REVIEW ARTICLE

CONTENTS

Igf-1 in acne pathogenesis and inositol as possible adjuvant treatment of acne

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ABSTRACT

Aim: To provide a comprehensive review of acne pathogenesis and data regarding inositol efficacy in targeting IGF-1 pathway and decreasing IGF-1 levels and find pathophysiological substantiation (rationale, reasoning) of inositol therapy feasibility in acne treatment.

Materials and Methods: Search of literature was performed on PubMed, Scopus, ResearchGate to identify scientific publications that aimed to research the role of inositol in acne and IGF-1 in acne pathogenesis and treatment and were published between 1999 and 2024 yielding information about possible therapeutic approach targeting IGF-1 induced increased sebum production. Peer-reviewed full-text articles, systematic reviews and evidence-based guidelines were included.

Conclusions: We provided a comprehensive review of acne pathogenesis and data regarding inositol efficacy in targeting IGF-1 pathway.

KEY WORDS: insulin-like growth factor-1, inositol, acne

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INTRODUCTION

Acne is a chronic, inflammatory disease of the pilosebaceous unit. According to one of the most influential epidemiological studies, The Global Burden of Disease Study, it is known that acne is the eighth most common disease in the world with a total prevalence (for all age groups) of 9.38% [1]. As we know from the literature, the pathogenesis of acne is explained by four key factors: excess production of sebum, hyperproliferation of bacteria *Cutibacterium acnes* (*C. acnes*, formerly called *Propionibacterium acnes*), hyperkeratinization of the sebaceous follicle, and inflammatory mechanisms [2]. Excessive sebum production occurs due to increased activity of androgenic hormones and insulin-like growth factor 1 (IGF-1) [2]. Most textbooks describe acne as a hormone- dependent dermatosis [3]. Without a doubt, the participation of male sex hormones is an important link in the pathogenesis of acne. However, serum androgen levels increase during puberty and may remain high for decades, whereas acne physiologically resolves spontaneously after puberty. From the paper of Deplewski and Roseneld it is known that it is not serum androgens, but the level of IGF-1 that correlates with the clinical manifestation of acne. After all, the peak incidence usually falls on the teenage period, when the level of insulin-like growth factor - 1 in the blood serum reaches its maximum. This happens during a growth spurt [4]. After the culmination of puberty, the level of Somatomedin-C (IGF-1), the main hormone of puberty, is known to decrease continuously [5]. There are scientific publications that confirm that the increase in the level of IGF-1 in addition to androgens correlates with worsening of acne in adult men and women [6]. There is increasing evidence that interactions between growth hormone, insulin, and IGF-1 signaling during puberty may play a causative role in acne pathogenesis by influencing adrenal and gonadal androgen metabolism [7]. This opinion is also supported by the fact that acne is absent in adolescents with Laron syndrome and in people with a hereditary predisposition to dwarfism resulting from congenital deficiency of IGF-1 due to growth hormone receptor (GHR) mutations. Conversely, in some patients, the development of acne is observed against the background of treatment with insulin-like growth factor (IGF-1) drugs. And also regresses when IGF-1 dosage is reduced or stopped. [2] This data can imply that new therapeutic strategies that target IGF-1 levels may be implied in acne treatment.

AIM

We aimed to provide a comprehensive review of acne pathogenesis and data regarding inositol efficacy in targeting IGF-1 pathway and decreasing IGF-1 levels and find pathophysiological substantiation (rationale, reasoning) of inositol therapy feasibility in acne treatment.

MATERIALS AND METHODS

Search of literature was performed on PubMed, Scopus, ResearchGate to identify scientific publications that aimed to research the role of inositol in acne and IGF-1 in acne pathogenesis and treatment and were published between 1999 and 2024 yielding information about possible therapeutic approach targeting IGF-1 induced increased sebum production. Peer-reviewed full-text articles, systematic reviews and evidence-based guidelines were included.

ETHICS

All sources used in this literature review are publicly available.

REVIEW AND DISCUSSION

Growth hormone and IGF-1 are important components of epidermal homeostasis Somatotropin is produced by the adenohypophysis. It binds to growth hormone receptors (GHR), which are expressed on most peripheral cells of the body. Somatotropic hormone induces hepatic synthesis and secretion of IGF-1 [8]. Somatotropin, insulin and insulin-like growth factor-1 have a clear effect on the growth and differentiation of sebocytes [4]. According to the literature, it is known that IGF-1 signaling is a central endocrine pathway of puberty and is a key mechanism through which nutrition influences the development of acne [2], which is closely associated with the Western diet [9].

Three main components of the Western diet have been identified as driving forces in the pathogenesis of acne: 1) hyperglycemic carbohydrates (high glycemic load); 2) insulinotropic milk/ dairy products, which promote secretion insulin/insulin-like growth factor (IGF)-1; 3) saturated fats, including trans fats and a deficiency of polyunsaturated fatty acids [5].

Epidemiological and clinical data evidence confirms that milk and other insulinotropic dairy products have an acne-promoting or acne-aggravating effect. Also, according to data from placebo- controlled studies, it is known that diets with a high glycemic load can exacerbate acne, increase levels of free IGF-1 in blood serum and stimulation of postprandial hyperinsulinemia [5].

INSULIN-IGF-1 PATHWAY AND ACNE

As it was mentioned before growth hormone and Western diet induce production of insulin and IGF-I in the liver and many other target tissues. Which, in turn, on the one hand activates the excess production of sebum, and on the other - androgens, which stimulate abnormal keratinization of the sebaceous glands. As a result, all these processes lead to the development of acne [5,8,9]. For a better understanding of all links of pathogenesis, let's take a closer look at the processes that occur after the activation of the insulin-insulin-like growth factor pathway. Insulin and IGF-1 activate insulin and insulin-like growth factor receptors [5]. These receptors by their structure are very similar to the insulin receptor, as it is a member of the insulin gene family. However, it is known that functionally they have differences: insulin plays a more metabolic role and IGF-I is more involved in cell growth [8]. In this way, it is a possible explanation of the adjacent overlapping of signal transduction between receptors.

Stimulation of insulin receptors and insulin-like growth factor receptors promotes cell growth and proliferation through activation of the phosphoinositol-3-kinase (PI3K)–protein kinase B (AKT) signaling cascade [5]. Activation of the PI3K/Akt cascade affects the regulation of FoxO1 and its nuclear export by insulin, insulin-like growth factor-1 (IGF-1). In the end this process has impact on the transcriptional activity of key target genes and nuclear receptors involved in the pathogenesis of acne [10].

IGF-1 downregulates FoxO1 and activates mTORC1. According to the literature, insulin-like growth factor-1 is known to reduce the nuclear levels of the Fork head box class O transcription factor 1 (FoxO1) and lead to the activation of the mammalian target of rapamycin complex 1 (mTORC1) [2] FoxO1 modulates the expression of genes involved in cell cycle control, DNA damage repair, apoptosis, oxidative stress, cell differentiation, glucose and lipid metabolism, inflammation, and innate and adaptive immune functions. FoxO1 is expressed in all mammalian tissues, including human sebaceous glands [11]. The main way of regulating FoxO1 transcription factors is their transport either to the nucleus or to the cytosol. Inhibition of FoxO1 occurs through its export from the nucleus to the cytoplasm. As it was mentioned before, insulin and insulin-like growth factor by specific phosphorylation of FoxO1 due to the activation of Akt kinase initiates its nuclear export. This process leads to the activation of the mammalian target of rapamycin complex 1 (mTORC1) [10]. This protein complex is involved in cell proliferation and metabolism. In acne, mTORC1 mediates sebaceous gland hyperproliferation, lipid synthesis, and keratinocyte hyperplasia [12]. Insu-

lin-like growth factor-1 also increases androgen levels, which in turn increases endogenous IGF-1, creating a positive feedback loop that increases lipogenesis [2].

IGF-1 AND INFUNDIBULAR KERATINOCYTES LOCAL PROLIFERATION

IGF-1 possesses the stimulatory effects on sebofollicular androgen signaling, by regulatory mechanisms that enhance androgen receptor (AR) transcriptional activity [13]. AR activate the expression of genes which are responsible for androgen-dependent growth and proliferation. For initiation of this nuclear transcription factors require two major aspects: 1) binding of its hormonal ligand (androgen) and 2) depression of its inhibitory nuclear coregulator FoxO1. Activation of AR depends on how it is related to androgen binding. Dihydrotestosterone (DHT), which is ten times more active than testosterone, has the highest ability to bind with AR. IGF-1 is also known to be a powerful inductor of the production of gonadal testosterone and adrenal dehydroepiandrosterone (DHEA) and also promotes the conversion of testosterone to DHT in the skin by increasing the activity of 5α-reductase [5,13].

IGF-1 AND LIPOGENESIS IN SEBACEOUS GLANDS

IGF-1 plays a key role in the lipogenesis of sebaceous glands. According to research it is known that, the level of concentration of IGF-I, has effect on increase in the accumulation of lipids in the sebocyte [14]. Signaling pathway of IGF-1/PI3K/AKT affects four key lipogenic transcription factors: the AR, peroxisome proliferator-activated receptor-γ (PPARγ), liver X receptor-α (LXRα), and sterol response element binding protein-1c (SREBP-1c). They are negatively regulated by FoxO1 [5, 13, 15]. Thus, activation of the insulin/IGF-1 pathway reduces nuclear FoxO1 and derepresses all major transcription factors of sebaceous gland lipogenesis [5]. High levels of IGF-1 induced by glycemic load result in both increased sebum production in sebocytes and upregulation of inflammatory cytokines such as IL-1β, IL-6, IL-8 and tumor necrosis factor (TNF)-α [25]. Besides, there is a positive correlation between serum IGF-1 levels and amount of facial sebum excretion [26].

NEW TRAJECTORIES IN THE TREATMENT OF ACNE

The treatment of acne is regulated by the European guidelines for local and systemic therapy. At the moment, oral isotretinoin is the most effective drug for acne treatment. It reduces sebum secretion in humans through sebocyte-mediated apoptosis. However, isotretinoin is associated with the risk of teratogenicity and other serious side effects. It is also possible to use antiandrogens in women without contraindications as an alternative method of treatment [16]. Thus, there is a need to develop alternative methods to suppress sebum production with fewer side effects. Therefore, according to modern scientists, several key development trajectories have been outlined:

- Medicines that increase insulin sensitivity (insulin sensitizers) such as MYO and D-Chiro- inositol (DCI)
- Probiotics are an important component in the complex treatment of acne and correction dysbiosis
- Transition from symptom control to a holistic patient-centered approach and stress control are further directions for future acne treatments [17]

INOSITOL AND ACNE

In the literature there is increasing information about the relationship between acne and insulin resistance [18,19]. Both pathologies have shared signaling pathways of mammalian target of rapamycin complex 1(mTORC1) and insulin-like growth factor-1 (IGF-1). Insulinemia, hyperandrogenism and elevated levels of insulin-like growth factor are important components in the development of the pathogenesis of acne [20]. Increased insulin levels can stimulate IGF-1 receptors boost, which leads to the proliferation and dysfunction of keratinocytes. On the other hand, hypersecretion of IGF-1 can produce abnormal production of sebum, hyperproliferation of sebocytes, and lipogenesis [1]. Also, insulin and insulin-like growth factor activate the androgen signaling pathway, and as a result - increase level of androgens. [2,6].

The results of the review of modern literature gave an understanding that inositol is a new player in the complex treatment of mild acne [21-23]. Chemically it can be characterized as hexahydroxycyclohexane and belongs to vitamin B group. Epimerization of the six hydroxyl groups leads to the formation of nine stereoisomers, including myo - (MYO) and D-chiro-inositol (DCI). [24] This vitamin-like substance mediates cellular signal transmission in response to various hormones, neurotransmitters, and growth factors [25]. It has been reported that an alteration of inositol levels plays a pivotal role in the pathogenesis of some metabolic diseases, such as metabolic syndrome (MetS), type 2 diabetes mellitus (T2D), and polycystic ovary syndrome (PCOS), which are conditions all related to altered insulin sensitivity it has been reported that an alteration of inositol levels plays a pivotal role in the pathogenesis of some

metabolic diseases, such as metabolic syndrome (MetS), type 2 diabetes mellitus (T2D), and polycystic ovary syndrome (PCOS), which are conditions all related to altered insulin sensitivity Both myo- and D-chiro-inositol can regulate insulin signal transduction by increasing its sensitivity and improving glucose metabolism. Inositol was also examined in patients with glucose intolerance, given its properties as an insulin-sensitizer and second messenger, thus exerting an insulin-like effect on as an insulin-sensitizer and second messenger, thus exerting an insulin-like effect on metabolic enzymes [27]. In type-1 diabetes (T1D), inositol was tested to replace metformin metabolic enzymes [27]. For this reason, inositol can be used as a complementary therapy for improving the cellular response to metabolic cascades following the binding of insulin to its receptor, specifically be reducing insulin resistance and improving glucose metabolism [6].

CONCLUSIONS

Recent studies have shown that inositol treatment improves tissue sensitivity to insulin and reduces circulating androgen levels. As a result, inositol preparations contribute to the reduction of manifestations of skin diseases in hyperandrogenic conditions; reduce the rate of hirsutism and acne manifestations. Inositol may be beneficial in treating female patients with acne as an adjunct therapy. Short-term treatments with low dosages of d-chiro-Ins, on the other hand, can be considered safe in man with normal testosterone levels.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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