ORIGINAL RESEARCH PAPER

General Medicine

CORRELATION OF ACANTHOSIS NIGRICANS AND ACROCHORDONS WITH INSULIN RESISTANCE- A CASE CONTROL STUDY.

Dr Girija Subramanian	Associate professor, Department of General Medicine, Sri Manakula Vinayagar Medical College, Kalitheerthal kuppam ,Puducherry ,India 605107.
Dr Tukuntla Vishwa Teja*	Assistant professor, Department of General Medicine, Malla Reddy Medical College for Women's, Hyderabad. *Corresponding Author
Dr. Kaliaperumal Karthikeyan	Professor & Head ,Department of Dermatology, Sri Manakula Vinayagar Medical College, Kalitheerthalkuppam, Madagadipet, Puducherry 605107, India

ABSTRACT

Introduction: Insulin resistance shown to be associated with and even precede cardiovascular diseases, diabetes mellitus and metabolic syndrome could be identified by cutaneous markers of insulin resistance namely, Acanthosois nigricans and Acrochordons.

Objective: The aim was to assess the presence of cutaneous lesions and relate with Insulin resistance.

Materials and methods: A total of 80 patients (40 cases and 40 controls) had their BMI, Waist Hip ratio (WHR), lipid profile, fasting glucose levels and fasting insulin levels checked, HOMA-IR was calculated and correlation between skin lesions and insulin resistance was evaluated.

Results: The mean age of the participants was 44 years (range 20-70) with a female preponderance. The mean BMI in cases was 26.19 +4.1 and in controls 23.60 + 2.5. This shows the significant risk by odds ratio of 2.07 times. The mean WHR in cases showed the significant risk by odds ratio of 1.57 times. The mean total cholesterol value in cases with odds ratio of 1.13 and the mean LDL cholesterol value in cases with odds ratio of 1.76 showed a significant risk. The mean HOMA-IR values in cases with odds ratio of 1.58 showed that individuals with HOMA-IR more than 1.7 have 1.58 times risk of developing skin lesions i.e. Acanthosis and Acrochordons.

Conclusion: This study shows a significant risk association between skin lesions and insulin resistance .

INTRODUCTION:

Insulin resistance is a metabolic disorder in which target cells fail to respond to normal levels of circulating insulin, resulting in compensatory hyperinsulinemia by the pancreatic β cells. Insulin resistance syndrome denotes the cluster of abnormalities that manifest in different tissues leading to abnormalities with serious clinical consequences, including cardiovascular disease and type2 diabetes mellitus, polycystic ovary syndrome, non-alcoholic fatty liver disease[1],other illnesses like malignancies, metabolic syndrome X, accelerated atherosclerosis, systemic hypertension, and various cutaneous lesions like Acanthosis nigricans, skin tags, hirsutism, acne and papillosis of finger.

Acanthosis nigricans (AN) is a dermatosis characterized by velvety, papillomatous, brownish-black, hyperkeratotic plaques found typically on the intertriginous surfaces and neck. The majority (80%) of AN occurs idiopathically or in benign conditions such as endocrinopathies like diabetes mellitus, polycystic ovary syndrome; metabolic syndrome and/or heritable disease. Malignancy-associated AN is rare. It is observed that most patients with Acanthosis nigricans have either clinical or subclinical insulin resistance.[2]

Acrochordons (skin tags) are small, soft, benign skin tumors that are seen most often on the sides of the neck or groin, and occasionally on the thorax varying in diameter from 1 to 6 mm. Deepa et al in their study on prevalence of insulin resistance syndrome in selected South Indian population- CUPS-7 have shown that the overall prevalence of insulin resistance syndrome was 11.2%.[3] Studies have shown that there is strong association between insulin resistance and multiple skin tags irrespective of other risk factors.[4] Insulin resistance stimulates insulin secretion, which in turn stimulates IGF-1 receptors of keratinocytes leading to epidermal growth. So these cutaneous markers could be an indicator of Insulin resistance status.[5]

Insulin resistance is shown to be the basis for development of glucose intolerance including diabetes and Coronary artery disease (CAD). Insulin resistance has been detected 10 to 20 years before developing diabetes in individuals who are offspring of patients with type 2 diabetes.[6] Skin manifestations of insulin resistance (e.g., acrochordons, acanthosis nigricans, androgenetic alopecia, acne, hirsutism) have shown to be to a reliable, easy and way of detecting insulin resistance.[7]

Aims and objectives:

The objectives of the study are as follows:
1) To detect the correlation between cutaneous lesions like (Acanthosis nigricans and Acrochordons) with Insulin resistance.
2) To relate severity of cutaneous lesions with insulin resistance.

MATERIAL AND METHODS:

The study was a hospital based , case control (age and sex matched) study conducted in the outpatient departments of General medicine and Dermatology of Sri Manakula Vinayagar Medical College Puducherry after clearance from Research and ethical committee.

A total of 80 patients were included in the study -40 cases and 40 controls .This study was conducted over a period of 12 months. Adult patients more than 18 years of age were included in the study after getting informed consent from the patients.

Case definition:

Cases were defined as patients with various grades of Acanthosis nigricans. The lesions of acanthosis nigricans were graded using a scale by BurkeJP etal.[8] Patients with acrochordons were graded by using a grading scale by Kahana M, El Safoury et al using thenumber, size, site, and color of lesions.[9,10] The grading of lesions was verified by a senior dermatologist.

Control definition:

Controls were defined as age and sex matched patients

without cutaneous lesions (i.e. Acanthosis nigricans and Acrochordons). Patients with Cushing's syndrome , Acromegaly, patients on steroids and insulin were excluded from the study. All the patients recruited in the study had their height, weight, Body mass index (BMI), Waist – Hip ratio, (Cutoff values of waist-hip ratio(WHRs) for male and female 0.88 and0.81, respectively)and blood pressure checked. The lipid profile, fasting plasma glucose and fasting Insulin levels were checked and HOMA-IR (Homeostasis model assessment index) was calculated using the formula: fasting plasma glucose X fasting insulin levels / 405. A value of more than 1.7 was considered as insulin resistance.

The categorical variables were described with frequencies and percentages while the continuous variables were described by mean and standard deviation. Chi square test and odds ratio were used to find out the risk association for categorical variable and student t test was used to compare mean difference. Continuous variables like BMI, WHR, HOMA-IR, lipid profile etc. were categorized based on cut off values . A 'P' value <0.05 is considered significant.When odds ratio is 1 --exposure does not affect odds of outcome, >1 - exposure associated with higher Odds of outcome, <1 -exposure associated with lower odds of outcome.

RESULTS:
Our study included a total of 80 patients, consisting of 40 controls and 40 patients, who were age, sex matched. The age of the study population ranged from 20 to 70 years with a mean of 44.93 + 9.4. Most of the patients studied were in the age group of 36 – 55 years (Female:Male 66:14) . In the study population all 40 (100%) had Acanthosis Nigricans and 36 (85%) had Acrochordons.

Acanthosis nigricans severity grading was done in cases according to the quantitative scale of by Burke et al. In neck, severity grading was moderate (grade 3) for 20 patients and severe (grade 4) for 3 patients, as shown in figure 1.
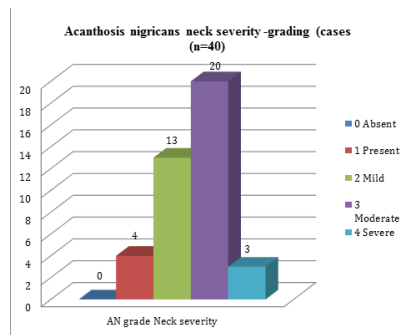

Figure 1 – Acanthosis nigricans neck severity grading in cases

In neck texture grading score, most of the patients (21) had score 1(rough to touch). In axilla most of the patients (15) had a score of 1 (present). In the study population 6 patients had Acanthosis Nigricans on knuckles and none of them had on knees. All the 40 cases had AN on the lateral aspect of the neck, the most common anatomical area. It was also the area where the texture and severity of AN were of higher grade.
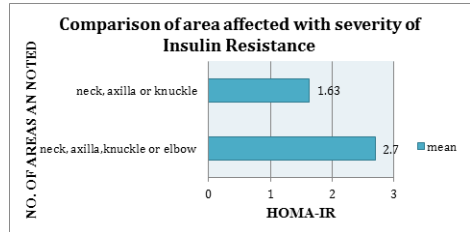

Figure 2: Comparison of areas affected with severity of insulin resistance.

HOMA-IR (mean) was 2.7 with Acanthosis nigricans when areas involved are more than 3 in number (HOMA-IR cut-off <1.7) (figure 2).
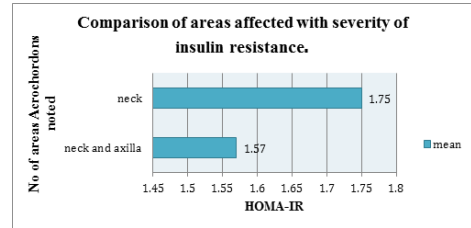

Figure-3: Comparison of areas affected with severity of insulin resistance (Acrochordons)

This study did not show any correlation between numbers of lesions of Acrochordons with the degree (severity) of insulin resistance as depicted in figure 3.

Normal BMI for healthy individuals in Indian population is < 23. The mean BMI in cases was 26.19 + 4.1 and in controls was 23.60 + 2.5. This shows significant risk by odds ratio of 2.07 with 95% confidence interval of 0.78 – 5.5. The inference is that individuals have 2.07 times risk of developing AN and Acrochordons when BMI is more than 23.

Waist Hip Ratio (WHR) the reference cut off value for males is < 0.89 and for females is < 0.81 for normal healthy individuals in Indian population.The mean WHR in cases was 0.91 + .08 and in controls 0.85 + .05. This shows the significant risk by odds ratio of 1.57 and 95% confidence interval of 0.53 – 4.6. The individuals have 1.57 times risk of developing AN and Acrochordons when WHR exceeds the normal cutoff value.

The normal total cholesterol value in healthy individuals is less than 200 mg/dl.The mean total cholesterol values in cases was 173.63 + 60.4 and in controls 170.48 + 54.5 with odds ratio of 1.13 and confidence interval of 0.42 – 3.0, which was statistically significant.

The normal triglycerides value in healthy individuals is less than 150 mg/dl. The mean total cholesterol values in cases 146.13 + 91.8 and in controls 149.70 + 79.2 with odds ratio of 0.8 and confidence interval of 0.32 – 3.01, which shows statistically insignificant.The normal HDL cholesterol value in healthy individuals is more than 40 mg/dl and 50 mg/dl in males and females respectively. The mean HDL cholesterol values (in cases) 40.75 + 9.7 and in controls 40.75 + 9.7 with odds ratio of 0.23 and confidence interval of .025 - 2.163, which is statistically insignificant.

The normal LDL cholesterol value in healthy individuals is less than 165 mg/dl.The mean LDL cholesterol values in cases 106 + 48.6 and in controls 102 + 42.8 with odds ratio of 1.765 and confidence interval of .39 – 7.92, which was statistically significant.

The normal fasting glucose value in healthy individuals is less than 100 mg/dl.The mean fasting glucose values in cases 105 + 50.5 and in controls 103 + 43.5 with odds ratio of 1.11 and confidence interval of .44 – 2.77, which shows statistically insignificant

The normal fasting insulin value in healthy individuals is 2 – 20 mIU / ml.The mean fasting insulin values in cases 6.9 + 3.7 and in controls 5.60 + 1.5, which shows statistically insignificant.

Table 1 - Correlation between AN and Acrochordons with HOMA-IR

Correlation between Acanthosis Nigricans and Acrochordons with HOMA-IR					
HOMA-IR	Cases	Controls	Odds Ratio	95 % CI	p-value

> 1.7	Count	15	11	1.582	.615 – 4.066	.340
	%	37.5%	27.5%			
< 1.7	Count	25	29			
	%	62.5%	72.5%			
Total	Count	40	40			
	%	100.0%	100.0%			
Mean (standard deviation)		1.69(.90)	1.44 (.58)			

Table 1 depicts the mean HOMA-IR values in cases 1.69 + .90 and in controls 1.44 + .58 with odds ratio of 1.58 and confidence interval of .61 – 4.06, this shows the individuals with HOMA-IR more than 1.7 have 1.58 times risk of developing skin lesions i.e. Acanthosis and Acrochordons.

Table 2 - The principle demographic, anthropometric and laboratory characteristics of the groups studied.

Variables	Cases (n = 40)	Control (n = 40)	P value*
Age Years	44.93 (9.4)	44.93 (9.4)	NA
Body Mass Index	26.19 (4.1)	23.60 (2.5)	0.001
Waist-Hip Ratio	0.91 (.08)	0.85 (.05)	0.0001
Total cholesterol mg/dl	173.63 (60.4)	170.48 (54.5)	0.807
Triglycerides mg/dl	146.13 (91.8)	149.70 (79.2)	0.853
High Density Lipid Cholesterol mg/dl	40.75 (9.7)	38.45 (6.7)	0.152
Low Density Lipid Cholesterol mg/dl	106.00 (48.6)	102.75 (42.8)	.752
Fasting glucose mg/dl	105.40 (50.5)	103.85 (43.5)	.884
Fasting Insulin mIU/L	6.91 (3.7)	5.60 (1.5)	.041
HOMA-IR	1.69 (.90)	1.44 (.58)	-

SD: standard deviation, *p value calculated using student's t test.

Table 2shows the frequency of the variables and the bivariate analysis between cases and controls.

AN and Acrochordons were present in 40 and 36 cases respectively and was noted in neck and axilla mostly. The skin lesions namely AN and Acrochordons were primarily and directly associated with BMI, waist-hip ratio, and fasting insulin levels, confirmed by using student's t test. This showed statistically significant p-value.

Table 3 – Multivariate logistic model adjusted for variable for calculated Odds ratio.

Variable	Odds Ratio	95% confidence interval
Body Mass Index	2.07	0.78 - 5.5
Waist-Hip Ratio	1.57	0.53 - 4.65
Total cholesterol mg/dl	1.13	0.42 - 3.08
Triglycerides mg/dl	0.8	0.320 - 2.01
High Density Lipid Cholesterol mg/dl	0.23	0.25 - 2.16
Low Density Lipid Cholesterol mg/dl	1.76	0.39 - 7.9
Fasting glucose mg/dl	1.14	.448 - 2.7
Fasting Insulin mIU/L	-	-
HOMA-IR	1.58	.65 - 4.06

Multivariate analysis corroborated the finding of higher levels of HOMA-IR in the cases and control groups, showed that patients with skin lesions Acanthosis Nigricans and Acrochordons have 1.58 times risk of Insulin Resistance .(Table 3)

DISCUSSION:
Acanthosis nigricans is a well defined skin disorder characterized by velvety hyperkeratotic macules that can be accompanied by various degrees of pigmentation. A scale developed by James P. Burke et al for grading Acanthosis nigricans correlated well with fasting insulin and BMI and had

a good inter observer reliability.

Insulin resistance (IR) is defined when a normal or elevated insulin level produces an attenuated biological response [11] and impaired sensitivity to insulin mediated glucose disposal.

Elevated insulin concentrations result in direct and indirect activation of IGF1 (insulin like growth factor) receptors on keratinocytes and fibroblasts, tyrosine kinase receptors such as EGFR (epidermal growth factor receptor and FGFR (fibroblast growth factor receptor) leading to proliferation. . The severity of AN in obesity correlates positively with the fasting insulin concentration.[12] Hyperinsulinemia may also facilitate the development of AN indirectly by increasing the levels of free IGF1 in the circulation.

The most commonly involved locations are the axillae, neck, external genitalia, groin, face, inner thighs, ante-cubital and popliteal fossae, umbilicus, and perianal area. Distal extremities are usually spared.Insulin neck (visibly increased texture on the poster lateral neck) is the most sensitive physical finding for IR and appears as visible lines and/or furrows and ridges on the poster lateral neck.[13]

Acrochordons are soft, flesh-coloured or brown filiform or dome shaped pedunculated papules, occasionally fleshy nodules that occur in intertriginous areas of neck, axillae, groin and inflammatory creases. Skin tags have been associated with pregnancy, acromegaly, symptomatic intestinal polyps, dyslipidemia, obesity, diabetes mellitus, atherosclerosis and various syndromes including polycystic ovary syndrome, Birt-Hogg-Dubé Syndrome and Cowden syndrome.[14]The lesions are attributed to variations in estrogen levels and trophic hormones such as IGF-1, insulin, TGF (transforming growth factor) and EGF (epidermal growth factor)[15] as suggested by Nanney et.al in their study.Studies have suggested the correlation between Acrochordons with hyperinsulinemic state[16]and impaired carbohydrate metabolism [17].Yilmaz et al. reported that 40% of the pregnant women who had both acrochordons and acanthosis nigricans had gestational DM.[18]

In our study skin lesions AN and Acrochordons were present in 40 and 36 cases respectively. Lesions of Acanthosis nigricans were commonly noted in neck and axilla. Higher grades of Acanthosis Nigricans were seen on the neck and showed higher Insulin Resistance. Patidar et.al. reported that AcanthosisNigricans neck severity grading correlated well with insulin resistance and can be used as a clinical surrogate for assessment of severity of insulin resistance.[19]

There was female predominance in both cases and control groups in our study. Tamega et.al also reported female predominance of skin tags in their study group.[14] Sadeghian et al. investigated the presence of insulin resistance in obese women with and without AN, and the skin lesions proved to be a marker for insulin resistance. There was no significant statistical difference in terms of lipid profile, triglycerides and presence of hypertension between the two groups in their study.[20]

Norris et al. suggested that Acrochordons correlated more closely with hyperinsulinemic state than diabetes[16].Agarwal and Nigam detected abnormality of glucose tolerance in 48 (40.6%) of 118 patients with Acrochordons. Obesity was present in 21.2% of patients.[21]Rasi A. studied 104 patients and 94controls with age, gender and BMI-matched, and found a positive correlation between the total number of Acrochordons and fasting plasma glucose.[22] In our study groups also we had significant risk association between elevated fasting plasma glucose levels and skin lesions AN and Acrochordons.

Kahana et al. observed IGT in 34.3% of 216 patients with Acrochordons and found no correlation between the localization, size, colour and number of the lesions with the presence of glucose intolerance.[9] The skin tags observed were hyperchromic in our study.

Sudy E et al. has shown that the presence of multiple skin tags was strongly associated with Insulin Resistance irrespective of other risk factors and found that eight or more skin tags were related with statistically significant laboratory glucose/insulin abnormalities i.e. Basal hyperinsulinemia, postprandial hyperinsulinemia and postprandial hyperglycaemia.[4] However our study did not relate the number of lesions with the severity of insulin resistance.

Few studies have investigated lipid profile and hypertension in patients with Acrochordons. Sari et al. investigated 113 patients with Acrochordons and 37 controls and found that the frequency of hypertension was 30.1%, dyslipidemia 59.3%, insulin resistance 21.2% and Metabolic syndrome 39.8% in the patient group.[23] Crook reported an atherogenic lipid profile, increased serum triglyceride concentration and decreased HDL cholesterol in a small study group including four patients with acrochordons.[24] William H. K. Schilling et al. suggested an association between metabolic syndrome, its resultant "atherogenic" lipid profile, and a number of cutaneous stigmata and proposed that insulin resistance and abnormal lipids may be implicated in the etiologies of both acrochordons and AN, and possibly in that of Ear lobe creases and some cases of xanthelasma.[25] Our study showed significant elevation of total and LDL cholesterol levels in patients with AN and Acrochordons, whereas triglycerides and HDL cholesterol did not show any association.

The Homeostasis Assessment Model is a mathematical model which allows values for insulin sensitivity and β-cell function (expressed as a percentage of normal) to be obtained if simultaneous fasting plasma glucose and fasting insulin/ C-peptide concentrations areknown[26]. Though Euglycemic insulin clamp test is considered to be the gold standard HOMA IR is widely used in clinical settings to detect Insulin resistance. It had been demonstrated that there was a strong positive correlation between HOMA IR and Euglycemic insulin clamp-IR in type-2 diabetic subjects, as reported by Emoto et al.[27] and Matthews et al.[28] in their studies. In our study, HOMA-IR was used as tool for assessment of insulin resistance.

CONCLUSION:
This study revealed that the patients with skin lesions with a HOMA-IR more than 1.7 have 1.58 times risk of insulin resistance. When BMI exceeded 23, patients showed AN and Acrochordons twice the controls. When WHR is > 0.81 in females and > 0.89 in males, cases had 1.6 times risk of insulin resistance compared to controls.

In this study total cholesterol and LDL cholesterol levels were significantly high in patients with AN and Acrochordons, whereas triglycerides and HDL cholesterol did not show any association. The limitations of the study were the small study group and male representation was small. These patients need longer period of follow up to find out the progression to metabolic syndrome and diabetes mellitus.

It is highly recommended to consider these cutaneous markers during clinical examination and evaluate early for the presence of insulin resistance.

REFERENCES:
1   Einhorn D, Reaven GM, Cobin RH, et al. American College of Endocrinology position statement on the insulin resistance syndrome. Endocr Pract. 2003 May-Jun. 9(3):237-52.
2.   Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM, Roth J. The syndromes of insulin resistance and acanthosis nigricans: insulin-receptor disorders in man. New England Journal of Medicine. 1976 Apr 1;294(14):739-45.
3.   Deepa R, Shanthirani CS, Premalatha G, Sastry NG, Mohan V. Prevalence of insulin resistance syndrome in a selected south Indian population--the Chennai urban population study-7 [CUPS-7]. Indian Journal of Medical Research. 2002 Mar 1;115:11.
4.   Sudy E, Urbina F, Maliqueo M. Screening of glucose/insulin metabolic alterations in men with multiple skin tags on the neck. JDDG: Journal der Deutschen Dermatologischen Gesellschaft. 2008 Oct 1;6(10):852-5.
5.   Barbato M, et al. Association of acanthosis nigricans and skin tags with insulin resistance. An Bras Dermatol. 2012;87:97–104
6.   Kong A, Williams R, Smith M, et al. Acanthosis Nigricans and Diabetes Risk Factors: Prevalence in Young Persons Seen in Southwestern US Primary Care Practices. Ann Fam Med. 2007;5:202–8.
7.   Yamazaki H, Ito S, Yoshida H. Acanthosis nigricans is a reliable cutaneous marker of insulin resistance in obese Japanese children. Pediatr Int. 2003;45:701–705.
8.   Burke JP, Hale DE, Hazuda HP, Stern MP. A quantitative scale of acanthosis nigricans. Diabetes care. 1999 Oct 1;22(10):1655-9.
9.   Kahana M, Grossman E, Feinstein A, Ronnen M, Cohen M, Millet MS. Skin tags: a cutaneous marker for diabetes mellitus. Act adermato-venereologica. 1986 Dec;67(2):175-7.
10. El Safoury OS, Ibrahim M. A clinical evaluation of skin tags in relation to obesity, type 2 diabetes mellitus, age, and sex. Indian J Dermatol 2011;56:3930-7.
11. Cefalu WT. Insulin resistance: cellular and clinical concepts. Experimental biology and medicine. 2001 Jan 1;226(1):13-26.
12. Hud JA, Cohen JB, Wagner JM, Cruz PD. Prevalence and significance of acanthosis nigricans in an adult obese population. Archives of dermatology. 1992 Jul 1;128(7):941-4.
13. Payne KS, Rader RK, Lastra G, Stoecker WV. Posterolateral neck texture (insulin neck): Early sign of insulin resistance. JAMA dermatology. 2013 Jul 1;149(7):875-7.
14. Tamega AD, Aranha AM, Guiotoku MM, Miot LD, Miot HA. Association between skin tags and insulin resistance. Anais brasileiros de dermatologia. 2010 Feb;85(1):25-31.
15. Nanney LB, Ellis DL, Levine J, King LE. Epidermal growth factor receptors in idiopathic and virally induced skin diseases. The American journal of pathology. 1992 Apr;140(4):915.
16. Norris PG, McFadden J, Gale E, Griffiths WA. Skin tags are more closely related to fasting insulin than fasting glucose levels. Act adermato-venereologica. 1988;68(4):367.
17. Demir S, Demir Y. Acrochordon and impaired carbohydrate metabolism. Act adiabetologica. 2002 Jun 1;39 (2):57-9.
18. Yılmaz E, Kelekci KH, Kelekci S. Skin tag and acanthosis nigricans: do they have a predictive value for gestational diabetes mellitus?. Experimental and clinical endocrinology & diabetes. 2011 Jul;119(07):419-22.
19. Patidar PP, Ramachandra P, Philip R, Saran S, Agarwal P, Gutch M, Gupta KK. Correlation of acanthosis nigricans with insulin resistance, anthropometric, and other metabolic parameters in diabetic Indians. Indian journal of endocrinology and metabolism. 2012 Dec;16(Suppl 2):S436.
20. Sadeghian G, Ziaie H, Amini M, ALI NILFROUSHZADEH M. Evaluation of insulin resistance in obese women with and without acanthosis nigricans. The Journal of dermatology. 2009 Apr 1;36(4):209-12.
21. Agarwal JK, Nigam PK. Acrochordon: a cutaneous sign of carbohydrate intolerance. Australasian Journal of Dermatology. 1987 Dec 1;28(3):132-3.
22. Rasi A, Soltani-Arabshahi R, Shahbazi N. Skin tag as a cutaneous marker for impaired carbohydrate metabolism: a case–control study. International journal of dermatology. 2007 Nov 1;46(11):1155-9.
23. Sari R, Akman A, Alpsoy E, Balci MK. The metabolic profile in patients with skin tags. Clinical and experimental medicine. 2010 Sep 1;10(3):193-7.
24. Crook MA. Skin tags and the atherogenic lipid profile. Journal of clinical pathology. 2000 Nov 1;53(11):873-4.
25. Schilling WH, Crook MA. Cutaneous stigmata associated with insulin resistance and increased cardiovascular risk. Int J Dermatol. 2014 Sep;53(9):1062-9.
26. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes care. 1998 Dec 1;21(12):2191-2.
27. Emoto M, Nishizawa Y, Maekawa K, Hiura Y, Kanda H, Kawagishi T, Shoji T, Okuno Y, Morii H. Homeostasis model assessment as a clinical index of insulin resistance in type 2 diabetic patients treated with sulfonylureas. Diabetes care. 1999 May 1;22(5):818-22.
28. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985 Jul 1;28(7):412-9.