Hong Kong J. Dermatol. Venereol. (2011) **19**, 108-114

Original Article

Leptin resistance and genetic predisposition as potential mechanisms in the development of skin tags

瘦素抵抗力與遺傳傾向在皮贅形成的潛在機制研究

E Erkek, U Kisa, Y Bagci, H Sezikli

Background and objective: The cause of skin tags (ST) remains elusive. The present study was designed to elucidate the role of leptin and to unravel other potential aetiological factors in the pathogenesis of ST. ***Methods:*** The study population comprised 58 patients with ST and 24 control individuals. Demographic and other variables were recorded. A detailed laboratory evaluation including serum leptin was performed. ***Results:*** Statistical analysis revealed significant differences between the two groups in terms of body weight, body mass index (BMI), family history of ST, triglyceride, cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and serum leptin levels. A family history of ST was the most important predictor of ST development by logistic regression analysis. ***Conclusions:*** These findings indicate that ST correlate with serum leptin levels and that leptin resistance may be involved in the pathogenesis of ST in susceptible individuals.

背景和目的：皮贅的成因仍然不明，本研究的設計是要闡明瘦素在皮贅發病中所扮演的角色及解開其他潛在的病因。**方法**：研究群組包括五十八名皮贅病者及二十四名對照組人仕，當中的人口統計學及其他變數都會被記錄，並進行包括瘦素血清水平的詳細檢查。**結果**：統計學分析顯示出兩組有重大區別，存在於體重、身體質量指數、皮贅家族史，三酸甘油酯、膽固醇、低密度脂蛋白、極低密度脂蛋白和血清瘦素水平。在邏輯迴歸分析中，皮贅家族史更被認爲是皮贅形成最重要的預測。**結論**：以上發現指出皮贅與瘦素血清水平的相互關係，並顯示出抗瘦素現象可能與易感人仕的皮贅發病有關。

Keywords: Acrochordon, diabetes, insulin, leptin, obesity, skin tag, soft fibroma

關鍵詞：軟垂疣，糖尿病，胰島素，瘦素，肥胖，皮贅，軟纖維瘤

Department of Dermatology, Acıbadem University School of Medicine, İstanbul, Turkey

E Erkek, MD

Department of Biochemistry, Kırıkkale University School of Medicine, Kırıkkale, Turkey

U Kisa, PhD
H Sezikli, MD

Department of Dermatology, Kırıkkale University School of Medicine, Kırıkkale, Turkey

Y Bagci, MD

Correspondence to: Dr. E Erkek

Acıbadem Maslak Hospital, Büyükdere Caddesi 40, Maslak 34457, İstanbul, Turkey

Introduction

Skin tags (ST) are benign connective tissue tumours of the dermis that present as soft, flesh to brown coloured, pedunculated or sessile protrusions on the flexures of middle aged and elderly patients.[1-4] They are quite common and develop in 25% of the population.[5] Biopsy reveals a papillomatous acanthotic epidermis overlying a loose fibrous tissue similar to that of the papillary dermis.[4] The cause of skin tags is unknown, although aging, obesity, insulin resistance, colonic polyposis, human papilloma virus (HPV) infection, pregnancy, menopause, acromegaly, excess of prolactin and genetic susceptibility have been proposed as potential aetiological or associated factors.[1,5-7]

Leptin is an adipocyte-derived hormone, that regulates food intake, energy expenditure and body weight by acting on the hypothalamus.[8-12] It is a product of the ob (obese) gene and exerts biological effects through the leptin receptor (ob-R), the product of the db gene.[8,9,13,14] It has been shown that the cells residing in epidermis and dermis possess leptin receptors[10,14] and that leptin has the ability to stimulate growth and proliferation of epidermal and dermal cells.[15-17]

Patients and methods

The study population consisted of 58 consecutive patients with ST diagnosed at the Dermatology Department of Kirikkale University Faculty of Medicine, Kirikkale, Turkey. Diagnosis of ST was based on typical clinical appearance and distribution. In equivocal cases a biopsy, obtained by scissor excision, has been sent for histological confirmation.

Twenty-four individuals were assigned as the control group. Two of these individuals were the medical personnel of our hospital, five were their relatives and 17 were dermatology outpatients without history or physical evidence of ST.

All patient and controls were questioned for applicable demographic and disease-associated variables as follows: age, sex, weight, height, duration of ST, history of diabetes mellitus (DM) and family history of ST. For each patient, the quantity and distribution of ST was recorded. The body mass index (BMI) was calculated as weight/(height)^2. A detailed laboratory work-up consisting of fasting blood glucose, HbA1c, insulin, basal cortisol, free triiodothyronine (fT3), free thyroxine (fT4), thyroid stimulating hormone (TSH), triglyceride, cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), high-density lipoprotein (HDL), apo A, apo B and, lipoprotein A was performed in both groups.

Five millilitres of venous blood was drawn from patients and controls to EDTA-coated tubes and immediately centrifuged. Serum samples were frozen and stored at -70°C. Serum leptin levels were determined by using a commercial solid phase enzyme-amplified sensitivity immunoassay kit (BioSource Europe S.A., Nivelles, Belgium) and test procedures were performed according to the manufacturer's instructions.

Statistical analysis was performed on personal computer by using SPSS 11.5 software (SPSS Inc., Chicago, IL). Student's T test and Mann Whitney U-test were utilized for comparison of numerical variables. Chi-square and when convenient, Fisher's exact test, were used for comparison of categorical data. Pearson correlation coefficient, linear regression stepwise and logistic regression tests were employed for correlation analysis. A p value of $\alpha \leq 0.05$ was considered as significant.

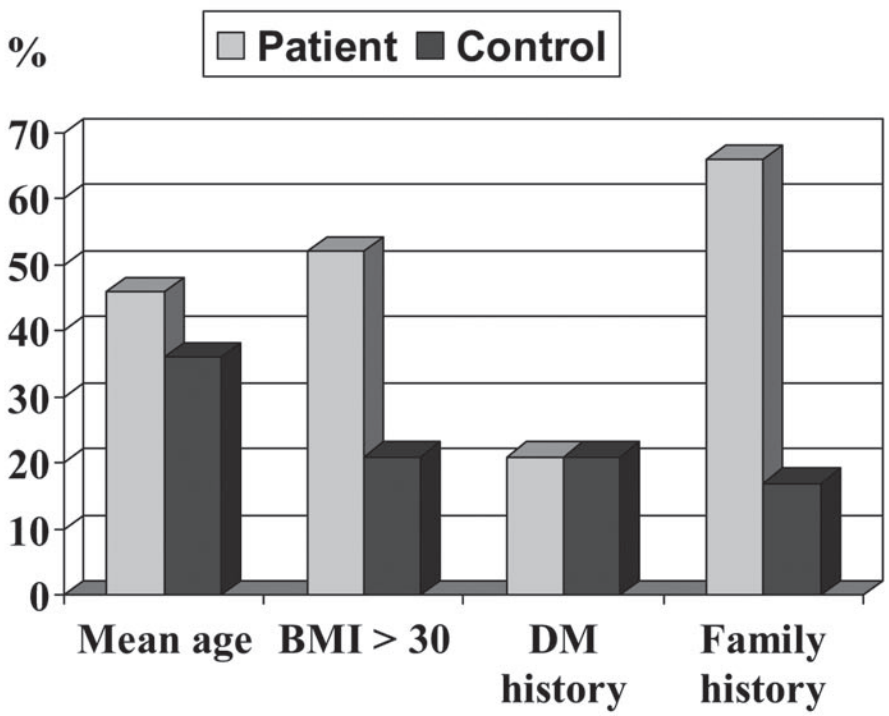
Results

The study group comprised 58 patients with ST (36 females, 22 males) with a mean age of 45.67±9.42 and an age range of 24-67 years. BMI values were <25 in 7 (12.1%) patients (normal weight), between 25-30 in 21 (36.2%)

patients (overweight) and >30 in 30 (51.7%) patients (obese). Twelve (20.7%) patients had previous or recent diagnosis of DM. Nine of these patients had type II DM; the type of DM was not specified in 3 patients. Except for one patient receiving insulin, five of these patients were using oral antidiabetic medications at the time of the study. A positive family history of ST was obtained from 38 (65.5%) patients. The duration of ST ranged from 1 to 28 years (mean 7.91±6.03 years) and the number of ST per patient varied between two and 32 (mean 11.88±7.95). Fasting serum glucose values were abnormal in 15 patients (25.9%); of these 6 (40%) had no history of DM. Only four patients (6.9%) had high insulin levels.

The control group consisted of 24 individuals (17 females, 7 males) with a mean age of 36.46±11.75 years (range 18-58). BMI values were <25 in 12 (50%) patients, between 25-30 in 7 (29.2%) patients and >30 in 5 (20.8%) patients. Five (20.8%) control subjects had a past or recent diagnosis of DM. Except for one control diagnosed 20 years ago as type I DM, the remaining four subjects had type II DM. Two of the controls were using oral antidiabetic medications and the subject with type I DM was receiving insulin injections. A family history of ST was present in four (16.7%) subjects. Fasting serum glucose values were abnormal in three individuals (12.5%); of these two (66.7%) had no history of DM. Only two subjects (8.4%) had high insulin levels (Figure 1).

Statistical analysis revealed significant differences between patient and control groups in terms of weight ($t=4.071$; $p=0.0001$), BMI ($t=4.182$; $p=0.0001$), family history of ST ($x^2=16.214$; $p=0.0001$), triglyceride ($t=2.253$; $p=0.027$), cholesterol ($t=2.272$; $p=0.026$), LDL ($t=2.291$; $p=0.025$), VLDL ($t=2.253$; $p=0.027$) and leptin ($t=3.047$; $p=0.003$) levels (Table 1).



BMI=body mass index; DM=diabetes mellitus

Figure 1. Comparison of patient and control groups for selected demographic and numerical variables.

Table 1. Comparison of patient and control groups for selected demographic and numerical variables.

	Patient Group Mean±SD	Control Group Mean±SD	P value
Weight (kg)	83.8793±15.4410	69.3958±12.5082	0.0001*
BMI (kg/m^2)	31.3084±5.6186	25.7000±5.2875	0.0001*
Fasting glucose (mg/dl)	105.8448±32.2190	92.8333±21.8267	0.074
Insulin (uU/ml)	13.2572±7.6563	25.9471±7.87364	0.430
fT3 (pg/ml)	3.4794±0.8100	3.3800±0.4434	0.591
Triglyceride (mg/dl)	186.1034±103.4441	130.7500±95.5853	0.027*
Cholesterol (mg/dl)	197.5345±41.2337	176.1250±32.1130	0.026*
LDL (mg/dl)	118.8103±29.2368	102.1667±31.5714	0.025*
VLDL (mg/dl)	37.2207±20.6886	26.1500±19.1171	0.027*
Serum leptin (ng/dl)	12.2929±14.7721	5.5462±5.230	0.003*

BMI=body mass index; fT3=free triiodothyronine; LDL=low-density lipoprotein; VLDL=very low-density lipoprotein

* Statistically significant.

For the patient group, leptin levels correlated positively with BMI ($r=0.482$; $p=0.0001$), number of ST ($r=0.620$; $p=0.0001$), duration of ST ($r=0.402$; $p=0.002$) and correlated negatively with free T3 ($r=-0.390$; $p=0.03$) levels. Linear regression stepwise analysis revealed that BMI was the sole significant predictor of serum leptin level in patients ($r^2=0.52$; $f=31.724$; $p=0.0001$), controls ($r^2=0.186$; $f=5.028$; $p=0.035$) and in combined patient + control cohort ($r^2=0.36$; $f=44.996$; $p=0.0001$).

Logistic regression analysis revealed that a family history of ST was the sole significant predictor for developing ST ($\beta=2.377$; $p=0.001$).

Discussion

ST have been consistently associated with DM and multiple ST have been proposed to serve as cutaneous markers for patients at risk of non-insulin-dependent DM.[1,3,4,18,19] According to previous studies, 26.3-62.8% of patients with ST have overt diabetes.[1,3] In the present study, the prevalence of DM in patient and control groups was 20.7% and 20.8% respectively. Statistical analysis revealed no significant differences between the two groups in terms of history of DM, fasting blood glucose and HbA1c levels. These findings contradict those of pertinent previous studies, which implicated derangement in carbohydrate metabolism as a conceivable mechanism in ST development. It has been suggested that ST correlate with fasting circulating insulin levels, rather than fasting glucose levels.[19] A paradigm of insulin resistance has been hypothesized; i.e. fibroblast proliferation in ST has been attributed to hyperinsulinemia through activation of epidermal growth factor (EGF) receptors and/or insulin-like growth factor-1 (IGF-I) receptors.[4] Both ST and its frequent companion acanthosis nigricans have been ascribed to insulin or IGF-I-mediated epidermal hyperproliferation.[5,19] In our study, insulin levels did not significantly differ between patient and control groups, casting doubt on the contribution of insulin to ST development.

Obesity is considered as another risk factor for the development of ST.[5] The number of ST have been reported to correlate with weight[6] and obesity prevalence in patients with ST was estimated as 28.7%.[3,18] In our study, not only obesity prevalence

(51.7% vs. 20.8%), but weight and BMI values were significantly higher in patient group as compared with the control group. Obesity is associated with high circulating insulin concentration and insulin resistance at the receptor level.[4,19] Moreover, obesity is coupled to elevated serum free leptin concentration, enhanced leptin mRNA expression, and low leptin sensitivity.[8-13,16] As our study revealed no significant difference in insulin levels of patients with ST and controls, we speculate that leptin is the culprit linking obesity and ST development.

Leptin is synthesized and secreted by peripheral and visceral adipose tissue.[8,11,13] Adipocyte cell size is the main determinant of leptin production, i.e. serum leptin level indicates the amount of adipose tissue in the body.[12,13] As can be anticipated, circulating leptin levels correlate with body weight and BMI.[11,13,20] The present study showed that BMI was the sole predictor of leptin levels with a positive predictive value of 52% in patients with ST. Human obesity is frequently associated with elevated serum free leptin levels and leptin resistance appears to be involved in its pathogenesis.[11-13] Since leptin has a glucose- and insulin-lowering effect on the whole body level *in vivo*, resistance for this effect could indirectly induce a state of insulin resistance.[21] Apart from such metabolic consequences, leptin resistance may have negative effects on several organ systems, including the skin.

Leptin is structurally related to growth hormone and could play a paracrine role in proliferation, differentiation, growth, and apoptosis of epithelial cells.[15-17] In vitro studies clearly demonstrated that leptin could trigger keratinocyte proliferation, similar to the most potent keratinocyte mitogens EGF and keratinocyte growth factor.[10,15,17] It has been shown that leptin acts as an angiogenic factor and that fibroblasts and keratinocytes express leptin receptors.[22]

The medical literature encloses a few studies linking leptin and ST development. In a study by Gorpelioglu et al,[23] there was no difference between serum leptin levels of 58 patients with ST and 31 healthy BMI-matched controls. The authors concluded that leptin may not be involved in the pathogenesis of ST. El Safoury et al[22] demonstrated significant increase in tissue leptin levels in lesional skin of 15 non-diabetic patients, as compared with the non-lesional control skin. Although the authors did not evaluate serum leptin levels, their study provides the only evidence for a role of leptin in ST, prior to ours. In the present study, serum free leptin levels were significantly higher in patients with ST as compared with controls. Furthermore, leptin levels correlated with both the number and duration of ST. These findings may allude to leptin resistance, as a novel mechanism in the development of ST. According to this hypothesis, excess leptin may bind to insulin-like growth factor receptors or to growth hormone-binding proteins in the dermis and epidermis. Through insulin-like effects, it may stimulate the growth and proliferation of dermal and epidermal constituents. As a result, leptin overproduction may potentially contribute to the formation of ST and related disorders such as acanthosis nigricans. It is fascinating that Yazici et al[17] advocate a mechanism of leptin resistance, rather than insulin resistance, in the pathogenesis of acanthosis nigricans.

It is believed that thyroid axis may regulate the secretion and metabolism of leptin and that circulating leptin in turn may modify TSH and hence thyroid hormone levels. Some studies demonstrated higher leptin levels in hypothyroid patients in contrast to lower leptin levels in hyperthyroid states.[24,25] It has been reported that serum leptin levels positively correlate with TSH levels,[22] or negatively correlate with free thyroxine levels.[26] In our study, serum leptin levels in patients with ST negatively correlated with circulating free thyroxine levels, but not with circulating TSH. However, since there was no significant difference between patient and control groups in terms of fT3, fT4 and TSH levels, the authors doubt that thyroid hormones are relevant to ST pathogenesis.

In our study, a family history of ST was present in 65.5% versus 16.7% of patient and control groups respectively. Moreover, a family history of ST was the singular significant predictor of developing ST by logistic regression analysis. These findings suggest that genetic predisposition undeniably contributes to ST development and/or progression. However, because of incomplete penetrance and variable phenotypic expressivity, the disorder is presumably multifactorial with participation of both genetic and endogeneous factors. The magnitude of contribution to ST development and/or propagation by each of these factors merits further investigations.

Our study has several limitations. First, ST is a frequent disorder and the statistical conclusions in this report were potentially biased by the relatively small cohort of patient and controls. Second, the sole criterion for selection of control group was the absence of history or physical evidence of ST. Thus, patient and control groups were unmatched for age, sex, weight, BMI or sample size. Finally, subjective underestimation or overestimation of duration of ST by patients or family history of ST by patients and controls might represent another limitation. Nevertheless, this study may be viewed as a preliminary one.

In conclusion, our findings indicate that ST correlates with serum leptin levels and that leptin resistance may be involved as an endogeneous factor in the pathogenesis of ST in genetically susceptible individuals. The precise role played by leptin and its receptor at the biochemical level within the milieu of ST remains to be determined.

References

1. Thappa DM. Skin tags as markers of diabetes mellitus: an epidemiological study in India. J Dermatol 1995; 22:729-31.
2. Banik R, Lubach D. Skin tags: localization and frequencies according to sex and age. Dermatologica 1987;174:180-3.
3. Kahana M, Grossman E, Feinstein A, Ronnen M, Cohen M, Millet MS. Skin tags: a cutaneous marker for diabetes mellitus. Acta Derm Venereol 1987;67:175-7.
4. Mathur SK, Bhargova P. Insulin resistance and skin tags. Dermatology 1997;195:184.
5. Luba MC, Bangs SA, Mohler AM, Stulberg DL. Common benign skin tumors. Am Fam Physician 2003;67:729-38.
6. Ochsendorf FR, Leopolder-Ochsendorf A, Holtermüller K-H, Milbradt R. Weiche Hautfibrome: Untersuchung ihrer Einflußgrößen und ihrer diagnostischen Bedeutung für Kolonneoplasien. Hautarzt 1990;41:207-11.
7. Dianzani C, Calvieri S, Pierangeli A, Imperi M, Bucci M, Degener AM. The detection of human papillomavirus DNA in skin tags. Br J Dermatol 1998;138:649-51.
8. Al-Daghri N, Bartlett WA, Jones AF, Kumar S. Role of leptin in glucose metabolism in type 2 diabetes. Diabetes Obes Metab 2002;4:147-55.
9. Brabant G, Nave H, Mayr B, Behrend M, van Harmelen V, Arner P. Secretion of free and protein-bound leptin from subcutaneous adipose tissue of lean and obese women. J Clin Endocrinol Metab 2002;87:3966-70.
10. Stallmeyer B, Pfeilschifter J, Frank S. Systemically and topically supplemented leptin fails to reconstitute a normal angiogenic response during skin repair in diabetic ob/ob mice. Diabetologia 2001;44:471-9.
11. Rajala MW, Scherer PE. Minireview: The adipocyte-at the crossroads of energy homeostasis, inflammation, and atherosclerosis. Endocrinology 2003;144:3765-73.
12. Guerre-Millo M. Adipose tissue hormones. J Endocrinol Invest 2002;25:855-61.
13. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce M, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996;334:292-5.
14. Goren I, Kampfer H, Podda M, Pfeilschifter J, Frank S. Leptin and wound inflammation in diabetic ob/ob mice: differential regulation of neutrophil and macrophage influx and a potential role for the scab as a sink for inflammatory cells and mediators. Diabetes 2003;52: 2821-32.
15. Frank S, Stallmeyer B, Kampfer H, Kolb N, Pfeilschifter J. Leptin enhances wound re-epithelialization and constitutes a direct function of leptin in skin repair. J Clin Invest 2000;106:501-9.
16. Wauters M, Considine RV, Van Gaal LF. Human leptin: from an adipocyte hormone to an endocrine mediator. Eur J Endocrinol 2000;143:293-311.
17. Yazici AC, Tursen U, Ikizoglu G, Akbay E, Tataroglu C, Cimen MY. Atypical localization of acanthosis nigricans in an obese patient with increased leptin level: is there an association? J Am Acad Dermatol 2006;55:S55-6.
18. Levine N. Brown patches, skin tags on axilla. Are this patient's velvety plaques related to his obesity and diabetes? Geriatrics 1996;51:27.
19. Norris PG, McFadden J, Gale E, Griffiths WAD. Skin tags are more closely related to fasting insulin than fasting glucose levels. Acta Derm Venereol 1988;68: 367-8.

20. Scholz GH, Englaro P, Thiele I, Scholz M, Klusmann T, Kellner K, et al. Dissociation of serum leptin concentration and body fat content during long term dietary intervention in obese individuals. Horm Metab Res 1996;28:718-23.
21. Jazet IM, Pijl H, Meinders AE. Adipose tissue as an endocrine organ: impact on insulin resistance. Neth J Med 2003;61:194-212.
22. El Safoury O, Fawzi M, Abdel Hay RM, Hassan AS, El Maadawi Z, Rashed L. Increased tissue leptin hormone level and mast cell count in skin tags: a possible role of adipoimmune in the growth of benign skin growths. Indian J Dermatol Venereol Leprol 2010;76:538-42.
23. 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;54:20-2.
24. Oge A, Bayraktar F, Saygili F, Guney E, Demir S. TSH influences serum leptin levels independent of thyroid hormones in hypothyroid and hyperthyroid patients. Endocr J 2005;52:213-7.
25. Janeckova R. The role of leptin in human physiology and pathophysiology. Physiol Res 2001;50:443-59.
26. Iossa S, Lionetti L, Mollica MP, Crescenzo R, Barletta A, Liverini G. Fat balance and serum leptin concentrations in normal, hypothyroid, and hyperthyroid rats. Int J Obes Relat Metab Disord 2001; 25:417-25.