Annals of Clinical Diabetes and Endocrinology

Review Article
Published: 25 Sep, 2018

Acanthosis, Rcrochordon and Diabetes: A Review

Anshul Kumar, Sandeep K. Mathur and Hardeva Ram Nehara*

Department of Endocrinology, Sawai Man Singh College, India

Introduction

Diabetes, long considered a disease of luxury and affluence is fast becoming a global pandemic. As per the WHO [1] the number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014 and according to the centers for disease control and prevention Type 2 diabetes accounts for 90% to 95% of all diagnosed cases of diabetes [2]. Also, the incidence of T2DM in developing nations like ours the numbers are increasing at a rate which far outmatches the resources available. Keeping this in mind the need of the hour is the discovery of certain easy to discern and measure physical markers to select people for screening of diabetes. This would help both in early diagnosis of diabetes as well as to decrease the load on already strained health resource of our country. In this review we intend to focus on two such easy to identify physical markers that are acanthosis and acrochordon and find literature and evidence to support our assumption that these 2 cutaneous markers are the way forward to identify those at diabetes risk in the general population.

Acanthosis Nigricans

Acanthosis Nigricans is a skin condition characterized by symmetrical plaques with hyperpigmentation and hyperkeratosis. It is usually observed on the posterior neck, axilla, and groin, but may also be observed on the elbows, knuckles, and knees [3]. The exact pathogenesis of acanthosis remains elusive it has been reported by some to be the result of an increase in melanocytes and melanin production [4],whereas others consider it to be a result of increased thickness of the keratin containing skin layers [5,6].

Pathogenesis of Acanthosis

The cause and pathogenesis of acanthosis remains elusive and yet to be completely understood. Abnormalities of three types of tyrosine kinase receptors, Insulin-Like Growth Factor Receptor-1 (IGFR1), Fibroblast Growth Factor Receptor (FGFR), and Epidermal Growth Factor Receptor (EGFR), have been proposed as potential contributing factors [7]. The fact that acanthosis is associated with multiple disorders causing hyperinsulinemia points to the fact that insulin/ insulin resistance plays an instrumental role in its pathogenesis. One of the hypothesis put forward in the same topical review is that the elevated insulin levels may stimulate the keratinocytes and dermal fibroblast proliferation via interaction with IGFR1, resulting in the plaque-like lesions that are identified with the disorder [7]. The fact that acanthosis is associated with syndromes of insulin resistance, obesity, T2DM further strengthen the hypothesis. These theories are further supported by the presence inherited form of these skin lesions in disorders of homozygous mutation of the insulin receptor gene.

Other mechanisms have also been hypothesised resulting from the instances where insulin resistance is absent like mutations in certain FGFRs may contribute to acanthosis nigricans through the promotion of keratinocyte proliferation and survival [8] These mutations have been proposed as the cause in disorders such as Crouzon syndrome, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), thanatophoric dwarfism, and hypochondroplasia [9,10]. FGFR3 mutations were identified in a family with familial acanthosis nigricans and at least 2 patients with malignancy associated skin lesions [9-11]. TGF alpha acting via the activation of EGFR may also play an important role in malignancy associated acanthosis; this fact is supported by the finding that TGF alpha levels as well as acanthosis both improve following removal of the malignancy [12-14].

Acanthosis and Insulin

In 1890s acanthosis nigricans was first reported as a sign of internal malignancy [15]. However since then it has been associated with T2DM, obesity and hyperinsulinemia [16-17]. Previously thought to be rare in children, its prevalence has increased, especially in populations with high

Correspondence:
Sandeep K. Mathur, Department of Endocrinology, S.M.S. Medical College, JLN Marg, Jaipur, India; Tel: +91(141)2518501; E-mail: drsandeepmathur@rediffmail.com

Received Date: *27 Aug 2018*
Accepted Date: *20 Sep 2018*
Published Date: *25 Sep 2018*

Citation:
Kumar A, Mathur SK, Nehara HR. Acanthosis, Rcrochordon and Diabetes: A Review. Ann Clin Diabetes Endocrinol. 2018; 1(1): 1004.

prevalence of adult diabetes [6] Acanthosis nigricans is a known and strong predictor of insulin resistance and hence of type 2 DM. Several studies have also established the association between acanthosis and anthropometric parameters. In a study done by Yoosoo Chang et al. [18] to assess the prevalence of acanthosis nigricans (AN) across various anthropometric measures in Asian preadolescent school children, it was seen that in the 2117 boys and 1916 girls assessed Acanthosis nigricans had a good correlation with adiposity, also it was seen that Acanthosis Nigricans was 8.4% in boys and 5.1% in girls, and was proportional to the Body mass index, Percentage weight for height, percentage body fat. In another study done by CA Stuart et al. [19] in 2009, they found that the incidence of acanthosis is equal in men and women in an unselected population. However, in clinical scenarios it is the women who predominate presenting with variety of symptoms most common being irregular menses whereas diabetes and obesity are relatively less common. Kong et al. [20] also proved the association between the occurrence of acanthosis nigricans and the risk factors of T2DM.IN their study which was conducted in 1730 patients it was seen that 19.4% had acanthosis nigricans and the occurrence of this cutaneous sign was conspicuously more frequent in those who had more risk factors for T2DM. It was also seen in the same study that the subjects with acanthosis nigricans were twice as likely to develop T2DM as those without acanthosis nigricans. In one study of 236 children with acanthosis nigricans and 51overweight children without the disorder, significant associations of acanthosis nigricans with insulin resistance and abnormal glucose homeostasis were detected [21].They found that 29% of the group with acanthosis had abnormal glucose homeostasis, 27% had systolic blood pressure > 95th percentile, and 50% had high-density lipoprotein–cholesterol ≤ 5th percentile. In another study by Kong et al. [22] done in 2007 in 1133 subjects proved an increasing association and incidence of acanthosis with obesity in the same study it was also seen that in the 1133 patients the incidence of diabetes was 15% in the patients with acanthosis as compared to 4% in those without the skin condition. Polycystic ovarian syndrome is another disorder that is known to be associated with insulin resistance and also has a higher occurrence of acanthosis nigricans with different studies suggesting an occurrence of 5-37% the skin lesion. It has also been suggested that in women with PCOS acanthosis may be a marker of metabolic abnormalities. In the study done by Schmidt et al. [23] they found that in the 401 women with PCOS studied those who had acanthosis higher rates of elevated free testosterone levels, insulin resistance, dyslipidemia, and increased body mass index Several other disorders are also known to be associated with acanthosis nigricans like Down syndrome, leprechaunism, Rabson-Mendenhall syndrome, congenital generalized lipodystrophy (Berardinelli-Seip syndrome), familial partial lipodystrophy, and Alstrom syndrome [16,24]. Occasionally, acanthosis nigricans may also be a paraneoplastic syndrome as a part of internal malignancy like abdominal adenocarcinomas, particularly gastric adenocarcinomas, represent the majority of acanthosis nigricans associated tumors [25-28].

Acrochordons

Acrochordon commonly known as skin tags are an outgrowth from normal skin which appears as pedunculated lesions on a narrow stalk. They occur in approximately 50% of the adults and the incidence increases with age [29]. It is a common clinical observation that skin tags occur more commonly in patients with obesity and diabetes [30]. In a cross-sectional study done in 500 consecutive diabetic patients who were evaluated for their skin manifestations it was seen that acrochordon was seen in 26.2% [31].Acrochordons usually occur in sites of friction, particularly the axilla, neck, inframammary, and inguinal regions

Pathogenesis

Margolis and Margolis [32] were the first to mention a possible relationship between multiple, large, hyperpigmented acrochordon and diabetes mellitus. In a study done by H Gundogdu-Koseoglu et al. [33] wherein they took 30 patients with at least 1 acrochordon but no history of diabetes and 30 controls with no acrochordon and no history of diabetes were taken and IGF1R and IGF-2R receptor expression was investigated using immunohistochemical assessment. They found IGF-1R and IGF-2R expression was significantly higher in the group containing acrochordons compared to the control group. These points in the direction that the acrochordons might be the result of altered IGF1 and IGF2 receptor expression. Morris et al. [34] measured fasting insulin levels in patients presenting with acrochordons and found raised fasting insulin levels, which indicates insulin resistance, thus derived that raised insulin levels were responsible for insulin-mediated effect on epidermal proliferation leading to acrochordon formation. Mathur and Bhargava [35] reported that Epidermal Growth Factor (EGF) or other growth factors may play a role in the pathogenesis of acrochordon. Demir et al. [36] also proposed hyperinsulinemia to be the cause of acrochordons. Despite these studies, not much concrete information is available regarding the pathogenesis of acrochordon and still works needs to be done.

Acrochordon and Insulin

Some clinical studies have been undertaken to substantiate acrochordon as cutaneous sign of diabetes, but the results have been conflicting. In the clinical study done by Aggarwal et al. [37,38] in non-hospitalized 118 patients no distinct correlation between the localisation, size, colour and number of the skin tags with glucose intolerance was seen. Whereas in the study done by Kahana et al. [38] in 216 patients with skin tags it was observed that although there was no correlation between the number, size, colour or location of skin tags and the incidence of Diabetes mellitus, skin tags were however associated with increased incidence of impaired carbohydrate metabolism. Morris et al [35] found an increased association of skin tags with increased insulin levels rather than increased fasting blood sugar levels. In another study done by Jusuf et al. [39] it was observed that the patients having acrochordon had increased BMI compared those without it. Demir et al. [36] found increased association between acrochordons and impaired carbohydrate metabolism. El Safoury et al. [40] found increased association of acrochordon and diabetes, increased BMI. In summary these findings from various studies have been fairly inconclusive and contradictory when it comes to the association between acrochordon and diabetes.

Conclusion

Acrochordon and acanthosis nigricans both are easy to locate and look for in any patient presenting to the out-patient department. Although none of the studies done till date conclusively establish the association of any of these cutaneous markers and the predisposition to diabetes, there is enough evidence to support a larger multicentre multi-ethnic follow up study with larger number of participants to assess the predictive capabilities of these cutaneous markers together and separately. If substantial evidence supports their association with impaired carbohydrate metabolism, they may prove indispensable

in the near future in predicting diabetes and thus enabling us to intervene and prevent diabetes and its feared complications.

References

1. Diabetes. 2017.
2. www.cdc.gov/diabetes/data/index.html
3. Hermanns-Le T, Scheen A, Pierard GE. Acanthosis nigricans associated with insulin resistance: pathophysiology and management. Am J Clin Dermatol. 2004;5(3):199-203.
4. Flier JS. Metabolic importance of acanthosis nigricans. Arch Dermatol.1985;121(2):193-94.
5. Acanthosis Nigricans:In Textbook of Dermatology. Rook A, Wilkinson DS, Ebling FJG, Eds. Oxford, U.K., Blackwell Scientific, 1979, p. 1307-1310
6. Stuart CA, Gilkison CR, Smith MM, Bosma AM, Keenan BS, Nagamani M. Acanthosis nigricans as a risk factor for noninsulin dependent diabetes mellitus. Clin Pediatr. 1998;37(2):73-9.
7. Ahmad S, Mahmoudi H, Naeem M, Betz R. C. "Autosomal recessive isolated familial acanthosis nigricans in a Pakistani family due to a homozygous mutation in the insulin receptor gene." British Journal of Dermatology. 2013;169(2):476-478.
8. Torley D, Bellus G.A, Munro C.S. "Genes, growth factors and acanthosis nigricans." British journal of Dermatology. 2002;147(6):1096-1101.
9. Berk David R, Elaine B. Spector, Susan J. Bayliss. "Familial acanthosis nigricans due to K650T FGFR3 mutation." Archives of dermatology. 2007;143(9):1153-1156.
10. Hida Yasutoshi, Yoshiaki Kubo, Yukiko Nishio, Shinji Murakami, Daisuke Fukumoto, Koji Sayama, et al. "Malignant acanthosis nigricans with enhanced expression of fibroblast growth factor receptor 3." Acta dermato-venereologica. 2009;89(4):435-437.
11. Fukuchi Kensuke, KazukiTatsuno, Kayo Matsushita, Akiharu Kubo, Taisuke Ito, YoshikiTokura. "Familial acanthosis nigricans with p. K650T FGFR 3 mutation." The Journal of dermatology. (2018);45(2):207-210.
12. Koyama Shohei, Kazuho Ikeda, Mikio Sato, Ken Shibahara, Kyoko Yuhara, HisayukiFukutomi, et al. "Transforming growth factor-alpha (TGF α)-producing gastric carcinoma with acanthosis nigricans: An endocrine effect of TGF α in the pathogenesis of cutaneous paraneoplastic syndrome and epithelial hyperplasia of the esophagus." Journal of gastroenterology.1997;32(1):71-77.
13. Dunaif Andrea, Magaret Graf, John Mandeli, VimlaLaumas, and AretaDobrjansky. "Characterization of groups of Hyperaiidrogenic women with Acanthosis Nigricans, impaired glucose tolerance, and/or Hyperinsulinemia." The Journal of Clinical Endocrinology & Metabolism. 1987;65(3):499-507.
14. Flier Jeffrey S, Richard C. Eastman, Kenneth L. Minaker, Doreen Matteson, John W. Rowe. "Acanthosis nigricans in obese women with hyperandrogenism: characterization of an insulin-resistant state distinct from the type A and B syndromes." Diabetes. 1985;34(2):101-107.
15. Sedano HO, Gorlin RJ. Acanthosis nigricans. Oral Surg Oral Med Oral Pathol. 1987;63(4):462-7.
16. Richards GE, Cavallo A, Meyer WJ, Prince MJ, Peters EJ, Stuart CA et al. Obesity, acanthosis nigricans, insulin resistance and hyperandrogenemia: pediatric perspective and natural history. J Pediatr. 1985; 107(6):893-897.
17. Mukhtar Q, Cleverley G, Voorhees RE, McGrath JW. Prevalence of acanthosis nigricans and its association with hyperinsulinemia in New Mexico adolescents. J Adolesc Health. 2001;28(5):372-6.
18. Chang Y, Woo HY, Sung E, Kim CH, Kang H, Ju YS. “Prevalence of acanthosis nigricans in relation to anthropometric measures: community-based cross-sectional study in Korean pre-adolescent school children.” Pediatricsinternational: official journal of the Japan Pediatric Society. 2008;50(5) 5: 667-73.
19. Stuart CA, Pate CJ, Peters EJ. Prevalence of acanthosis nigricans in an unselected population. Am J Med. 1989;87(3):269-72.
20. Kong AS, Williams RL, Rhyne R, Urias-Sandoval V, Cardinali G, Weller NF, et al. "Acanthosis Nigricans: high prevalence and association with diabetes in a practice-based research network consortium—a PRImary care Multi-Ethnic network (PRIME Net) study." The Journal of the American Board of Family Medicine. 2010;23(4):476-485.
21. Brickman WJ, Huang J, Silverman BL, Metzger BE. "Acanthosis nigricans identifies youth at high risk for metabolic abnormalities." The Journal of pediatrics. 2010;156(1):87-92.
22. Kong AS, Williams RL, Smith M, Sussman AL, Skipper B, Hsi AC, et al. "Acanthosis nigricans and diabetes risk factors: prevalence in young persons seen in southwestern US primary care practices." The Annals of Family Medicine. 2007;5(3):202-208.
23. Schmidt TH, Khanijow K, Cedars MI, Huddleston H, Pasch L, Wang ET, et al. "Cutaneous findings and systemic associations in women with polycystic ovary syndrome." JAMA dermatology. 2016;152(4):391-98.
24. Muñoz-Pérez, M. A., and F. Camacho. "Acanthosis nigricans: a new cutaneous sign in severe atopic dermatitis and Down syndrome." Journal of the European Academy of Dermatology and Venereology. 2001;15(4): 325-327.
25. Oesophagus, Adenocarcinoma. "Malignant acanthosis nigricans: an early diagnostic clue." Journal of the College of Physicians and Surgeons Pakistan 20, no. 2 (2010): 127-129.
26. Rigel, Darrell S, and Michael I Jacobs. "Malignant acanthosis nigricans: a review." The Journal of dermatologic surgery and oncology. 1980;6(11):923-927.
27. Anderson, S. H. C, M. Hudson-Peacock, A. F. Muller. "Malignant acanthosis nigricans: potential role of chemotherapy." The British journal of dermatology. 1999;141(4):714-716.
28. Krawczyk M, Mykała-Cieśla J, Kołodziej-Jaskuła A. Acanthosis nigricans as a paraneoplastic syndrome. Case reports and review of literature. Pol Arch Med Wewn. 2009;119(3):180-3.
29. Banik R, Lubach D. Skin tags: localization and frequencies according to sex and age. Dermatologica. 1987;174(4):180-3.
30. Boza JC, Trindade EN, Peruzzo J, Sachett L, Rech L, Cestari TF. Skin manifestations of obesity: a comparative study. J Eur Acad Dermatol Venereol. 2012;26(10):1220-3.
31. Ragunatha S, Anitha B, Inamadar AC, Palit A, Devarmani SS. Cutaneous disorders in 500 diabetic patients attending diabetic clinic. Indian J Dermatol. 2011;56(2):160-4.
32. Margolis J, Margolis LS. Letter: Skin tags--a frequent sign of diabetes mellitus. N Engl J Med. 1976;294(21):1184.
33. H Gundogdu-Koseoglu, A Akman-Karakas, C Bassorgun, S Akbas, S Ozdem, 3 M Ciftcioglu2 and E Alpsoy1 1 Dermatology and Venerology, Akdeniz University School of Medicine, Antalya, Turkey, 2 Pathology, Akdeniz University School of Medicine, Antalya, Turkey and 3 Medical Biochemistry, Akdeniz University School of Medicine, Antalya, Turkey
34. Norris PG, McFadden J, Gale E, Griffiths WA. Skin tags are more closely related to fasting insulin than fasting glucose levels. Acta Derm Venereol. 1988;68(4):367-8.
35. Mathur SK, Bhargava P. Insulin resistance and skin tags. Dermatology. 1997;195(2):184.
36. Demir S, Demir Y. "Acrochordon and impaired carbohydrate metabolism. "Acta diabetologica .2002;39(2):57-59.
37. Agarwal Jugal K, Pramod K Nigam. "Acrochordon: a cutaneous sign of carbohydrate intolerance." Australasian Journal of Dermatology. 1987;28(3):132-133.

38. Kahana M, Grossman E, Feinstein A, Ronnen M, Cohen M, Millet MS. Skin tags: a cutaneous marker for diabetes mellitus. Acta Derm Venereol. 1987;67(2):175-7.

39. Jusuf NK1, Putra IB1, Kartayana J1. The Correlation between Body Mass Index with the Occurrence of Skin Tag. Open Access Maced J Med Sci. 2017;5(3):271-274.

40. El Safoury OS1, Ibrahim M. A clinical evaluation of skin tags in relation to obesity, type 2 diabetis mellitus, age, and sex. Indian J Dermatol. 2011;56(4):393-7.