

# Correlation of Atherosclerosis with Acanthosis Nigricans of Temporal Region of Face Compared to Neck

Abel Francis<sup>1</sup>, Haseena Hassan C K<sup>2</sup>

## ABSTRACT

**Introduction:** Acanthosis nigricans (AN) is a dermatosis that clinically manifests as asymptomatic and symmetrical darkening of the skin, and it is associated with hyperinsulemia, obesity and metabolic syndrome. Previous studies have shown an increased risk of Acanthosis nigricans and atherosclerosis. Aim: To study correlation of atherosclerosis with Acanthosis nigricans of temporal region of face compared to neck, as assessed by carotid intima media thickness.

**Material and Methods:** The study included 66 patients who are clinically diagnosed as Acanthosis nigricans of temporal region of face and 66 patients with Acanthosis nigricans of neck, attending the outpatient department of dermatology, Amala Institute of Medical Sciences, Thrissur between January 2017 – September 2018. All patients were screened for diabetes mellitus and for insulin resistance by measuring fasting blood sugar, and insulin level. The two groups were sent to measure the Carotid Intima Media Thickness (CIMT). CIMT values  $\geq$  75<sup>th</sup> percentile are considered high and indicative of increased CVD risk.

**Result:** The mean CIMT in group 1 and group 2 were 0.8192 and 0.6159 respectively. The mean CIMT of patients with Acanthosis nigricans over temporal region of face in our study was 0.8192 which was higher compared with the mean CIMT of patients with Acanthosis nigricans over neck (p value is - 0.001). Carotid plaque was present in 4 patients with Acanthosis nigricans over temporal region of face. In group one, 28 patients (42%) had increased CIMT value ( $\geq$  75<sup>th</sup> percentile) and in group two, 11 patients (16.6%) had increased CIMT value. In our study, increased CIMT was associated with metabolic syndrome, insulin resistance, diabetes mellitus, hypertension and hypertriglyceridemia.

**Conclusion:** There is higher prevalence of atherosclerosis in patients with Acanthosis nigricans over temporal region of face (42.42%). This suggests that there is an increased chance for cardiovascular events.

**Keywords:** Acanthosis Nigricans, Carotid Intima Media Thickness

nasolabial folds and cheeks.<sup>3</sup>

Insulin derived growth factor (IGF1) receptors, are overexpressed in obese patients associated with hyperinsulinaemia and insulin resistance. IGF1 stimulate the proliferation of keratinocytes and dermal fibroblasts.<sup>1</sup> At higher concentrations, insulin can exert more potent growth-promoting effects by binding to insulin-like growth factor 1 receptors (IGF-1Rs) that are similar in size and subunit structure to insulin receptors.<sup>4</sup>

IGF receptors are present in fibroblasts and keratinocytes. Insulin can cross DEJ and at high concentrations can stimulate growth and replication of fibroblasts, which leads to the development of hyperkeratosis and papillomatosis observed in Acanthosis nigricans. Thus, insulin may promote development of AN through direct activation of the IGF-1 signaling pathway. Various studies reported the prevalence of AN ranges from 49.2% to 58.2% in children and adolescents with obesity<sup>5</sup> and prevalence of hyperinsulinemia in patients with Acanthosis nigricans was 50.0%.<sup>6</sup> Factors presumed to play a role in IR are tumor necrosis factor  $\alpha$ , adiponectin, leptin, resistin and other adipokines. Macrophages phagocytose adipocytes in the dystopic fat deposition areas and this initiates a chronic, low-grade inflammatory state.<sup>7</sup> Both insulin resistance and hyperinsulinemia play key role in the development of atherosclerosis.<sup>8</sup> Carotid intima-media thickness measurement with B-mode ultrasound is a useful, precise and noninvasive method for the estimation of atherosclerosis in subclinical stages of the illness.<sup>9</sup> Increased carotid intima-media thickness is related to the prevalence and extension of coronary artery disease, incidence of cerebral events and generalized atherosclerosis.<sup>10</sup>

A study done by Shyam Verma also showed, increased prevalence of obesity and insulin resistance in patients presenting with facial Acanthosis nigricans. Therefore, FAN can be considered a cutaneous marker of insulin resistance.<sup>11</sup> Hence we decided to study the correlation of atherosclerosis

## INTRODUCTION

Acanthosis nigricans (AN) is a dermatosis that clinically manifests as asymptomatic and symmetrical darkening affecting the skin over the intertriginous areas, in particular the axillae, groins, submammary folds and neck.<sup>1</sup> Helen Ollendorf Cruth classified it as either benign, malignant, syndromic or obesity-induced. AN can occur on face, presenting as hyperpigmented, raised velvety plaque on cheek and forehead.<sup>2</sup> The most commonly involved area in facial Acanthosis nigricans are the forehead, temples,

<sup>1</sup>Associate Professor, Department of Dermatology, <sup>2</sup>Junior Resident, Department of Dermatology, Amala Institute of Medical Sciences, Thrissur, India

**Corresponding author:** Haseena Hassan C K, Junior Resident, Department of Dermatology, Amala Institute of Medical Sciences, Thrissur, India

**How to cite this article:** Abel Francis, Haseena Hassan C K. Correlation of atherosclerosis with acanthosis nigricans of temporal region of face compared to neck. International Journal of Contemporary Medical Research 2019;6(8):H1-H4.

**DOI:** <http://dx.doi.org/10.21276/ijcmr.2019.6.8.7>

with Acanthosis nigricans of temporal region of face compared to neck by CIMT measurement.

## MATERIAL AND METHODS

After obtaining informed consent, the study included 66 patients who were clinically diagnosed as acanthosis nigricans of temporal region of face and 66 patients with acanthosis nigricans of neck, attending the outpatient department of dermatology, Amala Institute of Medical Sciences, Thrissur between January 2017 – September 2018. Inclusion criteria included patients of age 18-50 years of either sex who are diagnosed to have acanthosis nigricans of temporal region of face and acanthosis nigricans of neck. Exclusion criteria was patients who were chronic smokers (>20 pack year) and chronic alcoholics (In men >60-80g/d of alcohol for 10years, for women >20-40g/d for 10years).

### Method of study

The diagnosis of acanthosis nigricans was made clinically by two dermatologists with an MD qualification and > 5 years of experience. Lifestyle history, medical history and prescribed drug status were evaluated by questionnaire. All patients are screened for diabetes mellitus and for insulin resistance by measuring fasting blood sugar, and insulin level. All subjects underwent a detailed physical examination including height, weight, waist and hip circumference, from these data BMI, waist/hip ratio were calculated. All the two groups were sent to measure the Carotid Intima Media Thickness (CIMT). The CIMT was measured by B mode ultrasound using high frequency linear probe of 10MHz. The common carotid arteries were scanned at the level of bifurcation on either side and mean value was used for analysis. CIMT was assessed by a single observer. CIMT values  $\geq$  75th percentile are considered high and indicative of increased CVD risk.

### STATISTICAL ANALYSIS

Data was entered in Microsoft excel and statistical tests like independent 't' test and Chi square test are used for analysis. Data was analyzed using statistical software SPSS 23. Descriptive statistical methods such as percentage, mean, standard deviation were used to describe the background variables of the study population.

### RESULT

This study comprised of a total of 132 patient (in 2 groups) of age 26-50 years of either gender out of which 66 (in group 1) patients were clinically diagnosed to have facial acanthosis nigricans and 66 patients (in group 2) with acanthosis nigricans of neck. Mean age and standard deviation of the study population was  $40.83 \pm 6.870$ . In group 1 maximum no of patients (26 patients, 39%) fell under 46-50 years and in group 2 majority of the patients were in the age group of 36-40 years (21patients, 31%). In this study 20 (30%) were female and 46 (69%) were male in group 1. Males outnumbered female in group 1, whereas in group 2 females (53%) outnumbered males (46%).

At the time of analysis, 11 patients were obese (8.3%), 6 were obese in group 1 and 5 in group 2. Mean BMI obtained in

group 1 and 2 was 27.1527 and 26.5083 respectively. There was no significant difference in BMI between 2 groups (p value-0.173). Total cholesterol level >200 were found in 20 patients in group 1 and 11 patients in group 2. A history of diabetes mellitus (DM) was present in 35 (26%) in both groups. In group 1 history of diabetes mellitus was present in 22 (33%) and in group 2 was 13 (19.6%). There was no significant difference in diabetes mellitus between 2 groups (p value-0.076). Systemic hypertension was present in 16 (12.12%) patients in both groups. In group 1 systemic hypertension was present in 8 (12%) patients and in group 2 was 8 (12%). There was no significant difference in hypertension between 2 groups (p value-1.000). The mean fasting insulin level in group 1 was 13.6924 and in group 2 was 11.2597 respectively. There was significant difference with mean fasting insulin level between two group (P value - 0.0001). The mean triglyceride value in group 1 was 190.88 and group 2 was 163.92. There is significant difference in the mean triglyceride value between two groups (p value-0.001). The mean HOMA-IR in group 1 was 3.46864 and in group 2 was 2.70235 respectively. There was significant difference with mean HOMA-IR between two group (p value -0.002). Metabolic syndrome was present in 37 patients (28%) out of 132 patients. In group one, 20(30%) and in group two, 17 (25.7%) patients having Acanthosis nigricans. The mean of CIMT in group 1, group 2, are 0.8192 and 0.6159 respectively. Carotid plaque was present in 4 patients in the study and was found in group 1. There was significant difference with mean CIMT between group 1 and 2 (p value is 0.0001). CIMT values >75<sup>th</sup> percentile are considered high and indicative of increased CVD risk. Values in the 25<sup>th</sup> to 75<sup>th</sup> percentile are considered average and indicative of unchanged CVD risk. Values less than 25<sup>th</sup> percentile are considered as having lower CVD risk. In group one, 28 patient (42%) had increased CIMT value ( $\geq$  75<sup>th</sup> percentile) and in group two, 11 patient (16.6%) had increased CIMT value. There was significant difference in CIMT between two groups (p value - 0.001).

### DISCUSSION

Acanthosis nigricans is associated with a various systemic abnormalities, many of which are characterized by hyperinsulinemia and insulin resistance. Both hyperinsulinemia and insulin resistance have role in the pathogenesis of atherosclerosis. To the best of our knowledge, there is only one study, by Elizabeth Guevara-Gutiérrez et al, on the association of acanthosis nigricans with subclinical atherosclerosis<sup>12</sup> and they reported an increased prevalence of an abnormal carotid intima-media thickness in patients with facial acanthosis nigricans, (62.2%) compared to healthy group (35.5%) and a strong positive correlation between carotid intima-media thickness with insulin resistance. However in another study by ShyamVerma et al. There is increased prevalence of obesity and insulin resistance in patients with facial acanthosis nigricans. The above study reported that 85.29% of the males and 100% of females were obese and moderate insulin resistance was found in 16.66%

and severe in 62.74% of the patients. Hence they concluded that FAN can be considered as a cutaneous marker of insulin resistance.<sup>11</sup> Facial acanthosis nigricans is most commonly associated with metabolic syndrome and has more predilection for atherosclerosis. So there is likely chance of increased risk of atherosclerosis in these patients. Hence, it is decided to study the correlation of atherosclerosis with acanthosis nigricans of temporal region of face compared to neck by CIMT measurement.

Mean BMI obtained in group 1 and 2 was 27.1527 and 26.5083 respectively. Our study showed, there is no statistical difference in the incidence of obesity between group 1 and group 2 (p value-0.173). But the study done by Shyam Verma et al showed, that 85.29% of the males and 100% of females with facial acanthosis nigricans were obese.<sup>11</sup> The mean triglyceride value in group 1 was 190.88 and group 2 was 163.92. There is significant difference in the mean triglyceride value between two groups (p value- 0.001). This finding is consistent with previous studies.<sup>13</sup> The mean fasting insulin level in group 1 was 13.6924 and in group 2 was 11.2597 respectively. There was significant difference with mean fasting insulin level between two group (P value - 0.0001). The mean HOMA-IR in group 1 was 3.46864 and in group 2 was 2.70235 respectively. There was significant difference with mean HOMAIR between two group. (p value -0.002). Various studies showed significant association of acanthosis nigricans with fasting insulin and HOMA-IR(161)(162). A study by Shyam Verma et al, 82.1% of patients with facial acanthosis nigricans had insulin resistance.<sup>11</sup> In our study the prevalence of metabolic syndrome was 28.03% comparable to the Indian study.<sup>14</sup> In Indian study 23.35% of patients with acanthosis had MS.<sup>14</sup> The mean CIMT in group 1 and group 2 were 0.8192 and 0.6159 respectively. Carotid plaque was present in 4 patients in group 1 and not found in group 2. There was significant difference with mean CIMT between group 1 and 2 (p value is 0.017). In group one, 28 patients (42.4%) had increase in CIMT and group two, 11 patient (16.6%) had increase in CIMT. Indian study by Elizabeth et al, showed the prevalence of abnormal intima-media thickness was higher in patients with acanthosis nigricans versus healthy participants(62.2% vs. 35.5%,  $P = 0.02$ ).

We compared each variables between those who had increase in CIMT and those who did not in group 1 and 2 separately. Accordingly, there were 28 patients in group 1 and 11 patients in group 2 with increase in CIMT. In our study, increased CIMT was associated with metabolic syndrome (p value=0.0001),diabetes mellitus (pvalue=0.0001),hypertension (p value=0.0001) insulin resistance and hypertryglyceridemia. It is comparable with previous studies.<sup>12</sup> Insulin resistance play key role in pathogenesis of atherosclerosis. So early recognition of atherosclerosis in patients with facial acanthosis nigricans is warranted.

Limitations of our study are CIMT of control population of healthy individuals after taking into account by removing all the confounding factors like age, sex and BMI was not done in our study. We were not able to perform biopsies due to

its invasive nature and patients concern regarding a possible scar on their face in case of facial acanthosis nigricans.

## CONCLUSION

There is higher prevalence of atherosclerosis in patients with acanthosis nigricans over temporal region of face (42.42%). This suggest that there is an increased chance for cardiovascular events. So early recognition of atherosclerosis in patients with facial acanthosis nigricans is warranted and also acanthosis nigricans patients with metabolic syndrome, insulin resistance, diabetes mellitus, hypertension and hypertriglyceridemia should be cautiously monitored for the development of atherosclerosis.

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**Source of Support:** Nil; **Conflict of Interest:** None

**Submitted:** 16-06-2019; **Accepted:** 25-07-2019; **Published:** 07-08-2019