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# Correlation between insulin resistance and treatment-resistant acne

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**Abstract**

Physiologically during puberty and adolescence, when juvenile acne usually appears, the response to a glucose load is increased if compared to the one observed in adult and at pre-pubertal age, while insulin sensitivity is reduced. Insulin is a hormone that acts at different levels along the axis which controls the sex hormones. It increases the release of LH and FSH by pituitary gland, stimulates the synthesis of androgens in the gonads and stimulates the synthesis of androgenic precursors in adrenal glands. Finally, it acts in the liver by inhibiting the synthesis of Sex Hormone Binding Globulin (SHBG). Insulin is also able to act directly on the production of sebum and amplify the effects of Iinsulin Growth Factor-1 in the skin, inhibiting the synthesis of its binding protein (IGF Binding Protein-1).

In female subjects with acne and Polycystic Ovary Syndrome (PCOS), insulin resistance is a well known pathogenetic factor, while the relationship between acne and insulin resistance has been poorly investigated in males so far.

The purpose of this study is to investigate the correlation between insulin resistance and acne in young males who do not respond to common therapy. Clinical and biochemical parameters of glucose, lipid metabolism, androgens and IGF-1 were evaluated. Insulin resistance was estimated by Homeostasis Model assessment (HOMA-IR) and Oral Glucose Tolerance Test was also performed. We found that subjects with acne had higher Sistolic and Diastolic Blood Pressure, Waist/Hip Ratio, Waist Circumference, 120' OGTT serum insulin and serum IGF-1 and lower HDL-cholesterol than subjects of comparable age and gender without acne.

The results thus obtained confirmed what other authors have recently reported about a metabolic imbalance in young males with acne. Furthermore, these results support the hypothesis that insulin resistance might play an important role in the pathogenesis of treatment-resistant acne in males.

### 1.1 Polycystic Ovary Syndrome model

In 1990 the National Institute of Child Health and Human Disease (NICHD) of the United States National Institutes of Health (NIH) defined Policystic Ovary (or Ovarian) Syndrome (PCOS) as a syndrome which should include (in order of importance):

1. hyperandrogenism and/or hyperandrogenemia;
2. oligo-ovulation, [and the]
3. exclusion of other known disorders, which could cause hyperandrogenism.

This survey had the clarity of identifying PCOS as an androgen excess disorder of exclusion, with ovarian consequences.

Under the NIH/NICHD criteria, clinical hyperandrogenism has generally been interpreted as hirsutism, since >70% of hirsute women are hyperandrogenemic. Consequently, three principal phenotypes were originally recognized:

1. women with hirsutism, hyperandrogenemia, and oligo-ovulation;
2. women with hirsutism and oligo- ovulation;
3. women with hyperandrogenemia and oligo- ovulation.

According to the NIH/NICHD criteria, the presence of polycystic ovaries by ultrasound was suggestive, but not diagnostic, of PCOS.

In 2003 a new consensus was established by the European Society for Human

Reproduction and Embryology and the American Society for Reproductive Medicine in Rotterdam which defined the syndrome as the presence of at least two of the following three features:

1. oligo- and/or anovulation;
2. clinical and/or biochemical signs of hy- perandrogenism;
3. polycystic ovaries on ultrasound.

According to the Rotterdam criteria, the population of potential patients with the PCOS has increased through the creation of two new phenotypes, namely, patients who have polycystic ovaries, hirsutism, and/or hyperandrogenemia but normal ovulation and women who have polycystic ovaries and irregular ovulation but no sign of androgen excess.

Finally, in 2006 the Androgen Excess Society and Polycystic Ovary Syndrome Society gave emphasis to hyperandrogenism, suggesting that this would be a mandatory criterion for the diagnosis of the syndrome.

Even if the definition of PCOS is still debated, PCOS is the most frequent endocrine disorder that is associated with acne. Its prevalence is around 15-20% in infertile women. Furthermore, PCOS is a good example of coexistence of insulin resistance, hyperandrogenism and hyperinsulinemia. Indeed, in female with acne and PCOS, insulin resistance is a well known etiopathogenetic factor.

The insulin receptor in PCOS is genetically and functionally normal. Insulin resistance in PCOS is caused by a post-receptor defect in insulin signaling with increased serine phosphorylation implicated as the cause of decreased insulin-stimulated Iinsulin Receptor Substrate-1 (IRS-1) activation and decreased GLUT 4 expression.

Although insulin resistance per se is considered to be the responsible entity for

hyperandrogenism in PCOS, this mechanism does not explain the hyperandrogenism evident in women with the disorder without insulin resistance and/or excess adiposity. Inflammation may be the common thread in the induction of insulin resistance that is related to PCOS per se, or to superimposed excess adiposity.

This concept raises the possibility that inflammation may be capable of directly inducing hyperandrogenism in PCOS. The ability of TNF-alpha to stimulate increased serine phosphorylation makes it an ideal candidate for initiating these molecular events in PCOS.

Furthermore, while discussing the definition of PCOS and the validity of the criteria proposed for its diagnosis, some authors observed that the only presence of polycystic ovaries in women who otherwise are not hirsute and have normal ovulation can be associated with the presence of features reminiscent of those observed in patients with PCOS. This features include mild elevations in circulating LH , androgen, and insulin levels, in insulin resistance assessed using the homeostatic assessment (HOMA-IR) calculation or the insulin tolerance test, and in the LH, 17-hydroxyprogesterone, and testosterone response to acute long-acting GnRH-analog stimulation.

There are some evidence that hyperandrogenemic ovulatory women with and without polycystic ovaries did not have significantly different androgen levels and LH/FSH ratios, although the former had higher fasting insulin levels, lower glucose-insulin ratios, and a higher 17-hydroxyprogesterone response to leuprolide.

These data suggest that hyperandrogenemic ovulatory women with polycystic ovaries, whether hirsute or not, tend to have mild insulin resistance and mild evidence of ovarian dysfunction, although significantly less than women with anovulatory PCOS.

Other investigators found that fasting and glucose-stimulated insulin and glucose levels or gonadotropin levels were similarly altered in non hyperandrogenic women with polycystic ovaries and in patients with PCOS. In both groups, menstrual irregularity was associated

with significantly higher concentrations of serum fasting and stimulated insulin levels, independent of androgens and degree of obesity.

In conclusion, PCOS well represents the complexity of interaction between androgens and insulin/IGF-1 and can be used as a model of the complex interaction between immune and endocrine system.

### 1.2 Growth Hormone (GH) and Insulin-like Growth Factors (IGFs) in acne

Growth Hormone is secreted by the pituitary gland and acts on the liver and peripheral tissues to stimulate the production of IGFs (*Insulin-like Growth Factors*). They are formerly known as somatomedins. Growth hormone is released in intermittent secretory bursts; IGF-1 is relatively stable instead.

IGF is found in two forms, IGF-1 (the most prevalent) and IGF-2. Adolescence is a time of maximal growth hormone secretion. Furthermore, in adolescence the highest serum levels of IGF-1 are reached. In addition, IGF-1 can be produced locally within the skin, where it can interact with receptors on the sebaceous gland to stimulate its growth.

In some tissues, the actions of IGF-1 can be mediated by androgens and it has been hypothesized that androgens may influence IGF-1 action in the sebaceous gland as well. Sebocytes express receptors for growth factors, including *Epidermal Growth Factor* (EGF) and IGF-1.

All known functions of IGF-1 are mediated by its cell membrane receptor. The distribution of the IGF-1 receptor in normal and pathological tissue provides valuable clues to its role in vivo.

Hodak et al. demonstrated that IGF-1 receptor was expressed not only in the epidermis but also in several skin appendages. IGF-1 immunoreactivity was found in the outer root sheath, hair matrix cells, sebaceous gland, eccrine sweat duct, and myoepithelial cells of the secretory portion of eccrine sweat gland. IGF-1 receptor in a cell surface pattern occurred principally in undifferentiated epithelial cells in both the epidermis and in skin appendages. In normal epidermis, in hyperplastic epidermis, and within the pilosebaceous unit, the expression of IGF-1 receptors by undifferentiated epithelial cells was largely coincident with proliferating or cyclig cell populations, as assessed by expression of the

Ki67 nuclear protein.

Ligand-mediated activation of the IGF-1 receptor is required for proliferative responses of cutaneous epithelial cells to other mitogens such as EGF, *basic-Fibroblast Growth Factor* (bFGF), or *Keratinocyte Growth Factor (*KGF*)* and restricted expression of IGF-1 receptors to relatively undifferentiated epithelial cells could directly explain compartmentialized proliferation.

In pilosebaceous epithelia IGF-1 receptor immunoreactivity is localized to the basal layer of the outer root sheath and the germinative layer of sebaceous gland, whereas EGF receptor immunoreactivity is observed in all cells of outer root sheath and sebaceous gland. The presence of IGF-1 receptor expression in sweat duct epithelium, as well as myoepithelial cells, which are metabolically very active but mitotically inactive indicates that IGF-1 receptor expression in the skin is not restricted to structures that are greatly involved in cell replication. IGF-1 is not only a mitogenic factor, but also a factor regulating the synthetic activity of a variety of cells.

The influence of sex steroids on the folliculo-sebaceous unit is well established, and several lines of evidence link IGF-1 with sex hormones.

There is increasing evidence suggesting the involvement of IGF-1 in acne. Recent studies describe a correlation between IGF-1 serum levels and the severity of acne in women (Aizawa and Niimura, 1995; Cappel et al., 2005). IGF-1 serum levels also correlate directly with the amount of facial sebum in both men and women (Vora et al. 2008).

In the skin, IGF-1 induces keratinocyte proliferation in vitro and in vivo, and it induces lipid production in human sebocytes.

Isard et al. found that IGF-1 and IGF1-R were overexpressed in acne lesions as compared with healthy skin. They have firstly reported that Propionibacterium acnes stimulates IGF-1 and IGF-1R expression in keratinocytes and increases IGF-1 secretion. Furthermore, they

observed that IGF-1 and IGF-1R overexpression in acne lesions was associated with increase in Ki-67 and filaggrin expression in the epidermis, confirming that IGF-1/IGF-1R system is associated with the modulation of both proliferation and differentiation of keratinocytes.

Therefore, acne has been recently suggested to be an IGF-1 mediated disease.

IGF-1 production activate IGF-1R, mostly located in the basal layer of epidermis, and thus induce proliferation of keratinocytes and an increase in filaggrin expression through a paracrine pathway. Moreover, acne lesion formation is increased by the induction of lipogenesis and the production of androgens by IGF-1.

Similar to that of growth hormone and IGF1, the level of dehydroepiandrosterone sulphate (DHEAS), that is the major adrenal androgen precursor, progressively increases during puberty. It appears to be a crucial factor in the initiation of sebum secretion in the prepubertal period and perhaps beyond. IGF-1 and DHEAS follow a similar chronological trend, for this reason some authors hypothesized a possible relationship between these two hormones.

Cappel et al. studied the correlation between IGF-1 and DHT and DHEAS in an all-women group, a group of women with clinical acne, and a group of men with clinical acne. Their study supported the findings that IGF-1 levels are higher in adult women with acne than in those without acne. Furthermore, they found statistically significant correlations between IGF-1 and DHEAS and IGF-1 and DHT in the all-women group, statistically correlation between dihydrotestosterone (DHT) and IGF-1 in women with clinical acne and statistically correlation between DHEAS and androstenedione levels in men with clinical acne.

Despite these correlations, the data from their study demonstrate that IGF-1 and androgens can act independently or dependently on acne lesions counts, depending on the patient group or subgroup. However, in men and women with clinical acne, IGF-1

appears to play a greater role. Moreover, in women with clinical acne, IGF-1 actually acted independently of androgens.

A correlation between the mean facial sebum excretion rate and serum IGF-1 levels has been demonstrated in postadolescent acne patients as well.

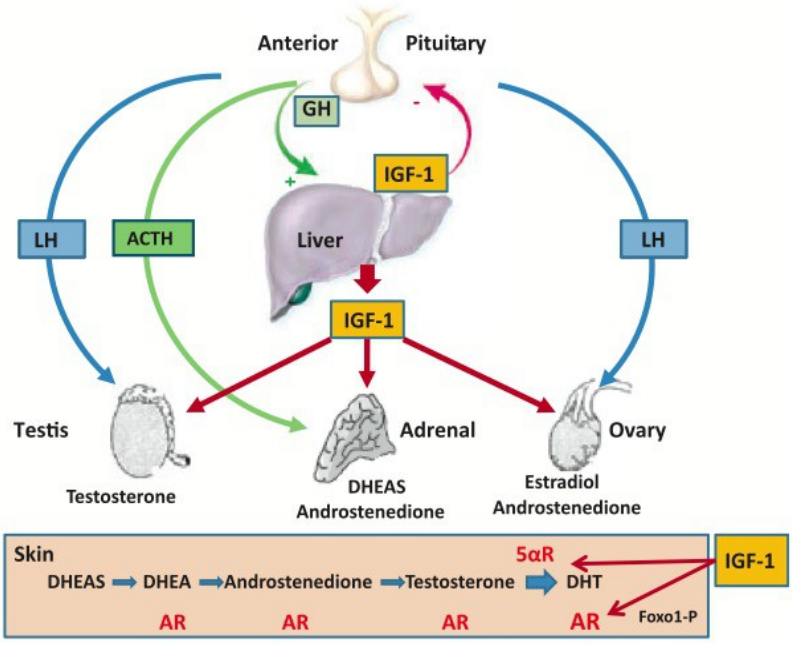


Figure 1. Regulatory network of ACTH, LH, GH, IGF-1 in adrenal and gonadal androgen synthesis and cutaneous intracrine androgen metabolism. (AR=androgen receptor) *[Melnik et al., Experimental Dermatology, 2009;18:833-841]*

### 1.3 The regulatory network of GH, Insulin and IGF-1

GH, insulin and IGF-1 have distinct effects on sebocyte growth and differentiation.

IGF-1 exerts its major effect on proliferation, while having an effect similar to insulin on differentiation.

More than 90% of circulating IGFs are bound to IGF- binding protein-3 (IGFBP-3), the rest to IGFBP-1, -2, -4, -5 and -6, and less than 1% of IGFs circulate as free IGFs.

IGF signal transduction is mediated by the IGF-1 receptor (IGF1R) and IGF2R. The IGF1R is a tyrosine kinase receptor, which is able to form heterodimers with insulin receptor (IR). The IGF2R is a scavenger receptor involved in the degradation of IGF-2. Insulin primarily binds to IR, but it can also bind to IGF1R. Furthermore, insulin at high levels, as found in insulin-resistant subjects, can interact with the IGF-1R.

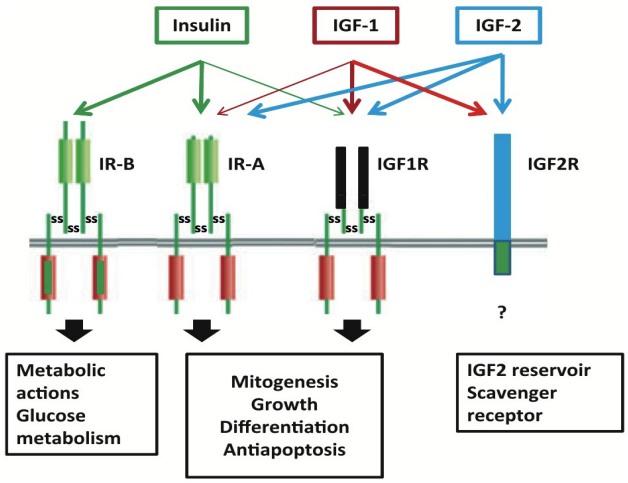


Figure 2. IGF-1, IGF-2 and insulin signal transduction and receptor cross-reactivity inducing mitogenic responses. (IR=insulin receptor) *[Melnik et al., Experimental Dermatology, 2009;18:833-841]*

IGF-1 and IGF-2 primarily bind to their specific receptors but are also able to bind to IR, explaining the significant overlap in signal transduction. IGF1R-mediated signals activate the Ras-Raf-MAP kinase and the phospho-inositide 3-kinase (PI3K)／Akt pathway. The IR-B isoform mediates the classic metabolic responses induced upon insulin binding and has very low affinity for IGFs. Activation of the IR-A isoform by either insulin or IGF-2 leads to mitogenic responses similar to those observed for IGF1R.

In immortalized human sebaceous gland cell lines SEB-1, IGF-1 increased lipogenesis by the induction of *sterol response element-binding protein-1*(SREBP-1).

SREBP-1 preferentially regulates genes of fatty acid synthesis.

In the hamster ear sebaceous model, androgens rapidly induced the expression of SREBP-1. Insulin regulates SREBP-1 on the trascriptional level. The importance of IGF-1 for lipid synthesis in immortalized human sebaceous gland cell lines SZ sebocytes and for keratinocyte proliferation has been demonstrated.

In human SEB-1 sebocytes, IGF-1 activated PI3K/Akt and MAPK /ERK-signal transduction pathways and induced the expression SREBP-1 resulting in increased sebaceous lipogenesis. Addition of a specific PI3K-inhibitor down-regulated IGF-1-induced expression of SREBP-1 and sebaceous lipogenesis.

SREBP-1c increases also in response to insulin signalling.

SREBP-1 has been implicated in the development of insulin resistance and regulates components of the insulin signalling pathway such as IRS-2 and PI3KR3. All the recently identified promoters of the human genome, which bind SREBP-1 and its two associated transcription factors Sp1 and NFY, form an interconnected regulatory circuit and bind to distinct sets of target genes. Members of the Sp-family may be key mediators of gene expression induced by insulin. Insulin regulates the subcellular localization, stability and trans-activation potential of Sp1 (29).

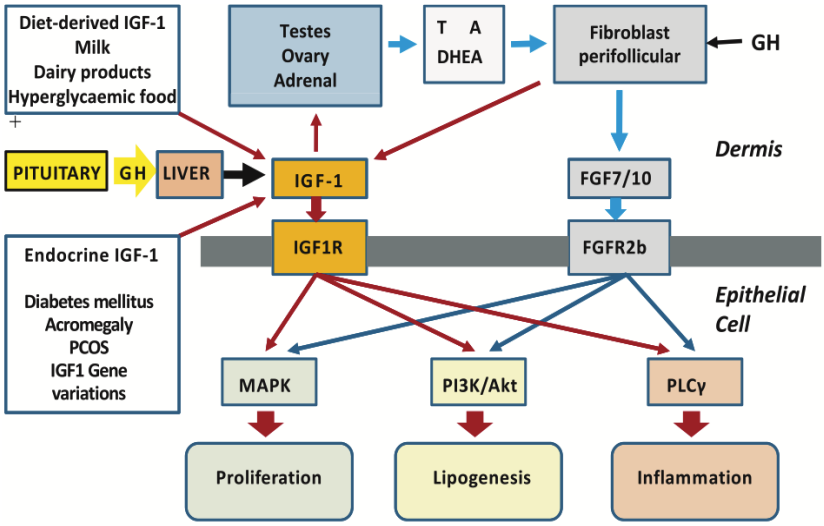


Figure 3. IGF-1 signalling in the pilosebaceous follicle and related interaction with androgen metabolism, androgen-dependent FGF-FGFR2b-signalling, endocrine and nutritional impact on IGF-1 homeostasis. (MAPK=mitogen-activated protein kinase; PI3K=phosphoinositide-3-kinase) *[Melnik et al., Experimental Dermatology, 2009;18:833-841]*

The role of androgen-dependent FGFR2b signalling in keratinocyte and sebocyte differentiation in acne has been recently elaborated.

IGF1R primarily regulates cellular proliferation and to a lesser extent differentiation, whereas FGFR2b is predominantly involved in cellular differentiation.

Comedogenesis is considered to be a process of increased keratinocyte proliferation as well as exaggerated keratinocyte differentiation (hyperkeratinization). From studies on human keratinocyte cell culture models, it has been concluded that the normalizing activity of retinoids on diseases with hyperkeratinization is mediated by modulation of differentiation rather than cell growth.

IGF1R expressed on basal cells, and FGFR2b expressed on suprabasal cells, regulate canonical cellular pathways involved in proliferation and differentiation of sebocytes and

keratinocytes and activate MAPK- and PI3K ／ Akt signalling pathways. Substantial qualitative overlap in their recruitment profiles has been demonstrated. The androgen-dependent expression of FGF7 and FGF10, the ligands of FGFR2b, is increased by IGF-1-mediated Androgen Receptor signalling.

In this regard, IGFR1-signalling has cooperative effects for FGFR2b signal transduction.

IGF-1 induces androgen receptor (AR) trans-activation. In the nucleus, AR binds to the AR repressive protein Foxo1. IGF-1, as well as insulin activates PI3K, which leads to Akt-mediated Foxo1 phosphorylation. Phosphorylated Foxo1 leaves the AR and translocates from the nucleus into the cytoplasm. By this mechanism, IGF-1 signalling alleviates AR repression resulting in AR gain-of-function. Thus, IGF-1 has direct influence on the intracrine androgen regulation of the skin and potentiates androgen signalling by the induction of 5a-reductase activity and activation of AR.

### 1.4 Insulin resistance

Insulin resistance is characterized by decreased cellular uptake of glucose and normal or increased serum levels of insulin.

In states of insulin resistance, the intracellular pool of the insulin-responsive glucose transporter 4 (GLUT4) is markedly reduced. GLUT4 proteins are stored in recycling endosomes until insulin stimulates the cell to deliver large numbers of recycling endosomes with GLUT4 to the plasma membrane to facilitate increased glucose uptake. However, in insulin-resistant states, higher than normal insulin levels are required to increase the membrane pool of GLUT4 for adequate glucose uptake.

The improvement in insulin sensitivity normalizes increased insulin levels.

As insulin is a stimulator of hepatic IGF-1 secretion, the insulin-lowering effect of metformin will reduce elevated serum IGF-1 levels.

SREBP-1c is also regulated at the transcriptional level by insulin.

In obesity-related diabetic syndromes, TNFa is a known mediator of insulin resistance by causing increased serine phosphorylation of insulin receptor substrate-1 (IRS-1) in insulin sensitive tissues. This leads to decreased expression of GLUT 4, the insulin sensitive glucose transport protein.

As already said in section 1.1, Insulin Receptor (IR) in PCOS is genetically and functionally normal. Insulin resistance in PCOS is caused by a post-receptor defect in insulin signaling with increased serine phosphorylation implicated as the cause of decreased insulin-stimulated IRS-1 activation and decreased GLUT 4 expression. Thus, the ability of TNF-alpha to stimulate increased serine phosphorylation makes it an ideal candidate for initiating these molecular events in PCOS.

Endocrine diseases or nutritional influences leading to increased insulin and IGF-1 serum levels are frequently associated with acne.

It has been well documented that immune processes are modulated by the endocrine system. In fact, glucocorticoid hormones have potent anti-inflammatory properties on cells of the innate immune system. TNFalpha-induced insulin resistance is the most studied example of interaction of immune and endocrine systems. It was first described in the early 1990s. It is now known that proinflammatory cytokines also induce a state of resistance in other important hormone systems, including glucocorticoids, GH, and IGF-1.

The intracellular signaling components for both proinflammatory cytokine and IGF receptor-activated pathways are present in most cell types, and are sometimes even shared (ERK-1/2 for both IGF-I and proinflammatory cytokine). This situation creates the potential for signal amplification or resistance. However, in the case of insulin, TNF-R activated pathways are well known to engage in intracellular crosstalk and reduce the availability of substrates used by insulin receptor-activated pathways, resulting in resistance. At least two proinflammatory cytokine-activated pathways interact with IGF-IR signaling to impair the induction of PI3-K dependent events.

### 1.5 The role of Insulin and IGF-1 in the pathogenesis of acne

Acne is associated with sebaceous gland hyperactivity. Sebum has been shown to be comedogenic and can cause inflammation when injected cutaneously.

The increase of sebum production coincides with adrenarche. Indeed, androgens play an important role in increasing the sebaceous gland size, stimulating sebum production and stimulating keratinocyte proliferation in the pilosebaceous unit.

In addition to androgen in the serum, it is known that insulin-like growth factor-1 (IGF-1) levels correlate with severity of acne in women. Serum IGF-1 levels are also known to be the highest during puberty, which is when sebum production begins and this coincides with the occurrence of acne. Vora et al. have recently observed that exists a correlation between the amount of mean facial sebum excretion (MFSE) and serum IGF-1. Moreover, this seem to be true in both men and women.

Increased IGF-1 could lead to increased sebum secretion. It was also noted that serum IGF-1 levels correlated with acne lesion counts in women, but not in men.

In acne patients, associations between serum levels of IGF-1, dehydroepiandrosterone sulphate, dihydrotestosterone, acne lesion counts and facial sebum secretion rate have been reported. IGF-1 stimulates 5a-reductase, adrenal and gonadal androgen synthesis, androgen receptor signal transduction, sebocyte proliferation and lipogenesis.

The number of total acne lesions, inflammatory lesions, serum levels of dihydrotestosterone (DHT) and dehydroepiandrosterone sulphate (DHEAS), each correlated with serum IGF-1 levels in women with acne.

IGF-1 enhances the sensitivity of the adrenal for ACTH, and induces the expression and activity of key enzymes of adrenal androgen biosynthesis. In healthy prepubertal girls as well as prepubertal girls with premature adrenarche, a positive correlation between IGF-1

and DHEAS serum levels has been reported. Serum IGF-1 levels rise and fall in a pattern similar to serum DHEAS, and normal puberty is characterized by a state of transient insulin resistance associated with an increase in gonadal sex steroid production and adrenal androgens.

Addition of IGF-1 to cultures of rat and human skin scrotal fibroblasts significantly increased 5a-reductase activity in a dose-dependent manner. Conversion of testosterone to DHT increases androgen signalling. The IGF-1-induced activation of 5a-reductase points to an important role of IGF-1 as a peripheral amplifier of androgen metabolism in the skin.

## 2.1 Introduction

Physiologically during puberty and adolescence, when juvenile acne usually appears, the response to a glucose load is increased when compared to the one observed in adult and at pre-pubertal age, while insulin sensitivity is reduced. Insulin is a hormone that acts at different levels along the axis which controls the sex hormones. It increases the release of LH and FSH by pituitary gland, stimulates the synthesis of androgens in the gonads and stimulates the synthesis of androgenic precursors in adrenal glands. Finally, it acts in the liver by inhibiting the synthesis of Sex Hormone Binding Globulin (SHBG). It was also demonstrated that insulin is able to act directly on the production of sebum and amplify the effects of IGF-1 in the skin, inhibiting the synthesis of its binding protein (IGF binding protein-1, IGFBP- 1). Therefore, disturbances in insulin metabolism may contribute to the occurrence of acne.

In clinical practice treatment-resistant acne is not a so rare event. We identify two groups of patients in which acne does not seem primarily due to a disorder of androgen hormones. In the first group there are female patients who have persistent acne or late-onset acne. In these patients blood concentrations of androgens are frequently normal and their treatment-resistant acne seems not to be strictly related to hyperandrogenism.

The second group of patients is composed by male subjects who present treatment-resistant acne. We decided to focus our attention on the latter group of patients because the relationship between acne and insulin resistance has been poorly investigated in males so far.

On the basis of recent findings that have demonstrated the role of insulin and IGF-1 in the pathogenesis of acne vulgaris, we assumed that IGF-1 and insulin could have a key role in treatment resistance development in these subjects.

## 2.2 Methods

Our observational study was performed in a population of males aged 15-26 years, with treatment-resistant inflammatory acne. We classified as resistant those patients suffering from acne for at least a year, who didn't experience in the latter six months any clinical improvement, despite adherence to all therapies prescribed according to the most recent guidelines for acne therapy.

Insulin resistance was estimated by HOMA-IR. In subjects with HOMA-IR higher than normal and/or fasting glucose higher than normal and insulin levels was performed evaluation of glucose tolerance by OGTT (glucose loading test at 0 and 120 'after administration of 75 g of glucose).

In a second step, the dosage of IGF-1, insulin and the calculation of insulin resistance by HOMA-IR was performed on a population of female patients not previously selected with PCOS and with androgen levels within normal limits, assuming the role of IGF-1 and insulin in the resistance to treatment.

At the dermatological examination, acne was classified according to the degree of disease in mild-moderate-severe acne by a global acne grading system (GAGS). The GAGS considers six locations on the face and chest/upper back, with a factor for each location based toughly on surface area, distribution, and density of pilosebaceous units. The global score is the summation of all local scores (0 = None, 1–18 = Mild, 19–30 = Moderate, 31–38 = Severe, >39 = Very severe).

| Location | Factor × Grade (0–4)* = Local score |
|---|---|
| I Forehead | 2 |
| II Right cheek | 2 |
| III Left cheek | 2 |
| IV Nose | 1 |
| V Chin | 1 |
| VI Chest and upper back | 3 |

Global score = _____

| | |
|---|---|
| 0 | None |
| 1–18 | Mild |
| 19–30 | Moderate |
| 31–38 | Severe |
| >39 | Very severe |

*0, No lesions; 1, ⩾ one comedone; 2, ⩾ one papule; 3, ⩾ one pustule; 4, ⩾ one nodule.

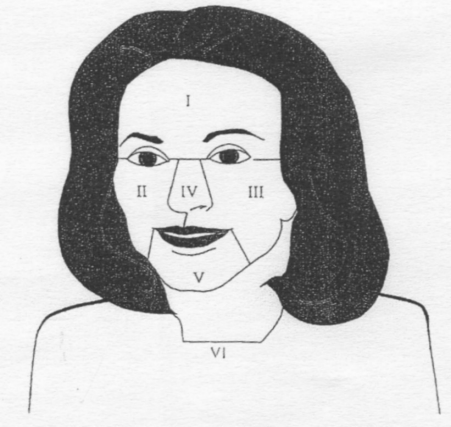


Figure 4. The six locations (I-VI) of the Global Acne Grading System (GAGS)

[Doshi A, et al.Int J Dermatol 1997;36:416-18]

Height, weight, body mass index (BMI), waist circumference (WC), waist to hip ratio (WHR), and measurements of systolic (SBP) and diastolic blood pressure (DBP) were evaluated by standard methods. BMI was measured as the ratio between the weight and the square of the height. A BMI between 25 and 30 was considered as index of overweight while >30 was considered as index of obesity. WC was measured as the smallest trunk circumference between the twelfth rib and the iliac crest. WHR was measured as the ratio between the WC and the circumference of the hip, considered as the maximal extension of the buttocks. The measurements were performed with the patients in standing position with relaxed abdomen, arms at sides, and joined feet. WHR>0.8 in females and WHR>0.95 in males are considered abnormal values.

Blood pressure was measured in the right arm, with the subjects in relaxed sitting position.

In all subjects, serum blood samples were obtained by standard methods to measure total (total-cholesterol <200 mg/dl) and high density lipoprotein cholesterol (HDL-cholesterol >45 mg/dl), triglycerides (<180 mg/dl), glycemia (60–110 mg/dl), insulin (5–20 μU/ml), and glycated hemoglobin (<6 %). An oral glucose tolerance test (OGTT) was also performed (75 g of glucose diluted in 250 ml of saline solution, measuring blood glucose every 30 minutes for 2 hours). Insulin resistance was estimated by HOMA-IR. The relationship between glucose and insulin is well known and has led to the development of the index HOMA (Homeostasis Model Assessment). The HOMA is a mathematical model by which insulin sensitivity can be calculated starting from the simultaneous concentrations of serum fasting glucose and serum fasting insulin.

The index of insulin resistance by homeostasis model assessment (HOMA-IR) is also based on a mathematical model that allows to quantify the extent of insulin resistance.

For calculating HOMA-IR was used the formula published by Matthews:

HOMA-IR = [basal insulin (μU / mL x fasting glucose (mg/ dL)] / 405
Normal range = 0.23 to 2.5 (average 0.99)

In subjects with HOMA-IR higher than normal and/or fasting glucose and/or insulin higher than normal an oral glucose tolerance test (OGTT) was also performed (75 g of glucose diluted in 250 ml of saline solution, measuring blood glucose every 30 minutes for 2 hours). The hormonal work-up included free testosterone (15–40 μg/ml), total testosterone (10.4–34.7 nmol/l), dehydroepiandrosterone sulfate (DHEAS; 35–430 μg/dl), sex hormone-binding globulin (SHBG; 6–50 nmol/l), and Insulin-like Growth Factor 1 (IGF-1; 90–280 mg/ml), which were evaluated by standard methods using commercially available kits.

| Inclusion criteria: |
| --- |
| - Males aged 15-16 with treatment-resistant inflammatory acne of the face and/or body<br>- BMI≤ 24,9<br>- Good general health<br>- No usual intake of drugs (except acne therapy)<br>- Blood Pressure <140/90 mmHg |

| Exclusion criteria: |
| --- |
| - Patients affected by Diabetes Mellitus Type 1 or Type 2 (Criteria for the diagnosis of Type 2 Diabetes Mellitus: fasting glucose≥126 mg/dL in two different measurements or blood glucose> 200 mg/dL in a single occasion and in the presence of suggestive symptoms)<br>- Patients affected by other dermatological diseases or performing treatment for other endocrinopathies |

## 2.3 Results

Seven patients were recruited according to our inclusion criteria.

By comparing the 7 subjects with data from a group of controls of comparable age and gender, we found that patients had higher Sistolic and Diastolic Blood Pressure, Waist/hip Ratio, Waist Circumference, 120' OGTT serum insulin and serum IGF-1. HDL-cholesterol was higher in controls than in subjects with acne.

These difference did not achieve statistical significance perhaps owing to our small sample size, but our pilot study supports the findings previously reported by Del Prete et al.

These authors observed a significant correlation between acne score and HOMA-IR, 120' OGTT serum glucose levels, serum IGF-1 levels, in a group of 13 subjects with treatment-resistant acne and BMI≤ 24,9.

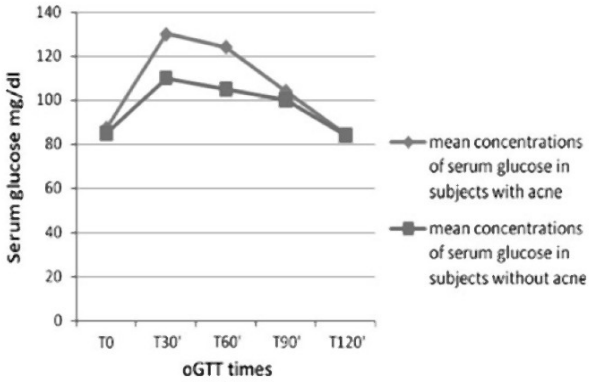


Fig 5. Comparison of mean concentrations of serum glucose for each time of OGTT in subjects with acne and subjects without acne(*)

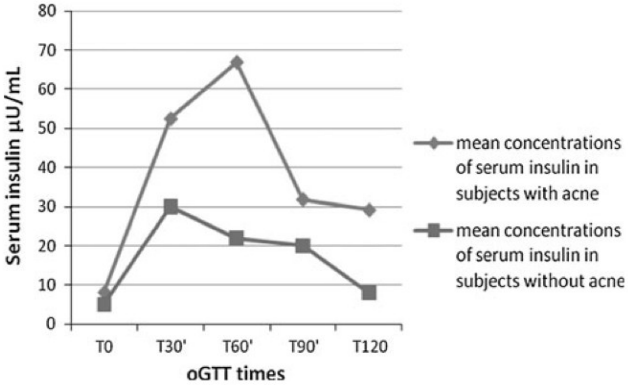


Fig 6. Comparison of mean concentrations of serum insulin for each time of OGTT in subjects with acne and subjects without acne(*)

These authors investigated the relationship betweeen acne and insulin resistance in males, comparing 22 young males with acne and 22 controls of comparable age and gender. They found that patients had higher BMI ($p = 0.003$), WC ($p = 0.002$), WHR ($p = 0.02$), SBP ($p = 0.0001$), DBP ($p = 0.001$), basal ($p = 0.01$) and 120 minutes OGTT serum insulin concentrations ($p = 0.002$), basal glucose concentrations ($p = 0.03$), HOMA-IR ($p = 0.016$), and lower HDL-cholesterol than controls ($p = 0.001$). Total cholesterol, triglycerides, serum IGF-1, and androgen levels were similar in subjects with acne and controls. Baseline serum insulin and glucose concentrations were significantly higher in subjects with acne. In parallel, OGTT curves were significantly different between subjects with acne and controls (Figs. 5,6 ). At 120 min. OGTT, serum glucose levels were similar between subjects with acne and controls, while serum insulin levels were significantly higher in sub- jects with acne than in controls.

The same authors performed a subgroup analysis by excluding subjects with overweight/obesity (BMI >24.9). At the linear correlation study, among the 13 subjects with acne and BMI>24.9, they found a significant correlation between acne score and HOMA-IR, 120 min. OGTT serum glucose levels, serum IGF-1 levels.

Moreover, they reported that HDL-cholesterol ($p = 0.05$) and 120 min. OGTT serum insulin concentrations ($p = 0.009$) resulted to be independent predictors of acne at multivariate analysis.

Table 1. Clinical and metabolic characteristics of subjects with and without acne: whole population with BMI<24.9 (Data are reported as Mean ± SEM. P<0,05 are considered significant)

| | Subjects with acne | Subjects without acne | P (Wilcoxon test) |
|---|---|---|---|
| Age | 18,6 ± 3 | 20 ± 3,1 | 0,1 |
| BMI (Kg/m2) | 22,2 ± 2,1 | 20,7 ± 1,7 | 0,1 |
| WC (cm) | 83,3 ± 10 | 79,4 ± 7,6 | 0,02 |
| WHR | 0,8 ± 0,05 | 0,7 ± 0,07 | 0,04 |
| SBP (mmHg) | 128,1 ± 7,9 | 112,5 ± 9 | 0,0001 |
| DBP (mmHg) | 80,9 ± 6,4 | 72,9 ± 7,8 | 0,03 |
| Fasting serum glucose (mg/dL) | 87,3 ± 8,6 | 84,3 ± 6,3 | 0,3 |
| Fasting serum insulin (µU/mL) | 10,3 ± 9,2 | 5,2 ± 1,2 | 0,09 |
| 120' OGTT serum glucose (mg/dL) | 84,3 ± 21,6 | 83,3 ± 9,7 | 0,05 |
| 120' OGTT serum insulin (µU/mL) | 20,5 ± 14,7 | 7,6 ± 1,2 | 0,009 |
| HOMA-IR | 1,5 ± 0,7 | 1,1 ± 0,3 | 0,05 |
| Total cholesterol (mg/dL) | 179,5 ± 32,2 | 165,0 ± 19,4 | 0,2 |
| HDL cholesterol (mg/dL) | 47,1 ± 7,2 | 58,8 ± 8,3 | 0,05 |
| Tryglicerides (mg/dL) | 85,1 ± 19,5 | 83,6 ± 15,3 | 0,83 |
| Serum IGF-1 (nmol/L) | 325,3 ± 97,2 | 318,3 ± 6,7 | 0,03 |
| Free testosterone (pg/mL) | 22,6 ± 19,8 | 21 ± 18,8 | 0,8 |
| Total testosterone (ng/dL) | 5,4 ± 1,6 | 5,4 ± 1,4 | 0,9 |
| DHEAS (µg/dL) | 222,6 ± 116,5 | 180,5 ± 167,9 | 0,46 |
| SHBG (nmol/L) | 32,4 ± 8,9 | 32,8 ± 7,8 | 0,9 |

Legend. BMI:body mass index, WHR:waist/hip ratio, HOMA-IR:Homeostasis Model assessment of insulin resistance; SBP:systolic blood pressure; DBP=diastolic blood pressure; DHEAS:dehydroepiandrosterone sulfate, SHBG:sex-hormone-binding globulin, WC:waist circumference, OGTT: oral glucose tolerance test (*)

(*)*Del Prete M, et al. Insulin-resistance and acne: a new risk factor for men? Endocrine 2012;42:555-60.*

## 2.4 Discussion

The purpose of this study was to investigate a possible correlation between acne and insulin resistance in a sample of acneic treatment-resistant males, who were in good general health, apart from their dermatological condition.

According to the inclusion criteria shown above, we decided to exclude patients who presents a metabolic syndrome to avoid this bias.

To make the diagnosis of Metabolic Syndrome at least two of the following criteria are required:

-the presence of abdominal obesity which is defined for Europeans >94 cm in men;

-serum triglycerides >150 mg/dl,

-cholesterol levels HDL <40 mg/dl (in men) or lipid-lowering therapy,

-blood pressure >130/85 mmHg or antihypertensive treatment, and

-fasting glucose >100 mg/dl or previous diagnosis of Diabetes Mellitus Type 2.

In female subjects with acne and PCOS, insulin resistance is a well known pathogenetic factor, while males have been poorly studied so far.

In all males with acne here evaluated, the androgenic profile was found to be normal, suggesting that acne in these patients can be related to changes in insulin and IGF-1 circulating levels rather than to changes in androgen levels, unlike female subjects with acne and PCOS who have hyperinsulinemia and hyperandrogenism.

Our data, even with the limits of a pilot study, support the hypothesis that insulin resistance might play an important role in the development of acne in males who are no responders

to common therapies. Our data confirmed the results which have been recently reported by Del Prete et al. and suggest that young acneic males should be investigated for insulin sensitivity to start a dietary and/or pharmacological treatment options.

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