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REVIEW

Acne Comorbidities

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Abstract: Acne vulgaris is a multifactorial chronic inflammatory disorder of the pilosebaceous unit, and it represents the most common skin disease affecting about 85% of adolescents in Western populations. The prevalence of acne vulgaris in developed countries is higher than that in developing countries.Emerging data has shown some systemic diseases closely associated with acne, including obesity, diabetes mellitus, cardiovascular diseases, metabolic syndrome (Mets), and so on.This review summarizes acne-associated diseases that have been reported in studies, and analyzes the possible co-pathogenesis of these diseases and acne.

Keywords: acne, comorbidity, metabolic diseases, diabetes mellitus, obesity

Introduction

Acne vulgaris is a chronic inflammatory skin disease involving the sebaceous glands of the hair follicles. Epidemiological and basic scientific studies have made us gradually realize that acne is not only a skin disease, but also an important systemic disease, which can occur successively or concurrently with a variety of systemic and metabolic diseases.One study showed that patients with acne have significantly higher total cholesterol (TC) and triglyceride (TG) levels, while their high-density lipoprotein cholesterol (HDL-C) levels were significantly lower.[1] Cerman et al[2] observed that the glycemic index of acne patients was significantly increased, the serum adiponectin level was significantly decreased, and the glycemic index and serum adiponectin were closely related to diabetes.Our team previously conducted an epidemiological survey on the correlation between acne and glucolipid metabolism diseases, and found that people who had acne before had a higher risk of abnormal glucolipid metabolism than people who did not have acne. Acne is a risk factor for abnormal glucose and lipid metabolism.[3] Recently, it has been reported that acne is a multi-gene and multi-target disease,[4] which may affect hyperlipidemia, diabetes, and cardiovascular disease through some genes or targets. For example, the latest report found that RETN-420 and IL6-572 gene polymorphisms are closely related to acne susceptibility, and RETN-420G and IL6-572C alleles increase the risk of acne.[5] These two gene polymorphisms can lead to the occurrence of metabolic diseases such as obesity, type 2 diabetes, cardiovascular disease, and cancer.[6–8] The occurrence of acne is not only regulated by genes, but also by signaling pathways such as insulin-like growth factor 1 (IGF-1) and the mechanistic target of rapamycin complex 1 (mTORC1). Some believe that IGF-1 signaling may be the main pathway in the pathogenesis of acne, which can alleviate acne by inhibiting the proliferation of sebaceous glands and the secretion of sebum,[9,10] while others believe that acne vulgaris is a civilized disease driven by mTORC1 signaling. mTORC1 promotes lipid synthesis by activating the transcription factor sterol regulatory element-binding protein 1 (SREBP1), which leads to acne.[11] These signaling pathways are also actively involved in the occurrence and development of metabolic diseases.[12] In addition to the above commonalities, acne shares common dietary habits with these metabolic diseases, ie high sugar, high carbohydrate, and high dairy.[13] Through experimental studies, our team found that milk can promote sebum secretion in golden hamsters through the IGF-1/SREBP/ACC-1 signaling pathway,[14] and the increase of sebum secretion is one of the pathogenesis of acne.Some scholars find that having milk and a high-sugar diet can increase the levels of insulin and IGF-1, which in turn over-activates mTORC1 signaling, leading to acne, insulin resistance and increased BMI in adolescents; and early intervention can reduce the incidence of obesity, type 2 diabetes, cancer and other diseases in adults.[15] It suggests the possibility of comorbidity between acne and the above-mentioned diseases on the timeline.Other scholars agree with this view,[16] arguing that dermatologists should be aware

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of the potential relationship between acne and insulin resistance and should consider referring acne patients to primary care for further evaluation. Early treatment of insulin resistance can prevent the development of diabetes and cardiovascular disease. Therefore, a thorough understanding of the relationship between acne and metabolic diseases is conducive to the early prevention, screening and treatment of metabolic diseases. This article will respectively discuss the possible common mechanisms of acne and metabolic diseases.

The Relationship Between Acne and Various Metabolic Diseases

The Obesity

major public health problem worldwide, and its prevalence has increased dramatically over the past 20 years. Despite the ambiguity in the use of body mass index (BMI) as a biomarker of current abnormalities and future risk, it is undeniable that obesity has been proven to contribute to cardiovascular and cerebrovascular disease, diabetes, and hypertension.[17] Currently, obesity has been found in some studies to increase the risk of acne, and high BMI is a risk factor for acne severity in adolescents.An epidemiological survey found overweight and obese individuals have a significantly higher prevalence in acne vulgaris than healthy individuals, and there is a positive correlation between BMI and acne severity.[18] How does obesity lead to acne? The mechanism may be related to the metabolic effect of obesity. Androgen, insulin and insulin growth factor are often increased in obese patients, which can induce the proliferation and differentiation of sebaceous cells through the expression of adipogenic genes, thereby increasing sebum secretion and affecting the severity of acne.[19,20] Other studies have shown that the number and percentage of T helper (Th) 17 cells in adipose tissue are increased in obese subjects compared with non-obese subjects, and Th17 cell signaling pathway is a key pathway.[21] Obesity impairs the innate immune function of white adipose tissue, and a specific diet (such as high-fat feeding) leads to the secretion of transforming growth factor-β (TGFβ) from over-accumulated mature adipocytes,[22] which plays a key role in the differentiation of Th17 cells.[23] Our team found that Th17 cells are closely related to the occurrence and development of acne by reviewing the literature.[24] In addition, acne and metabolic diseases also share common targets at gene loci. Tumor necrosis factor (TNF)-α rs1800629 (308 G/A) is associated with obesity and metabolic disorders in children, and this SNP has been shown to increase the susceptibility to acne.[4,25]

The Dyslipidemia

Among patients with acne, there is evidence of an abnormal lipid profile.[26,27] Shrestha et al studied 100 women with acne between 2015 and 2016 and found that 15.4% of them had changes in their lipid profiles.[28] Since androgens have clear roles in acne pathogenesis, and androgens are derived from plasma cholesterol, lipid alterations might cause acne.[29] In studies, plasma TC, TG and low-density lipoprotein cholesterol (LDL) were found to be elevated in patients with acne, and high TC was the most common derangement, particularly in men.[30] Common lipid components (TC, TG, LDL) in patients with adult or prepubertal acne flare-ups or severe, persistent acne all accompanied by hirsulosis exceed normal reference ranges. These reports call attention to the fact that changes in lipid levels are present in patients with acne and that dyslipidemia is positively correlated with the onset of acne. Therefore, correct and early intervention may be an important measure to prevent diseases caused by dyslipidemia.

Diabetes

Insulin resistance is a common feature of obesity and type 2 diabetes, but novel approaches of diabetes subtyping (clustering) revealed variable degrees of insulin resistance in people with diabetes.[31] Insulin resistance is considered to be an important factor in the pathogenesis of acne, and both insulin and IGF-1 levels are increased in patients with acne.[32] Insulin and IGF-1 can promote the synthesis of androgens in the adrenal gland and gonad, thus leading to acne susceptibility.[33,34] They can also increase the expression of SREBP-1 through mTORC1 pathway to induce lipid synthesis. However, IGF-1 has a stronger stimulating effect on the production and development of acne sebum than insulin.[20,34] Cytokines such as TNF-α, interferon-γ (IFN-γ), interleukin (IL)-6, IL-1β and IL-17 can not only inhibit insulin signal transduction, thereby inhibiting glucose and lipid metabolism, resulting in insulin resistance, but also mediate the inflammatory response of acne.[35,36] Given that acne

patients are more likely to develop insulin resistance, which may be a pre-stage of type 2 diabetes, close observation is important for controlling disease progression to type 2 diabetes.[16]

Hypertension

The effect of androgen on blood pressure is well established.[37,38] Related experimental results indicate that androgen can be mediated through regulate blood vessel tone of hypertension. For example, testosterone and its precursor androstenedione can increase the expression of thromboxane A2 receptors through androgen receptors'dependency mechanism[39] or testosterone can accelerate vascular remodeling by promoting the role of rat vascular smooth muscle cell mitosis, thus promoting the development of hypertension.[40] At the same time, excessive androgen secretion is also one of the main mechanisms of acne.According to statistics, male acne patients after puberty are more likely to have higher blood pressure, which may be related to the persistently-high androgen levels after puberty.[41] Studies have shown that serum IL-6 levels are positively correlated with blood pressure in hypertensive patients.[42,43] TNF-α is one of the important inflammatory indicators of hypertensive plaques, which can inhibit autophagy and aggravate the formation of hypertensive plaques by inducing p38MAPK phosphorylation.[44,45] Reducing serum IL-1β and nuclear factor kappa B (NF-κB) levels can improve hypothalamic leptin resistance, thereby inhibiting central sympathetic nerve excitation-mediated increase in blood pressure.[46,47] The above cytokines also mediate the inflammatory response of acne.

Cardiovascular Diseases

There is no report on the direct association between acne and atherosclerosis, or coronary vascular disease, but risk factors affecting cardiovascular disease, such as obesity, hyperlipidemia, hypertension, diabetes, etc., are significantly related to acne. McCullough et al[48] reported that androgens can significantly reduce high-density lipoprotein and increase low-density lipoprotein, and the increase of low-density lipoprotein levels can promote the formation of atherosclerosis. The apolipoprotein B/apolipoprotein A1 (ApoB/ApoA1) ratio is an important indicator for preventing the occurrence and development of cardiovascular disease.[49,50] If it increases, the risk of cardiovascular disease increases.Androgens that lead to acneigenesis can also lead to elevated ApoB/ApoA1.[51] Studies have found that IL-17, TNF-α, Toll-like receptors, and NF-κB pathways are actively involved in the occurrence and development of cardiovascular diseases,[52–55] and these targets and pathways are also involved in the occurrence and development of acne. Acne and cardiovascular disease may have common targets and pathways.

Metabolic Syndrome

MetS includes abdominal obesity, low-grade chronic systemic inflammation, altered glucose metabolism, dyslipidemia, and hypertension. Dietary habits, sedentary, less physical activity, and oxidative stress can contribute to the development of the disease. It is the current global epidemic and major public health care problem. Recently, several authors have highlighted the link between this syndrome and acne, which they suggest increases the odds of developing metabolic syndrome.[56,57] mTORC1 signaling pathway is the common feature between them.The expression of mTORC1 is increased in the skin lesions of acne patients,[58,59] and the attenuation of mTORC1 signaling can achieve the effect of acne treatment.[60–62] This signaling pathway is a central regulator of cell growth and anabolism, and plays an important role in various metabolic diseases such as obesity, insulin resistance, and type 2 diabetes.[11]

Other Diseases

Acne has been reported to be associated with increased sinus infections, asthma, non-asthmatic lung disease, reflux, abdominal pain, nausea and food allergies, depression, anxiety, attention deficit hyperactivity disorder, and insomnia.[11,63,64]

The Etiological Link Between Acne and Metabolic Diseases

Factors such as common dietary structure, genetic susceptibility, immune-inflammatory pathways, and the influence of high androgen levels may be the reasons for the increased incidence of acne comorbidity.On the one hand, patients with acne have a higher incidence of comorbidities. For example, patients with acne are prone to symptoms such as anxiety

and insomnia, which in turn affect obesity, cardiovascular disease, etc.; Patients such as diabetes, obesity, etc., have a higher probability of acne than normal people, and acne, obesity, diabetes and other diseases are regulated by the same gene locus RETN-420.[5,6] It is well known that insulin resistance, obesity, and type 2 diabetes can develop through a kinase pathway known as the target of mammalian mTORC1,[65,66] which is also one of the important mechanisms of acne pathogenesis.[67] On the other hand, comorbidities can interact with each other, such as obesity, hyperlipidemia, hypertension, and diabetes, which are all high-risk factors for cardiovascular disease.

Conclusions

Acne is a disease caused by multiple factors and abnormal expression of multiple genes. Although in-depth studies have been conducted on various factors including skin microecological changes, androgen induction, keratinization of pilosebaceous ducts, the release of pro-inflammatory factors, environmental pollution, sunlight, ultraviolet rays, dietary changes, etc., the pathogenesis of acne is yet to be thoroughly understood. It is a common understanding that endogenous factors are closely related to acne. In 2020, a prospective case-control study of serum FoxO1, mTORC1, IGF-1, IGFBP-3 levels and metabolic syndrome in patients with acne vulgaris in Turkey suggested that acne was associated with hypertension, insulin-like growth factor-binding protein-3 (IGFBP-3), HDL and factors related to Mets, the concept of acne comorbidity was proposed for the first time, and new treatment strategies were suggested.[32] The latest data indicate that the pathogenesis of acne shares features of other metabolic diseases in which TREM2 macrophages and lipid dysregulation are prominent.[68] Acne and the above diseases have many common pathogenesis mechanisms, and there is the possibility of comorbidity. The form of their comorbidity may be concurrent existence, sequential existence, or mutually-causal existence. They may be in the same spectrum of metabolic diseases, and under the regulation of gene polymorphisms, they manifest as different diseases at different ages.From the perspective of the "Butterfly Effect", attention should be paid to the "whistleblower" function of acne to other diseases, and reduce the over-activation of MTORC1 signal, which can warn and intervene the occurrence of metabolic diseases in advance, so as to prevent more serious diseases.Dermatologists can make lifestyle changes to acne sufferers at an early age to prevent or delay the onset of the disease.

Abbreviations

Mets, metabolic syndrome; TC, higher total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; IGF-1, insulin-like growth factor 1; mTORC1, mechanistic target of rapamycin complex 1; SREBP1, sterol regulatory element-binding protein 1; BMI, body mass index; Th17, T helper 17 cells; TGFβ, transforming growth factor-β; TNF, Tumor necrosis factor; LDL, low-density lipoprotein cholesterol; IFN-γ, interferon-γ; IL, interleukin; NF-κB, nuclear factor kappa B; ApoB/ApoA1, apolipoprotein B/apolipoprotein A1.

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