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Original Article

Biochemistry Section

Understanding the Inflammatory Biomarkers in Patients with Acrochordons: A Case-control Study

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ABSTRACT

Introduction: Acrochordons kown as Skin Tags (ST) are common benign skin tumours usually occurring on the neck and major flexors of older and obese people. A few studies with conflicting results have been reported regarding the abnormalities of carbohydrate or lipid metabolisms, and the involvement of some inflammatory markers in patients with acrochordons.

Aim: Comparison of Fasting Blood Sugar (FBS), lipid profile, and C-Reactive Protein (CRP) between patients with acrochordon, and healthy controls.

Materials and Methods: The case-control study was conducted in the Department of Biochemistry and Dermatology of Pramukhswami Medical College, Karamsad, Gujarat, India. A total number of 160 subjects (80 healthy controls and 80 cases with acrochordons) were included. The FBS, lipid profile, and CRP were measured. Statistical analysis was performed by Independent t-test, one-way Analysis of Variance (ANOVA), frequency, descriptive statistics and Pearson's correlation coefficient (r).

Results: Total 160 subjects were included in study, 80 in each case and control group (51 female and 29 male in both groups). Age and sex between two groups were matched with mean age 47.68 years. The mean FBS for cases and controls were 133.24 and 84.9 mg/dL respectively. The mean CRP for cases and controls were 17.33 and 1.66 mg/L respectively. Significant differences were recognised for means of BMI, FBS and CRP between two groups (p-value <0.001). These parameters had significant difference between two groups in aspect of various size, colour and number of acrochordons (p-value <0.001).

Conclusion: Threat of progress of metabolic syndrome is significantly higher in patients with acrochordons. Among the many elements of inflammations and metabolic syndrome, BMI, CRP, lipid profile and plasma sugar are remarkably linked with acrochordons.

Keywords: Acanthosis nigricans, Atherosclerosis, Diabetes mellitus, Insulin resistance, Skin tags

INTRODUCTION

Acrochordrons are also known as the Skin Tags (ST) [1]. They are tiny lesions or sprouting on the skin which hold the colour of the flesh or roll in a brown colour. They hang off from the skin, and closely resemble other skin problems like seborrheic keratosis, Dermatosis Papulosa Nigra (DPN), mole, or warts. ST can vary in size from a few millimetres up to a bit of cm [2,3]. They are usually found on the neck, on the eyelids, under the folds of the buttocks, armpits, around the groin, or under the breasts. ST often develops in areas of friction [4].

Acrochordons are smooth, knobby, soft and hang off the skin, whereas warts are rougher, usually flat with an irregular surface. Acrochordons aren't contagious, but warts spread very easily, so a sudden outbreak or cluster of growths is more likely with warts. A seborrheic keratosis is a very common benign lesion that typically appears as waxy stuck-on plaque. Dermatosis Papulosa Nigra (DPN) is a benign cutaneous condition common among blacks. It is usually characterised by multiple, small, hyperpigmented, asymptomatic papules on the face of adult blacks. A mole (nevus) is a pigmented (colored) spot on the outer layer of the skin (epidermis).

Acrochordrons are most common benign dermatological lesions generally found in the general population and have been associated with diabetes mellitus, obesity, acanthosis nigricans, insulin resistance and atherosclerosis [5-9]. Early apprehension of patients with insulin resistance may play an important defending role.

In obesity, formulation of inflammatory cytokines by Visceral Adipose Tissue (VAT) macrophages exaggerates significantly. This situation creates a general subclinical inflammatory state that will ultimately leads to altered insulin responsiveness. Macrophages have been perceived as major sources of proinflammatory mediators, which are largely culpable for the explanation of insulin resistance. The alleged classically activated or 'M1' macrophages secrete more numbers of inflammatory mediators while the alternatively activated "M2" macrophages are low cytokine producers [10].

Leptin is a protein secreted by adipose tissue, which has a crucial role in metabolism and immunity. It balances body weight, appetite and energy expenditure. Additionally, leptin conciliates proliferative and anti-apoptotic activities in different cell types, including T cells, macrophages and eosinophils.Plasma leptin frame-ups a strong association with cardiovascular risk factors, including obesity, insulin resistance, dyslipidemia, and hyperuricaemia [11-14].

Acrochordrons are strongly associated with prediabetes, also called insulin resistance, and type-2 diabetes. An epidemic in our country of type-2 diabetes, early detection can prevent the development of this deadly disease. The diabetics on average, live 10 to 15 years less than the non-diabetics. As few as three acrochordons on the body are coupled with increased diabetes risk. Research has also shown that those with ST have higher cholesterol, Triglycerides (TG), blood sugar, and CRP than those without acrochordrons (all risk factors for diabetes and cardiovascular disease). Those people with elevated CRP, a marker for inflammation in the body, more likely to develop diabetes. So although ST looks bad, they are actually an ominous sign for diabetes that should not be ignored.Variations in oestrogen levels and trophic hormones such as Insulin like growth factor, as well as increased mast cell counts are involved in the genesis and development of the acrochordons [15-18].

C-reactive protein, dyslipidemia, and hyperglycaemia are implicated as a strong risk factor of atherosclerosis and coronary heart diseases in the patients of the acrochordons. As the acrochordon, a marker of inflammatory state, that correlates with an increased risk of

cardiovascular disorders, prompts for preventive measures in patients with the acrochordon like weight reduction, avoidance of smoking and commitment to healthy lifestyle. So we have carried out this study with objectives to assess association between acrochordons, lipid profile, glycaemic control (FBS) and inflammatory marker (CRP).

MATERIALS AND METHODS

The case-control study was conducted in the Department of Biochemistry and Dermatology of Pramukhswami Medical College, Karamsad, Gujarat, India, from May 2014 to April 2015. Ethical clearance was obtained by Institution's Human Research Ethics Committee. (Ref:HMPCMCE: HREC/UGPG/23/SESSION 1/12).

Inclusion and exclusion criteria: This study had enrolled 80 patients with the acrochordon and 80 healthy controls without acrochordon. Age and sex between two groups were matched. Patients were excluded from the study, if they had acromegaly, pheochromocytoma, pregnancy, cushing's syndrome or any drug history.

For measurement of fasting blood glucose and lipid profile 5 mL of fasting (8-10 hours) venous samples were taken in fluoride bulb and CRP samples were taken in plain bulb by using aseptic precautions after obtaining informed consent.

All tests were estimated by fully automated analyser by colorimetric methods which were following:

- CRP was estimated by Latex particles enhanced turbidometry method.
- FBS was estimated by Colorimetric kinetic HEXOKINASE method.
- Total Cholesterol (TC) was estimated by Colorimetric assay Cholesterol oxidase (CHOD) Peroxidase (POD) method method.
- TG was estimated by Colorimetric endpoint Glycerine Phosphate Oxidase Peroxidase(GPO-PAP) method.
- High Density Lipoprotein (HDL) was estimated by Colorimetric Homogenous enzymatic method.

Other parameters were:

- Low Density Lipoprotein (LDL)=Total Cholesterol-(HDL+VLDL)
- Very LDL (VLDL)=TG/5
- TG/HDL ratio
- LDL/HDL ratio

STATISTICAL ANALYSIS

Analysis was performed using the commercially available Statistical Software STATA (14.2), and Microsoft Excel 2016. The p-value of less than 0.05 was considered statistically significant. All of the above were proved by applying Independent t-test, One-way Analysis of Variance (ANOVA), Frequency, Descriptive statistics, Pearson's correlation coefficient (r).

RESULTS

This study had enrolled total 160 subjects, out of which 80 subjects were in case group and 80 subjects were in control group. All the subjects were >25 years of age with most common age group in both cases and control groups was 46-55 years (38.75%) with mean age of 47.68 years (95% CI-28.54 to 66.82). In both the groups, out of 80 subjects, 51 subjects were female with a mean age of 46.88 years with (95% CI: 27.38-66.38), and 29 subjects were male with a mean age of 49.06 years with (95% CI: 30.58-67.54) [Table/Fig-1].

There were no significant differences between two groups in age and gender distributions (p>0.05). There were, 33 patients with known case of type-2 diabetes (41.25%), 24 cases with prediabetes (30%), and remaining 23 (28.75%) patients with normal fasting blood glucose in the case group. In cases 23 patients (28.75%) were with acanthosis nigricans (female-16, male-7).

Age (years)	Gender		n (%)
	Female n (%)	Male n (%)	
≤35	6 (7.5)	3 (3.75)	9 (11.25)
36-45	16 (20)	7 (8.75)	23 (28.75)
46-55	19 (23.75)	12 (15)	31 (38.75)
56-65	9 (11.25)	6 (7.5)	15 (18.75)
66-75	1 (1.25)	1 (1.25)	2 (2.5)
Total	51 (63.75)	29 (36.25)	80 (100)

[Table/Fig-1]: Demographic data same for both control and cases groups (n=80 in each group).

T-test was applied in group statistics for variables like BMI, CRP and FBS. Group-1 stands for cases, Group-2 stands for controls [Table/Fig-2,3]. The mean BMI for cases and controls were 31.66 kg/m^2 and 23.88 kg/m^2, respectively. The mean FBS for cases and controls were 133.24 and 84.9 mg/dL respectively. The mean CRP for cases and controls were 17.33 and 1.66 mg/L respectively. Significant differences were recognised for means of BMI, FBS and CRP between two groups (p-value <0.001). Authors had established significant positive correlation between number of acrochordons with the means of FBS, cholesterol and TG (r=0.827, 0.579, 0.837, p-value <0.01 respectively) [Table/Fig-4,5]. There were also significant positive correlation between LDL and number of acrochordons, at the p-value=0.01 level with Pearson's correlation (r=0.593). The HDL were negatively correlated with number of acrochordons, which was significant {p-value <0.001, Pearson's correlation (r=-0.798)} [Table/Fig-4,5]. One-way ANOVA and descriptive statistics were applied between various groups on the basis of in various sizes and colour of acrochordon with lipid profile and FBS.

Variables	Group	Number	Mean	Std. Deviation (SD)
BMI	1	80	31.66	4.43
	2	80	23.88	1.36
FBS	1	80	133.24	30.77
	2	80	84.9	8.9
CRP	1	80	17.33	7.31
	2	80	1.66	0.655

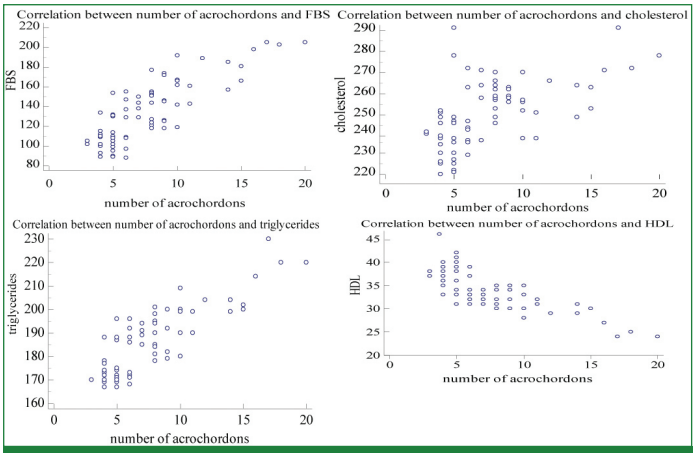
[Table/Fig-2]: Mean and SD of BMI, FBS and CRP for both groups.
BMI: Basal metabolic index; FBS: Fasting blood sugar; CRP: C-reactive protein

Variables	t-test for equality of means			
	t	df	Sig. (2-tailed)	Mean difference
BMI equal variance assumed	15.03	158	0.001	7.78
BMI equal not variance assumed	15.03	93.72	0.001	7.78
FBS equal variance assumed	13.49	158	0.001	48.34
FBS equal not variance assumed	13.49	92.13	0.001	48.34
CRP equal variance assumed	19.10	158	0.001	15.67
CRP equal not variance assumed	19.10	80.3	0.001	15.67

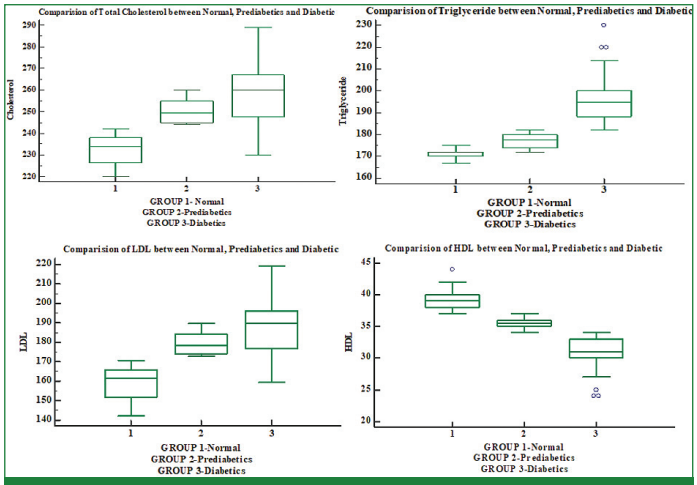
[Table/Fig-3]: Independent samples t-test for BMI, FBS and CRP.
BMI: Basal metabolic index; FBS: Fasting blood sugar; CRP: C-reactive protein

Statistical tests	HDL and No. of ST	FBS and No. of ST	CHO and No. of ST	TG and No. of ST
r	-0.798**	0.827**	0.579**	0.837**
Sig. (2- tailed)	0.001	0.001	0.001	0.001
N	160	160	160	160

[Table/Fig-4]: Correlation between number of Acrochordon and HDL, FBS, Cholesterol and Triglyceride (TG).
CHO: Cholesterol; TG: Triglyceride; ST: Skin tags; r: Pearsons correlation r; N: Number; **r is a correlation coefficient. It ranges from -1.0 to +1.0. The closer r is to +1 or -1, the more closely the two variables are related. If r is close to 0, it means there is no relationship between the variables. If between 0 to +1.0, it means positive relation between two variables with low to higher degree. If between 0 to -1.0, it means negative relation between two variables with low to higher degree



[Table/Fig-5]: Correlation between number of Acrochordons and biochemical markers like Fasting Blood Sugar (FBS), Triglyceride (TG), Cholesterol and High Density Lipoprotein (HDL).



[Table/Fig-6]: Significant difference in lipid profile among diabetic, prediabetic and normal subjects in cases.

Group classification between various size of Acrochordon: (L=Large, S=Small, M=Moderate, Mx=Mixed) were made. Group classification between various colour of Acrochordon: (F=Flesh, H=hyperpigmented, Mx=Mixed, DB=Dark brown) were also made.

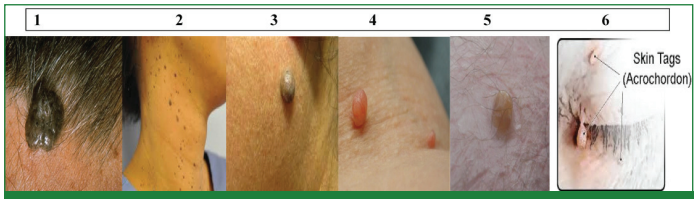
In cases, from small to large size, among groups on the basis of various size of the acrochordons, mean of cholesterol TG, LDL, and FBS were showing increase in value. In cases from light to dark colour, among groups on the basis of various colour of the acrochordons mean of cholesterol, TG, LDL, and FBS were showing increasing value. There were significant differences in various size and colour of the acrochordons for cholesterol, TG, LDL, and FBS in between groups and within groups (p-value <0.001) with positive correlation. LDL/HDL ratio for various size of the acrochordons L=6.67, M=5.30, Mx=5.55, S=4.46 respectively with significant differences (p-value <0.05). For VLDL various size of the acrochordons L=40.86, M=38.74, Mx=38.77, S=35.22 respectively with significant differences (p-value <0.05). For TC/HDL various size of the acrochordons L=9.09, M=8.11, Mx=8.19, S=6.65 respectively with significant differences (p-value <0.05). For HDL various size of the acrochordons were L=28.86, M=31.64, Mx=31.71, S=36.90 respectively with significant differences (p-value <0.05).

Prevalence of site of acrochordons were axilla was 57%, neck was 15%, both axilla, and neck 10% and remaining 18% contributed by mix sites (groin, eyelids and others). LDL/HDL ratio for various colour of the acrochordons like F, H, Mx, DB mean were 4.52, 4.90 and 5.29, 6.35, respectively (p-value <0.05). For VLDL for various colour of the acrochordons like F, H, Mx, DB mean were 35.03, 38.13, 38.82 and 40.54, respectively (p-value <0.05). For TC/HDL for various colour of the acrochordons like F, H, Mx, DB mean were 6.52, 7.97, 8.28 and 8.85, respectively (p-value <0.05). For HDL for various colour of the acrochordons like F, H, Mx, DB mean were 37.18, 32.17, 31.78 and 29.50, respectively (p-value <0.05). Applying Independent samples t-test in lipid profile for all parameters between two groups, and they were significantly higher in case group than control group (p-value <0.001 for all).

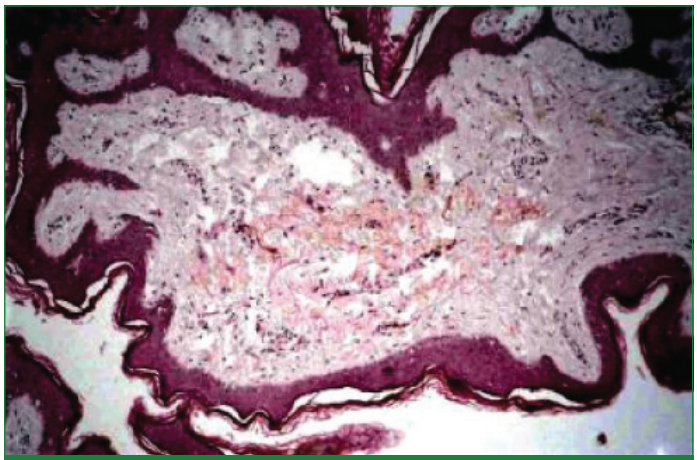
On comparison of acrochordon patients having diabetes, prediabetes and normal state, it was found that the levels of serum TC, TG, and LDL were significantly higher in the diabetic group than the prediabetic group [Table/Fig-6]. On the contrary, significantly higher HDL levels could be observed in prediabetics when compared with diabetic patients (p-value <0.001). CRP was not statistically significant between diabetics, and prediabetics (p-value >0.05). There were also significant differences in other lipid profile parameters like VLDL, TC/HDL, LDL/HDL among diabetic, prediabetic and normal subjects in case group (p-value <0.05). This further corroborates with the increased incidence of acrochordon in the diabetics than prediabetics.

DISCUSSION

In this study, other acrochordons like skin lesions in the patients were also noted. They were differentiated from acrochordons by clinical history and other features like histopathological findings [Table/Fig-7]. Authors had differentiated acrochordons and other acrochordons like skin lesions by histopathological features mentioned in [Table/Fig-8].



[Table/Fig-7]: Acrochordons and other similar skin problems. (1-Seborrheic keratosis, 2-Dermatosis Papulosa Nigra (DPN), 3-Mole, 4-Acrochordon, 5-wart, 6-Acrochordon).



[Table/Fig-8]: A hyperplastic epidermis showing papillomatosis, hyperkeratosis, and acanthosis overlying loosely arranged collagen fibers with many capillaries.

Puri N demonstrated flexural involvement in 40% patients, lip involvement in 6.6% patients, dorsal involvement in 3.3% patients, in a study of pathogenesis of Acanthosis nigricans and its clinical implications [19]. In this study, prevalences of site of acrochordons were in axilla was 57%, neck was 15%, both axilla and neck 10% and remaining 18% contributed by mix sites (groin, eyelids and others) which concluded some congruent results supporting with this study.

El-Zawahry KM and Abdallah MA EH, in their study reported some identical findings with the present study in reference to ST were more common in diabetics and obese patients [20]. But there was no correlation between the presence of ST and age (p>0.05). Also there was more prevalence in male compared to female unlike the present study. The prevalence of ST was detected more often among male (68%) than among female participants (32%). This was statistically significant (p-value <0.05). ST was higher among diabetic (60.5%) than among non diabetic (39.5%) participants.

Idris S and Sunitha S in their study established that, the acrochordons group had significantly higher values of BMI, TC, and TC/HDL ratio (p-value <0.05) [21]. That was also supporting with the present study findings. In the present study, there was a statistically significant higher mean BMI in cases (mean=31.66 kg/m^2) than healthy controls (23.88 kg/m^2, p-value <0.001).

Hegazy SK and El-Ashmawy NE constructed similar type of study in the sense of involvement of Leptin and C-reactive protein implication in the pathogenesis of ST [11]. They demonstrated that ST patients were insulin resistant with elevated HOMA-IR. They showed higher levels of plasma cholesterol, TGs, LDL-cholesterol, high-sensitivity C-reactive protein (hs-CRP) and Tumour necrosis factor α (TNFα) than the control group. The mean CRP was statistically highly significant in cases (mean=17.33 mg/L) than healthy controls (1.66 mg/L, p-value <0.05), in the present study.

Rasi A et al., had established a positive correlation between the total number of acrochordons and fasting plasma glucose (FPG) [6] which plays a supportive role with our findings. There are also some studies which favour relationship between metabolic syndrome, lipid profile and acrochordons [22-24].

In present study, authors had evaluated positive significant relation between biomarkers, which are involved in pathogenicity for inflammations, fibrosis, insulin resistance and other metabolic alterations. So, the present study can appraise future health of acrochordon patients and can prevent chain of incidences like cardiovascular atherosclerosis and other metabolic alterations.

Limitation(s)

This study could not evaluate the impacts of metabolic syndrome, homocysteine, endothelin-1, hs-CRP, leptin, other hormonal profiles, inflammatory markers and various lipoproteins {Apolipoprotein A-I (apo A-I); Apolipoprotein B100 (apoB100); Apolipoprotein B-48 (apo B-48); Lipoprotein (a)} with their ratio on acrochordons, if done could have added more repercussions on the study. Addition of detailed history of hormonal status, diet, lifestyle behaviour and other family history along with skin biopsy could have make the study more distinctive.

CONCLUSION(S)

This study showed that those with acrochordons have higher values of lipid profile (cholesterol, TGs, LDL and other variables), blood sugar, and CRP, marker for inflammation in the body (all risk factors for diabetes, atherosclerosis, and cardiovascular disease) than those without acrochordons. So, although acrochordon appearance is cosmetically bad, they are absolutely a threatening sign for diabetes that we should not overlook.

REFERENCES

[1] Cutaneous Skin Tags: Medline Plus Medical Encyclopedia [Internet]. [cited 2011 Jan 18]. Available from: http://www.nlm.nih.gov.
[2] A Skin Disease Atlas. Available from: http://www.dermnet.com.
[3] Differentiating Features between Acrochordon and Warts [Internet]. Available from: http://www.nhs.uk/conditions/skin-tags/pages/introduction.aspx.
[4] Allegue F, Fachal C, Pérez-Pérez L. Friction induced skin tags. Dermatol Online J. 2008;14(3):18.
[5] Yılmaz E, Kelekci KH, Kelekci S. Skin tag and acanthosisnigricans: Do they have a predictive value for gestational diabetes mellitus? Exp Clin Endocrinol Diabetes. 2011;119(7):419-22.
[6] Rasi A, Soltani-Arabshahi R, Shahbazi N. Skin tag as a cutaneous marker for impaired carbohydrate metabolism: A case-control study. Int J Dermatol. 2007;46(11):1155-59.
[7] Erdoğan BS, Aktan S, Rota S, Ergin S, Evliyaoğlu D. Skin tags and atherosclerotic risk factors. J Dermatol. 2005;32(5):371-75.
[8] Dm T. Skin tags as markers of diabetes mellitus: An epidemiological study. India J Dermatol. 1995;22(10):729-31.
[9] Mathur SK, Bhargava P. Insulin resistance and skin tags. Dermatology. 1997;195(2):184.
[10] Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003;112(12):1796-808.
[11] Hegazy SK, El-Ashmawy NE. Leptin and c-reactive protein are implicated in the pathogenesis of skin tags. J Diabetes Res ClinMetab. 2013;2(1):13.
[12] El Safoury OS, Abdel Hay RM, Fawzy MM, Kadry D, Amin IM, Abu Zeid OM, et al. Skin tags, leptin, metabolic syndrome and change of the life style. Indian J Dermatol Venereol Leprol. 2011;77:577-80.
[13] Wauters M, Considine RV, Van Gaal LF. Human leptin: From an adipocyte hormone to an endocrine mediator. Eur J Endocrinol. 2000;143(3):293-311.
[14] Gorpelioglu C, Erdal E, Ardicoglu Y, Adam B, Sarifakioglu E. Serum leptin, atherogenic lipids and glucose levels in patients with skin tags. Indian J Dermatol. 2009;54(1):20-22.
[15] Indulekha K, Surendar J, Mohan V. High sensitivity C-reactive protein, tumour necrosis factor-α, interleukin-6, and vascular cell adhesion molecule-1 levels in Asian Indians with metabolic syndrome and insulin resistance (CURES-105). J Diabetes Sci Technol. 2011;5(4):982-88.
[16] Rifai N, Ridker PM. High-sensitivity C-reactive protein: A novel and promising marker of coronary heart disease. Clin Chem. 2001;47(3):403-11.
[17] Hegazy SK, El-Ashmawy NE. Leptin and c-reactive protein are implicated in the pathogenesis of skin tags. J Diabetes Res ClinMetab. 2013;2(1):13.
[18] El Safoury O, Rashid L IM. A study of androgen and estrogen receptors α, β in skin tags. Indian J Dermatol. 2010;55(1):20-24.
[19] PuriN.A study of pathogenesis of acanthosisnigricans and its clinical implications Indian J Dermatol. 2011;56(6):678-83.
[20] El-Zawahry KM, Abdallah MA EH. Study of the possible relationship between skin tags and obesity in Egypt. Egypt J Dermatol Venerol. 2013;33:18-21.
[21] Idris S, Sunitha S. Assessment of BMI, serum leptin levels and lipid profile in patients with skin tags. J Clin Diagn Res. 2014;8(9):CC01-03. PMC. Web. 9 July 2016.
[22] Shah R, Jindal A, Patel NM. Acrochordons as a cutaneous sign of metabolic syndrome: A case-control study. Ann Med Health Sci Res. 2014;4(2):202-05.
[23] Sari R, Akman A, Alpsoy E, Balci MK. The metabolic profile in patients with skin tags. Clin Exp Med. 2010;10(3):193-97.
[24] El Safoury OS, Ezzat M, Abdelhamid MF, Shoukry N, Badawy E. The evaluation of the impact of age, skin tags, metabolic syndrome, body mass index, and smoking on homocysteine, endothelin-1, high-sensitive c-reactive protein, and on the heart. Indian J Dermatol. 2013;58(4):326.

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