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Hormonal Inconsistency: A Sign of the Onset of Acneogenesis

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Abstract:

Hormonal release throughout the body is dependent on the various signaling pathways, which are responsible for consistent activities until any fluctuations occur in them. The abnormal activities of hormones are the precursor to many disorders. Hormonal imbalance and abnormal production of sebaceous glands during the differentiation and maturation of pilosebaceous units render to an infectious and inflammatory skin disorder i.e. acne. Five major factors i.e. sebum production, dead skin cells, propionibacterium colonies, sebaceous glands, and hormonal imbalance are correlated with each other in acneogenesis. Acne is directly linked with the onset of puberty. However, it is most common in females as compared to males. In females, hormones overstimulate during the pregnancy and menstrual cycle. The development starts from inflammatory to non-inflammatory acne i.e. papules, nodules, pustules, and more severe cysts and acne scarring may result. Steroid sex hormones i.e. androgen, estrogen, and progesterone are mostly responsible for the overproduction of sebum in acne formation. Several growth hormones like insulin and insulin-like growth factor-1 and stress hormones i.e. cortisol, glucocorticoids are involved in the pathogenesis of acne. This review is conducted to address the common issues and factors involved in acneogenesis, for a better understanding of hormonal activities involved.

Keywords: Acneogenesis, sebum, hormonal imbalance, steroid, puberty.

INTRODUCTION

Acneogenesis, the process in which hormones affect the skin by producing elevated levels of sebum and cause inflammation resulting in acne lesions (Tahir, 2016). Acne is an inflammatory chronic disorder that affects the population of approximately 9.4% around the global world. Acne lesions become so severe and produce cyst and develop into acne scars. 80% of females and 90% of males are affected by acne especially in the case of adolescents. This disease is more common in adolescents as compared to adults (Kamra and Diwan, 2017). According to estimates, acne is considered the world's 8th most frequent disease, and globally, approximately 633 million people are prone to it (Vos *et al.*, 2015). The main cause of this disease is the fluctuation and disruption of the microbial activity of resident microbes on the skin, with each microbe has its role and purpose in protecting the human body from external sources. These microbes resist the defense barriers of the host skin to survive. The pathogenicity and virulence of the microbial population increase the acne lesions formation and they ultimately develop into acne or pimples (Kumar *et al.*, 2016).

In 1840, Fuchs was the first scientist to invent the term acne vulgaris and other different types of acne i.e. acne rosacea and acne mentagra. In 1842, Erasmus Wilson isolated the acne vulgaris from acne rosacea (Grant, 1951). It mostly founds in most children and young individuals during their lifetime at the onset of puberty. Most male individuals are affected at the age of 15-20 years and female individuals are affected by acne at the age of 13-18 years, respectively. This disorder is mostly found in females as compared to males. It is found to be more severe in females and becomes permanent in them (Tahir, 2016). A previous study observed the contact between sex steroid hormones and pubertal maturation in the pathogenesis of acne, especially in teenage girls (Lucky *et al.*, 1994). During the age of 8-10 years on the onset of the premenstrual condition

in young girls, the severity of acne and steroid hormones maturation was evaluated. The concentration of steroid hormones reached its peak level from pre-pubertal to pubertal maturation. Therefore, the level of dehydroepiandrosterone sulfate, a precursor of androgen would be higher in prepubertal girls with acne (Khunger and Kumar, 2012). The prevalence of acne is increasing from the age of adolescence to adult patients up to 25 years old around 95%. Two types of adult acne are involved: persistent acne and late-onset acne. When the adolescent acne stays continual until the age of 25 years old, it's termed as persistent acne. While in the case of late-onset acne, the people may suffer from acne for the first time after the adult age (Goulden *et al.*, 1997).

Factors Responsible for Acne Formation

There are several factors involved in acne formation. Some of them are discussed includes increased production of sebum, production of sebaceous glands to hair follicles and accumulation of dead skin cells, production of colonies of acne-causing bacteria i.e. "Propionibacterium" and increased activity of hormones, as shown in Figure 1 (Gollnick and Dreno, 2015).

Human skin contains many hair follicles that are linked to oil glands occurring inside the skin. These glands produce oil known as sebum. The composition of sebum contains a mixture of lipids or fats with triglycerides 57.5%, wax esters 26%, squalene 12%, cholesterol esters 3%, and cholesterol 1.5% approximately. These oil glands carry dead skin cells to the surface of the skin and maintain the level of hormones. When the pores present on the skin surface get blocked and the production of oil increases, in return the dead skin cells are also accumulated. Sebum and hair follicles produce clog together and this clog starts to colonize the bacteria and the inflammation may be going to start resulting in irritation and swelling and produce "comedones" either open or closed.

Microcomedones are the precursors of comedones when the keratinocytes increase in size and overproduction of dead skin cells and oily secretions happen (Lai *et al.*, 2012). When the clog is starting to rupture; the pimple may

appear on the surface of the skin. The bacteria start to multiply and produce many colonies of the Propionibacterium that causes infection as producing inflammation onto the skin (Beylot *et al.*, 2014).

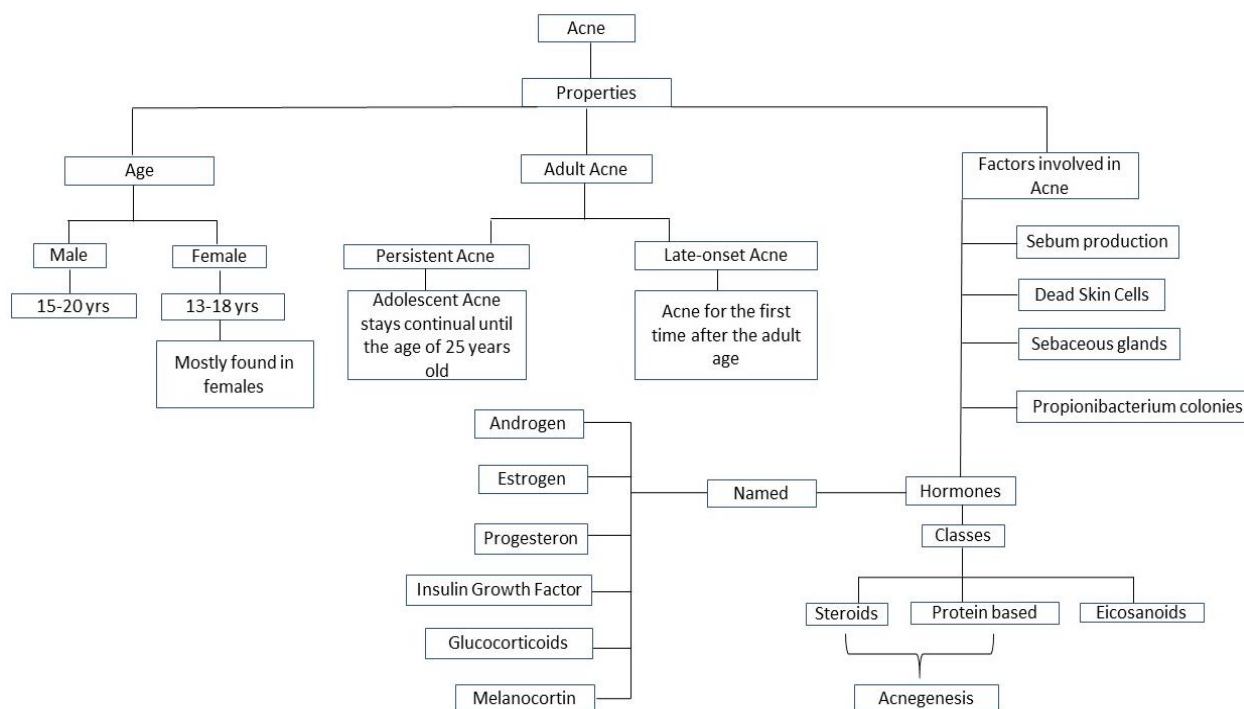


Fig. 1. This flow chart is constructed based on the common features of Acne. Acne mostly occurs in females as compared to males. Puberty and under growing stages are the ideal time for acne's occurrence and it mostly occurs in this stage. However, this disease also happens after the adult stage. Several factors are involved in acnegenesis. While hormonal imbalance is the major factor in this disease.

Propionibacterium releases several enzymes like lipase and protease to degrade the follicular wall and causes to start the inflammatory cascade by using the chemotactic factors (Gollnick, 2015).

1. Hydrolysis of Fats by bacteria-overproduction of sebum

When the fats are hydrolyzed by bacteria, the oily secretion goes to the skin surface and accumulated there. The third part of the total secreted and accumulated fat consists of free fatty acids. The rate of secretion is higher

in adult males as compared to the females and gradually decreases as the person grows older. Overproduction of sebum may cause a diseased condition, acromegaly due to the overstimulation of growth hormones (Thiboutot, 2008).

2. Chronic Stress and hormone- acne formation

The main cause of acne development is the chronic stress that is associated with the sebum production level. With increased stress levels, the sebum glands excreting more sebum outside the skin that leads to a higher

concentration of hormones in the body resulting in more severe types of permanent acne scars (Fabbrocini *et al.*, 2010).

Hormones and its role in the regulation of the different system

Hormones are the signaling molecules secreted from endocrine glands that are transported from tissues to the major organs of the body (Nussey and Whitehead, 2013). Hormones are classified into three main classes: eicosanoids, steroids, and amino acids-based derivatives in which steroid hormones are activated from cholesterol such as sex hormones and stress hormone i.e. estrogen and cortisol. While the protein hormones are derived from the combination of amino acids into peptides such as insulin and growth hormones. Other complex protein hormones include luteinizing hormone, thyroid-stimulating hormone, and follicle-stimulating hormones (Neave, 2007).

They are used to regulate metabolism and control the activities of the body. They also control the reproductive and immune system and prepare the body for a new phase of life i.e. puberty, menopause (Nussey and Whitehead, 2013).

Hormonal imbalance and its consequences

The steroid and protein hormones are involved in acnegenesis because the activity of sebaceous glands is linked to the level of hormones in the body. If the level of hormones rises from the normal, they disturb the normal function and cause overstimulation of the sebum and *Propionibacterium* colonies results in the development of acne (Zouboulis *et al.*, 2003).

Human sebocytes serve as the site where a significant amount of sex steroids is synthesized, and it depends upon the enzyme's expression during the synthesis of androgen and estrogen in the pilosebaceous unit. Androgen synthesizes its prohormones i.e.

dehydroepiandrosterone and androstenedione and converted them into its more potent forms i.e. testosterone and dihydrotestosterone with the major contributors, the sebocytes and sweat glands by using specialized enzyme cytochrome P450. Androgen stimulates the growth and differentiation of the sebocytes, hair growth, and wound healing; they are only effective when androgen binds to androgen receptors. The enzymes involved during the synthesis of sex steroids are used to either activate or deactivate the androgen in the skin. Alterations in the association of androgen to its receptor are the main cause of several skin disorders i.e. acne, seborrhea, and alopecia. Estrogen hormones activate the signaling pathways and perform their action by diffusing into the cell or binds to the cell surface receptors. Estrogen has been concerned with skin aging, pigmentation, sebum production, and skin cancer. Progestins are used in the treatment of the pathogenesis of skin disorders because they are used to control the hormone during birth and menopausal therapy (Zouboulis *et al.*, 2007).

Hormones perform their action by following different pathways; exocrine, endocrine, paracrine, and autocrine action. In the case of paracrine action, hormones diffuse at the target cells while autocrine acts on the same cell. The human skin is considered an endocrine organ because it produces the hormones and hormones-related receptors in the process of signaling. Different types of hormones i.e. steroid hormones, phospholipid hormones, growth hormones, and stress hormones, are involved in the development of the pilosebaceous unit, growth of hair follicles, and synthesis of lipids in the sebaceous glands. Among these, androgen hormones have clinical importance in the field of dermatology such as skin-related disorders i.e. acne, alopecia, etc. When the androgenic enzymes are overexpressed, it stimulates the diseased condition hyperandrogenemia in response to the androgen receptors present on the surface of the skin. Steroid hormones are synthesized in adrenal glands and ovaries. Pilosebaceous unit

is best to study endocrinology in dermatoses (Chen and Zouboulis, 2009).

Hormones Involved in Pathogenesis of Acne

Different types of hormones are involved in the pathogenesis of acne which includes steroid sex hormones i.e. testosterone and its derivatives, estrogens, progesterone, and growth hormones i.e. insulin-like growth factor, insulin hormone, and stress hormones i.e. cortisol, glucocorticoids, mineralocorticoids. However, some other factors are also involved in this regard (Zouboulis *et al.*, 2007).

Steroid Sex Hormones

Sex hormones are those hormones that contain three-ring six-carbon and one ring five-carbon structure, and this structure is known as cholesterol, the basic component of steroid hormones. They are involved in growth, reproduction, sexual development, and in controlling the metabolism of the whole body. Steroid hormones such as testosterone, androgen, dehydroepiandrosterone, estrogen, and progesterone are the main cause of skin-related diseases (Zouboulis *et al.*, 2007). Several changes occur during new life phases such as menstrual cycle, puberty, pregnancy, and menopause in the body, especially in females. Overstimulation of hormones may occur in these stages of life that may lead to skin-related diseases (Balachandrudu *et al.*, 2015).

Androgen (Testosterone)

Androgen is the most important hormone in the development of sexual characteristics and hair growth during puberty. The differentiation and maturation of the pilosebaceous unit depend upon the androgen level. Follicular keratinization results due to epithelial-stromal interactions for optimal growth

(Deplewski and Rosenfield, 2000). Testosterone is the most important steroid sex hormone produced both in males and females but a greater amount in males. Testosterone is produced in the testis of males and ovaries and adrenal glands of females. This hormone is circulated in the blood and transported to the cell where it binds to the sex-hormone-binding globulin (SHBG) domain. Testosterone influences the activity of cell metabolism and the development of body tissues and sexual characteristics. Sebum over stimulates due to the increased level of testosterone and increases the pathogenesis of acne (Rohr, 2002).

Androgen Biosynthesis

Androgen can be synthesized by the synthetic pathway in which testosterone is stimulated through testis and ovaries excreted from adrenal glands or when the testosterone is converted into androstenedione. Conversion of testosterone into dihydrotestosterone (DHT), also takes place by utilizing NADPH-dependent enzyme 5-alpha reductase which is further aromatized into estrogen or 17 beta oestradiol. These androgens come in contact with the skin via the bloodstream and stimulate sebum production. Testosterone and DHT are more effective to bind to the androgen receptors (AR) where DHT becomes ten-times more active than testosterone. 5 α reductase enzymes play important role in many androgens causing disorders, for example, acne, hirsutism, and baldness (Thiboutot, 2007).

The other derivatives of androgen hormone are androstenedione and dehydroepiandrosterone that can also be converted into testosterone and DHT, and follow the same mechanism by regulating extracellular and intracellular events of endocrine glands (Zouboulis *et al.*, 2007). The signaling pathways and mechanism of actions of Androgen involved in acne formation are summarized in Table 1.

Table 1. Role of Androgen on the onset of acne.

Role of Androgen on the Onset of Acne		
Signaling pathways	Mechanism of action	References
Activation of Protein Kinase A (PKA) pathway with intracellular calcium	Stimulate the activation of kinase- signaling pathway and induce the production of intracellular calcium, these are referred to as non-genomic actions.	(Heinlein and Chang, 2002)
Fibroblast growth factor receptor-2b (FGFR2b)- signaling pathway	FGFR2b signaling plays a vital role in maintaining homeostasis of pilosebaceous follicle, comedogenesis, sebaceous gland stimulation, and lipid synthesis. The signaling can be upregulated by enhancing the expression of cytokines, IL-1 α , and may result in diseased conditions i.e. acne vulgaris.	(Melnik, 2009)
Upregulation of P13k/Akt MAPK, PKC pathways	In this signaling pathway, signals are transmitted and activate the phosphorylation process by using transcription factor and regulates the cellular functions i.e. metabolism, growth, proliferation, survival, and protein synthesis. The dysregulation of the PI3K/Akt pathway is concerned with several human diseases such as acne.	(Li <i>et al.</i> , 2015)
Activation of Sterol regulatory element-binding protein (SREBP) pathway	SREBP regulates the biosynthesis of cholesterol through the repression of the transcriptional factor. Regulated genes are involved in the development of cellular lipid metabolism and homeostasis.	(Heemers <i>et al.</i> , 2006)

Mechanism of Action

Steroid sex hormones play an important role in transcription and translation to synthesize proteins, this is also known as the genomic effect. The androgen receptor binds to testosterone and DHT. These receptors are located in the cytoplasm and attached to residing heat-shock proteins. When it binds to the receptor, heat shock protein starts to dissociate resulting in a ligand-androgen receptor complex. This complex enters into the nucleus where it is phosphorylated and forms a dimer that binds to the specific promoter region of androgen-related genes, therefore, influences the gene transcription. DHT is more active or potent rather than testosterone because its binding affinity becomes double to the androgen receptor than that of testosterone (Starka *et al.*, 2008).

Non-genomic processes can be synchronized by classic genomic processes that determine the hormonal action, its role, and sequence. They differ from genomic actions because they can occur within seconds or minutes. The reaction occurs usually within the cytoplasm, not in the nucleus. Inhibitors are

used to stop transcription or translation, but they can withstand the effects of the inhibitors. Inhibitors are used to stop transcription or translation, but they can withstand the effects of the inhibitors. In the case of non-genomic actions, the hormones act on the membrane containing phospholipids (Losel *et al.*, 2003). They may bind to the receptors either the surface receptors located onto the membrane that generate signals or with androgen receptors associated with their gene expression (Revelli *et al.*, 1998). These non-genomic reactions can be triggered by using calcium ions or following the cyclic AMP pathway where calcium ions act as a second messenger (Heinlein and Chang, 2002).

Sex hormone-binding globulin (SHBG) has a significant effect on the regulation of sex hormones. Their receptors may be G-coupled protein receptors that are found on the surface of the testis or in the liver. SHBG binds to the receptor making a complex and then interacts with steroid hormone by activating the cAMP pathway or calcium ions into the cell (Heinlein and Chang, 2002).

Estrogen

Estrogen is the most important female sex hormone that belongs to the steroid family. They are involved in the development of the reproductive cycle and sexual characteristics mostly in females. Estrogen also acts on the cell membrane and reaches into its interior region. The Interior region contains receptors for these hormones, which allow them to bind. Estrogen receptors can be of two types: Estrogen α receptor and β receptors. Estrogen α receptors are the classical receptors for the activation and deactivation of transcription or translation inside the cell. They are mostly found in sebocytes while estrogen β receptors are located at different sites i.e. keratinocytes, melanocytes,

endothelial cells, and sebocytes (Zouboulis *et al.*, 2014) When high-dose estrogen is used it reduces the sebaceous gland size and sebum production (Zouboulis *et al.*, 2014).

Estrogen stimulates the production of sebaceous glands by following different ways: 1) inhibition of gonadotropin-releasing hormone and luteinizing hormone (negative feedback mechanism) 2) elevated level of SHBG secreted by the liver 3) reduce the level of testosterone 4) resist the action of testosterone 5) affecting the gene expression of sebaceous glands and sebum production (Thiboutot, 2004). The signaling pathways and mechanism of actions of estrogen involved in acne formation are summarized in Table 2.

Table 2. Role of Estrogen on the onset of acne.

Role of Estrogen on the Onset of Acne		
Signaling pathways	Mechanism of action	References
Activation of various protein-kinase cascades i.e. tyrosine-protein kinase, serine or threonine-protein kinase pathway	Estrogen hormones influence their activity by the action of estrogen receptors (ER) and target the genes to activate transcription without binding to DNA. This pathway is also known as genomic to non-genomic signaling.	(Lösel and Wehling, 2003)
Signal transducer and activator of transcription 5 (STAT5)-dependent transcription signaling pathway	STAT-5 is involved in biological processes such as nuclear translocation and DNA binding activity. Estrogen and its receptors regulate the gene expression containing STAT binding sites i.e. β -casein activated by 17 β -estradiol.	(Toran-Allerand, 2004)
Regulation of intracellular calcium, and the stimulation of cAMP and adenylate cyclase activity	G coupled proteins receptors and changes in protein-protein interactions are involved in Downstream pathways including calcium mobilization and kinase activation.	(Wong <i>et al.</i> , 2002)
Activation of the mitogen-activated protein kinase (MAPK) signaling and Phosphoinositide 3-kinase (P13K) pathway	Hormones stimulation can be mediated by using different promoters to regulate the gene expression but do not have any steroid response element. Their effect concerning transcription can lead to the proliferation and progression of sebocytes.	(Prossnitz and Maggiolini, 2009)

Progesterone

Like other steroids, Progesterone also has specific receptors with which it binds and enters the cell either nucleus or cytoplasm and a complex is formed. The attachment of these complex to the receptors allows them to step

forward for transcription. Progesterone stops the conversion of testosterone into its more potent form i.e. DHT by inhibiting the NADPH-dependent enzyme 5 α reductase. Progesterone receptors are only found in keratinocytes. Menstrual flares and sebum exacerbations mostly take place due to reduced levels of

progesterone (Lakshmi, 2013). The signaling pathways and mechanism of actions of

progesterone involved in acne formation are summarized in Table 3.

Table 3. Role of Progesterone on the onset of acne.

Role of Progesterone on the onset of Acne		
Signaling pathways	Mechanism of action	References
Activation of c-Src and Downstream MAPK (Erk-1/-2) pathway	Signaling can control the expression of targeted genes that do not have any PR dependent response element. Progesterone receptors are also used to initiate the activation of extranuclear receptor signaling pathway such as cyclin D1 (CCND1) and promote the progression of the cell.	(Boonyaratanakornkit <i>et al.</i> , 2008)
Nuclear Receptor Signaling Pathways	Nuclear receptors are implicated in the process of signaling containing ligands and co-regulators by physiological alterations to coordinate the expression of genes at a specific position. NR signaling controls the reproduction cycle and the changes occur during embryonic development at the stage of puberty. Their main function is to modulate the alterations in physiology resulting in a broad range of diseased states.	(Burriss <i>et al.</i> , 2013)

Insulin and Insulin Growth Factor 1

Growth hormone receptors are located in sebocytes that play a significant role in the stimulation and maturation of sebaceous glands (Melnik *et al.*, 2013). Besides this, the activity of SHBG is inhibited and has a positive effect on androgen synthesis on adrenal glands and ovaries. The insulin is released when the level of glycemic diet reaches a maximum which in turn increases the production of androgen and sebum formation (Smith *et al.*, 2008). The signaling pathways and mechanism of actions of growth hormones involved in acne formation are summarized in Table 4.

Corticotrophin Releasing Hormone

Corticotrophin releasing hormones (CRH) have a considerable impact on the growth of acne lesions. CRH consists of 40-50 amino acids in its polypeptide chain and can bind with the CRH receptors bound onto the membrane (Slominski *et al.*, 2013). There are two types of receptors; CRH 1 receptor and CRH 2 receptor,

which are associated due to its binding proteins. CRH 1 receptor is the principal receptor present in human skin and show response to the exterior stress (Krause *et al.*, 2007). CRH is converted into other precursor hormones i.e. adrenocorticotrophic hormones (ACTH), α melanocyte-stimulating hormones, and others by the activation of the CRH-1 receptor in the pituitary gland. Cortisol, the stress hormone is released by the breakdown of ACTH. The production of CRH occurs in keratinocytes and then the proliferation of Propionibacterium starts (Slominski *et al.*, 2013). CRH stimulates the inflammation and releases the pro-inflammatory modulators as cytokines. It also induces lipid biosynthesis. CRH function is contradictory to testosterone and growth hormones because testosterone reduces the activity of CRH-1 and CRH-2 receptors and growth hormones utilize both receptors for the expression of mRNA. CRH also stimulates the conversion of DHEA into testosterone and induces the fats synthesis resulting in a high level of androgen and overstimulation of sebaceous glands (Art and Stewart, 2005).

Table 4. Role of Growth Hormones on the onset of acne.

Role of Growth Hormones on The Onset of Acne		
Signaling pathways	Mechanism of action	References
Tyrosine-protein kinase	Growth hormones i.e. insulin and its associated receptors produce heterodimers by its binding to tyrosine-protein kinase receptors.	(Denley <i>et al.</i> , 2005)
MAPK and P13k/Akt pathways	Insulin-like growth factor-1 (IGF-1) stimulates the proliferation, differentiation, and progression by activating this Ras-Raf-MAP kinase and the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway with various stimuli i.e. g-proteins or tyrosine kinase. Insulin and its receptors bind together to stimulate the transcription of genes and regulate the synthesis of lipids and proliferation of keratinocytes in sebocytes by following the SREBP-1 pathway.	(Downie <i>et al.</i> , 2002)
Induction of sterol response element-binding protein-1 (SREBP-1)	The most important fibroblast growth factor receptor-2b (FGFR-2b) can be downregulated with a shared common signaling cascade. IGF-1 induces the expression of genes by binding proteins to raise sebaceous lipogenesis e.g. the human genome containing promoters of different length binds to its specific transcription factor and regulate the gene expression.	(Smith <i>et al.</i> , 2006)
FGFR2b signaling transduction cascade	An FGFR-2b signaling pathway is dependent on the concentration of androgen and enhances sebocytes differentiation. IGF-1 receptors can be expressed on basal cells and regulate proliferation mostly while FGFR2b expressed on suprabasal cells, may involve in the differentiation of sebocytes.	(Smith <i>et al.</i> , 2008)

Melanocortin

Melanocortins are released into pituitary gland when conversions of proopiomelanocortin take place. This hormone is also involved in the stimulation of sebaceous glands by the action of MC receptors. Alpha melanocyte-stimulating hormone is a specialized hormone that acts as a modulator and binds to the G-protein coupled receptors on the surface of the cell. There are five different types of receptors; MC-R to MC-5R. MC-5R acts as an antagonist to suppress sebum production. While MC-1R is more active that affects the production of the sebaceous gland. Antagonists of these receptors are used to treat skin-related disorders and reduce the surplus sebum level (Zhang *et al.*, 2011). MC-1R and MC-5R that are mostly found in sebocytes and control the lipid synthesis and sebaceous gland maturation (Böhm *et al.*, 2014).

Glucocorticoid

Glucocorticoid hormones belong to a class of steroid hormones released from adrenal glands. They have an important role in glucose metabolism. Glucocorticoids diffuse on the cell membrane and they bind to the glucocorticoid receptors (GRs) and produce complexes in the presence of chaperones i.e. heat-shock proteins, results in conformational changes. Then these complexes are transported into the nucleus for transcription and then polypeptide synthesized (Nicolaidis *et al.*, 2010).

Annexins are actually regulatory proteins induced by glucocorticoids that act as mediators against inflammatory actions occurring inside the body. They can be synthesized by a signaling pathway between proteins and ligands and their association with the membrane on its target cell. The more synthesis of annexins suppresses the production

of inflammatory cytokines, in turn, several proinflammatory mediators are released to control various skin inflammatory responses (Shibata *et al.*, 2009).

CONCLUSION

Acne occurs due to the abnormal functioning of hormones. Females are more prone to this disease than males. Symptoms start in the early stages of puberty. Most fluctuations in hormonal balance occur at the stages of the menstrual cycle, puberty, and pregnancy in females. Along with hormones, bacterial activities and dead skin cells are also the major factors in acneogenesis. As it occurs in the specific cycles and stages of life, so permanent medication for this is mandatory. Although many medications are available and scientists are conducting several pieces of research, but specific and effective medication is still required.

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CONFLICT OF INTEREST

There is no conflict of interest.

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