The Role of Insulin-Like Growth Factor in the Acrochordon Etiopathology

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Abstract

Background There are reports that acrochordons (skin tag), the most common fibroepithelial tumor of the skin, may be associated with metabolic syndrome components, particularly insulin metabolism disorders. However, to the best of our knowledge, there is no study examining its association with the insulin resistance, insulin-like growth factor 1 receptor (IGF-1R) and insulin-like growth factor 2 receptor (IGF-2R) levels at tissue level yet

Methods Thirty patients with at least 1 acrochordon in their body who had no known history of diabetes mellitus and the control group comprised 30 individuals who had no acrochordon or no known history of diabetes mellitus were included. IGF-1R and IGF-2R expression was investigated using immunohistochemical assessment administered to the tissue samples from the study and control groups.

Results In the group with acrochordon, IGF-1R and IGF-2R expression was found to be significantly higher compared to the control group (p<0,01). IGF-1R expression was found to correlate with serum IGF-1 and BMI (p=0,03 r=0,028 and p=0,048 r=0,257 respectively). IGF-2R expression was found to correlate with BMI and HOMA-IR (p=0,03 r=0,357 and p=0,046 r=0,256 respectively). Using logistic regression analysis, an increase in serum insulin, serum IGF-1 and HOMA-IR levels was shown to increase IGF-1R and IGF-2R expression rates.

Conclusion These findings support the view that insulin metabolism disorders in patients with acrochordon should be evaluated. Our study indicates that insulin like growth factor receptors may have an effect on the acrochordon pathogenesis and that acrochordon etiology and related conditions can be clarified by detection of parameters that influence the receptor levels.

Background

Acrochordons are tiny pinhead size or larger papules with or without stem which have colors ranging from skin color to dark brown (1). Though the association of acrochordon development has been reported with obesity, pregnancy, acromegaly, aging, colonic polyps, and genetic predisposition, its cause is not fully understood yet (2, 3). Previous studies have suggested the association of acrochordons with type 2 diabetes mellitus (DM), glucose intolerance, hyperinsulinemia, and obesity.

Insulin-like growth factor (IGF), namely somatomedins, is a peptide family that mediates the emergence of many of the anabolic and mitogenic effects of the growth hormone (4). Since IGFs are protein in structure, they do not cross the cell membrane and show their effects by binding to their receptors on the cellular membrane. Three different IGF receptors have been identified; insulin receptor, IGF–1R, and IGF–2R (5). The insulin receptor and IGF–1R are approximately 60% similar regarding their amino acid structures. IGF–1R has an essential role in cell growth and differentiation because it has tyrosine kinase activation (6). Hyperinsulinemia increases the serum level of free IGF–1 and decreases serum level of insulin-like growth factor binding protein (IGFBP)–3.

On the other hand, IGFBP–3, which decreases due to increased insulin level, is the alpha receptor ligand of nuclear retinoic acid X, so the transcription of the antiproliferative gene also reduces. Hyperinsulinemia and increase in IGF–1 result in the growth of the epithelial and fibroblastic cells directly via receptor activation. This association explains the relatively frequent development of acrochordon and pseudoacanthosis nigricans in hyperinsulinemic patients (7).

The signal cascade following the activation of the IGF–2R receptor is not fully known. It is believed that the task of the IGF–2R receptor is to decrease the serum level of IGF–2 by binding, which is the only ligand of this receptor. When the level of IGF–2 decreases in the serum, it binds to IGF–1R in a lesser extent. Thus, IGF–2R is thought to suppress tumor growth and proliferation by indirectly suppressing IGF–1R activation. (8).

In contrast to the results of studies investigating the relations of acrochordons with DM and dyslipidemia, there is no study examining its association with the insulin resistance, IGF–1R and IGF–2R levels at tissue level yet. In this study, we aimed to investigate IGF–1R and IGF–2R levels in acrochordon tissue as well as metabolic disease indicators.

Methods

A total of 30 patients aged between 21 and 66 years who admitted to Dermatology outpatient clinic of Akdeniz University School of Medicine Hospital during a 6-month period, and have at least one acrochordon lesion and no known diabetes mellitus, were enrolled in the study. The control group consisted of 30 healthy age- and gender-matched individuals, aged between 18 and years, who don’t have any acrochordon lesion and free of diabetes mellitus. The study was approved by the local ethics committee of our hospital. All participants signed an informed consent form.

The locations, numbers, dimensions, shape and edge properties of the acrochordons, surface and base shape, sensorial features and duration of the lesions were recorded. Body mass index (BMI = Body weight/height2 [kg/m2]) of patients with acrochordon and control group was calculated. The BMI results were evaluated according to the World Health Organization (WHO) classification for the excess weight. Venous blood samples were taken following 12 hours of fasting and biochemical analysis of fasting blood glucose, total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, basal insulin, IGF–1, HbA1c, leptin, and free fatty acid levels were measured in the serum. Then all participants underwent an oral glucose tolerance test (OGTT).

Venous blood samples were taken following 12 hours of fasting. Fasting blood glucose, total cholesterol, triglyceride, LDL, HDL cholesterol levels were measured by enzymatic colorimetric methods in Modular PPP autoanalyser (Roche Diagnostics, GmbH, Mannheim). Whole blood HbA1c levels were measured by turbidimetric immun inhibition assay (TINIA) in Modular PPP autoanalyser (Roche Diagnostics, GmbH, Mannheim). Fasting insulin levels were determined by electrochemiluminescence immunoassay (ECLIA) method in E–170 immunoanalyser (Roche Diagnostics, GmbH, Mannheim). Serum IGF–1 and leptin levels were measured by commercially available ELISA kits. Serum non-esterified fatty acid (FFA) levels

were determined by automatically with application of an enzymatic colorimetric method(NEFA-HR) Wako Diagnostics, USA) to Viva-E analyser (Siemens Healthcare,Marburg, Germany). A 2 hour, 75 gram oral glucose tolerance test (OGTT) were administered for all patients.

Tissue specimens were taken from 30 patients with acrochordon lesions by superficial excision after local anesthesia. The control group for pathological examination was formed by selecting 30 non-tumoral skin tissue samples from the intact tissue archive of the Pathology Department. Tissue samples were fixed with formalin and embedded in paraffin. Sections of 4–5 micrometers thick were prepared from these paraffin blocks and immunohistochemically exposed to IGF–1R and IGF–2R (Santa Cruz Biotechnology, INC. IGF–1[G–17]: sc–1422 ve Genetex IGF2 Receptor antibody [N1], N-term) antibodies by 'Streptavidin-Biotin complex' method. Briefly tissue sections were incubated at 56 °C for overnight, and then paraffin was removed with xylol twice for 5 minutes of duration at each time. Then they were passed through descending degrees of alcohol and rehydrated by taking into distilled water. Antigen retrieval process was applied for 30 minutes in the hot (90°C) water tank containing EDTA buffer pH 8.0. It was then cooled for 20 minutes and washed in PBS. The sections were then incubated with 3% hydrogen peroxide solution for endogenous peroxidase enzyme blocking for 10 minutes. It was then allowed to stand in PBS for 20 minutes to prevent background staining. Sections were incubated overnight at room temperature with primary antibodies of IGF–1R and IGF–2R. Following the incubation, it was treated with 'linking reagent' for 15 minutes and then treated with streptavidin conjugated 'horseradish peroxidase' for a further 15 minutes. The staining was made visible with diaminobenzidine and covered with lamella after contrast staining with hematoxyline. Histological evaluation was done semi-quantitatively by light microscopy. Cytoplasmic and membranous staining was considered positive. The staining intensity was graded as negative (-), mild (+), moderate (++) and intense (+++).

Statistical Analysis

The data was analysed with SPSS 18.0 For Windows statistical application software. The differences between study groups in terms of categorical variables were tested by Fisher's exact test or Pearson Chi-Square test; the numerical variables was tested by Mann-Whitney-U test or Student-T test, correlations between two independent variables was tested by Spearman correlation test, and factors affecting the development of acrochordon were analyzed and interpreted by logistic regression analysis methods. A P value of <0.05 was considered statistically significant.

Results

Of the 30 patients included in the study group, 18 (60%) were female and 12 (40%) were male. The age of patients with acrochordon ranged between 21-66 years, with a mean age of 48.17 ± 12.08 years. The control group consisted of 17 women (56.7%) and 13 men (43.3%). The age of the control group ranged between 18-77 years and the mean age was 48.37 ± 13.81 years. There was no statistically significant difference between the

two groups in terms of age and sex distribution (p = 0.953 and p = 0.793, respectively). The disease duration of the group with acrochordon ranged from 1 to 35 years, with a mean duration of 7.9 ± 7.07 years (min- max = 1-35 years, median = 5 years). Twenty-three of the patients with acrochordon had multiple locations. Twelve (40%) of the patients had acrochordon lesions in axillary and neck locations, 3 (10%) patients had in axillary region, neck and on trunk, 2 (6.6%) patients had on trunk, neck, and face, 2 (6.6%) patients had on the neck, infra-mammarian region and extremities, 1 (3.3%) patient had in axillary region, neck and extremities, 1 (3.3%) patient had on the neck and face, and 1 (3.3%) patient had on the axilla and the trunk.

BMI values of the group with acrochordon ranged from 22.2 kg / m^2 to 48.1 kg / m^2, with a mean value of 30.55 ± 5.09 kg / m^2. BMI values of the control group were between 18.6-42.6 kg / m^2 and the mean was 28.17 ± 6.19 kg / m^2. According to BMI values in the acrochordon group; 3 patients (10%) were normal, 13 (43.3%) were overweight and 14 (46.7%) were obese. Of the control group, 11 (36.7%) were normal, 8 (26.7%) were overweight and 11 (36.7%) were obese. The mean BMI of the study group with acrochordon was significantly higher than that of the control group (p = 0.04). There was no significant correlation between the current acrochordon count and BMI value of the patient group (p = 0.206).

When we examined the fasting blood glucose (FBG) level of the patient group, there were normal values in 19 patients (63.3%), whereas 9 (30%) patients had impaired FBG levels and 2 patients (6.7%) had FBG levels within DM range. Ten (33.3%) subjects in the control group had normal FBG levels, whereas 17 (56.7%) had impaired FBG levels and 3 (10%) had FBG levels within DM range. The difference in FBG category distribution between groups did not reach statistical significance (p=0.06).

According to the OGTT results, 22 (73.3%) patients in the acrochordon group were normoglycemic (below 140 mg/dL), while 5 (16.7%) patients had impaired glucose tolerance (IGT) (140-200 mg/dL) result and 3 had DM (over 200 mg/dL) diagnosis. In the control group, 15 (50%) subjects were within normoglycemic ranges, 8 (26.7%) patients had IGT and 7 (23.3%) patients had DM diagnosis. There was no statistically significant difference between the groups regarding the OGTT results (p = 0.16).

Patients with acrochordon were divided into two groups according to the lesion count; those with fewer than 15 lesions and those with 15 or more. There was no statistically significant difference in carbohydrate metabolism between these two groups. In addition, there was no statistically significant relationship between carbohydrate metabolism and acrochordon location (p>0.05).

The mean HbA1c value was 5.83 ± 0.62% in the group with acrochordon and 6.06 ± 0.67 % in the control group (p = 0.037).The mean serum insulin level was 13.87 ± 12.53 uU / ml in the group with acrochordon and 10.45 ±

9.61 uU / ml in the control group (p = 0.031). According to the HOMA-IR values of the participants, 17 patients (56.7%) in the study group had insulin resistance and 13 patients (43.3%) did not. In the control group, 10 subjects (33.3%) had insulin resistance while 20 (66.7%) did not. The mean HOMA-IR value of the study group was tended to be higher compared to the controls (p=0.069). In addition, insulin resistance was found in 9 of 14 obese patients (64.28%) in the acrochordon group and in 5 (35.71%) of 11 obese patients in the control group. There was no significant difference between the groups in terms of insulin resistance ratio in obese patients (p = 0.34). There was no significant correlation between HOMA-IR value and acrochordon count (p = 0.547). No relation was found between HOMA- IR value and acrochordon localization (p>0.05).

There was no statistically significant difference between the control group and acrochordon group in terms of triglyceride, total cholesterol, VLDL, HDL, LDL cholesterol levels and total cholesterol/HDL and LDL/HDL ratios (p>0.05, for all). There was no statistically significant relation of lipid profile with the number and location of acrochordon lesions (p>0.05). The mean serum free fatty acid level was 0.53 ± 0.17 mmol / L in the acrochordon group and 0.49 ± 0.22 mmol / L in the control group. There was no statistically significant difference in serum free fatty acid levels between the study groups (p = 0.228).

The mean serum leptin level was 11228.97 ± 4.56 pg / ml in the acrochordon group and 9970.30 ± 4.49 pg / ml in the control group. There was no statistically significant difference in serum leptin levels between the study groups (p = 0.352).

The mean serum IGF-1 value was 63.89 ± 40.96 ng / ml in the acrochordon group and 92.3 ±73.98 ng / ml in the control group. The difference between the groups in terms of mean serum IGF-1 level was not significant statistically (p=0.193) In addition, there was no significant correlation between serum IGF-1 level and acrochordon count (p = 0.671). Serum IGF-1 levels were not significantly different in normoglycemic patients with acrochordon compared to the control group (p = 0.125).

IGF-1R staining was observed in 29 of 30 patients in the group with acrochordon. Pathologic specimens of 12 patients (40%) were mildly stained (+), 14 (46.7) were moderately stained (++) and 3 (10%) were intensely stained (+++). Only 5 (16.7%) of the control group had mild (+) staining, and 25 (83.3%) had no staining (-).

Negative IGF-1R staining in normal tissue is shown in Figure 1a, IGF-1R with mild (+), moderate (++) and severe (+++) staining in Figure 1b, 1c and 1d, respectively.

Presence of IGF-1R was significantly higher in the acrochordon group compared to the control group (p <0.001). The distribution of IGF-1R staining levels according to groups is shown in Table 1.

Table 1. The distribution of IGF-1R staining levels according to groups

	No staining (-) n (%)	Mild (+) n (%)	Moderate (++) n (%)	Intense (+++) n (%)
Patients	1 (3.3)	12 (40)	14 (46.7)	3 (10)
Controls	25 (83.3)	5 (16.7)	0 (0)	0 (0)

When the IGF-2R staining levels were examined in the acrochordon group, staining was observed in all patients. One patient (3.3%) had mild (+) staining, 5 (16.7) had moderate (++) staining, and 24 (80%) had intense (+++) staining. Mild (+) staining was present in only 6 (20%) of the control group and 24 (80%) of them had no staining observed in the control group. Mild (+), moderate (++) and intense (++) staining with IGF-2R in acrochordon tissue are shown in Figure 2.

IGF-2R staining was significantly higher in the acrochordon group than the control group ($p<0.001$). The distribution of IGF-2R staining levels according to groups is shown in Table 2.

Table 2. The distribution of IGF-2R staining levels according to groups

	No staining (-) n (%)	Mild (+) n (%)	Moderate (++) n (%)	Intense (+++) n (%)
Patients	-	1 (3,3)	5 (16,7)	24 (80)
Controls	24 (80)	6 (20)	-	-

There was a positive correlation between IGF-1R staining intensity and serum IGF-1 level in patients with acrochordon ($r = 0.028$, $p = 0.003$). However, there was no statistically significant correlation between IGF-2R staining intensity and serum IGF-1 level ($p = 0.11$).

There was a positive correlation between IGF-1R staining intensity and BMI in patients with acrochordon ($r = 0.257$, $p = 0.048$). The relationship between IGF-1R level and BMI is shown in Table 3.

Table 3. Relationship between IGF-1R level and BMI

	IGF-1R		Total n (%)
	Staining positive n (%)	No staining n (%)	
Normal	4 (28.6)	10 (71.4)	14 (100)
Overweight	14 (66.7)	7 (33.3)	21 (100)
Obese	16 (64)	9 (36)	25 (100)
Total	34 (56.7)	26 (43.3)	60 (100)

There was a positive correlation between IGF-2R staining and BMI ($r = 0.357$, $p = 0.003$). In addition, the IGF-2R staining intensity is significanly correlated with BMI ($r = 0.375$, $p = 0.003$) There was no correlation between IGF-1R or IGF-2R with age and lesion duration in patients with acrochordon ($p > 0.05$, for all).

There was no relationship between IGF-1R staining and the number and localization of acrochordons ($p = 1.00$). In addition, there was no correlation between the intensity of IGF- 1R staining and the number of acrochordons ($p = 0.423$). There was no significant correlation between IGF-1R staining intensity and insulin level ($p = 0.166$). Whereas, there was a positive correlation between IGF-2R staining intensity and serum insulin levels ($r = 0.27$, $p = 0.037$). Meanwhile, there was no correlation between the number of lesions and IGF-2R staining intensity ($p = 0.352$).

There was no statistically significant difference between the patients with normal serum insulin levels and the control group in terms of IGF-1R and IGF-2R staining ($p = 1.00$).

The levels of IGF-1R and IGF-2R were similar between genders ($p = 0.93$ and $p = 0.593$, respectively).

There was no statistically significant difference between the patients with acrochordon and the control group in terms of HOMA-IR and staining with IGF-1R and IGF-2R ($p = 0.438$ and $p = 0.459$). In addition, HOMA-IR level was not correlated with IGF-1R and IGF-2R staining intensity ($p>0.05$, for both).

The staining with IGF-1R and IGF-2R was significantly higher in the normoglycemic patients with acrochordon compared to the control group ($p <0.01$).

In logistic regression analysis, independent factors were investigated associated with the presence of acrochordon. None of the variables included in the model (BMI, serum insulin levels, IGF-1R and IGF-2R staining) were found to be independently associated with the presence of acrochordon (Table 4)

Table 4. Logistic regression analysis results of the potential factors associated with the presence of acrochordon

	p value	%95 Confidence interval	
		Upper limit	Lower limit
BMI	0.743	0.827	1.306
IGF-1R	0.337	0.175	162.59
IGF-2R	0.996	0	
Insulin	0.179	0.554	1.11

In the logistic regression analysis we found that HOMA-IR, insulin and serum IGF-1 are independent variables associated with IGF-1R staining. (Table 5)

In the logistic regression model of BMI, serum IGF-1, serum insulin, and HOMA-IR as independent variables which may affect IGF-2R staining. (Table 6)

Table 5. The logistic regression analysis of independent variables associated with IGF-1R staining

	p value	%95 Confidence interval	
		Upper limit	Lower limit
HOMA-IR	**0.021**	0.027	0.749
BMI	0.314	0.945	1.191
Insulin	**0.020**	1.100	2.987
IGF-1	**0.032**	0.976	0.999

Table 6. Logistic regression analysis of independent variables associated with IGF-2R staining

	p value	%95 Confidence interval	
		Upper limit	Lower limit
HOMA-IR	0.023	0.023	0.758
BMI	0.084	0.985	1.275
Insulin	0.022	1.091	3.114
IGF-1	0.039	0.977	0.999

Discussion

In the present study, metabolic parameters were investigated in non-diabetic patients, together with serum IGF–1 level and the presence of IGF–1R and IGF–2R in tissue were investigated for the pathogenesis of acrochordon. Mathur and Bhargava have reported that acrochordon and acanthosis nigricans may develop in patients with obesity-related insulin resistance and have shown that as the BMI values increase, the number of acrochordons also increases (9). In a study conducted by Demir et al to investigate the relationship between acrochordons and impaired carbohydrate metabolism, BMI values of the patients were found between 22–56 kg / m2 with a mean value of 33.2 ± 6 kg / m2 and obesity was determined in 70% of their study population. They also reported that the number of acrochordons increases as the BMI value increases ($r = 0.36$, $p < 0.01$) (2). In our study, the mean BMI value of the acrochordon group was significantly higher than the control group. In another study, it was reported that the number of acrochordons was high in patients with high BMI; furthermore, it was stated that in patients with high BMI, acrochordons were more commonly located on the neck, axilla, and extremities and this could be related to friction (10).

Insulin resistance, hyperinsulinemia, IGF-R activation, and obesity are closely related with each other. Therefore, Bhargava et al. suggested that obesity, multiple acrochordons, abnormal glucose tolerance, pseudoacanthosis nigricans, and seborrheic keratoses may be components of a syndrome (11). In our previous study, we had included 113 patients with acrochordon and had determined insulin resistance in 21.2% of these patients (12). In a study by Sudy et al conducted with male patients having multiple acrochordons, 11.5% of 26 patients with 8 or more acrochordons had DM, 34.6% had impaired glucose tolerance, and 30.7% had hyperinsulinemia/insulin resistance. Therefore, they suggested that 8 and more acrochordons may be a cutaneous manifestation of hyperinsulinemia, indicating pre-diabetic status (13). In a study conducted by Tamega et al., the authors have suggested that acrochordons are associated with fasting insulin levels rather than fasting glucose levels (7). In our study, we found that fasting insulin level was significantly higher in the group with acrochordon compared to the control group which is consistent with the previous studies. However, there was no statistically significant correlation between the number of acrochordons and insulin level according to our results.

The signal cascade following the activation of the IGF–2R receptor is not fully known yet. It is thought that the task of the IGF–2R receptor is to decrease the serum level of IGF–2 after binding. When the level

of IGF–2 decreases in the serum, it binds to IGF–1R in a lesser extent. Thus, IGF–2R is thought to suppress tumor growth and proliferation by indirectly suppressing IGF–1R activation (8). The first study examined the association of IGF–1 and insulin with acrochordon development in non-diabetic individuals was conducted by Jowkar et al. In this study, serum insulin was found to be higher in patients with acrochordon, whereas the IGF–1 levels were not different between groups (1). In our study, serum IGF–1 values were found to be comparable between the acrochordon group and the control group, which is consistent with the results of Jowkar's study. It has been suggested that acrochordons may result from dermal fibroblast proliferation by activation of IGF–1R (12); however, there is no previous study to clarify this issue. Our study is the first to investigate IGF–1R and IGF–2R levels in acrochordon tissues. We believe that the role of IGF-R activation is more important than the increase in serum IGF–1 level and hyperinsulinemia in the acrochordon development process. In our study, IGF–1R and IGF–2R levels were significantly higher in the acrochordon group compared to the control group ($p<0.001$). In patients with acrochordon, IGF–1R staining frequency and intensity were positively correlated with serum IGF–1 level and BMI. Moreover, BMI and HOMA-IR values were also correlated with IGF–2R staining frequency and intensity. These results indicate that an increase in BMI may directly be associated with the presence of IGF receptor and intensity of receptor staining in tissue. The fact that the mean BMI of the patients in our study were higher than those of the control group supported this suggestion. According to the results of this study, which is the first study showing that insulin can affect IGF–2R, there is a significant correlation between serum insulin levels and IGF–2R staining intensity. The concentration of IGF receptors was not different between patients with normal serum insulin levels and controls. These results suggest that high insulin levels may directly affect the presence and intensity of IGF receptors, leading to the development of acrochordons. The presence of both IGF–1R and IGF–2R were found to be significantly more frequent in normoglycemic patients with acrochordon compared to the control group. These results suggest that the presence and intensity of IGF receptor may play a role in the pathogenesis of acrochordon regardless of impairment in carbohydrate metabolism.

In our study, we found that the most important variable independently associated with the presence of both IGF–1R and IGF–2R is serum IGF–1 level. The effects of IGF–1 on IGF–1R are known. However, we think that the increase in IGF–2R levels may be due to negative feedback secondary to the increase of IGF–1 and IGF–1R and its potential antiproliferative effects. We also found that increased levels of HOMA-IR, serum IGF–1 and serum insulin are potential independent variables associated with the presence of both IGF–1R and IGF–2R. The high IGF receptor concentration in normoglycemic subjects and the independent association of HOMA-IR with the presence of receptor suggest that insulin resistance is independently associated with the presence and intensity of IGF receptors rather than DM.

The results of our study have suggested that IGF–1R and IGF–2R may play role in the pathogenesis of acrochordon. We found that IGF receptor levels are correlated with BMI, serum insulin and IGF–1 levels in patients with acrochordon. Furthermore, the fact that the presence of IGF receptor is more frequent in normoglycemic patients compared to the control group, shows that the presence of the receptor is independent of carbohydrate metabolism. These results suggest that hyperinsulinemia and insulin resistance play a role in the development of acrochordon at tissue receptor level mediated by IGF–1. By

determining the variables affecting the presence and intensity of tissue IGF receptor, we believe that the acrochordon etiopathogenesis and the related conditions can be elucidated.

Abbreviations

IGF: Insulin-like growth factor, IGF–1R: Insulin-like growth factor receptor–1, IGF–2R: Insulin-like growth factor–2, IGFBP: Insulin-like growth factor binding protein, BMI: Body mass ındex, HOMA-IR: Homeostatic Model Assessment-Insulin Resistance, DM: Diabetes mellitus, WHO: World Health Organisation, TINIA: Turbidimetric immun inhibition assay, ECLIA: Electrochemiluminescence immunoassay, FFA: Non-esterified fatty acid, NEFA-HR: Enzymatic colorimetric method, OGTT: Oral glucose tolerance test, IGT: Impaired glucose tolerance, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein

Declarations

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None

Authors Contributions

AAK, HGK, CIB, RS and SHA designed the study. AAK, HGK, BCB and CIB collected the data. AAK supervised the project. HGK, BCB and AAK wrote the study. HGK, AAK, CIB, RS and SHA corrected the manuscript. All authors revised and approved the final manuscript

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Availibility of data and materials

The data set fort his publication is not publically available and can be obtained from the corresponding author on request. The administrative permission to Access the data was obtained from HGK

Ethics approval and consent to participate

All procedures performed were in accordance and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards and ethical approval was obtained from Akdeniz University Medicine Faculty ethics committee Referance Number: 2010.04.0103.006].

This article does not contain any studies with animals performed by any of the authors.

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable

Competing interest

The authors declare that they have no competing interests

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Figures

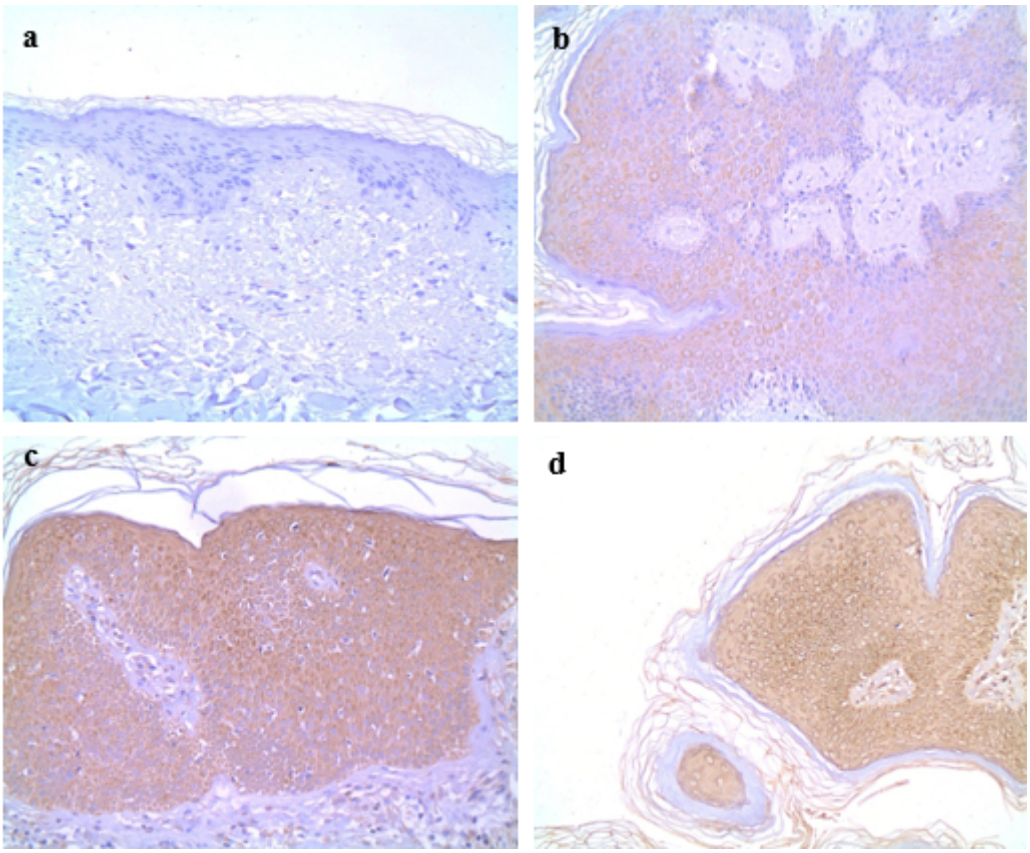

Figure 1

IGF-1R staining. Figure 1a. negative IGF-1R staining in normal tissue (1x100) Figure 1b. mild (+) staining with IGF-1R in acrochordon tissue (1x100) Figure 1c. moderate (++) staining with IGF-1R acrochordon tissue (1x200) Figure 1d. intense (+++) staining with IGF-1R in acrochordon tissue (1X100)

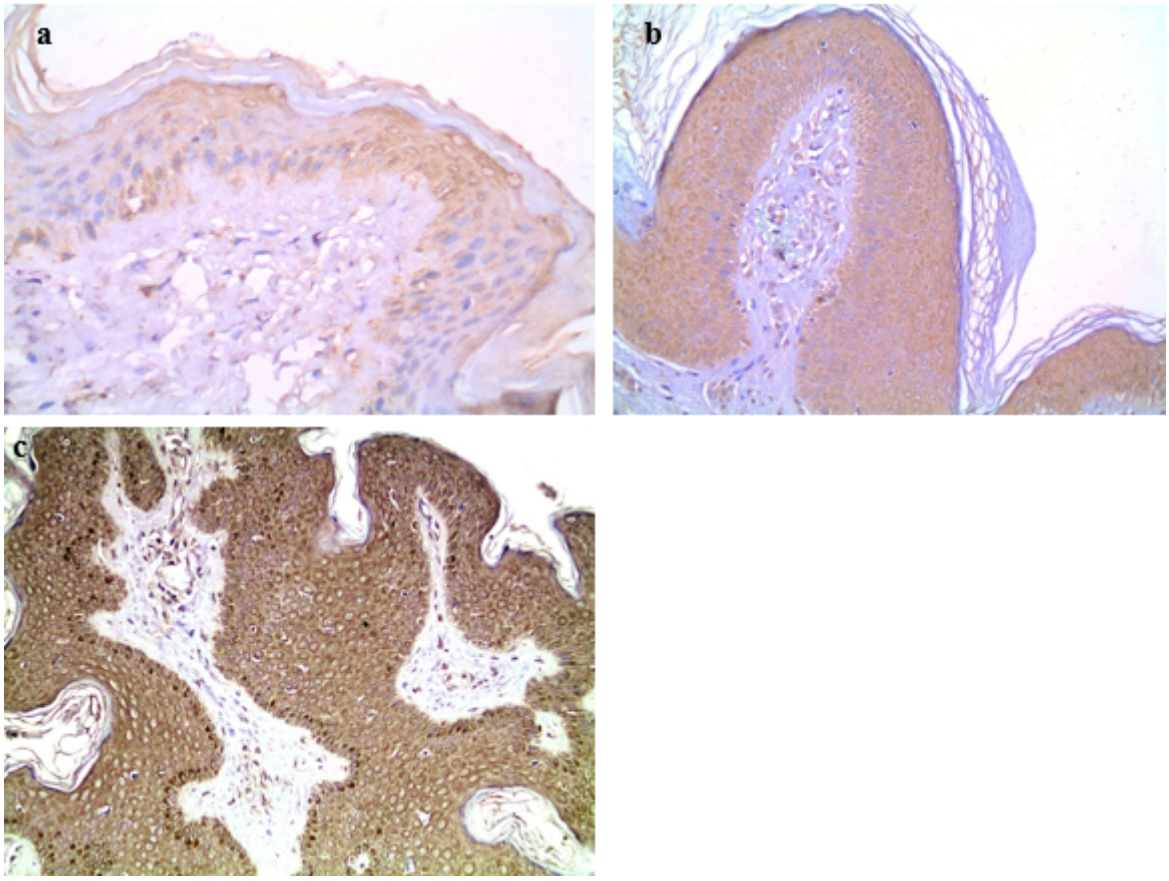

Figure 2

IGF-2R staining in acrochordon tissue. Figure 2a. Mild (+) staining with IGF-2R in acrochordon tissue (1x200) Figure 2b. Moderate (++) staining with IGF-2R in acrochordon tissue (1x100) Figure 2c. Intense (+++) staining with IGF-2R in acrochordon tissue (1x100)