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A systematic review on the role of infrared thermography in the Brown adipose tissue assessment

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Abstract
Brown adipose tissue (BAT) is an endocrine adipose tissue with attributes to dissipate energy as heat in response to changes in temperature and diet. Infrared thermography (IRT) has been studied in recent years in the assessment of BAT thermogenesis, as an option to positron emission tomography - computed tomography (PET-CT), because of several advantages. We performed a systematic review on the use of IRT in BAT assessment. Comprehensive online search was performed in different databases. The QUADAS 2 tool was used to evaluate studies' quality. 12 studies fit the inclusion criteria, whereas only one of these was considered of low risk of bias. 10 studies were favorable to IRT appliance in BAT evaluation, observing elevation of supraclavicular skin temperature correlated with BAT activity. Studies were heterogeneous in design, and a meta-analysis was precluded. Further studies with similar methodologies are needed. Conclusion: Despite the large number of published methodologies, IRT is a promising method for detecting BAT activation. Current knowledge already allows a better understanding of thermography to improve and standardize the technique.

Keywords Brown adipose tissue · Infrared thermography · Supraclavicular temperature · Positron emission tomography · Standardized uptake value · Energy expenditure · Region of interest

Abbreviation

BAT	brown adipose tissue
IRT	infrared thermography
SCT	supraclavicular temperature
PET	positron emission tomography
SUV	standardized uptake value
EE	energy expenditure
ROI	region of interest

1 Introduction

Obesity is one of the main concerns in public health, as it leads to several diseases and has reached pandemic proportions worldwide [1]. To the date, adoption of effective prevention strategies has been inconsistent [2, 3]. Therefore, new insight is focusing on the role of thermogenic function of brown adipose tissue (BAT) [4–10] as a promising complementary therapy for obesity and its associated complications [11, 12]. BAT activation seems to be involved in body weight regulation [13–15], improvement of glucose and lipid homeostasis, chronic low-grade inflammation [16–19], and even fertility [20, 21].

The current gold standard technique for BAT detection is positron emission tomography - computed tomography (PET-CT) [22]. Although free fat acids mediated metabolism is the most favored, a variety of extracellular substrates are metabolized by the BAT [18]. F-fluorodeoxyglucose PET/CT (FDG-PET) imaging can display its prominent glucose uptake [13]. Reported limitations of this technique include heterogeneity of response, sensitivity to experimental or environmental factors, and confounding variables for standardized uptake value (SUV)–based quantitation [12]. Furthermore, technical hindrances, such as the 2-h cooling protocol, the restriction to

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a single time-domain of capture depending on the kinetics of the radiopharmaceutical, costs and availability make this technique unfeasible to be utilized in daily practice [23].

Due to the heat-generating properties of BAT [24, 25], infrared thermography (IRT) is a natural candidate for measuring its activity. Studies indicate that the main local of BAT is the supraclavicular (SC) and cervical areas in humans [6, 26, 27] as the SC BAT depot is relatively superficial, allowing detection of the heat signature [28]. IRT is a safe, non-invasive, non-contact, non-ionizing, inexpensive, real-time serial, repeatable and wide available technique for measuring temperature remotely. Recent developments in imaging techniques such as IRT have facilitated the study of BAT [29]. Hence, we performed a systematic review assessing the accuracy of IRT in the detection of BAT.

2 Methods

2.1 Search strategy

An extensive search was performed in online databases, including *Medline,* the *Cochrane Library, Google Scholar, Embase, LILACS and Scopus*. This review followed the guidelines for diagnostic test reviews of the Joanna Briggs Institute [30, 31]. The Boolean operator "and" was used to combine the ancillary test IRT and BAT in the search. The Boolean operator "or" was used to discriminate terms, such as IRT, infrared thermogram and infrared thermography, BAT and brown adipose tissue. Table 1 describes the results of the search.

The same searches were repeated in all databases, although the number of relevant studies retrieved did not increase. The present study conception and writing was performed by two authors (SB and ACR). Also, quality of retrieved studies was assessed independently by the same authors. Expert insight on IRT technique and the critical revision of the final manuscript version was given by the other authors (FM and MLB, EFC and MJT respectively). Studies attributes were classified as unclear, high- or low-risk according to the *Quality Assessment of Diagnostic Accuracy Studies* 2 (QUADAS 2) tool, an acknowledged instrument recommended for the use in systematic reviews to evaluate diagnostic test quality and assess the risk of bias in study design and applicability [32]. Risk of bias was evaluated in reference to patient selection (if consecutive, randomized, no case-control, avoiding inappropriate exclusions), index test (results interpretation without knowledge of reference standard and threshold pre-specification), reference standard (if the reference standard chosen correctly classified the target condition and its results were interpreted without knowledge of index test results) and flow and timing (appropriate interval between tests, if all samples received the same reference standard and if the entire sample was included in the analysis).

The QUADAS 2 additionally evaluates study applicability questioning if the included patients do not match the review question, if the index test, its conduct, or interpretation differ from the review question and if the target condition as defined by the reference standard does not match the review question. In order to be considered high quality, studies should not display high risk of bias in any judgment.

Table 1 Search databases and search results

Database	Total Studies	Studies Matching
Medline	77	8
Cochrane library	9	2
Google Scholar	2280	15
Embase	70	11
LILACS	30	7
Scopus	33	9

2.2 Inclusion criteria and data extraction

The exclusion criteria involved: 1) all studies that did not apply IRT as the comparable tool for detecting BAT; 2) studies that were not published in English if it was not possible to contact the authors; 3) case reports; 4) abstracts, reviews or research protocols; and 5) animal studies.

Several citations from the reference lists of each retrieved study were assessed, including other reviews on the use of IRT or further ancillary testing for BAT activation assessment [28, 29].

3 Results

3.1 Number of studies retrieved

Fourteen studies matched inclusion criteria, thirteen of which prospective, observational case-control series [23, 28, 33–44], and one randomized trial [40]. Thirteen studies presented some high risk of bias according to the applied criteria, whereas the remaining one was considered methodologically next to ideal [23], and none were considered non-valid.

3.2 Characteristics of included trials

The studies were conducted from 2012 to 2019 and included single- and multicenter studies from many medical centers in Australia, Asia, Europe and North America. The retrieved studies included children [33] and/or adults, exclusively male [28, 38, 40, 43], female [36, 37] or both sexes, exclusively lean [23, 28, 33, 36, 40, 43, 44] or varied BMI, with no medical history of metabolic syndromes, diabetes mellitus, thyroid diseases or chronic diseases. The IRT protocol for BAT

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evaluation was described satisfactorily in all studies, and was similar to that applied to study BAT by PET-CT.

Various different IRT devices were used in the retrieved studies (FLIR B425 [34, 36], FLIR T440 [23, 40], FLIR Bb60 [33], FLIR E60 [42], FLIR i60 [44], FLIR T450sc [41] T650sc [38, 39], DE-TC 1000T [43], Varioscan 3021 ST [35] and Fluke Ti9 [37]) whereas the protocol for BAT stimulation and heat production varied among the studies such as the use of cold stress challenge, capsinoids ingestion, mental stress challenge, oral glucose tolerance test or even no stimulation. A considerable variety of golden standards was verified for BAT detection and comparison with IRT, such as a PET images bank [33], PET [28, 34, 35, 44], energy expenditure [38, 41] with fat oxidation measure [40], salivary cortisol [36], near-infrared spectroscopy (NIRS) [37] and skin temperature (iButtons) [42] and even the comparison of interclavicular area with SCV IRT [39]. Table 2 features the PIRO acronym of each study retrieved.

3.3 Cooling methodologies

Following the principle of BAT thermogenic properties associated with fatty acids and glucose metabolism, in addition to the sympathetic nervous system influence in order to maintain body temperature homeostasis, cooling techniques have been applied to BAT study. Notwithstanding, cooling protocols varied significantly between the studies. All authors applied varied acclimation periods in rooms with temperature around 19 °C to 24 °C, whereas the cooling stimulation was performed with no further action in one study [34]. Water vest or blanket with controlled temperature from 12 °C to 14.5 °C (or individualized protocols following a shivering threshold test) was applied in five studies [23, 28, 38, 42, 44]. Immersion of body parts in cool water was used in other five studies [33, 37, 40, 41, 43], whether only hands or both feet and one hand, from 5 to 10 min, obtaining images ~~at~~ from the beginning to the end of the challenge. Table 3 shows the main differences between cooling protocols in the studies.

3.4 Positivity thresholds

IRT correlation with BAT was positive in the studies if the peak T° or the SCT area after stimulation were the highest in the same region where BAT was observed in the reference standards or elevations over 100 to 200 kcal/d after cold exposure with concomitant elevation in SCT area. Hartwig et al. and Symonds et al. evaluated initial and final peak SCT, whereas in the other studies mean SCT was evaluated. Law

Table 2 Description of population studied, IRT, reference standard applied and outcomes. BATa: brown adipose tissue area, EE (RQ): energy expenditure respiratory quotient, ICA: interclavicular area, IR-SCT: supraclavicular area temperature, IRT: infrared thermography, NIRS: near infrared spectroscopy, OGTT: oral glucose tolerance test, PET-CT: positron emission tomography - computed tomography and PET-MR: positron emission tomography-magnetic resonance

Studies	Population	IRT	Reference	Outcome
Symonds et al. 2012	26 subjects 3–8(7)/13–18(12)/35–58(7) yo	Cold stress	PET-CT images bank, iButtons	IR-SCT correlated to PET BATa
Jang et al. 2014	17 lean adults	Cold stress	PET-CT	IR-SCT correlated to BATa
Gatidis et al. 2016	102 adults	No challenge	PET-CT	IR-SCT inversely related to SCA thickness
El Hadi et al. 2016	14 lean and 16 mildly obese adults	Cold stress	EE (RQ)	IR-SCT was coupled with EE
Robinson et al. 2016	5 healthy female adults	Mental stress challenge	Salivary cortisol	IR-SCT was coupled with cortisol levels
Ang et al. 2017	24 male adults	Cold stress/capsinoids/-placebo	EE (RQ) and fat oxidation	IR-SCT was related to EE and fat oxidation
Haq et al. 2017	28 male	Cold stress	EE	IR-SCT correlated to EE
Hartwig et al. 2017	5 lean and 5 obese female adults	Cold stress/OGTT	NIRS	IR-SCT increased, whereas NIRS remained stable
Law et al. 2018	8 male	Cold stress	PET-CT	IR-SCT correlated to BATa
Habek et al. 2018	15 male and 16 female adults	Caloric meal challenge	IRT ICA	IR-SCT correlated in male, but not in overweight female
Martinez-Tellez et al. 2019	11 adults	Cold stress	PET-CT and iButtons	IR-SCT did not represent BATa
Sun et al. 2019	20 lean adults	Cold stress/capsinoids	PET-MR and EE	IR-SCT correlated to BATa
Andersson et al. 2019	12 healthy adults	Cold stress	PET-MR	IR-SCT correlated to BATa
Nirengi et al. 2019	24 healthy adults	Cold stress	PET-CT	IRT-SCT correlated to BATa

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Table 3 Description of IRT protocol studied, acclimatization, challenge test and IRT thresholds. SCT: supraclavicular temperature

Studies	Acclimatization	Challenge	IRT protocol	IRT Thresholds
Symonds et al. 2012	19°-20 °C room (length?)	5 min, both feet or 1 hand in 19°-20 °C tap water	1 image at each minute, 5 images	ΔSCT area and Peak SCT
Jang et al. 2014	2 h in 19 °C room	No further challenge	1 image at each hour, 3 images	ΔSCT area
El Hadi et al. 2016	1 h in 24 °C room	20 min both hands in 5 °C water basin	Unclear	ΔSCT area and Δsternum area
Ang et al. 2017	45 min in 24 °C room	5 min, both feet or 1 hand in 18 °C tap water	5 min movie	ΔSCT area
Haq et al. 2017	1 h in 32 °C room	1 h of 12 °C blanket on torso	1 image at each 5 min	ΔSCT area
Hartwig et al. 2017	15 min in 20 °C room	Left hand in 5–9 °C water basin, one minute	1 image before and after cooling	ΔSCT area and peak SCT
Law et al. 2018	Unclear	8 °C vest on torso (length?)	Multiple images in the first 10 min and after prolonged cooling	ΔSCT area
Martinez-Tellez et al. 2019	30 min. ~24.5 °C and then, 15 min. 19.5 °C	Vest on torso 4 °C over the individualized shivering threshold, 120 min.	4 images prior and after cooling	ΔSCT area
Sun et al. 2019	10 min (T°?)	14.5 °C vest on torso	1 image at each 15 min for 2 h	ΔSCT area
Andersson et al. 2019	Room at 15 °C (T?)	5 min basal, and then 5 min hands/ft 32 °C and last 25 min 18 °C water immersion	1 image at each minute for 35 min	ΔSCT area
Nirengi. et al. 2019	30 min. 27 °C room	two tests: 5-min hand immersion into 18 °C water and only 120-min cold exposure at 19 °C	1 image at each 10–30 min for 120 min.	ΔSCT area

et al. calculated both. Only Sun et al., Andersson et al. and El Hadi et al. compared mean SCT with another region of interest (e.g. skin overlying sternum or paranasal) in the same subjects. In Fig. 1 the authors of the present study show a representative example of the measurement of BAT according to the cooling protocol recommended by Symonds et al. [33]. The authors used a proper more specific color scale to highlight BAT (BATscale 1.0, Thermofy version 2019).

3.5 Outcome measures

Table 4- QUADAS 2 tool, risk of bias and applicability judgements. LR: low risk, HR: high risk, PS: patient selection, IT: infrared thermography, RS: reference standard, TF: timing and flow.

A main risk of bias was observed concerning the reference standard applied. Despite energy expenditure measured by respiratory quotient technique has been reported to correlate satisfactorily with BAT activity [45], only Jang et al. [34], Law et al. [28], Martinez-Tellez et al. [42] and Sun et al. [23], compared IRT of the same subjects with PET-CT or PET-MR, which are the current golden standard for BAT assessment, although is not known in these studies whether IRT imaging was obtained unaware of PET results. The studies retrieved were not clear about whether IRT and the reference standard were submitted to blinded performance and interpretation, except by Ang et al. [40]

Risks of bias with reference to IRT performance was verified in the studies of Martinez-Tellez et al. [42] and Jang et al., since these authors obtained IRT images before cooling stimulation, and after 60- or 120-min posterior cooling beginning, otherwise, Hartwig et al. [37] performed an excessive short stimulation of one minute, acquiring a single image before and after this procedure. Gatidis et al. [35] performed a single IRT image in the absence of any stimulation of the BAT, whereas Habek et al. [39] and Robinson et al. [36] utilized different strategies to BAT stimulation that are not applied on PET-CT, as mental stress test [36] and caloric meal [39]. Moreover, the thresholds for positivity are also not clear in these studies.

Timing bias was observed exclusively in the study of Symonds et al. [33], because the subjects studied with IRT were not also studied by a reference standard. In terms of applicability, risk of bias in reference to patient selection was observed in studies that included overweight subjects to be evaluated with IRT without comparison with PET-CT [35, 37, 39, 41, 46]. There were also uncertainties about IRT conduction, and the reference standard being in fact not a real gold standard.

Thus, a meta-analysis on the applicability of IRT for detecting the activation of the BAT is currently not possible to be performed because of high heterogeneity of the studies available, and the small number of subjects studied in the studies of higher quality.

4 Discussion

The present review indicates IRT as a promising method for BAT assessment. Among twelve studies, only two obtained no favorable results, however, Gatidis et al. [35] presented a

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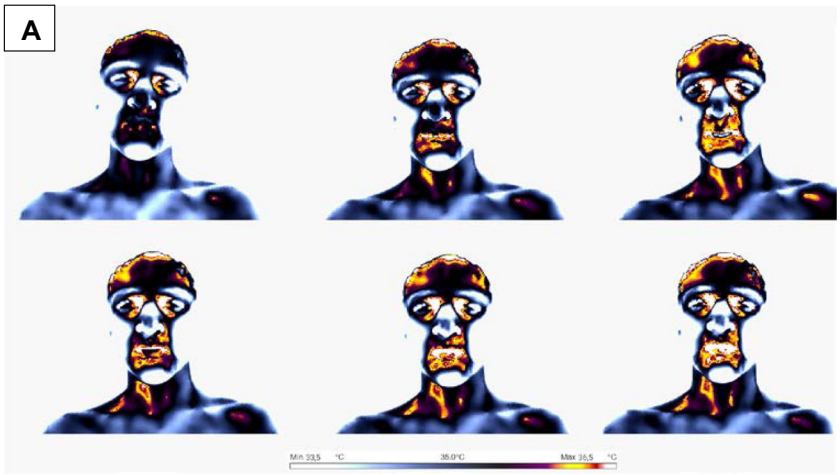
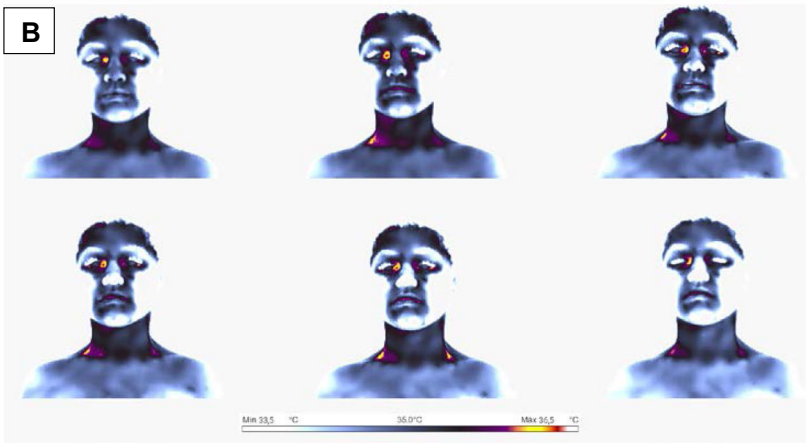


	0	1	2	3	4	5
Right	34,89	35,12	35,20	35,26	35,25	35,27
Left	34,51	34,62	34,69	34,64	34,73	34,75



	0	1	2	3	4	5
Right	34,50	34,41	34,37	34,23	34,22	34,45
Left	34,11	34,21	34,21	34,24	34,19	34,11

Fig. 1 The cooling protocol demonstration as recommended by Symonds et al. [33] with authors BAT scale. The mean of the upper 10th percentile temperatures of the supraclavicular regions were calculated before cooling. In total 6 thermal images were taken: one image before and one image at each minute of thermal challenge, for five minutes. Representative positive example of the measurement of BAT in a 11 y.o. lean girl (A), the increase in mean change in temperature of SC area following placement each minute before and after five minutes of one hand into cold water at 15 – 17° C each a minute. Negative example in a 9 y.o. obese boy (B), with no significant change in temperature after challenge

remarkable source of bias, since cold stimulation is the most suitable technique to challenge the activation of BAT, and these authors did not submit their sample to any challenge, in a single imaging fashion.

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Table 4 describes the results of the QUADAS 2 signaling questions to assist in judgments regarding the risk of bias

Studies	Risk of Bias				Applicability Concerns		
	PS	IT	RS	TF	PS	IT	RS
Symonds et al. 2012	LR	LR	HR	HR	LR	LR	HR
Jang et al. 2014	LR	HR	LR	LR	LR	LR	LR
Ang et al. 2016	LR	LR	HR	LR	LR	LR	HR
Gatidis et al. 2016	LR	HR	LR	LR	LR	HR	LR
El Hadi et al. 2016	LR	Unclear	HR	LR	HR	LR	HR
Robinson et al. 2016	LR	HR	HR	LR	LR	HR	HR
Haq et al. 2017	LR	LR	HR	LR	HR	LR	HR
Hartwig et al. 2017	LR	Unclear	HR	LR	HR	LR	HR
Law et al. 2018	LR	HR	LR	LR	LR	LR	LR
Habek et al. 2018	LR	HR	HR	LR	HR	HR	HR
Martinez-Tellez et al. 2019	LR	HR	LR	LR	LR	LR	LR
Sun et al. 2019	LR	Unclear	LR	LR	LR	LR	LR
Andersson et al. 2019	LR	HR	LR	LR	LR	LR	LR
Nirengi et al. 2019	LR	HR	LR	LR	LR	LR	LR

Martinez-Tellez et al. [42], despite concluding that skin temperature measured with iButtons and IRT is not comparable, they also observed that during cold stimulation, the temperature decrease is less at supraclavicular skin, compared to other skin sites in human adults [47]. These findings may raise the possibility of an over cooling of the subjects studied, since these authors submitted theirs sample to a shivering cooling protocol, and in a second opportunity to two hours of cold water vest, obtaining IRT images before cooling, and just prior to PET-CT scanning, possibly losing the perfect BAT thermogenesis timing. Further studies suggest short cooling protocols avoiding shivering with frequent IRT imaging [7, 28, 29, 33]. After cold exposure, SCT appears to reach its maximum between 5 and 10 minutes [33, 38, 40].

Gathered studies in this review revealed a high level of heterogeneity, especially with issues about IRT imaging protocols and interpretation, BAT stimulation and cooling protocols. The reference standards applied were also varied, leading to applicability concerns. Because of small sample with unification of the three higher quality studies [23, 34, 42] samples ($n = 48$), a meta-analysis was not indicated at this time.

Sun et al. [23] recently evaluated EE, the SUVs and fat fraction (FF) by PET-MR in 20 adults and found correlation between these measures and the hottest SC areas. The authors suggested the novelty of MR FF stays beyond assessing the anatomical localization of BAT, because of PET displays glucose uptake exclusively and IRT assesses the acute effect of thermogenic stimuli. MR FF of the supraclavicular region should provide unique insight into longer-term metabolic health [23].

IRT critics and limitations rely on the possibility of SCT to increase after a stimulus because of large vessel underlying this area, such as the carotid and subclavian arteries, or even the possibility of SCT raise in fact because of elevation of blood flow. The study of Hartwig et al. [37] with NIRS imaging indicated there is no elevation in SC blood flow, since NIRS imaging of SC skin remained unaltered during challenge, while IRT SCT increased. Another research including healthy women did not found correlation between NIRS in the supraclavicular and BAT volume and activity [48].

It has been demonstrated that obesity decreases BAT activity [1]. The hypothesis that SCT could be underestimated due to the subcutaneous adipose tissue thickness interference with heat transference to SC skin is not verified in the recent studies [23, 28, 39]. Besides IRT, in the near future, evidence based on specific PET tracers, MR imaging and even ultrasound will be approaches for BAT investigation [12].

Based on the review, we believe that the ideal protocol should take into account faster acclimatization, such as 15 min in a room at 23° C, so that there is no shivering. The challenge test should be rapid for 5 min with both hands immersed in cold water at 18° C, similar to room temperature, considering the test can be tolerated in both children and older adults. Image acquisition should be just prior to the challenge, and then at each minute for ΔSCT area calculation using a specific scale to highlight the region of interest as shown in Fig. 1.

To the date, there are still no studies of IRT evaluation changes in human BAT after a significant weight loss. BAT appears to react to diet influences, such as ketogenic diets as demonstrated in animal models [49], and to resveratrol [13] and caffeine consumption as demonstrated in humans [50].

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IRT has been established and accepted as a technique for studying BAT function in small animals [34], and should be directed in further research in humans [49], inclusive in order to aid elucidation of the physiologic facts involved with BAT. IRT has potential to be a useful tool in future studies of BAT and obesity therapy.

5 Conclusion

Despite the large number of published methodologies, IRT is a promising method for detecting BAT activation. Current knowledge already allows a better understanding of thermography to improve and standardize the technique.

Compliance with ethical standards

Disclosures The authors declare no conflicts of Interest. Declaration of informed consent was not applicable.

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