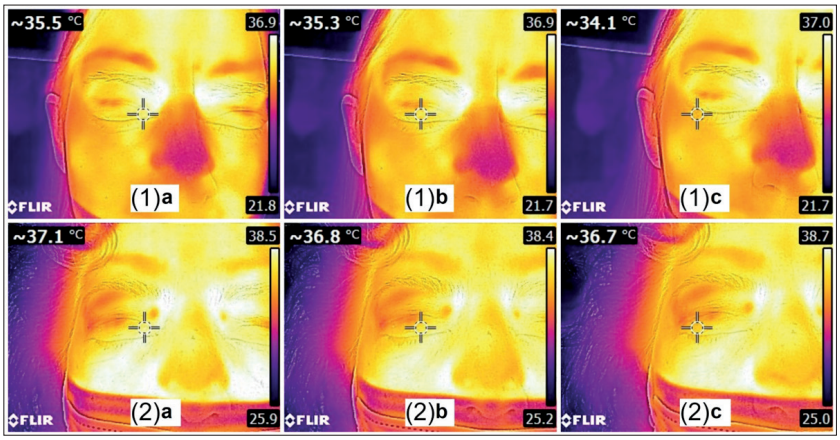

Figure 1.. Example thermal images of the right eye from (1) a patient with inactive TED and (2) a patient with active TED. The thermal images of the patient with active TED (2) show increased temperature of the orbital and periorbital area compared to the patient with inactive TED (1). Anatomical regions of interest: (a) medial part of upper eyelid, (b) middle of upper eyelid, and (c) lateral part of upper eyelid.

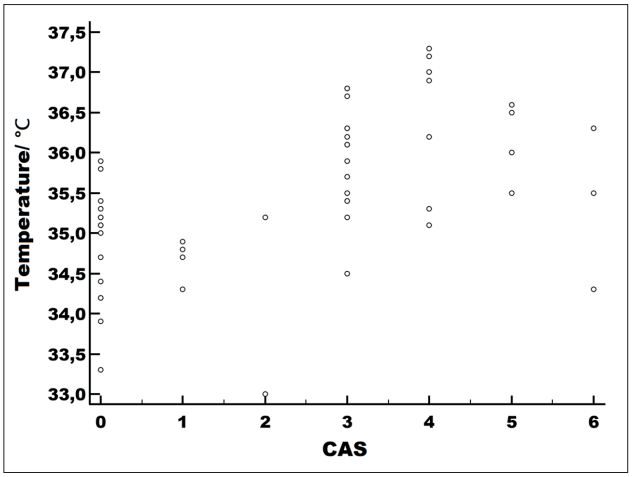

Figure 2. Spearman's correlation graph shows correlation between temperature and CAS.

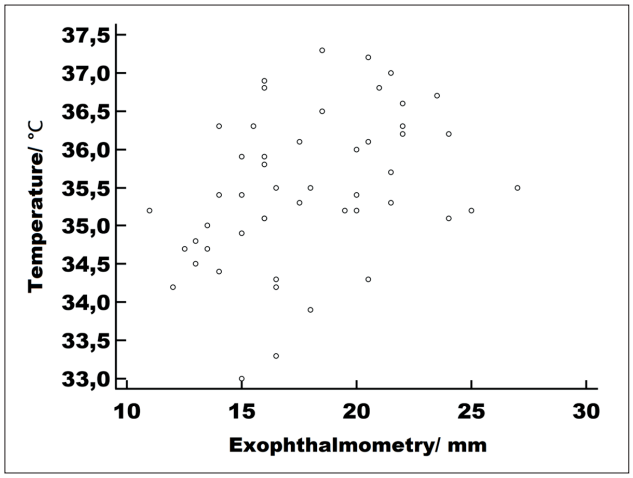

Figure 3. Spearman's correlation graph shows correlation between temperature and exophthalmometry.

the two groups showed statistically significant differences between them as the active group has reported their symptoms more often (chi-square test, p<0.0001). Eyelid swelling and swelling/ erythema od caruncle had the lowest p value (p<0.001) and were the most specific clinical sign/ symptom for the active group. The average temperature of orbital area in patients in the inactive group was 34.7 °C while in patients in the active group was 36.0 °C (t-test, p<0.0001). We found statistically significant differences in all measured areas of both eyes which is shown in Table 1. ROC analysis indicated that the temperature cut-off at 35.3 °C best discriminates patients with and without active TED (AUC 0.9, p<0.001) with a sensitivity of 82.8% and a specificity of 85.7%. Average exophthalmometry values were also higher on both eyes in patients in the active group (t-test, p = 0.0002). The average exophthalmometry value of the right eye in the active group was 19.1 mm and in the inactive group was 15.7 mm (p=0.0004). The average exophthalmometry value of the left eye in the active group was 19.7 and in the inactive group was 15.6 (p=0.0003). Out of all thyroid hormone and anti-

body levels only FT4 (Mann-Whitney, p=0.0176) and TRAb (Mann-Whitney, p=0.0091) values were higher in the active group while other thyroid hormone and antibody levels showed no statistically significant difference. The strongest correlation coefficient was found between the average temperature and CAS (r=0.516, p=0.0001), exophthalmometry values (r=0.424, p=0.0022) and anti-TPO values (r=0.485, p=0.019). The correlation can also be seen on Spearman's correlation graphs. Figure 2 shows correlation graph between the temperature and CAS while figure 3 shows correlation graph between the temperature and exophthalmometry. As the values of temperature rise, the values of CAS and exophthalmometry also rise.

5. DISCUSSION

As the treatment of TED depends on the stage of the disease, it is important to assess in which stage the patient is. The CAS scale is a subjective tool in this assessment, so with this study we tried to expand the spectrum of tools that would help us in greater objectivity. Di Maria et al measured the highest mean temperature, average mean temperature and average difference in temperatures in patients with active and inactive TED. They reported that all five parameters were increased in active TED (22). In our study we also reported increased temperature in all measured areas in the active TED group and the highest mean temperature in the medial part of both upper eyelids which was present in both groups of patients. These results are in accordance with the results of the study of Matteoli et al who also proved that the nasal canthus is the hottest region and the central cornea the coolest (23). Riguetto et al used a novel smartphone attached thermal camera and recorded thermal images from caruncles and upper eyelids. They reported that all areas of thermal evaluation had higher temperatures in active TED and the values correlated with the CAS. The group of patients with ophthalmopathy had significantly greater measures of proptosis and all eye areas had higher temperatures when compared to patients without inactive ophthalmopathy or healthy controls. They got a positive correlation of average temperature and CAS score (24). Our study also showed greater measures of proptosis obtained with exophthalmometry in patients with active TED. The mean temperature also positively correlated with CAS score, exophthalmometry values and anti-TPO antibody values. Our study wasn't designed to have a healthy control group as our control group were patients with inactive TED. The similar results were shown in the study of Dave et al who concluded that the temperature at the caruncle, medial and lateral conjunctiva was significantly higher in the active TED group compared to inactive TED and healthy eyes. They got similar results with AUROC value of 0.91, a sensitivity of 91% and a specificity of 79% and showed correlation between caruncular temperature and CAS.25 A statistically significant correlation between serum TRAb levels and CAS has been found in the study of Nicoli et al The correlation was also confirmed for age and FT3 levels (8). Our study has found statistically significant higher levels of TRAb in patients with active TED when compared to patients with inactive TED (14.7604 versus 0.725, p=0.009) but no correlation was found with temperature (p=0.6432) or CAS (p=0.3766). We also haven't found a statistically significant correlation between FT3 levels and CAS (p=0.7463). A study by Subekti et al that was conducted in Indonesia also showed that there was no correlation between TRAb and CAS nor the severity of TED (7). Our study was first up to date to find statistically higher levels of FT4 in patients with active TED (p=0.0176) and positive correlation of temperature and anti-TPO levels (p=0.019). In a review article Purslow et al concluded that current instrumentation offers the great potential to measure ocular surface temperature with more accuracy, resolution, and speed than previously possible. They also suggested the use of dynamic ocular thermography as it offers great opportunities for monitoring the temperature of the anterior eye (26). One of the limitations of our study was the number of patients and in the future research of this topic a larger number of patients would be needed to confirm the previous results. As we didn't measure the temperature change after TED treatment it would be interesting to monitor the change in temperature and other measured values.

6. CONCLUSION

Changes in orbital temperature may occur over a period of days or weeks, which may limit the ability of the study to detect short-term changes. Thermal camera showed higher values of the temperature of the orbital area in patients in the active phase of the disease and positively correlated with the CAS scale, exophthalmometry findings and anti-TPO levels. There were statistically higher levels of FT4 in patients with active TED.

- **Acknowledgements:** The The authors would like to acknowledge patients who participated in this study.
- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms.
- **Author's contribution:** AP, AK, OZ, RI gave a substantial contribution to the conception and design of the work. IGG, IMK, GM gave a substantial contribution of data. IS gave a substantial contribution to the acquisition, analysis, or interpretation of data for the work. IPV, VLL, ZV had a part in article preparing for drafting or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved..
- **Conflict of interest statement:** The authors have no conflicts of interest to disclose.
- **Financial support and sponsorship:** The authors received no specific funding for this work.

REFERENCES

1. Wiersinga WM, Prummel MF, Terwee CB. Effects of Graves' ophthalmopathy on quality of life. J Endocrinol Invest. 2004; 27: 259–264. 10.1007/BF03345275
2. Weiler DL. Thyroid eye disease: a review. Clin Exp Optom. 2017; 100(1): 20-25. 10.1111/cxo.12472
3. Łacheta D, Miśkiewicz P, Głuszko A, Nowicka G, Struga M, Kantor I, et al. Immunological Aspects of Graves' Ophthalmopathy. Biomed Res Int. 2019;2019:7453260. 10.1155/2019/7453260
4. Verity DH, Rose GE. Acute thyroid eye disease (TED): principles of medical and surgical management. Eye (Lond). 2013; 27(3): 308-319. 10.1038/eye.2012.284
5. Wang Y, Patel A, Douglas RS. Thyroid Eye Disease: How A Nov-

el Therapy May Change The Treatment Paradigm. Ther Clin Risk Manag. 2019; 15: 1305-1318. 10.2147/TCRM.S193018
6. Barbesino G, Tomer Y. Clinical review: Clinical utility of TSH receptor antibodies. J Clin Endocrinol Metab. 2013;98(6): 2247-2255. 10.1210/jc.2012-4309
7. Imam Subekti I, Boedisantoso A, Moeloek ND, Waspadji S, Mansyur M. Association of TSH receptor antibody, thyroid stimulating antibody, and thyroid blocking antibody with clinical activity score and degree of severity of Graves ophthalmopathy. Acta Med Indones. 2012; 44(2): 114-121.
8. Nicolì F, Lanzolla G, Mantuano M, Ionni I, Mazzi B, Leo M, et al. Correlation between serum anti-TSH receptor autoantibodies (TRAbs) and the clinical feature of Graves' orbitopathy. J Endocrinol Invest. 2021; 44(3): 581-585. 10.1007/s40618-020-01353-y
9. Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Berghout A, Van Der Gaag R. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. Br J Ophthalmol. 1989; 73: 639–644. 10.1136/bjo.73.8.639
10. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf). 1997; 47(1): 9–14. 10.1046/j.1365-2265.1997.2331047.x
11. Gerding MN, Prummel MF, Wiersinga WM. Assessment of disease activity in Graves' ophthalmopathy by orbital ultrasonography and clinical parameters. Clin Endocrinol (Oxf). 2000; 52: 641–646. 10.1046/j.1365-2265.2000.00973.x
12. Tachibana S, Murakami T, Noguchi H, Noguchi Y, Nakashima A,Ohyabu Y, et al. Orbital magnetic resonance imaging combined with clinical activity score can improve the sensitivity of detection of disease activity and prediction of response to immunosuppressive therapy for Graves' ophthalmopathy. Endocr J. 2010; 57: 853–861. 10.1507/endocrj.k10e-156
13. Almohammed HI, Mansour S, Alhulwah AH, Mayhoub FH, Arafah AM. Scintigraphy has the potential to replace thyroid stimulating hormone and ultrasonography in hyperthyroidism diagnosis. Saudi J Biol Sci. 2020; 27(7): 1722-1725. 10.1016/j.sjbs.2020.05.015
14. Ring EF, Ammer K. Infrared thermal imaging in medicine. Physiol Meas. 2012; 33: R33–R46. 10.1088/0967-3334/33/3/R33
15. Pauling JD, Shipley JA, Harris ND, McHugh NJ. Use of infrared thermography as an endpoint in therapeutic trials of Raynaud's phenomenon and systemic sclerosis. Clin Exp Rheumatol. 2012; 30: S103–S115.
16. Anderson KN, Di Maria C, Allen J. Novel assessment of microvascular changes in idiopathic restless legs syndrome (Willis-Ekbom disease). J Sleep Res. 2013; 22: 315–321. 10.1111/jsr.12025
17. Allen J, Oates CP, Chishti AD, Ahmed IA, Talbot D, Murray A. Thermography and colour duplex ultrasound assessments of arterio-venous fistula function in renal patients. Physiol Meas. 2006; 27: 51–60. 10.1088/0967-3334/27/1/005
18. Shih SR, Li HY, Hsiao YL, Chang TC. The application of temperature measurement of the eyes by digital infrared thermal imaging as a prognostic factor of methylprednisolone pulse therapy for Graves' ophthalmopathy. Acta Ophthalmol. 2010; 88:e154–e159. 10.1111/j.1755-3768.2010.01941.x
19. Chang TC, Hsiao YL, Liao SL. Application of digital infrared thermal imaging in determining inflammatory state and follow-up effect of methylprednisolone pulse therapy in patients with Graves' ophthalmopathy. Graefes Arch Clin Exp Ophthalmol. 2008; 246: 45–49. 10.1007/s00417-007-0643-0
20. Tosima Manullang MC, Lin YH, Lai SJ, Chou NK. Implementation of Thermal Camera for Non-Contact Physiological Measurement: A Systematic Review. Sensors 2021; 21(23): 7777. 10.3390/s21237777
21. Tattersall GJ. Infrared thermography: A non-invasive window into thermal physiology. Comp Biochem Physiol A Mol Integr Physiol. 2016; 202: 78-98. 10.1016/j.cbpa.2016.02.022
22. Di Maria C, Allen J, Dickinson J, Neoh C, Perros P. Novel thermal imaging analysis technique for detecting inflammation in thyroid eye disease. J Clin Endocrinol Metab. 2014; 99(12): 4600–06. 10.1210/jc.2014-1957
23. Matteoli S, Vannetti F, Sodi A, Corvi A. Infrared thermographic investigation on the ocular surface temperature of normal subjects. Physiol Meas. 2020 4; 41(4): 045003. 10.1088/1361-6579/ab6b48
24. Riguetto CM, Minicucci WJ, Neto AM, Tambascia MA, Zantut Wittmann DE. Value of infrared thermography camera attached to a smartphone for evaluation and follow-up of patients with Graves' ophthalmopathy. Int J Endocrinol. 2019; 2019: 7065713. 10.1155/2019/7065713
25. Dave TV, Patodi P, Richhariya A, Dave VP. Thermal Imaging of the Ocular Surface in Thyroid Eye Disease: A Comparison between Active, Inactive and Healthy Eyes. Curr Eye Res. 2021; 46(10): 1482-1488. 10.1080/02713683.2021.1907418
26. Purslow C, Wolffsohn JS. Ocular surface temperature: a review. Eye Contact Lens. 2005; 31(3): 117-123. 10.1097/01.icl.0000141921.80061.17