



Leptin and c-reactive protein are implicated in the pathogenesis of skin tags

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Abstract

Background: Skin tags (ST) are the most common benign skin lesions. In obesity, production of inflammatory cytokines by visceral adipose tissue (VAT) macrophages increases significantly. This situation creates a general subclinical inflammatory state that will ultimately lead to altered insulin responsiveness. The aim of the study is to investigate the possible involvement of leptin and some inflammatory markers in the development of skin tags.

Patients and Methods: Twenty obese patients seeking advice for their STs, and 10 healthy volunteers serving as controls. Venous blood samples were collected after overnight fast. Laboratory measurements included determination of fasting blood glucose (FBG), glycated hemoglobin, insulin, leptin, high sensitive c-reactive protein (hs-CRP), tumor necrosis factor- α (TNF- α), cholesterol, and triglycerides (TG). Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated.

Results: ST patients were insulin-resistant with elevated HOMA-IR. They showed higher levels of plasma cholesterol, triglycerides, LDL-cholesterol, hs-CRP and TNF- α than the control group. There was a positive correlation between leptin level and each of plasma TG, cholesterol, and insulin. Moreover, there was a positive correlation between the number of ST and each of hs-CRP, TNF- α , leptin and HOMA-IR.

Conclusion: The subclinical higher levels of leptin, hs-CRP and TNF- α in ST patients may be implicated in the development of skin tags. Association between skin tags and insulin resistance is already known, however this article showed that leptin, hs-CRP and TNF- α in ST patients may be implicated in the development of skin tags.

Keywords: Skin tags, leptin, insulin resistance, hs-CRP, TNF- α

Background

Skin tags (ST) are the most common benign skin lesions; they are also known as soft fibroma or acrochordon [1]. Skin tags are small, soft, pedunculated flesh to dark brown colored lesions that occur mainly on the neck and axilla [2]. These lesions are extremely common in the adult population over 40 years of age and increase in incidence in the elderly [3].

ST often develop in areas of friction and are associated with several conditions, including diabetes mellitus, obesity, acromegaly, Crohn's disease, aging, child abuse, organ transplants, colonic polyps, pregnancy and human papilloma virus [4]. Variations in estrogen levels and trophic hormones such as insulin-like growth factor-1 (IGF-1) and epidermal growth factor [5], as well as increased mast cell count [6], are involved in the genesis and development of skin tags. Various skin conditions are associated with insulin resistance including pseudocanthosis nigricans, hirsutism, acne, hidradenitis suppurativa, alopecia, and skin tags [7].

Leptin is a protein secreted by adipose tissue, which has an important role in metabolism and immunity. It regulates body weight, appetite and energy expenditure. Additionally, leptin mediates proliferative and anti-apoptotic activities in different cell types, including T cells, macrophages and eosinophils [8]. Plasma leptin

displays a strong association with cardiovascular risk factors, including obesity, insulin resistance, dyslipidemia, and hyperuricemia [9].

Macrophages have been recognized as major sources of proinflammatory mediators, which are largely responsible for the manifestation of insulin resistance. The so-called classical activated or 'M1' macrophages secrete high amounts of inflammatory mediators while the alternatively activated 'M2' macrophages are low cytokine producers [10]. In obesity, the balance between M1 and M2 macrophages is disturbed. Thus, production of inflammatory cytokines by visceral adipose tissue (VAT) macrophages increases significantly [11]. This situation creates a general subclinical inflammatory state that will ultimately lead to altered insulin responsiveness [12].

The present study was conducted to investigate the inter-relation between leptin level, insulin resistance, inflammatory mediators and genesis of skin tags in obese subjects.

Patients and Methods

The study included 20 obese patients seeking advice for their STs, and 10 healthy volunteers serving as controls. The patients were recruited from the Outpatient Clinic of Dermatology and Venereology Department, Tanta University Hospitals. The study was approved by the Ethics

Committee of the Faculty of Pharmacy, Tanta University. All participants were asked to sign an informed consent prior to inclusion in the study. Cases were defined as patients with > 5 skin tags in the neck region or axillae. They were subjected to thorough personal history taking including smoking, diabetes, hypertension, lipid abnormality, and family history of ST.

Patients were excluded from the study if they reported acromegaly, pheochromocytoma, Cushing's syndrome, liver or kidney disease, or taking oral contraceptive pills or corticosteroids.

Height, weight and waist circumference were measured. BMI was calculated as weight in kg divided by the square of the height in meters. Overweight was defined as BMI 25-30 kg/m², and obesity was defined as BMI >30 kg/m² [13].

Venous blood samples were taken at the enrollment visit after the participants had fasted overnight. Glucose was measured in serum immediately. Plasma was separated using EDTA as anticoagulant, divided into aliquots and kept frozen at -20°C until analyzed. Commercial kits (Biodiagnostics, USA) were used for determination of fasting blood glucose [14], plasma total cholesterol [15], triglycerides [16], and HDL-cholesterol [17]. LDL-cholesterol was calculated using Friedewald formula.

Fasting plasma insulin was estimated by electrochemiluminescence immunoassay [18] using kits obtained from Roche Diagnostics GmbH, Mannheim, Germany. Insulin resistance (IR) was calculated by the Homeostatic Model of Assessment of insulin resistance (HOMA-IR) [19]. An enzyme-linked immunosorbent assay (ELISA) was utilized for determination of plasma leptin (Linco Research, St. Charles, MO, USA), high sensitive C-reactive protein (hs-CRP) (Labor Diagnostika Nord GmbH & Co. KG), and plasma tumor necrosis factor- α (TNF- α) (R&D Systems, Minneapolis, MN, USA).

Statistical analysis

Data were statistically analyzed by unpaired Student's t-test and ANOVA test using the computer program SPSS version 10 for Windows. Correlation between variables was evaluated using Pearson's correlation coefficient. Level of significance was set at $P < 0.05$.

Results

The characteristics of the study population are provided in (Table 1). 55% of the patients had family history of diabetes, and 10% had type 2 diabetes. BMI of the patients ranged from 31 to 41.6 kg/m² and there was a statistically significant difference between BMI of patients and controls ($P < 0.05$). The waist circumference of the patients was greater in the males by ~ 30.7% and in the females by ~ 22.7%, than in the corresponding controls. The number of skin tags ranged from 8 to 28; 18 patients (90%) had more than 10 skin tags. Skin tags were detected on the neck in 15 patients (75%), on axillae in 2 patients (10%),

Table 1. Demographic data of skin tags patients and controls.

Parameter	Patients (n=20)	Controls (n=10)
Age, years (min-max)	44-65	40-60
Gender (M/F)	7/13	4/6
BMI, kg/m ² (range)	31-41.6	25-30
(mean \pm SD)	(35.4 \pm 2.4)	(27 \pm 1.8)
Waist circumference (mean \pm SD), (M/F), cm	115 \pm 1.6/92 \pm 1.4	88 \pm 1.6/75 \pm 0.8
Number of skin tags (range)	8-28	None
Family history of diabetes (Yes/No)	11/9	4/6
Diabetic (Yes/No)	2/18	0/10

BMI : Body mass index. Data are presented as mean \pm SD.

*: Significant compared to control ($P < 0.05$).

Table 2. Biochemical parameters of skin tags patients and controls.

Parameter	Patients (n=20)	Controls (n=10)	P-value
FBG, mg/dL	99.6 \pm 50	85.9 \pm 45	0.096
HbA1c %	5.5 \pm 1.1	4.9 \pm 0.15	0.15
insulin, μ U/mL	22.5 \pm 2.3*	9.2 \pm 1.5	<0.01
HOMA-IR	5.4 \pm 2.1*	1.79 \pm 0.75	<0.01
Cholesterol, mg/dL	269.6 \pm 14.45*	168.55 \pm 9.13	<0.01
TG, mg/dL	244 \pm 57.2*	114.9 \pm 14.07	<0.01
LDL-C, mg/dL	186.75 \pm 8.89*	140 \pm 8.27	<0.01
HDL-C, mg/dL	34.1 \pm 3.78	38.45 \pm 1.46	1.05
hs-CRP, ng/mL	331 \pm 98.7*	1.37 \pm 0.9	<0.01
TNF- α , pg/mL	18.4 \pm 3.9*	2.0 \pm 0.8	<0.01
Leptin, ng/mL	69.4 \pm 21.7*	19.75 \pm 2.19	<0.01

FBG: Fasting blood glucose, HbA1c: glycated hemoglobin, HOMA-IR: Homeostatic model of assessment of insulin resistance, TG: Triglycerides, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, hs-CRP: High-sensitive C-reactive protein, TNF- α : Tumor necrosis factor- α . Data are presented as mean \pm SD. *: Significant compared to control ($P < 0.05$).

and on both neck and axillae in 3 patients (15%).

Skin tags and glycemic control

The results revealed that ST group showed significantly higher insulin levels and insulin resistance (HOMA-IR) compared to controls ($P < 0.05$). However, there was no significant difference between the patients and the controls regarding fasting blood glucose and HbA1c (Table 2).

Skin tags and lipid profile

Skin tags patients showed significantly higher cholesterol, triglycerides, and LDL-cholesterol levels compared to controls, whereas HDL-cholesterol level showed no significant difference (Table 2).

Skin tags and inflammatory markers

Leptin level as well as TNF- α and hs-CRP were significantly higher in patients compared to controls as shown in Table 2. There was a positive correlation between leptin level and each of plasma TG and cholesterol ($r = 0.81$, $r = 0.47$, respectively, $P < 0.05$) as well as a positive correlation between leptin and insulin ($r = 0.53$, $P = 0.05$). In addition,

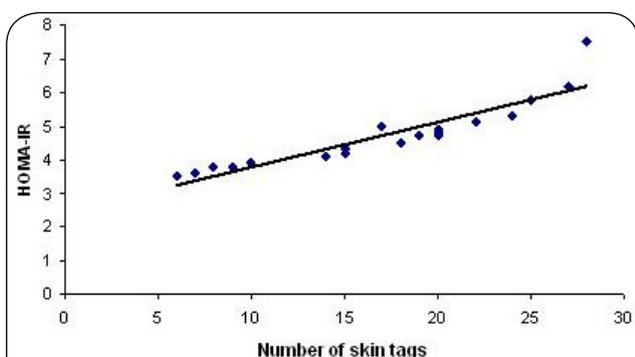


Figure 1. Correlation between number of skin tags and HOMA-IR in skin tags patients.
HOMA-IR: Homeostatic model of assessment of insulin resistance.

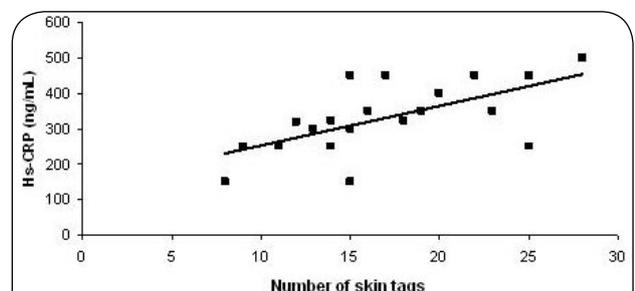


Figure 2. Correlation between number of skin tags and high sensitive C reactive protein (hs-CRP) in skin tags patients.

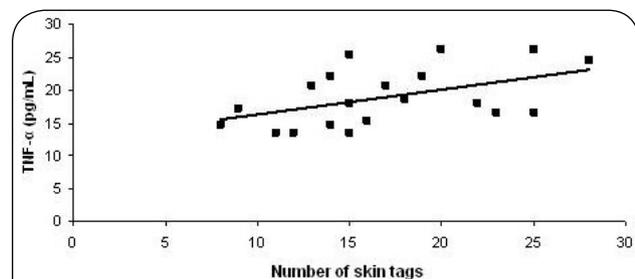


Figure 3. Correlation between number of skin tags and tumor necrosis factor-α (TNF- α) in skin tags patients.

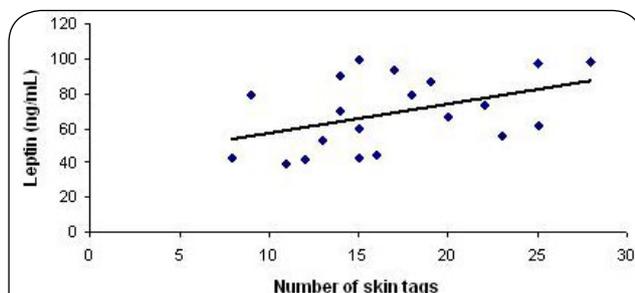


Figure 4. Correlation between number of skin tags and leptin in skin tags patients.

$r = 0.44$, $r = 0.46$, respectively, $P < 0.05$) (Figures 1,2,3 and 4).

Discussion

Skin tags are considered the most common fibrous lesions of the skin. A relation to obesity, diabetes mellitus, friction, acromegaly, organ transplant, human papilloma virus and other conditions has been reported [4]. However, how these factors may cause the development of ST is not yet clear. In this study, we measured the level of leptin hormone, TNF- α , and high sensitive C-reactive protein in attempt to investigate their role in the pathogenesis of these benign lesions.

In spite of the finding that 90% of ST patients participated in the present study were with normal blood glucose and HbA1c, the patients showed significant increase in fasting plasma insulin and HOMA-IR compared to the control group. These findings suggest that insulin resistance constitutes an important physiological abnormality in obese subjects even in absence of hyperglycemia or diabetes.

Our results were in agreement with Tamega *et al.*, [3], who found a greater association of ST with insulinemia than with fasting glucose, reinforcing the argument that skin tags together with pseudoacanthosis nigricans, may represent a marker for the identification of IR prior to the manifestation of diseases resulting from the hypermetabolic syndrome.

In the present study, there was a positive correlation between number of skin tags and HOMA-IR. This finding could be explained by the work of Sudy *et al.*, [5], who demonstrated that multiple skin tags were more sensitive than acanthosis nigricans in identifying alterations in the glucose/insulin metabolism and that they should raise suspicion of insulin resistance or hyperinsulinemia.

Moreover, the present data revealed a positive correlation between BMI and number of skin tags. These results were supported by El Safoury *et al.*, [20], who revealed that skin tags are related to obesity and a hormonal mechanism has been suggested, where there is increased peripheral aromatization of androgens to estrogens in obese females, while the estrogen levels in blood increase in a direct proportion with BMI in obese males. Furthermore, Goyal *et al.*, [21] detected different patterns of cutaneous manifestations including skin tags in type 2 diabetes mellitus and metabolic syndrome, which are characterized by insulin resistance.

The obtained positive correlation between insulin resistance and number of skin tags could be attributed to the fact that insulin is a hormone that promotes tissue growth and stimulates glucose uptake in tissues at an intensity that varies from one individual to another. When insulin resistance is present, the cells are less responsive to the effect of this hormone. To compensate, the pancreas begins to produce greater quantities of insulin [22]. This hyperinsulinism promotes an increase in IGF-1 and a reduction in insulin-like growth factor-binding protein 3

the number of ST was positively correlated with each of plasma hs-CRP, TNF- α , leptin and HOMA-IR ($r = 0.7$, $r = 0.48$,

(IGFBP-3), one of the ligands to retinoid X receptor (RXR), responsible for antiproliferative gene transcription. Both the hyperinsulinism and the increase in IGF-1 directly induce epithelial and fibroblastic growth by activating receptors, possibly explaining the prevalence of skin tags and pseudoacanthosis nigricans in these groups [23].

As shown by our results the insulin resistance was associated with higher levels of total cholesterol, LDL-cholesterol, and triglycerides in patients with skin tags. There are many studies suggesting a relation between skin tags and atherogenic lipid profile. Crook [24] reported increased serum TG and decreased HDL cholesterol in patients with skin tags. Gorpelioglu *et al.*, [25] found that total cholesterol and LDL-C levels were higher in patients with ST compared to healthy controls.

Interestingly, the present results revealed a significant increase of leptin levels in ST patients compared to control group. Leptin acts as an angiogenic factor in the vascular endothelium [26]. Fibroblasts and keratinocytes are also known to express leptin receptors, and the mitogenic effect of leptin on keratinocytes has been demonstrated during wound healing by *in vivo* studies [27]. Furthermore, the role of leptin in the proliferation of both normal and cancer cells has been previously reported [28]. It is therefore plausible that the increased level of leptin in ST patients, as shown in this study, through its angiogenic effect and the induction of cellular proliferation, may play an important role in the development of ST.

Additional evidence was provided by El Safoury *et al.*, [29], who showed that the presence of both ST and hyperleptinemia may be associated with high levels of triglycerides and low levels of HDL-C.

The present findings showed a positive correlation between leptin level and each of plasma insulin, triglycerides and cholesterol levels. Our results are in agreement with Sari *et al.*, [30], who proposed that skin tags are frequently associated with the risk factors for metabolic syndrome (MS) and heart disease. Furthermore, Rao *et al.*, [31] reported a positive correlation between serum insulin and BMI, plasma C-peptide, and plasma leptin, whereas, Shaheen *et al.*, [32] demonstrated a positive correlation between leptin and HOMA-IR in obese patients suggesting that leptin displays an association with obesity and insulin resistance.

In the present study, elevated serum TNF- α and hs-CRP were recognized in ST patients. TNF- α is a cytokine involved in systemic inflammation, produced chiefly by activated macrophages, although it can be produced by other cell types as the adipose tissue [33]. TNF- α stimulates the acute phase reaction leading to an increase in C-reactive protein and a number of other mediators. TNF- α also induces insulin resistance by promoting serine-phosphorylation of insulin receptor substrate-1 (IRS-1), which impairs insulin signaling [34].

Recent studies [35] have shown that M1 macrophages are key mediators of obesity-induced IR, with a progressive

infiltration of macrophages into obese adipose tissue. They release cytokines such as interleukin-1 β (IL-1 β), IL-6 and TNF- α creating a pro-inflammatory environment that blocks adipocyte insulin action, contributing to the development of IR and type 2 diabetes mellitus. So, it can be hypothesized that increased leptin level in hyperinsulinemia and/or insulin resistance conditions stimulate the production of TNF- α , which in turn exaggerates insulin resistance [35].

Data of the present work indicated a positive correlation between the number of skin tags and each of hs-CRP and TNF- α in the patients group. These results were further supported by other previous studies. Indulekha *et al.*, [36] showed that in Asian Indians, the inflammatory cytokines hs-CRP, TNF- α , IL-6, and vascular cell adhesion molecule-1 (VCAM-1) are elevated in subjects with MS, while hs-CRP and TNF- α are further elevated in those with MS and IR. Furthermore, it has been suggested that mast cells, TNF- α and TNF-related apoptosis-inducing ligand (TRAIL) may play a role in the pathogenesis of STs [37].

Thus, the present findings indicate a possible adipimmune role in the pathogenesis of ST. Obesity-associated chronic inflammation by recruitment of M1 inflammatory macrophages and increased cytokine production is a key contributor to decreased insulin signaling throughout the disease progression [38].

Since elevated blood lipids together with hs-CRP represent a strong risk factor of atherosclerosis and coronary heart disease, skin tags may be a marker of state of inflammation, which correlates with increased risk of cardiovascular disorders. So, protective measures for patients with ST and/or hyperleptinemia are highly recommended regarding weight reduction, smoking cessation, and commitment to healthy dietary habits.

Further studies are warranted to elucidate the molecular basis of the role of the inflammatory mediators and adipocytokines in the development of ST and other benign skin growths.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Dr Nahla E El Ashmawy: Concept, design, revision of the article
Dr Sahar K Hegazy: Drafting article, data analysis, statistics

Acknowledgement

The authors express deep thanks to Dr. Samia Osman Nassar, Professor of Dermatology and Venereology, Faculty of Medicine, Tanta University, for kind help and support in the diagnosis and selection of patients.

Publication history

Received: 25-Jan-2013 Revised: 18-Feb-2013
Accepted: 07-Mar-2013 Published: 12-Mar-2013

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Citation:

Hegazy S K and El-Ashmawy N E: **Leptin and c-reactive protein are implicated in the pathogenesis of skin tags.** *Journal of Diabetes Research and Clinical Metabolism* 2013, **2**:13.
http://www.hoajonline.com/jdrcm/2050-0866/2/13