SMJ- Sohag Medical Journal, Vol. 28 No(3) 2024

Print ISSN1687-8353 Online ISSN2682-4159

Review Article

Pathophysiology of Insulin Resistance and Related Skin Diseases (Review Article)

Asmaa Rafat Lotfy [1], Mary Atef Shokry[1], Amera Ahmed Genedy [2], Doaa Gaber Abdelbaset [3] , Esraa salah Ismail [3]

1.Department of Medical Physiology, Faculty of Medicine, Sohag University,
2 Department of Medical Biochemistry, Faculty of Medicine, Sohag University,
3 Department of Dermatology, Venereology, and Andrology, Faculty of Medicine, Sohag University,

Abstract

Insulin resistance is characterized by decreased sensitivity of insulin-targeting tissues to elevated physiological hormone levels. The liver secretes glucose into the blood during a fast to sustain euglycemia and supply energy to tissues that require glucose. Insulin released by pancreatic β-cells stimulates anabolism and inhibits catabolic processes following food consumption. Insulin resistance may be due to inherited, acquired, and mixed causes. Skeletal muscle, the liver, and adipose tissue are the three main locations of insulin resistance. Up to 70% of tissue glucose absorption occurs in muscle, Energy substrates must be processed by the liver. lipolysis is insulin-sensitive. Moreover, insulin plays a critical role in skin physiology and homeostasis, while its precise involvement in insulin signaling is still up for debate. In a healthy state, insulin controls the balance between keratinocyte proliferation and differentiation, which is necessary for the development of the epidermal structure. High levels of proinflammatory cytokines stimulate p38 Mitogen activated protein kinases in chronic inflammatory diseases (e.g., acne or psoriasis).

Key words : Insulin, inflammation, Androgenetic alopecia, Acanthosis nigricans (AN), psoriasis.
DOI : 10.21608/SMJ.2024.331502.1504 **Received:** October 29, 2024 **Accepted:** December 01, 2024
Published: January 01, 2025
Corresponding Author: **Asmaa Rafat Lotfy** **E.mail**: rafta1983@gmail.com
Citation: **Asmaa Rafat Lotfy . et al., Pathophysiology of Insulin Resistance and Related Skin Diseases (Review Article)** SMJ,2025 Vol. 29 No (1) 2025: 16- 23

Introduction

Insulin resistance is a condition characterised by decreased sensitivity of insulin-targeting tissues to elevated physiological hormone levels. It is believed to be the causative agent of numerous illnesses, such as atherosclerosis, type 2 diabetes, metabolic syndrome, and nonalcoholic fatty liver disease (NAFLD). The main clinical sign of type 2 diabetes (T2DM) which is non-physiologic increased blood sugar levels, comes before insulin resistance. Insulin levels rise in prediabetes to satisfy typical insulin requirements, which eventually results in T2DM, hyperglycemia, and persistent hyperinsulinemia. [(1)]

Although hereditary factors and increased body fat are the primary causes of insulin resistance. Since there is no widely recognized insulin resistance test, the condition's clinical definition is still unclear. The metabolic consequences of insulin resistance, delineated in the metabolic syndrome categories and insulin resistance condition, are a clinical indicator of insulin resistance. [(2)]

Biochemistry of insulin hormone:

Pancreatic islets of Langerhans beta cells produce the polypeptide hormone known as insulin. It controls the levels of blood glucose. When the insulin receptor interacts to insulin, the receptor auto-phosphorylates, which attracts adaptor molecules like insulin receptor substrates (IRS1-6) or Shc. Following their phosphorylation, these molecules serve as binding sites for a number of signaling cascades, including those triggered by mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3-K). These routes govern not only the way that proteins, lipids, and carbs are metabolized but also the regulation of proliferation, differentiation, and apoptosis in order to manage mitogenic responses. By inhibiting the serine phosphorylation of IRS 1, insulin signaling is down regulated, making cells resistant to insulin. [(3)]

Only exons 2 and 3 of the gene for human insulin contribute to the coding of mature insulin. The three exons of the gene are divided by two introns. Exon 1 regulates insulin expression and comprises the 5′ untranslated region. Exon 2 encodes a portion of the linking peptide (C-peptide) and the signal peptide (B-chain). The remainder of the C-peptide and the A-chain are finally encoded by exon 3. The four domains that make up pre pro insulin, the single-chain progenitor of fully developed insulin, are the carboxy-terminal A-chain, the B-chain, the C-peptide, and the amino-terminal signal peptide. The A-chain (which has 21 residues) and the B-chain (30 residues) are two different peptide chains make up mature insulin. Two disulfide bonds connect them at locations A7–B7 and A20–B19 between the cysteine residues. Furthermore, the A-chain contains an intra-chain disulfide link that joins residues A6–A11. The three α-helices that make up insulin's core structure are stabilized by these three disulfide bonds. [(4)]

Physiological insulin signaling :

The liver secretes glucose into the blood during a fast in order to sustain euglycemia and supply energy to tissues that require glucose. This process, known as the generation of glucose by the liver, uses fatty acids and glycerol from fatty tissue to break down hepatic glycogen (glycogenolysis) and create glucose (gluconeogenesis). [(5)] Insulin released by pancreatic β-cells stimulates anabolism and inhibits catabolic processes following food consumption. Insulin enhances the uptake of glucose by a number of glucose-consuming tissues, including adipose and skeletal muscle tissues, during glucose metabolism. This, in turn, facilitates the liver, skeletal muscle, and Glycogen production in adipose tissue and lipid. Furthermore, insulin inhibits lipolysis in adipose tissue and the production of gluconeogenic genes, which both reduce hepatic glucose production. Additionally, insulin inhibits the release of glucagon from pancreatic α-cells and decreases appetite through the central nervous system. [(6)]

Etiology

Insulin resistance may be due to inherited, acquired, and mixed causes. An acquired etiology, such as increased visceral fat accumulation associated with ectopic fat deposition and spillover from subcutaneous fat accumulation accounts for the vast majority of individuals with insulin resistance. Other causes such as the aging process, lack of physical activity, nutritional imbalance, pharmaceuticals (atypical antipsychotics, Anti-adrenergic, glucocorticoids, inhibitors of proteases,

inhibitors of selective serotonin reuptake, and some insulins that are exogenous); high-sodium diets; toxicity of glucose; The toxicity of lips brought on by an excess of free fatty acids in the blood. [7]

Types

Type-A resistance to insulin is marked by extreme insulin resistance brought on by mutations in the insulin- receptor gene, which results in impaired regulation of glucose, ovarian virialization, and a condition called acanthosis nigricans. [8]

Type-B insulin resistance is characterized by severe impairment of the insulin action triggered by the formation of autoantibodies to insulin receptor with resultant abnormal glucose balance, hyperandrogenism, and acanthosis nigricans. [8]

There is another way to classify insulin resistance, and it is based on where an insulin receptor is malfunctioning. There are pre-receptor, receptor, and post-receptor etiologies in this categorization system. [9]

Pathophysiology

Skeletal muscle, the liver, and adipose tissue are the three main locations of insulin resistance. Chronic calorie excess causes the body's tissues to develop resistance to insulin signaling. The hyperinsulinemic-euglycemic clamp indicates that as much as 70% of glucose elimination occurs in skeletal muscle, which is a sizable reservoir for glucose in the bloodstream. Reduced muscle tissue absorption of glucose is a direct consequence of muscular insulin resistance. De novo lipogenesis (DNL) takes place in the liver after glucose is transported there from muscle. Insulin resistance also develops in the liver as a result of elevated glucose substrate as shown in **figure 1**. Elevated DNL levels raise the amount of plasma triglycerides and produce an environment with too much energy substrate, which makes the body more insulin resistant and leads to ectopic deposits of lipids. [10]

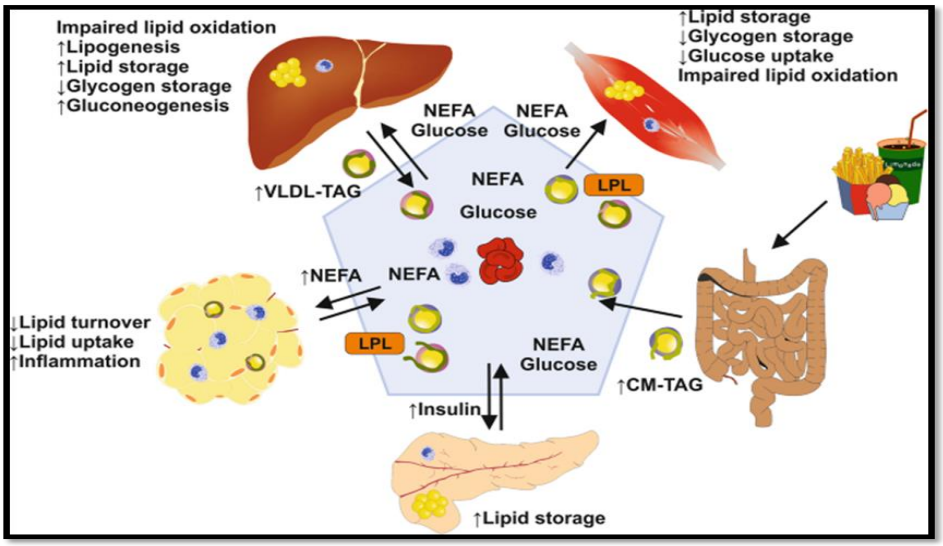

Figure 1. Mechanisms of insulin resistance.[11]

Skeletal Muscle Tissue

Up to 70% of tissue glucose absorption occurs in muscle, which serves as the main location for glucose disposal following calorie intake and transformation to glucose. In myocytes fatty acids build up in muscle tissue when there is a persistent calorie excess. An intramyocellular fatty acid called diacylglycerol alerts the cell to excess energy. Protein kinase C theta (PKC-theta) is activated by diacylglycerol, which reduces proximal signaling of insulin. Impaired muscle tissue absorption of glucose and lowered translocation of glucose transporter type 4 (GLUT4) to the cell membrane are the direct outcomes. The liver receives the extra glucose in the blood and uses it for storage or metabolism. [12]

Hepatic Tissue

Energy substrates must be processed by the liver. It uses, stores, and produces glucose and packages, recirculates, and produces fatty acids. These functions are negatively impacted if the liver develops insulin resistance, which has serious metabolic repercussions. The liver receives extra circulating glucose when muscular tissue becomes insulin resistant. The liver tissue goes through a similar procedure as skeletal muscle when it detects an overabundance of energy substrate, especially diacylglycerol. Protein kinase C epsilon (PKC-epsilon) is activated in the liver by the diacylglycerol concentration, which reduces proximal insulin signaling. [13]

Insulin-independent mechanisms allow extra glucose to get into hepatocytes, where it stimulates DNL through substrate push to produce additional fatty acids. The extra fatty acid is either deposited in the liver or spread throughout the gastrointestinal tract as ectopic fat. Further contributing to circulating fatty acid and ectopic lipid accumulation include immune-mediated proinflammatory alterations and excessive lipolysis from fatty tissue, which the liver re-esterifies. Lastly, the liver continues to produce additional glucose, contributing to the circulating glucose surplus, due to a malfunction in the normal insulin-mediated inhibition of gluconeogenesis. [14]

Adipose Tissue

Researchers discovered that lipolysis is insulin-sensitive. Circulating free fatty acids (FFAs) rise when insulin fails to inhibit lipolysis in insulin-resistant adipose tissue, particularly abdominal adipose tissue. Increased levels of circulating FFAs have a direct impact on both liver and muscle metabolism, aggravating insulin resistance in these areas and causing beta-cell malfunction brought on by lipotoxicity. [15]

Role of Inflammation in Insulin Resistance

The overall chronic inflammatory reaction brought on by altered cytokine production and activation of inflammatory signaling pathways is the primary cause of obesity-induced IR. [16] Increased macrophage infiltration brought on by obesity aids in the generation of cytokines. IR is linked to the inflammatory response in two ways. First, IR is caused by the direct serine phosphorylation of IRS1 in hepatocytes and myocytes, which is triggered by inflammatory signaling intermediates. Second, inflammatory cell infiltration within adipose tissue may modify adipocyte lipid metabolism, with TNF-α increasing lipolysis and alterations in the production of cytokines such as IL-6. [17]

Relation between insulin resistance and skin diseases

It's interesting to note that cytokines and other inflammatory mediators can cause IR by activating IRS kinases. [18] Moreover, insulin plays a critical role in skin physiology and homeostasis, while its precise involvement in insulin signaling is still up for debate. In a healthy state, insulin controls the balance between keratinocyte proliferation and differentiation, which is necessary for the development of the epidermal structure. High levels of proinflammatory cytokines stimulate p38 Mitogen-activated protein kinases in chronic inflammatory diseases (e.g., acne or psoriasis), which activates IR by serine phosphorylating IRS. This results in the blockage of differentiation and an increase in basal keratinocyte proliferation. [19]

- **Androgenetic alopecia (AGA)**

Androgenetic alopecia (AGA) is a prevalent pattern of hair loss affecting both men and women. The pathogenesis of AGA is multifactorial including genetics, androgen sensitivity, and environmental factors. The prevalence varies by gender and race, with over half of elderly males and 15% of postmenopausal women affected. [20] Androgens, particularly dihydrotestosterone (DHT), play an important role in the pathophysiology of AGA by binding to androgen receptors on androgen-sensitive follicles, resulting in follicular shrinkage [21]. Clinically, men typically have bitemporal and vertex hair loss, which leads to total baldness. The frontal hairline is often retained in women, and full baldness seldom develops. [22]

Metabolic syndrome (MS) is a set of metabolic disorders that includes central obesity, hypertension, glucose intolerance, insulin resistance (IR), and dyslipidemia. [23] The relationship between AGA and MS remains unclear. However, IR has a pathogenic effect on the miniaturization of hair follicles. Vasoactive chemicals linked to endothelial dysfunction in IR disrupt microcirculation, cause

perifollicular vasoconstriction, and promote smooth muscle cell proliferation in the vascular wall. This syndrome causes microvascular insufficiency, local tissue hypoxia, and gradual shrinkage of hair follicles. [24]

Hyperinsulinemia contributes to local androgen synthesis, either directly from cholesterol or by converting testosterone to DHT. DHT suppresses adenyl cyclase activity, which slows the anagen cycle and may be responsible for follicle shrinking in AGA. [25] Matilainen et al. found that men with early AGA have considerably higher levels of hyperinsulinemia. [26]

- **Hirsutism**

Hirsutism, the presence of terminal hairs in females in a male-like pattern, is a common clinical condition that affects 5–10% of women of reproductive age. Hirsutism is extremely distressing for patients and has a significant negative impact on their psychosocial development.[21]

Hirsute women usu-ally present with excessive growth of terminal hair at the sides of the face, upper lip, chin, upper back, shoulders, and upper abdomen. Ferriman and Gallwey developed a score for clinical assessment of hirsutism. [27]

The two most common causes of hirsutism include polycystic ovary syndrome (PCOS) and idiopathic hirsutism (IH).[28]

PCOS is characterized by hyperandrogenism and chronic anovulation in addition to many clinical features such as hirsutism, acne, polycystic-appearing ovaries, obesity, and acanthosis nigricans. [29]

Epidemiologic studies indicate that hyperinsulinemia and insulin resistance are frequent in both patients with IH and PCOS and are associated with an increased risk of glucose intolerance, dyslipidemia, and cardiovascular disease .[30]

Insulin resistance and compensated hyperinsulinemia are the most common features of PCOS, and insulin resistance-lowering drugs are usually used to manage PCOS. [31]

• Skin tags (acrocordons)

Skin tags are skin-coloured to deep brown sessile or pedunculated papillomas that usually appear on the neck, axillae, eyelids, and, less commonly, the trunk and groin. They typically measure between 1 mm and 1 cm in diameter. [32] The exact cause of skin tags is yet unknown. Skin rubbing, hormone imbalance, obesity, metabolic syndrome, and other disorders were described as contributory factors. [33]

Previous research revealed that skin tags were associated with problems in glucose metabolism, including type 2 diabetes, hyperinsulinemia, and insulin resistance. [34, 35]

• Acanthosis nigricans (AN)

Acanthosis nigricans is a pigmented hyperkeratosis of the neck and flexures. [36] It is associated with hyperinsulinemia and malignancy. Children with AN are between 1.6 times and 4.2 times more vulnerable to having hyperinsulinemia. [37, 38]

Friction may play a role in the development of AN, which is proved by its location, most probably through inflammation. This may occur via the inhibitory antagonistic effects of inflammation on certain PPARs. In fact, a dominant, negative mutation in PPAR-γ appears to be responsible for an insulin resistance syndrome also associated with AN. [39]

• Ear lobe creases (ELCs)

It has been observed that ear lobe creases (ELCs) are associated with coronary artery disease (CAD), an observation first published by Frank in 1973. Other studies have evaluated this association later. [40, 41] The presence of ELCs is a predictor of future cardiac events in a 10-year follow-up. [42] In fact, ELCs are thought to be a more important predictor than diabetes, hypertension, hypercholesterolaemia, cigarette use, a family history of CAD, and obesity. [43]

• Xanthelasma

About 50% of patients with xanthelasma have an abnormal lipid profile. [44] Xanthelasma is associated with low serum HDL cholesterol and decreased subclass HDL2 particles or raised serum apolipoprotein B concentrations. [44, 45] Xanthelasma is associated with a history of CVD and with increased levels of plasma cholesterol and LDL cholesterol, principally in young males. It is also associated with fatty liver, which can be a feature of insulin resistance. [46]

• Acne

Acne may be a part of diseases that are also associated with insulin resistance. [47] This is the case in seborrhoea-acne-hirsutism-androgenetic alo-

pecia (SAHA) syndrome, polycystic ovarian syndrome (PCOS), and hyperandrogenism, IR, and acanthosis nigricans (HAIR-AN) syndrome. [48] PCOS represents the most common and well-known clinical scenario that links IR and acne. Indeed, PCOS shows acne in 70% of cases. About 19% to 37% of women with moderate to severe acne meet this disorder's criteria. [49, 50]

• Psoriasis

Psoriasis is a chronic inflammatory disease of the skin that is now considered a systemic autoimmune disorder .[51] Patients with psoriasis are at elevated risk of developing cardiovascular and metabolic diseases, including diabetes, as well as metabolic syndrome. [52] Also, overweight and obesity are exacerbating factors for psoriasis itself .[53, 54]

Summary And Conclusion

The current review found numerous pathways of insulin resistance in liver, adipose, and muscular tissue. It also described the creation of insulin resistance in various tissues as well as significant variations in insulin signaling. Skeletal muscle energy consumption and glucose metabolism depend on normal insulin activity. Insulin resistance is mostly the underlying pathologic mechanism of metabolic syndrome which is significantly associated with many skin diseases such as psoriasis, acne, hirsuteism, skin tags and acanthosis nigricans.

References:

1. Lee SH, Park SY, Choi CS. Insulin Resistance: From Mechanisms to Therapeutic Strategies. Diabetes Metab J. 2022;46(1):15-37.
2. Nellaiappan K, Preeti K, Khatri DK, Singh SB. Diabetic Complications: An Update on Pathobiology and Therapeutic Strategies. Curr Diabetes Rev. 2022;18(1):e030821192146.
3. Napolitano M, Megna M, Monfrecola G. Insulin resistance and skin diseases.

ScientificWorldJournal. 2015;2015(1):479354.

4. Ataie-Ashtiani S, Forbes B. A Review of the Biosynthesis and Structural Implications of Insulin Gene Mutations Linked to Human Disease. Cells. 2023;12(7):1008.
5. Rizza RAJD. Pathogenesis of fasting and postprandial hyperglycemia in type 2 diabetes: implications for therapy. Diabetes. 2010;59(11):2697-707.
6. Petersen MC, Shulman GI. Mechanisms of Insulin Action and Insulin Resistance. Physiol Rev. 2018;98(4):2133-223.
7. Samuel VT, Shulman GIJTJoci. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. 2016;126(1):12-22.
8. Szablewski L. Insulin Resistance: The Increased Risk of Cancers. Curr Oncol. 2024;31(2):998-1027.
9. Fryk E. The role of galectin-1 in type 2 diabetes. Clinical and experimental studies; 2022; https://gupea.ub.gu.se/handle/2077/543
10. Sangwung P, Petersen KF, Shulman GI, Knowles JWJE. Mitochondrial dysfunction, insulin resistance, and potential genetic implications: potential role of alterations in mitochondrial function in the pathogenesis of insulin resistance and type 2 diabetes. Endocrinology. 2020;161(4):bqaa017.
11. Chandrasekaran P, Weiskirchen RJCTMR. Cellular and molecular mechanisms of insulin resistance. 2024:1-12.
12. Yang W, Jiang W, Guo S. Regulation of Macronutrients in Insulin Resistance and Glucose Homeostasis during Type 2 Diabetes Mellitus. Nutrients. 2023;15(21):4671.
13. Jani SB. Dietary Manipulation of Glucose and Fat Metabolism in Skeletal Muscles and Liver. 2023.
14. Dimitriadis GD, Maratou E, Kountouri A, Board M, Lambadiari V. Regulation of Postabsorptive and Postprandial Glucose Metabolism by Insulin-Dependent and Insulin-Independent Mechanisms: An Integrative Approach. Nutrients. 2021;13(1):159.
15. da Silva Rosa SC, Nayak N, Caymo AM, Gordon JW. Mechanisms of muscle insulin resistance and the cross-talk with liver and adipose tissue. Physiol Rep. 2020;8(19):e14607.
16. Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. J Clin Invest. 2003;112(12):1785-8.
17. Aguirre V, Uchida T, Yenush L, Davis R, White MFJJoBC. The c-Jun NH2-terminal kinase promotes

insulin resistance during association with insulin receptor substrate-1 and phosphorylation of Ser307. J Journal of Biological Chemistry. 2000;275(12):9047-54.

18. Taniguchi CM, Emanuelli B, Kahn CRJNrMcb. Critical nodes in signalling pathways: insights into insulin action. 2006;7(2):85-96.

19. Buerger C, Richter B, Woth K, Salgo R, Malisiewicz B, Diehl S, et al. Interleukin-1β interferes with epidermal homeostasis through induction of insulin resistance: implications for psoriasis pathogenesis. 2012;132(9):2206-14.

20. Katzer T, Leite Junior A, Beck R, da Silva C. Physiopathology and current treatments of androgenetic alopecia: Going beyond androgens and anti-androgens. Dermatol ther. 2019;32(5):e13059.

21. Barth JH, Catalan J, Cherry CA, Day A. Psychological morbidity in women referred for treatment of hirsutism. J Psychosom Res. 1993;37(6):615-9.

22. Katzer T, Leite Junior A, Beck R, da Silva C. Physiopathology and current treatments of androgenetic alopecia: Going beyond androgens and anti-androgens. Dermatol Ther. 2019;32(5):e13059.

23. Bakry OA, Shoeib MA, El Shafiee MK, Hassan A. Androgenetic alopecia, metabolic syndrome, and insulin resistance: Is there any association? A case-control study. Indian Dermatol Online J. 2014;5(3):276-81.

24. Pinkney JH, Stehouwer CD, Coppack SW, Yudkin JS. Endothelial dysfunction: cause of the insulin resistance syndrome. Diabetes. 1997;46 Suppl 2:S9-13.

25. González-González JG, Mancillas-Adame LG, Fernández-Reyes M, Gómez-Flores M, Lavalle-González FJ, Ocampo-Candiani J, Villarreal-Pérez JZ. Androgenetic alopecia and insulin resistance in young men. Clin Endocrinol (Oxf). 2009;71(4):494-9.

26. Matilainen V, Koskela P, Keinänen-Kiukaanniemi S. Early androgenetic alopecia as a marker of insulin resistance. Lancet. 2000;356(9236):1165-6.

27. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. J Clin Endocrinol Metab. 1961;21:1440-7.

28. Rosenfield RL. Clinical practice. Hirsutism. N Engl J Med. 2005;353(24):2578-88.

29. Zhang HY, Zhu FF, Xiong J, Shi XB, Fu SX. Characteristics of different phenotypes of polycystic ovary syndrome based on the Rotterdam criteria in a large-scale Chinese population. Bjog. 2009;116(12):1633-9.

30. Glueck CJ, Phillips H, Cameron D, Sieve-Smith L, Wang P. Continuing metformin throughout pregnancy in women with polycystic ovary syndrome appears to safely reduce first-trimester spontaneous abortion: a pilot study. Fertil Steril. 2001;75(1):46-52.

31. Nazari T, Bayat R, Hamedi M. Metformin therapy in girls with polycystic ovary syndrome: a self-controlled clinical trial. Arch Iran Med. 2007;10(2):176-81.

32. El Safoury OS, Fawzy MM, El Maadawa ZM, Mohamed DH. Quantitation of mast cells and collagen fibers in skin tags. Indian J Dermatol. 2009;54(4):319-22.

33. Sari R, Akman A, Alpsoy E, Balci MK. The metabolic profile in patients with skin tags. Clin Exp Med. 2010;10(3):193-7.

34. Allegue F, Fachal C, Pérez-Pérez L. Friction induced skin tags. Dermatol Online J. 2008;14(3):18.

35. Sudy E, Urbina F, Maliqueo M, Sir T. Screening of glucose/insulin metabolic alterations in men with multiple skin tags on the neck. J Dtsch Dermatol Ges. 2008;6(10):852-5, -6.

36. Torley D, Bellus GA, Munro CS. Genes, growth factors and acanthosis nigricans. Br J Dermatol. 2002;147(6):1096-101.

37. Stoddart ML, Blevins KS, Lee ET, Wang W, Blackett PR, Cherokee Diabetes S. Association of acanthosis nigricans with hyperinsulinemia compared with other selected risk factors for type 2 diabetes in Cherokee Indians: the Cherokee Diabetes Study. Diabetes Care. 2002;25(6):1009-14.

38. Mukhtar Q, Cleverley G, Voorhees RE, McGrath JW. Prevalence of acanthosis nigricans and its association with hyperinsulinemia in New Mexico adolescents. J Adolesc Health. 2001;28(5):372-6.

39.Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA, et al. Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. Nature. 1999;402(6764):880-3.

40.Pasternack A, Porsti P, Poyhonen L. Effect of pindolol and propranolol on renal function of patients with hypertension. Br J Clin Pharmacol. 1982;13(Suppl 2):241S-4S.

41.Salamati P, Nazeri I, Alehossein M, Sotoudeh K, Rezaee AJPJMSJ-S. Earlobe crease and coronary artery disease. 2008;24(4):600-3.

42.Elliott WJ, Powell LH. Diagonal earlobe creases and prognosis in patients with suspected coronary artery disease. Am J Med. 1996;100(2):205-11.

43.Jorde LB, Williams RR, Hunt SC. Lack of association of diagonal earlobe crease with other cardiovascular risk factors. West J Med. 1984;140(2):220-3.

44.Bergman R, Kasif Y, Aviram M, Maor I, Ullman Y, Gdal-On M, Friedman-Birnbaum R. Normolipidemic xanthelasma palpebrarum: lipid composition, cholesterol metabolism in monocyte-derived macrophages, and plasma lipid peroxidation. Acta Derm Venereol. 1996;76(2):107-10.

45.Ribera M, Pinto X, Argimon JM, Fiol C, Pujol R, Ferrandiz C. Lipid metabolism and apolipoprotein E phenotypes in patients with xanthelasma. Am J Med. 1995;99(5):485-90.

46.Menotti A, Mariotti S, Seccareccia F, Torsello S, Dima F. Determinants of all causes of death in samples of Italian middle-aged men followed up for 25 years. J Epidemiol Community Health. 1987;41(3):243-50.

47. Chen W, Obermayer-Pietsch B, Hong JB, Melnik BC, Yamasaki O, Dessinioti C, et al. Acne-associated syndromes: models for better understanding of acne pathogenesis. J Eur Acad Dermatol Venereol. 2011;25(6):637-46.

48.Zouboulis CC. Acne as a chronic systemic disease. Clin Dermatol. 2014;32(3):389-96.

49.Borgia F, Cannavo S, Guarneri F, Cannavo SP, Vaccaro M, Guarneri B. Correlation between endocrinological parameters and acne severity in adult women. Acta Derm Venereol. 2004;84(3):201-4.

50.Timpatanapong P, Rojanasakul A. Hormonal profiles and prevalence of polycystic ovary syndrome in women with acne. J Dermatol. 1997;24(4):223-9.

51.Balato A, Di Costanzo L, Patruno C, Ayala F, Megna M, Balato N. Psoriasis or "psoriases"? G Ital Dermatol Venereol. 2013;148(6):649-50.

52.Davidovici BB, Sattar N, Prinz J, Puig L, Emery P, Barker JN, et al. Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. J Invest Dermatol. 2010;130(7):1785-96.

53.Naldi L, Chatenoud L, Linder D, Belloni Fortina A, Peserico A, Virgili AR, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Invest Dermatol. 2005;125(1):61-7.

54. Barrea L, Balato N, Di Somma C, Macchia PE, Napolitano M, Savanelli MC, et al. Nutrition and psoriasis: is there any association between the severity of the disease and adherence to the Mediterranean diet? J Transl Med. 2015;13:18.