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Changes of Skin Temperature of Parts of the Body and Serum Asymmetric Dimethylarginine (ADMA) in Type-2 Diabetes Mellitus Indian Patients

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***Abstract*— In India, number of people with type 2 Diabetes Mellitus (DM) would be 87 million by the year 2030. DM disturbs autonomic regulation of skin micro-circulation, and causes decrease in resting blood flows through the skin. The skin blood flow has a major effect on its temperature. The aim of the study was to evaluate changes of skin temperature of all parts of the body and serum asymmetric dimethylarginine, ADMA (µmol/L) in type-2 DM Indian patients. Group-I: Normal (n=17; M/F: 10/15, mean±SD= 43.2±9.4 years); Group-II: Type-2 DM without cardiovascular (CV) complications (n=15; M/F: 10/7, mean±SD= 46.3 ± 14.0 years); Thermograms of all parts of the body were acquired using a non-contact infra-red (IR) thermography camera (ThermaCAM T400, FLIR Systems, Sweden). Blood parameters and thyroid hormone were measured biochemically. Indian diabetic risk score (IDRS) was calculated for each subject. In type-2 DM patients without CV group (n=15), there was a statistically significant (p=0.01) negative correlations between HbA_{1c} and skin temperature of eye and nose (r= -0.57 and r= -0.55 respectively). ADMA was correlated significantly (p=0.01) with HbA_{1c} (r=0.65) and estimated average glucose, eAG (r=0.63). In normal subjects, mean minimum and maximum values of skin temperatures were observed at posterior side of sole (26.89°C) and ear (36.85°C) respectively. In type-2 DM without CV, mean values of skin temperature in different parts of the body from head to toe were lesser than those values in control group; but this decreases were statistically significant in nose (32.66 Vs 33.99°C, p=0.024) as well as in tibia (32.78 Vs 33.13°C, p=0.036) regions.**

I. INTRODUCTION

DIABETES mellitus (DM) is a typical disease of metabolism system. On comparison, the prevalence of type-2 DM is greater than type-1 DM. In India, the number of people with type-2 DM would be eighty seven million by the year 2030 [1]. Blood glucose level is estimated biochemically to diagnose the disease; but in involves minimal invasive procedures. Blood glycosylated hemoglobin (HbA_{1c}) is being considered as the 'gold' standard for diagnosing the disease [2]. The skin blood flow response has a major effect on its temperature. The blood flow and temperature in cutaneous microcirculation are highly correlated [3]. Both advanced ageing and DM disturb the autonomic regulation of skin microcirculation, and cause a decrease in resting blood flows [4] through the skin. It may be due to impairment in nitric oxide synthesis, a vascular endothelial mediator of vascular smooth muscle dilation [5]. Also, DM patient has thinnest skin, which has both low blood vessel density, and low blood flow[6]. Increased serum asymmetric dimethylarginine (ADMA) and decreased nitrogen oxide (NO) in type-2 DM is significant because endothelial dysfunction associated with increased ADMA concentrations seems to begin before the detectable vascular damage in the disease. Additionally the patient has an increased level of ADMA leading to an endothelial damage, even if hypertension or hyper-lipidemia does not exist. Hence, they serve as predictors for future cardiovascular (CV) disease events in type-2 DM[7]. Infrared (IR) thermography is a test of 'physiology' and its sensitivity and specificity was reported as very high to detect the abnormality well in advance. It can be used as a 'surrogate' or an 'adjunctive' method in diagnosing/ or detecting any diseased conditions, namely: i) breast cancer; ii) DM; iii) CV complications; iv) hypo-, and hyper thyroidism; v) Joint inflammation; and vi) pain-related thermal dysfunction, etc [8]. Although, it is bound with some of the limitations, viz., environment-dependent, operator-dependent, not descriptive, difficult to interpret, non-specific, inconsistent, and no standard analysis procedure, it has more strength in an early detection of any diseased condition[9].

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In Western Countries, there are more than 400 IR imaging clinics working either as part of a hospital or an independent diagnostic centers. It is being extensively used for diagnosing/ or predicting various diseases, along with other standard diagnostic methods for several decades of years. Hence, more literature is available on 'medical thermography' in Western countries. On the other hand, only few research centres and multi-specialty hospital have this facility in India. Indira Gandhi Centre for Atomic Research (IGCAR), Kalpakkam, Tamil Nadu, India is the one, which has this facility right from the year 1996. To the best of knowledge, research study on DM using thermography and serum ADMA is limited in India. The aim of the study was: to evaluate the changes in skin temperature of all parts of the body and serum ADMA in type-2 DM patients without CV complications, when comparing to serum HbA_{1c} value as the standard.

I. Materials And Methods

A. Patients

A free public screening camp for DM, CV disease, and rheumatoid arthritis was organized at SRM Medical College & Research Centre, Kattankulathur (Chennai), Tamil Nadu, South India during March, 2010. A total number of 75 patients were attended the camp. A self-made questionnaire was administered, and the clinical detail of each patient was recorded meticulously. Patient was classified as DM, if the measured serum HbA_{1c} (%) was≥6.5 [2]. The CV disease was defined, if a patient had old history of any one of the heart diseases, viz., old history of myocardial infarction, heart attack, coronary artery bypass graft, stroke and angina. Patients with type-1 DM, CV complications, rheumatoid arthritis, hypo- and hyper- thyroidism, renal and liver failure, were excluded in this study.

A total number of 46 patients were found to have type-2 DM without CV complications; out of these, 15 patients (male/female: 10/5) had undergone all the relevant measurements for the study and were included for analysis. Out of these, 40% (6/15) of the patients were known type-2 DM for several years (mean duration was 6.0 years), and the remaining 60% (9/15) patients were diagnosed as having a disease during course of the study. No patient received any pharmacologic treatment during the past 1 week just before attending this camp. No one had ulcer in the foot. A normal control subject had free from any recognizable diseases and any abnormality, and was matched with age-and sex- as type-2 DM patients without CV. Participants were divided into 2 groups: Group-I: Normal (n=17, M/F: 10/15, mean ± SD= 43.2 ±9.4 years); Group-II: Type-2 DM without CV complications (n= 15, M/F: 10/7, mean ± SD= 46.3 ± 14.0 years);

B. Methods

i) *Indian Diabetes Risk Score (IDRS):* It is based on the following modifiable risk factors for the disease present in the subject: i) age; ii) family positive history of DM; iii) regular exercise; and iv) waist circumference (cm). As suggested by Mohan and other investigators [10, 11], IDRS was calculated for each subject.

ii) *Biochemical Blood Analysis:* HbA_{1c} was estimated by immune-turbidity method using Olympus auto analyzer (Hamburg, Germany). From its measured value, an average glucose was estimated (eAG) using an empirical equation established earlier [12]. Total cholesterol and HDL were estimated by enzymatic method using Olympus auto analyzer (Hamburg, Germany). Free T3, T4, and TSH were estimated by enzyme-linked immunosorbent assay (ELISA) method using Lilac. Serum ADMA concentration was measured using commercially available ELISA kits [13].

iii) *Non-Contact Digital Thermography:* As outlined by American Academy of Thermology, a thermogram was obtained under standardized conditions, namely laminar air flow, humidity of 50%, room temperature of 23°C, and time of acclimatization 30 minutes. In each participant, thermogram of each region of the whole-body from head to toe was obtained using a non-contact digital thermo-camera (ThermaCAM T400, FLIR Systems, Sweden). Using its accessory software, thermogram was analysed. The skin temperature at different regions of interest in a image was measured. In the following regions of interest: fore head, eye, nose, neck, ear, carotid artery, knee, tibia, and ankle toe, skin temperature measurements were carried out at both left and right sides separately, and then an average value was calculated for further statistical analysis. Its accuracy was reported as 0.01^{o}C.

iv) *Statistical Analysis:* Data was analyzed statistically to find out its significance using a Statistical Package for the Social Science for Windows (SPSS, version 10.0, 1999, Chicago, IL, USA). Student's t-test was used to find out whether these values were different between the groups. Associations between variables were examined with linear regression and Pearson's correlation analysis.

III. Results

A. Calculation of IDRS

The calculated IDRS in a subject in each group is tabulated (Table-I). It was found that 58.8% (10/17) and 73.3% (11/15) of normal and type-2 DM patients respectively were at greater risk for DM and CV complications.

B. Correlation Study of the Measured Variables

In normal subjects (n=17), ADMA was correlated significantly with HbA_{1c} (r=0.67, p=0.01) and with eAG (r=0.55, p=0.05). In type-2 DM patients without CV

group (n=15), there were a statistically significant (p=0.01) negative correlations (Table-II) between HbA_{1c} and temperature of eye (r= -0.57) and nose (r= -0.55). Also, ADMA was correlated significantly (p=0.01) both with HbA_{1c} (r=0.65) and eAG (r=0.63). In all normal subjects and patients (n=32), there was a significant negative correlation (Fig:1) between HbA_{1c} and nose temperature (r= -0.61, p=0.01). Also, ADMA was correlated positively (p=0.01) with both HbA_{1c} (r=0.86), and eAG (r=0.84); whereas, it correlated negatively with nose temperature (r= -0.504, p=0.01).

TABLE I
CALCULATED INDIAN DIABETIC RISK SCORE (IDRS)

CALCULATED IRDS AND RISK FOR DM AND CV COMPLICATIONS	NUMBER (PERCENTAGE)	
	NORMAL (N=17)	TYPE-2 DM WITHOUT CV (N=15)
Low risk: < 30	5 (29.4%)	2 (13.3%)
Moderate risk: 30-50	2 (11.8%)	2 (13.3%)
High risk: > 60	10 (58.8)	11 (73.3%)

TABLE II
CORRELATION MATRIX FOR TYPE-2 DM WITHOUT CV

TYPE-2 DM WITHOUT CV INDIAN PATIENTS (N=15)				
MEASURED VARIABLES	HbA_{1C} (%)	EAG (MG dL^{-1})	EYE (°C)	NOSE (°C)
eAG (mg dL^{-1})	1.00**			-0.55*
ADMA (µmol L^{-1})	0.65**	0.63*		
Fore head (°C)			0.59*	
Eye (°C)	-0.57*			
Nose (°C)	-0.55*	-0.72**		
Neck (°C)			0.74**	0.57*
Fore arm (°C)		-0.54*		0.63*
Palm (°C)		-0.57*		0.72**
Right side fingers (°C)		-0.55*		0.72**
Knee (°C)				0.68**
Tibia (°C)				0.70**

** Correlation is significant (p) at the 0.01 level;
*Correlation is significant (p) at the 0.05 level;

C. Comparison of type-2 DM without CV with Normal

Table-III shows the characteristics of the study groups. With respect to mean values of subject's age, BMI, waist-, and hip- circumference, SBP, DBP, and thyroid hormones, there was no statistically significant difference between the two groups. In the patient group, the mean values of HbA_{1c} and ADMA were higher than those in normal group; It was found that, the mean values of HbA_{1c} was increased significantly (p=0.000) by 28.6%, when comparing to the normal group. Also, the mean (±SD) value of ADMA (µmol L^{-1}) in the patient group was 1.01 (±0.17) Vs 0.61 (±0.14) in normal group, and it was found to be increased significantly (p=0.000) by 39.6% when comparing to normal group. In normal subjects, the mean value of skin temperature ranged from 26.89°C to 36.85°C. The minimum and maximum values of temperatures were observed at posterior side of sole and ear respectively. Generally, mean values of measured skin temperature in different parts of the body from head to toe were lesser in patient group than in normal group; but this decreases were statistically significant in nose (p=0.024) as well as in tibia (p=0.036) regions (Fig. 2-5), and the calculated percentage decrease in temperature in the regions were found to be 3.9% and 1.1% respectively.

TABLE III
CHARACTERISTICS OF THE STUDY GROUPS

MEASURED VARIABLES	GROUP-I: NORMAL (N=17)	GROUP-II: TYPE-2 DM WITHOUT CV (N=15)
General		
Age (years)	43.2±9.4	46.3±14.0
Gender (male/ female)	10/7	10/5
Duration of diabetes mellitus (years)	-	6.0 ± 5.6
Anthropometry		
BMI (Kg m^{-2})	28.2±4.1	29.4±6.1
Waist circumference (cm)	87.1±10.9	95.3±12.4
Hip circumference (cm)	93.6±9.4	103.7±12.1
SBP (mm Hg)	123.5±14.1	124.0±9.9
DBP (mm Hg)	78.4±7.7	82.6±9.7
Biochemical analysis		
HbA_1c (%)	5.58±0.41	7.81±1.21[a]
eAG (mg dL^{-1})	115.12±13.93	176.93±35.16[a]
ADMA (µmol L^{-1})	0.61±0.14	1.01±0.17[a]
Total cholesterol (mg dL^{-1})	172.65±44.28	186.33±47.86
HDL (mg dL^{-1})	38.94±9.0	35.80±4.95
Thyroid hormone assay		
Free T3 (Pg/ml)	2.29±1.43	2.11±0.80
Free T4 (Ng/ml)	1.24±0.31	1.25±0.31
TSH (µIu/ml)	2.47±1.55	2.30±1.46
Thermography (° C)		
Fore head	35.62±0.62	35.42±0.37
Eye	35.51±0.60	35.36±0.46
Nose	33.99±1.03	32.66±1.85[c]
Neck	35.38±0.39	35.23±0.56
Ear	36.85±0.55	36.83±0.44
Carotid artery	35.62±0.49	35.43±0.50
Right hand	33.84±1.52	33.62±1.44
Right side fingers	32.94±2.28	32.51±2.24
Right forearm	34.10±0.57	33.88±0.85
Knee	32.52±0.89	32.07±0.93
Tibia	33.13±0.71	32.78±0.69[d]
Ankle toe	31.14±1.66	30.62±1.37
Right side toes-posterior	26.91±2.95	25.84±3.09
Left side toes-posterior	26.89±2.97	25.87±3.18
Right side sole	28.79±2.50	27.79±2.02
Left side sole	28.88±2.41	27.82±2.03

When compared to the normal group: a) p=0.000; b) p=0.005; c) p=0.024; and d) p=0.0

V. DISCUSSION

In this study, HbA_{1c} was correlated significantly (p=0.05) with subject's age (r=0.44) in all normal and type-2 DM without CV patients (n=32), whereas, ADMA had no correlation with subject's age. It is contradict with the findings reported in another studies that, ADMA was correlated with subject's age, and its mean value was higher significantly in post-menopausal women than in men of same age [14, 15]. In type-2 DM without CV group (n=15), ADMA was correlated significantly with

both HbA_{1c} (r=0.65, p=0.01) and eAG (r=0.65, p=0.01). It is not consistent with the findings reported in another study [16] that ADMA correlated significantly with HbA_{1c} in DM with CV patients only, and not in DM without CV patients. In the patient group, there was a significant (p=0.01) negative correlations between HbA_{1c} and skin temperature measured at the following regions: i) nose (r= -0.57); and ii) eye (r= -0.55); further eAG had significant negative correlations with the skin temperature of the following regions: i) nose; ii) forearm; iii) palm; and iv) right-side fingers. It requires further studies in the literature that may either confirm or disagree these findings. A review on correlation studies between skin temperature, skin blood flow, biochemical parameter and others in DM patients is listed in Table-IV.

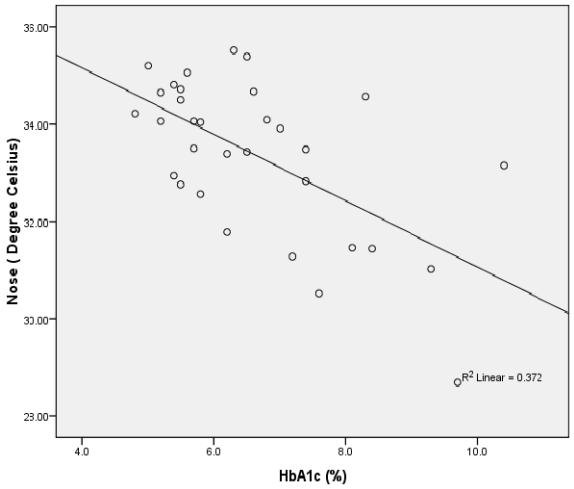

Fig.1. Significant correlation in all normal and type-2 DM without CV patients (n=32)

In a thermographic study on 32 healthy subjects [24], the highest skin temperature was found on the forehead (34.5°C), and the lowest was found at the toes (27.1°C), whereas, in the present study, the measured maximum and minimum values of skin temperatures in normal Indian subjects (mean± SD age: 46.3±14.0 years) were observed at ear (36.85°C) and posterior side of sole (26.89°C) respectively. Also, it was reported [18] that there was a significant decrease in foot temperature in diabetic patients compared to normal (26.0±0.3 Vs 27.0±0.3°C). In a pilot study [19], sixteen patients with DM (aged 56±8 years) were enrolled in a double-blind, with washout periods of 1 week; Each patient was rubbed with an active cream (4 mg L-arginine cm^{-2}) into one foot and vehicle into the other. At the last day, the skin temperature (measured by infrared thermometer) at the metatarsal area had risen from the initial value of 82.0 ±2.3 to 86.9± 2.4°F (p<0.0001), and the skin temperature of the big toe had risen from the initial value of 74.4 ±4.2 to 82.4 ± 4.8°F (p<0.0001); further, blood flow (measured by Doppler flow meter) at the metatarsal area had risen from 8.7 ± 4.3 to 11.6 ± 5.5 arbitrary units (AU) (p<0.0001), and flow at the Achilles area had risen from 8.4 ±2.5 to 11.4 ±5.5 AU (p <0.02). In this study, it was found that, in type-2 DM without CV group, mean values of skin temperature of parts of the body from head to toe were lesser compared to control group; but this decrease were statistically significant in nose and tibia regions. The mean values of nose temperature were 33.99°C and 32.66°C in control and patient groups respectively, and the decrease in temperature in the patient group was found to be 3.9% (p<0.024). Further, the mean values of tibia temperature were 33.13°C and 32.78°C in control and patient groups respectively, and the decrease in temperature in the patient group was found to be 1.1% (p<0.036). DM patients had lower skin temperature as well as lower peak CBV (mm/s) of great toe [18], compared to control subjects (28.1 ± 1.6 Vs 28.9 ± 2.1°C in normal; and peak CBV: 0.10 ± 0.06 Vs 0.58 ± 0.32 mm/s in normal). DM patients with sensory neuropathy[19] had lower mean plantar foot skin temperature than control (28.4 Vs. 28.9°C, p=0.01). On the other hand, diabetic neuropathic foot has elevated skin temperature primarily through an increased arterio-venous shunt flow [27]. The mean value of ADMA (µmol/L) in normal subjects was found to be 0.61, and it is agreed with the value published earlier [15]. In type-2 DM without CV group, the mean value of ADMA was elevated two-fold times significantly, when it was compared with normal control group. The same pattern was reported in one study [16], whereas, in another study, it was reported that, ADMA was higher by three fold times in the DM group than in normal group [28]. Using ADMA value, a threshold for type-2 DM was arbitrarily defined as the 90th percentile for type-2 DM patients without CV studied. The calculated threshold value of ADMA (µmol/L) was 0.755. When it was used, it was found that 17.6%(3/17) of the normal subjects had ADMA values greater than the threshold value and therefore they appeared to have a risk for having DM in the future. It was postulated that in type-2 DM patients, whose serum ADMA level was more than 0.63 µmol/L had a greater risk for fatal and non-fatal CV complications (p<0.014 by the log-rank test) during the median follow-up period of 21 months [29]. In the present study, all the patients had ADMA (µmol/L) value greater than 0.788, and hence all the patients may have a risk for CV complications in the future. It was reported that [30], Indian patients with IDRS score≥60 had significantly higher prevalence of coronary artery disease, diabetic peripheral neuropathy, and peripheral vascular disease. In the present study, 58.8%(10/17) and 73.3%(11/15) of normal and type-2 DM patients respectively were found to have IRDS score≥60, and hence they were at greater future risk for DM and CV complications.

V. CONCLUSION

A normal reference data on skin temperature of all parts of the body in Indian subjects, measured by

thermography, was established. It can be used for both clinical work and research studies in DM. In both type-2 DM patient group alone as well as in all normal and patient group, measured serum HbA_{1c}(%) was correlated negatively with nose temperature(°C) and these were statistically significant. Also, HbA_{1c} was correlated significantly with serum ADMA(µmol/L). In type-2 DM patients, measured nose and tibia temperatures were lesser significantly than in normal. The skin temperature measured from thermography may be useful in screening the population for DM disease. The predicting potential of thermography for the disease requires further study in that direction. ADMA helps to discriminate DM from normal like HbA_{1c} as well as to predict the future risk for CV complications.

TABLE IV
REVIEW ON CORRELATION OF SKIN TEMPERATURE IN DM PATIENTS

Investigator (Year)	Patient details (Country)	Key findings
Purewal *et al*, 1995 [17]	17 with chronic Charcot joints; 11 patients with neuropathic foot ulceration; 14 with DM; 11 normal subjects (UK);	No correlation between skin temperature and HbA_{1c};
Jorneskog *et al*, 1998 [18]	20 DM; 13 normal; (Sweden)	Significant inverse correlation between HbA_{1c} and peak capillary blood cell velocity, CBV (mm/s) of great toe in DM patients;
Boykoa *et al*, 2001 [19]	712 DM (366 sensory neuropathy & 346 autonomic neuropathy), (USA)	Weak negative correlations between right forefoot skin temperature and fall in systolic blood pressure with standing;
Colberg *et al*, 2002 [20]	10 normal exerciser; 8 normal sedentary; 9 DM exerciser; 8 DM sedentary; (USA)	During localized heating, significant inverse correlation between skin blood flow and fasting serum glucose levels and HbA_{1c} in DM patients; No correlation between skin NO and skin blood flow;
Nobuyuki, 2002 [21]	60 with DM and normal subjects (Japan)	There was no significant correlation between ankle brachial pressure index and HbA_{1c} and thumb skin temperature.
Shun *et al* 2004 [22]	38 DM patients (25 males and 13 females); (Taiwan);	Significant (p= 0.024) negative correlation between Intra-epidermal nerve fibre, IENF (fibres/mm) density of the leg and diabetic duration; No correlation of IENF density of the leg with HbA_{1C}, fasting and post-prandial glucose levels;
McLellan *et al*, 2009 [23]	15 DM; 15 older normal; 15 young normal; (USA)	During localized heating, significant inverse correlation between presence of diabetes and thermal change index of foot

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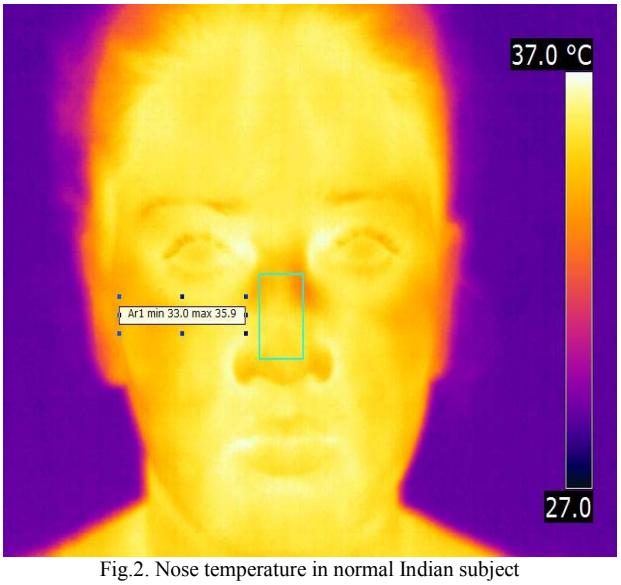

Fig.2. Nose temperature in normal Indian subject

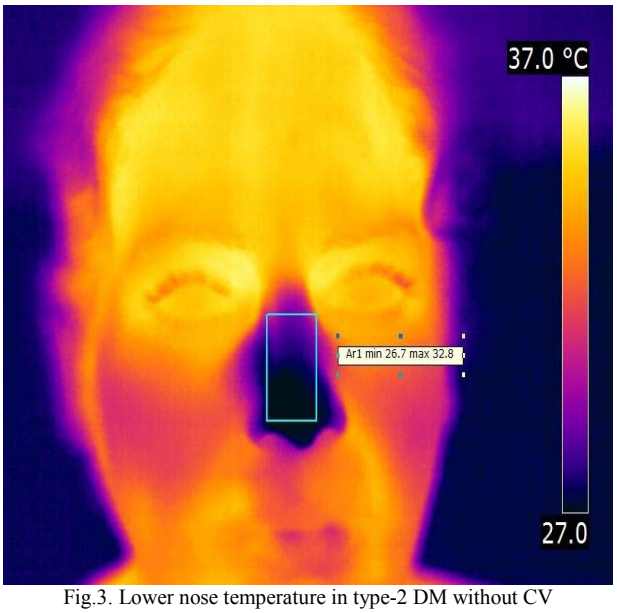

Fig.3. Lower nose temperature in type-2 DM without CV

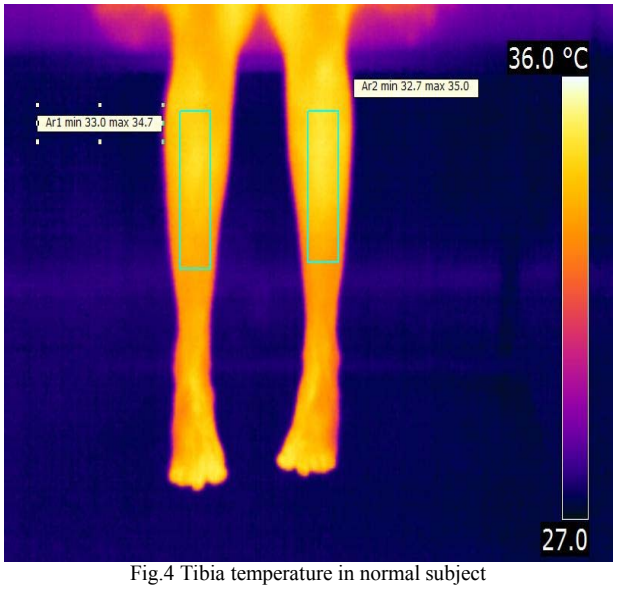

Fig.4 Tibia temperature in normal subject

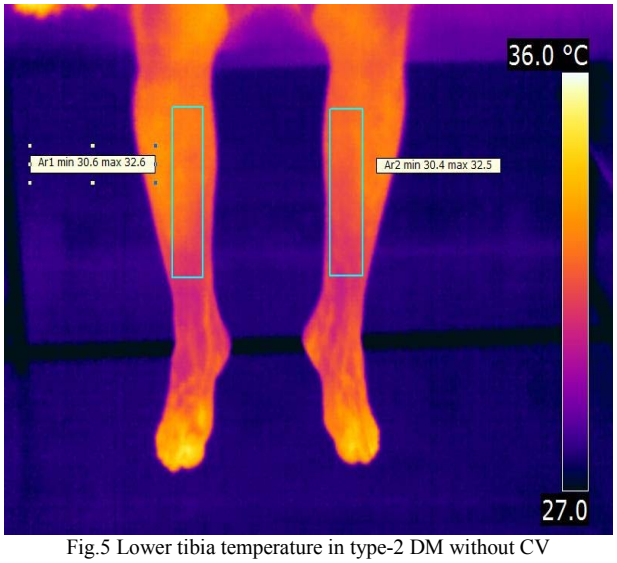

Fig.5 Lower tibia temperature in type-2 DM without CV