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Carotid Intima-Media Thickness; Could Be an Early Predictor of Atherosclerosis in Skin Tags Patients

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Running title: CIMT in STs patients.

Abstract

Background: Skin tags (STs) are commonbenign skin tumors. An association between STs and atherogenic risk factors including impairment of lipid has been proposed. Carotid intima media thickness(CIMT) is a surrogate marker for the existenceof atherosclerosis and its progression.
Objectives: To assess the possible risk of atherosclerosis in patients having STs, through evaluation of CIMT in STs patients compared to controls, in addition to study the relationship of the evaluated CIMT with clinical aspects of STs in the studied cases.
Methods: This case control study was performed on 80 non obese-subjects with STsand 60 matched healthy controls. All participants were subjected to a full history, clinical examination and lipid profile evaluation [serum cholesterol (CH), high density lipoprotein(HDL), low density lipoprotein(LDL), and triglyceride (TG)]. CIMT was measured by utilizing B mode carotid ultrasonography.
Results: There was a significant higher CH, TG, LDL and CIMTmean values in STs patients than controls (p= <0.001, p=0.02, p=<0.001 and p=0.007 respectively). In STs patients, CIMT was positively correlated with numbers of STs as well as serum levels ofCH, TG and LDL.
Conclusions: STs patients are more prone to develop dyslipidemia and atherogenic changes that could be detected early by CIMT assessment .CIMT could be an early predictor of atherosclerosis even in non-obese STs patients. STs patients especially those with high number of STs lesions need close supervision and regular follow up using CIMT to predict any atherogenic changes and to get benefit from the prevention program.
Keywords: Skin tags, Cholesterol, Triglyceride, Low density lipoprotein, Carotid intima-media thickness.
Running title: CIMT in STs patients.

Introduction

STs are soft, small, common, usually pedunculated, benign tumours of the skin frequently appearing on the neck and axilla.1

Internationally, STs have been documented to show an incidenceof 46% in the general people. They have the same incidence in both sexes.2However, it was stated that STs show more incidence in females than males, with two peaks, one at pregnancy and the other at menopause.3

STs are a part of ageing process; they are very common in middle aged and elderly people. About 60% of subjects may complain of appearance of STs by the time they are aged 60 years. Moreover, STsappearance in a child may be a sign resulting in early detection of nevoid basal cell carcinoma and biopsy should be taken.4

STs are considered the most common lesions of the skin, and their exact etiology is still unclear. Some of the associated factors are frequent irritation of the skin, obesity, diabetes mellitus, acanthosisnigricans, metabolic syndrome (METs), acromegaly, crohn's disease, colonic polyps, thyroid diseases and hormonal imbalance as well as human papillomavirus skin infection.5The relation between STs and impaired lipid profile as a risk factor for atherosclerosis was suggested.6-8

CIMT is asurrogate marker for the existence of atherosclerosis and its progression. It is simple, reproducible, and noninvasive measure. CIMT is measured between the medial-adventitial and the intimal-luminal interfaces of the carotid artery. The space between the 2 hyper-echoic linespoints to CIMT.9CIMT is associated with aging and prevalence of cardiovascular disease (CVD). Associations were also found between the CIMT, insulin resistance, and METs.10

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This study was done for the first time to assess the possible risk of atherosclerosis in patients having STs, through evaluation of CIMT in those patients compared to healthy subjects. In addition, we aimed to study the relationship of the evaluated CIMT with theSTs clinical aspectsin the studied subjects.

Patients and Methods

This study was conducted on 140 subjects selected from Outpatient Dermatology Clinic, Menoufia University Hospital at ShebinElkomFaculty of Medicine in a period of eight months from February to September 2018. They were 80 patients with STs as patient's group, and 60 gender and age matched healthy subjects in the control group.

The study was approved by the ethical committee of Faculty of Medicine, Menoufia University. A written informed consent was obtained fromeachparticipantsubsequent to explaining the research.

We included patients from both sexes, aged 27-58 years and having any number of STs. All patients and controls have normal physical activity and dietary habits. Subjects with history of cardiac diseases e.g. rheumatic cardiac diseases, risk factors of atherosclerosis (e.g. hypertension and diabetes), immunological diseases (e.g. SLE, rheumatoid arthritis, psoriasis and sjogren syndrome), hyperuricemia, chronic inflammatory conditions, infectious diseases (such as H pylori), liver and kidney dysfunction were not included in our study. Also, smokers, alcoholics and obese (body mass index (BMI)≥30 kg/ m2) were excluded from this study.

Methodology

The enrolled patients were subjected to detailed history, complete general examination and calculation of body mass index (BMI). Number and site of STs were reported. The disease severity was evaluated depending on STs number; mild (1-10), moderate (10-30) and severe (≥30).11

BMI was calculated using weight and height of an individual through dividing the weight (kg) over the square of the height (m2) of the individual. BMI was expressed as underweight: <18.5, normal weight: 18.5 to 25, overweight: 25 to 30 and obese: > 30.12

Under complete aseptic conditions, five ml of venous blood was taken in plan tube from all patients and control individuals, after fasting 12 hours. Sera were separated after centrifugation at 5000rpm (RCF = 1500 xg) for 5 minutes, stored at -20°C and thawed just before analysis. The collected sera were used to assess lipid profile (Spinreact, Girona, Spain):serum CH was measured by enzymatic colometeric method using Cholesterol Liquizyme (CHOD-PAP). HDL was determined by precipitation method using the HDL- cholesterol -precipitant kits. LDLwas calculated according to Friedewald's formula: LDL = cholesterol-HDL-TG/5.TGwas determined by GPO-PAP enzymatic colometeric method, using TriglycerideLiquizyme (GPO-PAP, single reagent).

To measure CIMT;all participants included in the study had undergone carotid artery doppler ultrasound examination using high-resolution B-mode, and colordopplersonography of the carotid arteries bilaterally. The carotid artery doppler ultrasound examination was operated with Toshiba Xario 200 (made in Russia, production date 2017) fitted with a linear array transducer with standard frequency of 5 to 10 MHz. All the subjects included in the study were evaluated while they were lying in a supine position with their heads tilted backwards. Subsequent torecognition of the carotid arteries location by using transverse scan, the probe was rotated 90 to get a longitudinal image of the posterior and anterior walls. Imaging of the common carotid artery (CCA), the carotid bulb and the internal carotid artery (ICA) was performed in the transverse and sagittal plane. The maximal CIMT was evaluated at the CCA far and near walls, CCA bifurcation and ICA and consequently presented as a mean value. All scans were obtained by the same experienced radiologist for each individual, the maximum CIMT was measured then the result was interpreted as follow:1) CIMT≤ 0.8 mm was considered normal.2) CIMT >0.8 mm was considered atherosclerotic.13The CIMT findings was verified by an independent second radiologist.

Statistical analysis

The collected data were processed, coded and introduced to the computer to undergo analysis by SPSS version 20 (USA). Statistics were calculated in terms of percentage, mean, median, range and standard deviation (SD). Student’s t-test is a test of significance used for comparison of quantitative variables between two groups of normally distributed data, while Mann Whitney's test was used for comparison of quantitative variables between

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two groups of not normally distributed data. Chi-Squared (x2) was used to study association between qualitative variables. Pearson's correlation (r) was used to show correlation between two continuous normally distributed variables. P- value of < 0.05 was considered statistically significant.

Results

The investigated patients were 20 males (25%) and 60 females (75%), their age ranged from 19 to 45 years and their BMI ranged from 20.8–29.6 kg/ m2. They were matched with the controls in age, sex and BMI (Table 1).

The age of STs onset in studied patients ranged from 25-43years and the disease duration ranged from 2 months to 10 years. Most of STs patients had lesions in head and neck (77.5%). Regarding STs number, it ranged from1 to 12 and most of our patients (92.5%) had a mild form of the disease.60 (75%)of our studied STs cases had positive family history of STs(Table 1).

Studying CIMT in STs patients and control group(Figure 1) showed that CIMT was significantly elevated in STs patients (0.62±0.17mm) than controls (0.51±0.11mm) (P=0.007), There was significant higher mean levels of CH (P<0.001), TG (P=0.020) and LDL (P=<0.001) in STs patients than controls(Table 2).

Numbers of STs were significantly positively correlated with CH(r=0.73,p=<0.001), LDL(r=0.69,p=<0.001) and TG (r=0.32,p=0.041) serum levels(Figure 2). There were significant positive correlations between CIMT with number of STs lesions (r= 0.49, P=0.001), CH (r=0.48, P=0.002), TG(r=0.33, P=0.038) and LDL(r=0.44, P=0.004) in studied patients(Figure 3).

Discussion

Carotid duplex ultrasound is a noninvasive imaging modality that can safely and accurately measure atherosclerotic carotid stenosis. As such, it is often used in the early detection of atherosclerosis.14Several studies have evaluated the lipids effectsand ratios on atherosclerosis in its early-stage.15,16 In STs patients,multiple studies have been conducting confirming the relation between STs and impaired lipid profile as a risk factor for atherosclerosis.6-8

To best of our knowledge, this study is the first one that investigated CIMT in STs patients to predict their risk to develop any atherosclerotic changes. In which we demonstrated asignificant atherogenic CIMT in STs Patients. Moreover, the number of STs (denoting disease severity) was significantly associated with atherogenic CIMT.

The relationship between STs and atherogenic lipid profile was suggested.17 Dyslipidemia was frequently demonstrated in STs patients. The mean levels of CH, LDL and TG were majorly higher in the subjects having STs than the subjects in the control group.18In consistent with these findings, our results showed that serum CH, LDL and TG were significantly higher in STs patients. Regarding HDL level, there was no significant change between ST patients and matched controls. Also, many authors found a significant association of STs with high TG levels and low HDL levels19, as well as higher total CH and LDL levels. 17

Dyslipidemia can have an effect on the insulin sensitivityby reducing the insulin receptor substrate-1expression. Therefore, the pancreas will produce more amounts of insulin to compensate. The increased level of insulin in the bloodencourages an elevation in insulin growth factor-1(IGF-1) which can lead to stimulation of keratinocytes proliferationand production of epidermal hyperplasia. In addition, IGF-1 encouragesthe dermal fibroblasts to undergo proliferation and formation of connective tissue.19Furthermore, the increasedIGF-1 level decreases the level of IGF binding protein-3 (IGFBP-3) which isaccountable for regulation of thetranscription of the anti-proliferation gene in the epidermis by inhibition ofIGF-1 bindingto its receptor. A reduced IGFBP-3 level will result in high rate of proliferation and excessive growth of cells that can appear as STs.11

In this study, there were significant positive correlations between CH, TG and LDL with number of STs lesions. In agreement with our results, Skoumas et al.7 found that the number of STs increased with high plasma CH levels 1, as well as TG and LDL.6 These results support suggestion that STs are associated with an important component of METs and the risk of atherosclerosis and cardiovascular disease.6

Based on the current demonstrated atherogenic CIMT in the investigated STs patients and its significant association with disease severity, together with the current reported high lipid profile (CH, LDL and TG) in our non-obese investigated STs cases, we suggested that STs might indicate abnormal lipid profile and increase

cardiovascular risk in STs patients even in non-obese cases andeven in those having mild and moderate degree of disease severity, as our result showed.

Recently, it was showed that feeding CH in rabbits led toatheroma formation, like those detected in humans, confirmed causal responsibility of CH in the atherosclerosis pathogenesis. Families with inherited high CH demonstrated increased risk for cardiovascular disease. LDL-C levels were shown to be directly related to cardiovascular events; whereas HDL-C levels were found to be inversely correlated withpossibility of cardiovascular events development.20

The atherogenesis 1st stepisentering of the LDL-C into the sub-endothelial spaces, and is trapped because of the glycoprotein molecules have high affinity to LDL-C. Theparticles of LDL cannot pass through the junctions between endothelial cells (EC) because of their very big size, but the majority of LDLin the circulation can be transported across the endothelial cells by nonspecific or receptor mediated uptake into micropinocytic channels. Each endothelial cell shows receptors for LDL and the altered forms. A free receptor alters and oxidizes LDL into alteredLDL forms like oxidized LDL which encouragethe monocytes trans-endothelial migration to the sub-endothelial spaces that is guided by chemokines. Furthermore, oxidized LDLencourages the monocytes differentiation to macrophages which form receptors for the oxidized LDL to be lipid-laden foam cells. Consequently, CH is trapped within the wall of arteries leading todevelopment of the early-stage atherosclerosis.21This data could explain our findings regarding significant correlation of CIMT with the serum levels of CH, LDL and TG in the current investigated STs Patients.

Conclusions

STs Patients are more prone to have dyslipidemia and development of atherogenic changes that could be detected early by CIMT assessment even in non-obese subjects. STs patients especially those with high number of STs lesions need close supervision and regular follow up using CIMTto predict any atherogenic changes and to get benefit from the prevention program.

Study limitations

The small number of the studied subjects was the main limitation of the current study.

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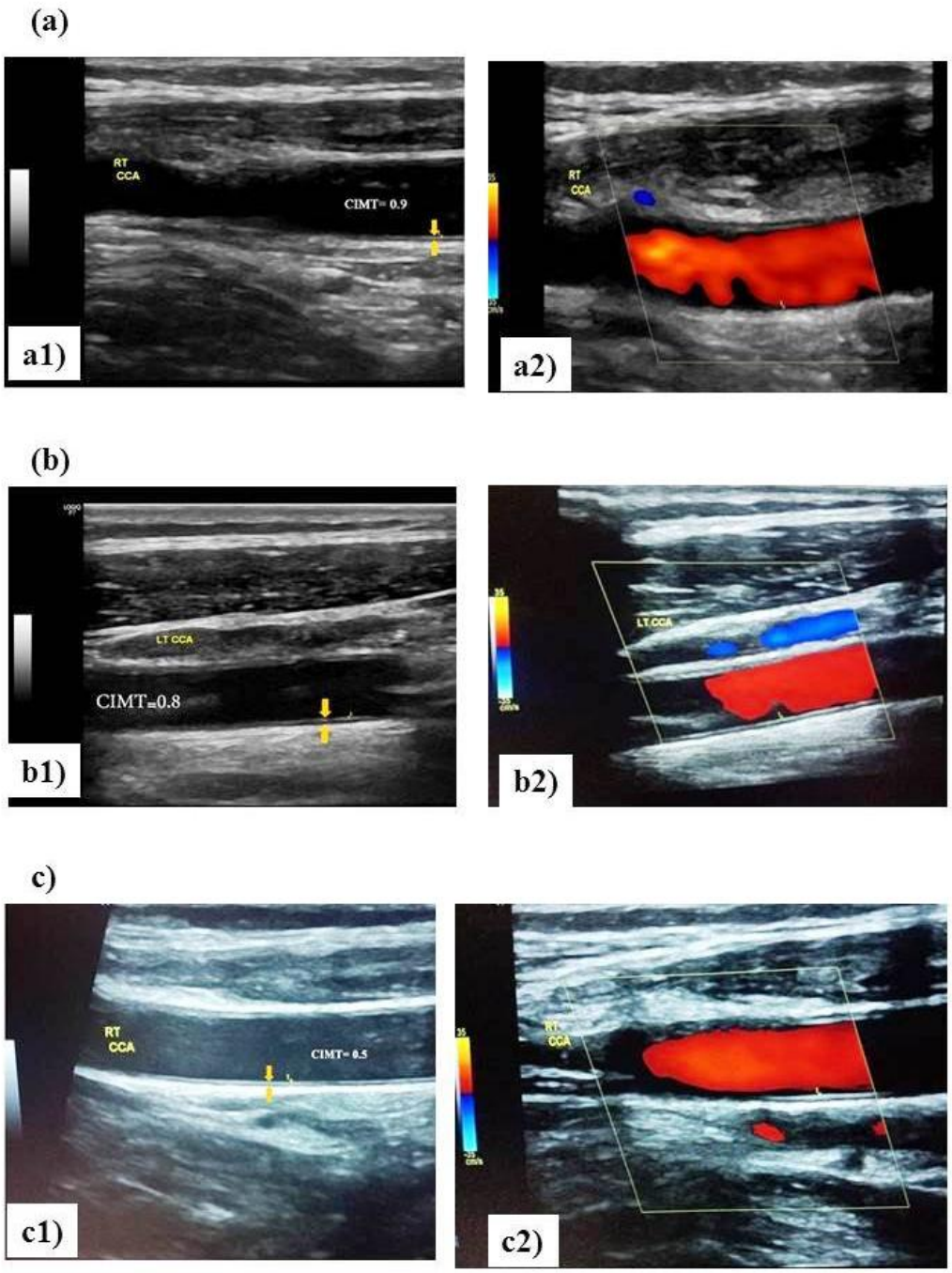

Figure 1.Carotid doppler study of the CCA in**(a):**ST patient showing: mild atherosclerotic changes, mild increased intimal thickness (CIMT=0.9mm)(a1) and preserved flow hemodynamics(a2), **(b):** ST patient showing normal intimal thickness (CIMT=0.8mm)(b1) and preserved flow hemodynamics(b2) and**(c):** normal controlsubject showing normal intimal thickness (CIMT=0.5mm) (c1)andnormal flow hemodynamics(c2).

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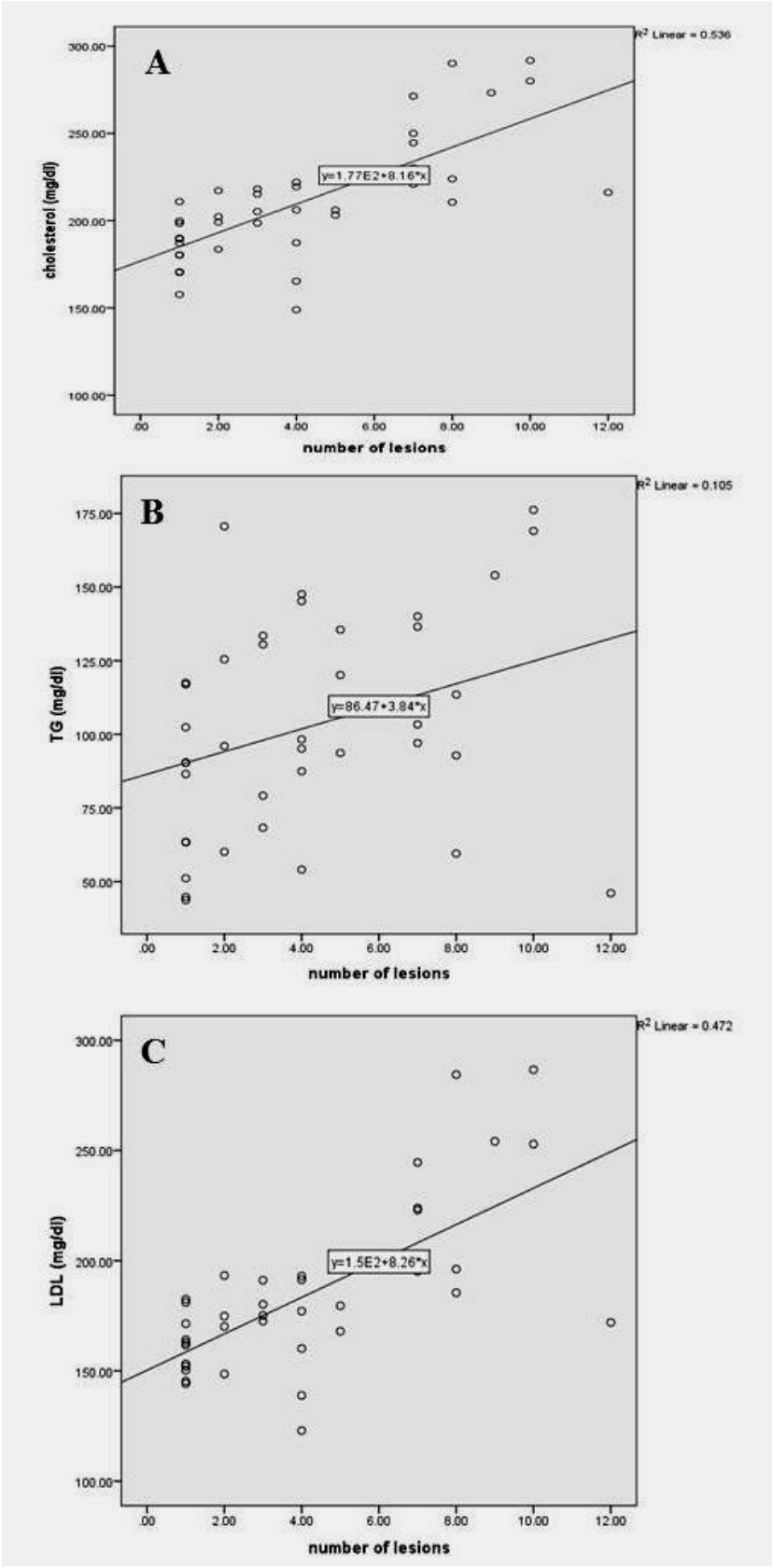

Figure 2.Correlations between number of STs Lesions and lipid profile; (a): CH (r=0.73, p=<0.001), (b): TG(r=0.32, p=0.041), and (c): LDL(r=0.69, p=<0.001) in STs patients.

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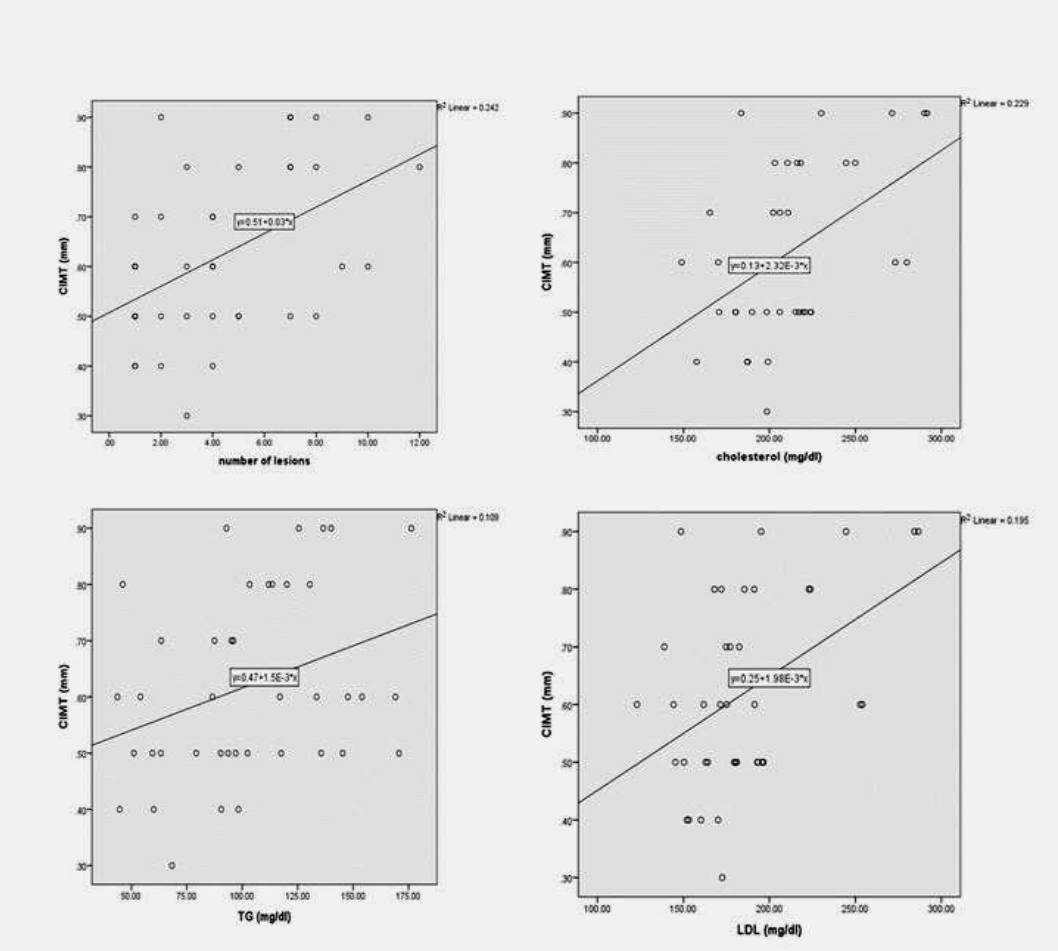

Figure 3. Correlations between CIMT and STs number(r= 0.49, P=0.001) (a), CH(r=0.48, P=0.002)(b),TG(r=0.33, P=0.038)(c)andLDL(r=0.44, P=0.004)(d).

Table 1. Personal data of studied groups and clinical characteristics of STs patients.

	STs patients (n=80)	**Controls (n=60)**	**Test of significance**	**P- value**
Demographic characteristics				
Age (years)				
-Mean ± SD	32.61±7.14	32.50±3.66	t=0.13	0.895
-Median	32.50	31.00		
-Range	27-58	25-55		
Sex: [No (%)]				
-Males	20 (25)	20 (33)	$\chi 2$=1.17	0.280
-Females	60 (75)	40 (67)		
BMI (kg/m^2):				
-Mean ± SD	26.61±2.42	26.91±1.55	t=0.49	0.628
-Median	27.31	27.38		
-Range	20.8-29.6	24.3-29.3		
Clinical characteristics of STs patients				
Age of onset (years):				
-Mean ±SD	28.74±7.39	--------	--------	--------
-Median	28.05			
-Range	25-43			
Site of lesion: [n (%)]				

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-Head & neck	62 (77.5)	--------	--------	--------
-Axilla	18 (22.5)			
Number of lesions:				
-Mean ±SD	4.25±3.09	--------	--------	--------
-Median	4			
-Range	1-12			
STs severity: [n (%)]				
-Mild (1-10)	74 (92.5)	--------	--------	--------
-Moderate (10-30)	6 (7.5)			
Duration of disease (years):				
-Mean ±SD	3.07±2.96	--------	--------	--------
-Median	2.00			
-Range	0.17-10			
Family history: [n (%)]				
-Positive	60 (75.0)	--------	--------	--------
-Negative	20 (25.0)			

- n: number.- t: test.-BMI: Body mass index.-SD: standard deviation.
- χ^2: Chi-square test.-STs: skin tags.-*: significant

Table 2. Lipid profile and CIMT of STs patients and controls.

Variables	STs patients (n=80)	Controls (n=60)	t- test	P- value
CH (mg/dl)				
-Mean ± SD	211.48±34.47	168.57±19.50	5.16	<0.001*
-Median	206.08	167.28		
-Range	149-291.7	134.7-210.1		
TG (mg/dl)				
-Mean ± SD	102.79±36.64	79.96±30.79	2.39	0.020*
-Median	97.67	80.27		
-Range	43.7-176.2	43.3-166.2		
HDL (mg/dl)				
-Mean ± SD	42.66±8.71	47.76±10.31	1.90	0.063
-Median	43.54	47.52		
-Range	24.2-55.0	24.2-75.5		
LDL (mg/dl)				
-Mean ± SD	185.42±37.23	137.78±14.91	4.49	<0.001*
-Median	178.35	143.65		
-Range	123.0-286.6	106.7-170.2		
CIMT(mm)				
Mean ± SD	0.62±0.17	0.51±0.11	2.79	0.007*
-Median	0.60	0.50		
-Range	0.3-0.9	0.3-0.7		

-STs: skin tags.-TG: triglyceride.-HDL: high density lipoprotein.

-LDL: low density lipoprotein.-CH: cholesterol.

-*: significant. - n: number. -SD: standard deviation. - t: test.