

HIGH PREVALENCE OF THYROID NODULES IN PATIENTS WITH ACHROCORDONS (SKIN TAGS). POSSIBLE ROLE OF INSULIN-RESISTANCE

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Abstract Due to the observation of a great number of patients having achrocordons, when they underwent fine needle biopsies for thyroid nodules, we decided to perform a prospective study to investigate the relationship between this finding and the presence of insulin resistance (IR), since achrocordons are commonly seen in hyperinsulinemic subjects. A total of 120 consecutive women, aged 18-35 yrs were studied. All subjects were also evaluated by thyroid ultrasound (US) for measuring thyroid volume and the presence of non-palpable nodules. Basal and post-prandial serum insulin was measured in all of them, as well as the Homeostasis Model Assessment (HOMA). Subjects were divided in two groups: Group A, with achrocordons (n = 44) and Group B, without achrocordons (n = 76). Group A showed 24 patients (54.5%) with thyroid nodules, whereas Group B only 13 subjects (17.1%); p = 0.0087. When we considered, as having high normal thyroid volume, the glands weighting more than 16 grams by US, without nodules, it was found that 8/44 cases from Group A (18.6%) and 3/76 from Group B (3.9%) fitted in such category, p = 0.0076. In patients with nodules and/or bigger thyroids, IR was observed in 36/44 (81.8%) of Group A and 14/76 (18.4%) of Group B, p = 0.0069, while the overall prevalence of IR was 0.47 in Group A and 0.05 in Group B, p = 0.00094. It is concluded that patients with achrocordons have a higher prevalence of US-detected thyroid nodules and larger thyroid glands. Then, it may be beneficial to search for thyroid abnormalities in those subjects with skin tags.

Key words: thyroid nodules, insulin resistance, skin tags

Resumen *Alta prevalencia de nódulos tiroideos en pacientes con acrocordones (fibromas blandos). Posible papel de la insulino-resistencia.*

Debido a la alta frecuencia de acrocordones en pacientes que concurrían a nuestro servicio para realizar punciones aspirativas de nódulos tiroideos, realizamos un estudio prospectivo para investigar la relación entre este hallazgo y la presencia de insulino resistencia (IR), dado que los acrocordones son frecuentemente observados en pacientes hiperinsulinémicos. Se incluyeron 120 pacientes consecutivas, con edades entre 18 y 35 años. Todas fueron evaluadas con una ecografía tiroidea para determinar su volumen y la presencia de nódulos no palpables. Se midió insulínemia basal y post prandial, así como el índice *Homeostasis Model Assessment* (HOMA). Las pacientes se dividieron en 2 grupos: Grupo A, con acrocordones (n = 44) y Grupo B, sin acrocordones (n = 76). En el Grupo A se encontraron 24 (54.5%) con nódulos tiroideos, mientras que el Grupo B, sólo 13 (17.1%); p = 0.0087. Cuando consideramos la presencia de una glándula tiroidea de tamaño elevado pero dentro de los límites normales, medida por ecografía (peso mayor a 16 gramos sin nódulos), encontramos que 8/44 casos del Grupo A (18.6%) y 3/76 del Grupo B (3.9%) entraron en esta categoría, p = 0.0076. En aquellas pacientes con nódulos tiroideos o glándula tiroidea de mayor tamaño, observamos IR en 36/44 (81.8%) del Grupo A y en 14/76 (18.4%) del Grupo B, p = 0.0069, mientras que la prevalencia total de IR fue del 0.47 en el Grupo A y del 0.05 en el Grupo B, p = 0.00094. En conclusión, las pacientes con acrocordones tuvieron mayor prevalencia de nódulos tiroideos detectados por ecografía, glándula tiroidea de mayor tamaño y mayor proporción de insulino resistencia.

Palabras clave: nódulos tiroideos, insulino resistencia, acrocordones

Skin tags (achrocordons) are skin-colored, pedunculated tumors with a smooth surface. Histologically they are composed by loose collagen fibers and dilated capillaries¹. The association of acanthosis nigricans, skin tags, diabetes

mellitus, insulin resistance (IR), and obesity in adolescents and young adults represents a well defined association². The endocrine origin of this condition is beyond doubt. Insulin and insulin-like growth factor-1, and their receptors on keratinocytes are obviously involved in the complex regulations leading to the peculiar epidermal hyperplasia. Control of obesity contributes largely to reverse the whole process, essentially by reducing both insulin resistance and compensatory hyperinsulinemia, although skin tags usually remains without change after IR normalization².

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TABLE 1.— Frequency of thyroid alterations and prevalence of insulin resistance in subjects with or without achrocordons

Variable	Group A		Group B		p
	n	(%)	n	(%)	
Thyroid nodules	24	(54.5)	13	(17.1)	0.0087
Thyroid gland weight > 16 g	8	(18.6)	3	(3.9)	0.0076
Thyroid nodules + gland weight > 16 g	36	(81.8)	14	(18.4)	0.0069
Prevalence of IR		0.47		0.05	0.00094

Group A: Subjects with achrocordons; Group B: Subjects without achrocordons; IR: insulin resistance

Due to the observation of a great number of patients having skin tags, when they underwent fine needle biopsies for thyroid nodules in our Clinic, we decided to perform a prospective study to investigate the relationship between this finding and the presence of IR, since achrocordons are commonly seen in hyperinsulinemic subjects².

Materials and Methods

One hundred and twenty consecutively by assisted women, mean age 24.2 ± 7 years, range 18-35 years, living in an iodine sufficient area³, who attended our Clinic for endocrinological evaluation, were included in the study. To be incorporated in this protocol, patients had to have: 1) normal thyroid function, as determined by the measurements of T_3 , T_4 and TSH, 2) negative titers of antithyroid antibodies (TPO-Ab), 3) no past history of thyroid abnormalities, and 4) no past history of any thyroid and/or having received homeopathic medication.

Subjects were divided into two groups as follows: *Group A*, with achrocordons (n=44) and *Group B*, without achrocordons (n=76).

All subjects gave written voluntary consent to participate in the study. Procedures were applied in agreement with the ethical guidelines of our Institutions.

Body weights (kg) and heights (cm) were measured without shoes and/or cap. Body mass index (BMI) was expressed as weight per height square (kg/m^2). Obesity was defined as BMI higher than 30.

All blood samples were taken between 8:00 and 9:00 a.m. after 12 hours of fasting period. After collection, serum samples were stored at -20°C until assayed.

Basal and 2-hour postprandial glycemia and insulinemia were monitored. The post prandial samples were obtained 2 h after a standard mixed meal intake, as previously described⁴. Breakfast included proteins, carbohydrates and fats.

Insulin was determined as previously described⁴.

Hyperinsulinemia was considered when basal levels were > 20 uIU/ml or > 60 uIU/ml in the post prandial state.

Glycemia was determined as previously described⁴.

Homeostasis Model Assessment index (HOMA) was calculated from insulin and glycemia values as previously described⁵. A high HOMA index (> 2.5) generally reflects insulin resistance.

The thyroid hormones, thyrotrophin (TSH) and antithyropoxidase antibodies (TPO-Ab) were measured by elec-

trochemiluminescent technology (ECL) with an automatic analyzer (Roche Diagnostics Elecsys 2010 Immunoassay System, Mannheim, Germany).

Thyroid ultrasound scanning (US) was performed in all patients by using a 7.5 MHz linear transducer. Thyroid volume (TV) was calculated by the elliptical shape volume formula ($0.479 \times \text{length} \times \text{width} \times \text{height}$) for each lobe as previously described⁴. We considered as thyroid nodules, all the US nodular lesions greater than 3 mm.

Results are expressed as means \pm SD. Between-group comparisons were made using Student's t-test for independent samples of cases of normal distribution. The Wilcoxon rank-sum test was used for independent samples of cases of abnormal distribution. The Chi-square test was used for nominal variables. The level of significance was set at 0.05.

Results

In Group A, 24 (54.5%) patients presented thyroid nodules, whereas Group B only 13 (17.1%) subjects, $p = 0.0087$ (Table 1).

When we considered, as having high normal thyroid volume, the glands weighting more than 16 grams by ultrasonography (US), excluding those which had thyroid nodules, it was found that 8/44 (18.6%) cases from Group A and 3/76 (3.9%) from Group B fitted in such category, with an statistically significant difference, $p = 0.0076$ (Table 1). Taking together those patients with thyroid nodules and/or bigger thyroid glands, IR was observed in 36/44 (82%) subjects of Group A and in 14/76 (18%) subjects of Group B, $p = 0.0069$ while the overall prevalence of IR was 0.47 in Group A and 0.05 in Group B, $p = 0.00094$ (Table 1).

Discussion

Skin tags are known to be more common after the age of 40 years⁶. In this series, the frequency of achrocordons was 37%, higher than the prevalence of skin tags in the general population which is estimated around 20 to 25%⁶.

There have been a few reports in the literature showing that the presence of skin tags is associated with diabetes mellitus^{7,8}. It has also been reported that these lesions might be associated with insulin resistance⁹⁻¹³, with

an atherogenic lipid profile¹⁴ and a lot of discussion has been made about if achrocordons constitute a marker for colon polyps¹⁵.

On the other side, we have recently shown that those subjects with IR have a higher prevalence of greater thyroid volumes and thyroid nodules⁴. We believe that the higher circulating levels of insulin might be causing increased thyroid proliferation. The clinical manifestations would be the larger thyroid volume and the formation of nodules⁴.

Insulin resistance is a characteristic feature of most patients with simple obesity, polycystic ovarian syndrome, and impaired glucose tolerance, as well as other disorders^{16,17}. In a recent publication, it has been reported that increased BMI is associated with increased risk of common and less common malignancies¹⁸. These epidemiological observations should inform the exploration of biological mechanisms that link obesity with cancer, and probably insulin resistance have much to do with this, considering that it is a growth factor which can act systemically.

In our study, we have observed that patients with achrocordons have a higher prevalence of US-detected thyroid nodules and larger thyroid glands. According to these results, we recommend that in those patients with achrocordons, it may be beneficial to search for thyroid abnormalities. On the other side, insulin resistance will usually be present in patients with skin tags¹⁹, as it was observed in our series. Therefore, we suggest that IR would be directly involved in thyroid proliferation and the development of achrocordons, as well. For this reason, in all subjects with achrocordons the possibility of the presence of IR and thyroid nodules is encouraged to be investigated.

References

1. Banik R, Lubach D. Skin tags: localization and frequencies according to sex and age. *Dermatologica* 1987; 174: 180-3
2. Maitra SK, Rowland Payne CM. The obesity syndrome and acanthosis nigricans. Acanthosis nigricans is a common cosmetic problem providing epidemiological clues to the obesity syndrome, the insulin-resistance syndrome, the thrifty metabolism, dyslipidaemia, hypertension and diabetes mellitus type II. *J Cosmet Dermatol* 2004; 3: 202-10.
3. Saborido L, Latres de Rauek B, Rezzonico JN, et al. Iodine in schoolchildren. Relationship with incidence of goiter, socioeconomic group and salt intake. *Medicina (Buenos Aires)* 1996; 56: 448-54.
4. Rezzónico J, Rezzónico M, Pusiol E, Pitoia F, Niepomniszcze H. Introducing the thyroid gland as another victim of the insulin resistance syndrome. *Thyroid* 2008;18: 461-461
5. Bonora E, Targher G, Alberiche M, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 2002; 3: 57-63.
6. Turner ML. Skin changes after forty. *Am Fam Physician* 1984; 29: 173-81.
7. Anonymous. Skin tags in diabetes mellitus. *N Engl J Med* 1976; 295: 172-3.
8. Tompkins RR. Skin tags and diabetes. 1977. *Arch Dermatol* 1977; 113: 1463.
9. Mansur JL, Donadio C, Martella A, et al. Acrocordones o fibromas blandos (skin tags) serían un signo clínico no descripto hasta ahora de insulino resistencia. *Rev Arg Endocrinol Metab* 2003; 40: 118.
10. Thappa DM. Skin tags as markers of diabetes mellitus: an epidemiological study in India. *J Dermatol* 1995; 22: 729-31.
11. Norris PG, McFadden J, Gale E, et al. Skin tags are more closely related to fasting insulin than fasting glucose levels. *Acta Derm Venereol* 1988; 68: 367-8.
12. Banik R, Lubach D. Skin tags: localization and frequencies according to sex and age. *Dermatologica* 1987; 174: 180-3.
13. Levine N. Brown patches, skin tags on axillae. Are this patient's velvety plaques related to his obesity and diabetes? *Geriatrics* 1996; 51: 27.
14. Crook MA. Skin tags and the atherogenic lipid profile. *J Clin Pathol* 2000; 53: 873-4.
15. Piette AM, Meduri B, Fritsch J, et al. Do skin tags constitute a marker for colonic polyps? A prospective study of 100 asymptomatic patients and metaanalysis of the literature. *Gastroenterology* 1988; 95: 1127-9.
16. Bloomgarden ZT. Insulin resistance concepts. *Diabetes Care* 2007; 30: 1320-6.
17. Eckel, RH., Grundy, SM, and Zimmet, PZ. The metabolic syndrome. *Lancet* 2005; 365: 1415-28.
18. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008; 371: 569-78.
19. Sudy E, Urbina F, Maliqueo M, Sir T. Screening of glucose/insulin metabolic alterations in men with multiple skin tags on the neck. *J Dtsch Dermatol Ges* 2008; 6: 852-5.

"La vida es seria"

[...]

Desterremos, hermanos, el hábito maligno
de ser superficiales y de adorar las formas,
e indaguemos la esencia bajo la piel del signo,
que el signo da las leyes y la esencia las normas

[...]

Ezequiel Martínez Estrada (1895-1964)

Obra poética. Oro y piedra. Hyspamérica: Buenos Aires, 1985, p 14