Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol.(8) Issue(9) (2023), (105-114) **online : ISSN 2356–976x**
http://bjas.bu.edu.eg

Serum Clusterin Level in Patients with Post Adolescent Acne

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Abstract
Background: Post-adolescent acne is a distinct and increasingly prevalent dermatological concern among adults, particularly in women. Understanding the pathogenesis and contributing factors to this condition is essential for effective management. Serum clusterin, a multifunctional glycoprotein, has emerged as a potential biomarker in various systemic and dermatological disorders. **Objective:** This review article aims to comprehensively explore the role of serum clusterin in patients with post-adolescent acne. We delve into the clinical characteristics of post-adolescent acne, factors aggravating the condition, comorbidities associated with it, relevant investigations, and the multifaceted roles of clusterin in systemic diseases, inflammation, immunity, NFκB pathway, apoptosis, and dermatological diseases. Additionally, we discuss the potential clinical implications of serum clusterin levels in the context of post-adolescent acne. **Conclusions:** Serum clusterin holds promise as a diagnostic and prognostic marker in post-adolescent acne. While its exact mechanisms in the pathogenesis of acne remain to be fully elucidated, its multifunctional properties suggest that it may play a pivotal role in the inflammatory and immunological processes underlying this condition.

Keywords: Post-Adolescent Acne; Serum Clusterin; Inflammation; Biomarker.

1. Introduction

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit that affects predominantly adolescents and young adults. It is characterized by noninflammatory, open or closed comedones and inflammatory papules, pustules, and nodules. It results from androgen-induced increased sebum production, altered keratinization, inflammation, and bacterial colonization of hair follicles by cutibacterium acnes pervious known as P acne [1].

Patients with post-adolescent acne appear to represent an increasingly important population of acne sufferers. External factors do not seem to have a significant aetiological role. Two main clinical groups were identified: those with persistent acne and those with late-onset acne. A minority of women also had features of hyperandrogenicity. These patients, and those with late-onset acne, may represent a subgroup who have underlying abnormalities of ovarian, adrenal or local androgen metabolism, and require separate investigation [2].

Clusterin (apolipoprotein J) is a 75 - 80 kDa disulfide-linked heterodimeric protein associated with the clearance of cellular debris and apoptosis. In humans, clusterin (CLU) is encoded by the CLU gene on chromosome 8. CLU is a molecular chaperone responsible for aiding protein folding of secreted proteins, and its three isoforms have been differentially implicated in pro- or antiapoptotic processes [3].

It was revealed that serum (CLU) levels were higher in subjects with metabolic syndrome than in those without metabolic syndrome [4].

This review article aims to comprehensively explore the role of serum clusterin in patients with post-adolescent acne. We delve into the clinical characteristics of post-adolescent acne, factors aggravating the condition, comorbidities associated with it, relevant investigations, and the multifaceted roles of clusterin in systemic diseases, inflammation, immunity, NFκB pathway, apoptosis, and dermatological diseases. Additionally, we discuss the potential clinical implications of serum clusterin levels in the context of post-adolescent acne.

2. Post-adolescent acne

Post-adolescent acne, distinct from its adolescent counterpart, primarily affects females aged 25 and older, typically presenting with mild-to-moderate severity. This condition encompasses two subtypes: adult-onset acne and adult persistent acne. Adult-onset acne suddenly emerges in adulthood with no specific distinguishing features, while adult persistent acne refers to acne that has persisted since adolescence. Notably, chin acne tends to be inflammatory and worsens premenstrually, while sporadic acne can appear suddenly in adulthood, potentially without any apparent trigger or in association with a systemic condition. Interestingly, sporadic acne may manifest in various locations, with torso lesions being more common in adults over 60, and severe acne has been observed in individuals with chronic renal insufficiency [5]. The epidemiological data suggests that acne typically clears up by the age of 25, but

between the ages of 25 and 50, approximately 14% of individuals experience post-adolescent acne, with a higher prevalence among women. Hormonal factors, increased cosmetic use, and exposure to hot and humid environments are potential contributors to its prevalence, with 82% of cases developing later in life. Importantly, post-adolescent acne exhibits gender, age, and ethnicity-based variations in prevalence, with scarring and dyspigmentation being more common among certain ethnic groups [6].

Furthermore, the etiopathogenesis of post-adolescent acne remains a complex puzzle. Persistent acne, resembling adolescent acne, is characterized by a higher sebum excretion rate in affected adults, suggesting an underlying increase in sebum production. Multiple factors contribute to its development, including genetic predisposition, smoking, antibiotic-resistant propionibacteria, cosmetic use, and stress. While hyperandrogenism or hyperandrogenemia are implicated in some cases, the majority of patients do not exhibit endocrine disorders. Instead, hormonal changes during the menstrual cycle may trigger an altered reaction in cutaneous androgen receptors, leading to inflammatory lesions and increased sebum production. Up to 60-70% of women experience an uptick in acne lesions, particularly during the premenstrual period, highlighting the intricate interplay of hormonal fluctuations in the pathogenesis of post-adolescent acne [7].

- **Factors aggravating postadolesent acne were shown in table 1.**

Table (1) Factors aggravating postadolesent acne [8].

Factors Aggravating Post-adolescent Acne
Hormonal Factors
- Elevated Serum Testosterone Levels: Women with post-adolescent acne tend to have considerably higher serum testosterone levels, particularly during periods of low estrogen, such as near the end of the menstrual cycle. This hormonal imbalance can lead to acne flare-ups.
- Androgen Involvement: Androgens, both endogenously and exogenously derived, are implicated in the development of post-adolescent acne. High androgen levels can contribute to acne formation, and anti-androgenic therapies have been shown to improve acne.
- Underlying Conditions: Conditions like Polycystic Ovarian Syndrome (PCOS), late-onset adrenal hyperplasia, ovarian hyperthecosis, and virilizing ovarian or adrenal malignancies can cause hyperandrogenemia, exacerbating acne.
- Exogenous Factors: Anabolic steroids, testosterone supplements, and progestin-only contraceptives (containing pro-androgenic progestins) can also contribute to acne development in some individuals. However, most adults with acne have normal androgen levels and do not receive exogenous androgens.
- Proposed Mechanisms: Androgens may worsen acne by increasing the conversion of androgen precursors to active androgens within sebaceous glands and by enhancing the sensitivity of these glands to androgens.
Genetic Predisposition
- Hereditary Factors: Genetic studies, including identical twin studies and family-based research, have indicated the importance of inherited factors in acne pathogenesis. The identification of specific genes involved began in the 1990s.
- Family History: Acne predisposition may be explained by a genetic component, with a positive family history of acne being a significant risk factor. First-degree relatives of individuals with acne are more likely to experience acne themselves.
- Heritability Estimates: Studies have shown that the heritability of acne is substantial, with more than three-fold increased risk among individuals with affected first-degree family members. Twin studies also support the heritability of acne.
- Genetic Polymorphisms: Various genetic polymorphisms affecting the expression and function of genes have been investigated in relation to acne, including genes like Insulin-like growth factor (IGF1), peroxisome proliferator-activated receptor Gamma (PPARG), IL-6, and IL-1A, among others.
Diet
- Unclear Dietary Relationship: The relationship between diet and acne remains unclear, with limited high-quality evidence. Some studies have suggested a positive correlation between the consumption of certain foods, such as milk, chocolates, and salt, and the severity of acne vulgaris.
- Hormone-Containing Foods: Non-fat portions of milk contain hormones and bioactive molecules that can stimulate acne. Additionally, hyperglycemic diets can reduce levels of adiponectin, leading to increased pro-inflammatory cytokines and decreased anti-inflammatory cytokines, potentially aggravating acne.
- Chocolate and Whey Protein: Some studies have examined the impact of chocolate and whey protein

consumption on acne. While results vary, certain individuals may experience changes in acne severity when consuming these products.

Smoking

- Smoking and Acne Types: Smokers are more likely to have non-inflammatory acne, while nonsmokers are more prone to inflammatory acne. Smokers who develop acne during puberty are also more likely to experience postadolescent acne.
- Effects on Skin: Smoking can lead to significant changes in skin microcirculation, keratinocytes, collagen, and elastin formation. Nicotine, present in cigarettes, affects vasoconstriction, inflammation, and wound healing, potentially aggravating acne.
- Antioxidant Deficiency: Smoking is associated with a relative deficiency in antioxidants, which could impact sebum composition and acne development.
- Protective Effects: Paradoxically, some studies have suggested that severe acne is less likely in smokers, potentially due to the anti-inflammatory effects of smoking.

Cosmetics

- Comedogenic Ingredients: Certain cosmetic ingredients, such as lanolin derivatives (etoxylated lanolines and acetylated lanolins), isopropyl myristate, isopropyl palmitate, and certain vegetable oils, have been found to be comedogenic in animal tests. However, the comedogenic effect in humans is still a subject of debate.

Stress

- Psychological Impact: Acne severity is influenced by psychopathological variables, and stress levels have been linked to acne flare-ups, creating a vicious circle.
- Neurogenic Factors: Neurogenic variables, including emotional stress, neuropeptides, and neurotrophic factors, can influence the clinical course and inflammatory process of acne.
- Stress-Induced Mechanism: Psychological stress can activate the hypothalamus-pituitary-adrenal (HPA) axis, leading to increased glucocorticoid secretion and the production of sex hormones. These hormonal changes can promote sebaceous hyperplasia and increased sebum secretion, aggravating acne.
- CRH System and Skin: The CRH system, including CRH receptors, is expressed in sebocytes and may play a role in stress-induced exacerbation of acne by affecting immune and inflammatory processes.

Studies have shown that nonobese, nonhirsute female acne patients have higher total cholesterol and low-density lipoprotein cholesterol levels than unaffected individuals. Severe acne patients also exhibit elevated total cholesterol, low-density lipoproteins, and lichen planus values. This link between blood lipid levels and acne offers new avenues for research into acne causes and treatments. Obesity is associated with changes in skin barrier function, sebaceous glands, and sebum production. Peripheral hyperandrogenism, often seen in obesity, can lead to increased sebum production and severe acne. Weight loss and metformin use can lower insulin, androgen, and IGF levels, all of which are elevated in acne [9, 10].

Approximately 70% of female acne patients experience premenstrual flare-ups, characterized by fresh inflammatory lesions, often near the chin, in the week before menstruation. This phenomenon is attributed to premenstrual changes in sebaceous follicles and sebum secretion, possibly due to increased follicular epithelium hydration induced by estrogen. Flare-ups are influenced by hormonal changes during the menstrual cycle, including higher androgen and estrogen levels in the follicular phase and periovulation. Combined estrogen/progesterone contraceptives reduce acne by suppressing androgens and boosting sex hormone-binding globulin. Reduced progesterone levels in the latter half of the menstrual cycle may explain premenstrual acne worsening [11].

Environmental factors like atmospheric pollution, occupational conditions, temperature, humidity, and sunlight exposure can influence acne development by affecting inflammation, sebum production, and hyperkeratinization. While sunlight is generally beneficial for acne, there have been reports of acne developing after beach vacations (e.g., "acne Mallorca" in Europe and "Goa acne" in India). Morphological differences exist between adolescent and post-adolescent acne, with lesion distribution, characteristics of nodules, and the presence of retentional lesions varying between the two. Late-onset acne has fewer total lesions and a higher proportion of inflammatory lesions compared to early onset acne, with differences mainly attributed to age of onset rather than acne progression.Classification of postadolescent acne [6].

- **Classification:**

Post-adolescent acne, as classified by Capitanio et al. (2010), is divided into two categories: Papulopustular post-adolescent acne (PPAA) and comedonal post-adolescent acne (CPAA). PPAA is characterized by moderate inflammatory acne, mainly involving deep-seated, tender inflammatory papules and nodules on the lower face, jawline, and neck, with comedonal lesions typically found on the forehead and side margins. On the other hand, CPAA is marked by a prevalence of retention lesions (microcomedones and macrocomedones) with minimal inflammatory lesions. In CPAA, comedones are prominent and evenly distributed across the entire face, sparing the lower third and jawline. The widespread distribution of lesions in CPAA is a distinctive feature and can have a significant psychosocial impact, making it challenging to treat and potentially disfiguring for patients [12].

❖ **Comorbidities with post adolescent acne**

Post-adolescent acne can be associated with various comorbidities. Polycystic ovary syndrome (PCOS) is a common cause of hyperandrogenism in women, presenting with dermatologic signs like seborrhea, androgenic alopecia, and acanthosis nigricans. While persistent post-adolescent acne is linked to higher androgen levels in some individuals, no direct correlation exists between circulating androgens and acne severity, suggesting other factors like locally generated androgens or end-organ hyper-responsiveness may contribute. Other potential causes of hyperandrogenism should be considered, such as ovarian or adrenal tumors, late-onset congenital adrenal hyperplasia, and exogenous androgen ingestion, as post-adolescent acne may signal underlying endocrine abnormalities [13]. Metabolic syndrome, characterized by insulin resistance (IR), is also associated with post-adolescent acne, potentially exacerbated by high BMI, hyperglycemic carbohydrates, and insulinotropic dairy products. Thyroid autoimmunity has emerged as another factor, with evidence suggesting a link between persistent acne vulgaris and thyroid autoimmunity, as well as an increased prevalence of thyroid autoimmunity in women with post-adolescent acne, warranting consideration for endocrinologist referral and care [14].

❖ **Investigations**

Although most patients have no hormonal disturbances, screening tests should be done for diagnosis of any underlying endocrinal abnormalities**.** Patients with cutaneous hyperandrogenism, hormonal evaluation is a prerequisite for hormonal therapy. The patient should be off any OCs or any other hormonal therapy for at least 1 month before testing and the tests should be performed at the onset of menses (luteal phase). The hormones that need to be investigated for are mentioned in **Table 2 [15]**:

Table \92) recommended investigations for patients with post-adolescent acne and potential hormonal disturbances [16]:

Hormone/Parameter	Purpose and Interpretation
Testosterone (free and total)	Assess for elevated levels; >200 ng/dL may indicate androgen-secreting neoplasia.
Androstenedione	Measure early morning levels; elevated levels may suggest an adrenal source.
Dehydroepiandrosterone (DHEA)	Evaluate for adrenal origin; higher levels may prompt adrenal tumor evaluation.
17-OH-progesterone	Elevated levels (>200 ng/dl) may indicate adrenal hyperplasia or CAH.
SHBG	Assess for relative hyperandrogenism; decreased levels may lead to elevated free testosterone.
LH: FSH ratio	A ratio > 3 may indicate a hormonal imbalance.
Prolactin	Elevated levels may suggest hyperprolactinemia due to hypothalamic disease or pituitary tumor.
Serum cortisol	Evaluate adrenal function; hyperactivity may indicate adrenal neoplasia.
Fasting and postprandial insulin	Measure to assess hyperinsulinemia, which can be associated with PCOS and acne.

❖ **Treatment**

Post-adolescent acne management involves a long-lasting and well-tolerated maintenance therapy due to the skin's aging predisposition to irritation, making topical monotherapy like azelaic acid a viable option for mild to moderate cases. Treatment approaches are similar to adolescent acne and

include topical therapies such as benzoyl peroxide, salicylic acid, and antibiotics for inflammatory acne, while retinoids are used for comedonal or severe forms. Glycolic acid peels effectively target comedonal acne, while oral antibiotics are typically prescribed for papular/pustular lesions. Secondary prevention often includes retinoids to prevent recurrence, and low intermittent doses of oral isotretinoin can maintain improvement for those who did not respond well to topical retinoids [17]. Hormonal therapies like antiandrogenic oral contraceptives (e.g., desogestrel, gestodene) are an option for individuals with elevated systemic androgens, especially in cases of persistent or relapsing acne. Metformin and thiazolidinedione drugs, which improve insulin sensitivity and lower testosterone levels, can also be beneficial, particularly for individuals with PCOD. Intralesional corticosteroids are employed to treat nodular or inflammatory cystic lesions, reducing scarring and inflammation, and combination treatments like low-dose spironolactone with topical benzoyl peroxide have shown efficacy for moderate to severe post-adolescent acne [18].

3. Clusterin

Clusterin (CLU), also known as apolipoprotein J (ApoJ), complement lysis inhibitor (CLI), sulfated glycoprotein 2 (SGP-2), testosterone-repressed prostate message 2 (TRPM2), and secreted protein 40,40 (SP-40,40), is a multifunctional glycoprotein with a ubiquitous presence throughout the body. It plays diverse roles, often leading to opposing outcomes, making it an enigmatic protein with a wide range of physiological functions and widespread expression in various bodily fluids and intracellular matrices [19].

❖ **Historical background:**

Clusterin (CLU) was initially isolated from the fluid of a ram's rete testis, where Fritz (1983) identified it as a heat-stable, trypsin-sensitive protein responsible for cell aggregation [20]. This discovery led to the name "Clusterin," suggesting its potential role in cell-cell interactions. Subsequently, CLU was found to be a glycoprotein with an isoelectric point of 3.6 and a molecular mass of approximately 80 kDa. In humans, it was first described as complement lysis inhibitor (CLI) by Jenne and Tschopp (1989), a component of soluble terminal complement complexes in human serum. This CLI was later identified as identical to sulfated glycoprotein 2 (SGP2) and Clusterin, suggesting its involvement in sperm maturation. Sensibar et al. (1995) demonstrated that CLU plays a role in protecting against induced cell death, particularly reducing the cytotoxic effects of TNF-α in prostate adenocarcinoma metastatic cells [21].

❖ **Structure of clusterin (Figure 1):**

Clusterin (CLU) exists in three isoforms: a small nuclear isoform (49 kDa), a medium-sized isoform residing in the cytoplasm and mitochondria (53 kDa), and larger glycosylated isoforms cleaved in the endoplasmic reticulum/Golgi apparatus and secreted as heterodimers outside the cell (75-80 kDa). These isoforms serve different functions. In humans, a single-copy gene on chromosome 8p21–p12 generates a 2 kb mRNA that produces a 449-amino-acid primary polypeptide chain. After proteolytic processing, a 22-mer secretory signal peptide is removed, and the remaining chain is cleaved into alpha and beta chains. The molecule features five disulfide bridges connecting the alpha and beta chains, forming a structure with amphipathic alpha-helices and coiled-coil alpha-helices flanking the core. Around 30% of the mature protein's mass is accounted for by N-linked carbohydrates attached at six glycosylation sites. Additionally, a nuclear localization signal and a potential dinucleotide-binding site have been identified in CLU's structure [3, 22].

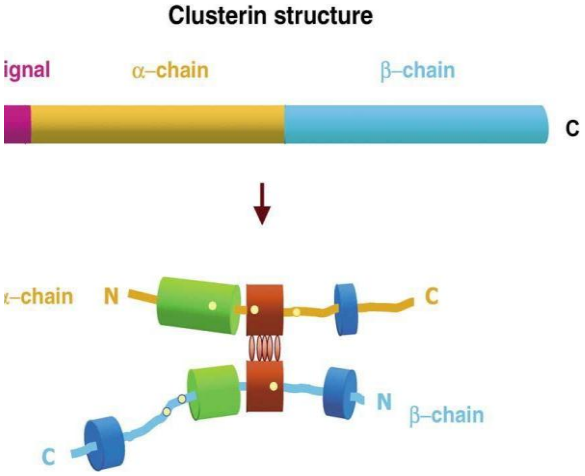

Fig. (1) Schematic representation of the structure of human clusterin [3].

The precursor polypeptide chain (top) is cleaved proteolytically to remove the 22-mer secretory signal peptide (magenta) and subsequently between residues 227/228 to generate the α (orange)- and β(light blue)-chains. These are assembled in anti-parallel to give a heterodimeric molecule (bottom) in which the cysteine-rich centers (red) are linked by five disulfide bridges (red ellipses) and are flanked by two predicted coiled-coil α-helices (green) and three predicted amphipathic α-helices (dark blue). The six sites of N-linked glycosylation are indicated as yellow spots [3].

❖ **Role of clusterin in systemic diseases:**

Clusterin (expression was investigated in many autoimmune diseases where it was found to be low in SLE, rheumatoid arthritis and psoriasis, while it was found high in diabetes mellitus type II, dermatomyositis and Alzhimer"s dementia [23].

❖ **Clusterin and cardiovascular diseases:**

Low plasma levels of CLU were found to be strongly linked with the presence of coronary heart lesions in patients with Kawasaki illness, suggesting that this protein could be a helpful biomarker for the disease. CLU serum levels were shown to be higher in healthy people than in patients with diabetes, myocardial infarctions, or coronary artery disease [24].

Clusterin (suppresses the progression of autoimmune myocarditis and protects the heart from long-term damage. In addition, serum CLU levels are much higher in patients with type 2 diabetes and heart failure [25].

❖ **Clusterin and Chronic Liver Failure:**

Infectious disorders, such as hepatitis B, are also affected by CLU activity. The stress of hepatitis C virus infection, which alters glucose control, causes CLU. By stabilising the core and NS5A components of the hepatitis B virus, the chaperone protein aids in viral assembly [25].

❖ **Clusterin and neuropsychatric diseases:**

Previous research has found that people with Alzheimer's disease had higher CLU levels in their blood, and that CLU levels in blood correspond with faster cognitive loss in Alzheimer's patients [26].

❖ **Clusterin and metabolic dysfunction:**

Clusterin (levels were lower in subject with low HDL and high triglycerides, Key components of the metabolic syndrome, Insulin resistance and obesity are hallmarks of type 2 diabetes and the metabolic syndrome, which confer an increased risk of cardiovascular disease. Previous studies suggest that the protein cargo of HDL makes important contributions to the lipoproteins cardioprotective effects [26].

Clusterin (levels in HDL are lower in men with reduced insulin sensitivity, higher BMI, and an unfavorable lipid profile. Furthermore, the possibility that CLU depletion contributes to the loss of HDL's cardioprotective properties. So, circulating CLU may become a marker of metabolic dysfunction [27].

Secreted CLU is increased by cellular stress and serves a protective function in cell survival, whereas nCLU appears to be connected with cellular death via apoptotic signalling. Other apolipoproteins, amyloid peptide, complement factors, immunoglobulins, megalin, leptin, TGF-receptor, and stressed unfolded proteins are also possible binding ligands for sCLU. The role of secreted CLU in plasma in endothelial function and metabolic control has been acknowledged, but the exact processes are unknown. Furthermore, animal models in which CLU mRNA expression has been knocked down or over-expressed have not adequately demonstrated its role in the metabolic and cardiovascular systems, as shown in Table (2) [28].

Table (2) CLU Hypothetical Mechanisms in Chronic Diseases [28].

Diseases	CLU expression	Hypothetical mechanism	References
Lupus	Low	Low complement inhibition	(Moll *et al.*, 1998), (Newkirk *et al.*, 1999)
Rheumatoid arthritis	Low	Apoptosis Regulator of NF-κB	(Connor *et al.*, 2001), (Devauchelle *et al.*, 2006)
RA model	Normal	Autoantigen?	(Kuhn *et al.*, 2006)
Juvenile dermatomyositis	High	Unknown	(Chen *et al.*, 2008)
Diabetes	High	Marker of disease Protector or pathogenic regarding the subcellular localization	(Calvo *et al.*, 1998b), (Savkovic *et al.*, 2007)

❖ **Role of clusterin in inflammation**

Clusterin has diverse roles in inflammation, with studies revealing its involvement in various inflammatory processes. It has been associated with the severity of asthma in children, suggesting its relevance in asthmatic pathology. Conversely, overexpression of clusterin has been observed in patients with osteoporosis, particularly in degenerating muscular tissues co-localized

with IL6 overexpression, indicating its potential role in inflammatory myoblast degeneration. Silencing clusterin has been proposed as a means to down-regulate the inflammatory response responsible for muscle atrophy in osteoporosis [29]. Moreover, clusterin has been linked to obesity, systemic inflammation, and cardiovascular risk, as adipocytes secrete it in response to a high-fat diet. This overexpressed clusterin may contribute to insulin resistance, gluconeogenesis, and glucose absorption, playing a significant role in the development of obesity, cardiovascular disease, and diabetes. Conversely, clusterin has been reported to improve endothelial dysfunction in diabetic patients by inhibiting mitochondrial fragmentation and potentially blocking AMPK signaling. These diverse roles highlight clusterin's complex involvement in inflammatory processes and metabolic disorders [25].

- **Clusterin and immunity**

Clusterin plays a significant role in the immune system, particularly in the context of dendritic cells (DC). DCs are essential antigen-presenting cells that activate naive T cells and support local immune responses. During DC maturation, CLU expression increases significantly, and given the crucial role of DCs in both innate and adaptive immunity, understanding the interplay between CLU and DCs is vital. DCs express various receptors, including toll-like receptors, Fc gamma receptors (FcγR), and lectins. FcγRs are essential for linking humoral and cell-mediated immunity, and the balance between activating and inhibitory FcRs affects immune complex-mediated inflammation. An imbalance in T helper cell responses, such as Th-1, Th-2, and Th-17, can lead to various immune-related conditions, and CLU expression has been linked to these responses, with Th-17 cells showing lower CLU expression in certain autoimmune conditions [30].

- **CLU: a complement inhibitor.**

Clusterin serves as a complement inhibitor in the complex system of complement proteins that play roles in both host defense and autoimmune conditions. Complement regulatory proteins like CLU and vitronectin bind to the membrane attack complex (MAC) and prevent cytolysis, which is the disruption of pathogen or target cell membranes. In conditions like systemic lupus erythematosus (SLE), where complement deficiency can lead to disease development, a significant decrease in serum sCLU is observed. Low sCLU levels are associated with various SLE symptoms, including skin ulcers, hair loss, proteinuria, and arthritis, suggesting that individuals with insufficient sCLU may struggle to control antibody-mediated inflammation at sites of apoptosis where autoantigens are exposed [31].

- **Role of clusterin in NFκB pathway:**

Clusterin (CLU) plays a significant role in the nuclear factor kappa B (NF-κB) pathway, a critical transcription factor involved in the regulation of genes encoding immune and proinflammatory mediators. NF-κB is crucial in cellular responses to various stimuli, and its aberrant activation can contribute to prolonged inflammatory processes. In the context of lichen planus (LP), NF-κB expression patterns in oral and cutaneous LP may explain the different clinical courses of these variants, with oral LP often being more resistant to treatment. Additionally, there are two isoforms of CLU, with isoform 2 (soluble clusterin, sCLU) being overexpressed under cellular stress conditions. sCLU has a protective role against apoptosis and is associated with various cellular responses, including the modulation of the NF-κB pathway, making it a key player in cellular responses to inflammation and various insults [32].

- **Role of clusterin in apoptosis**

Clusterin (CLU) plays a crucial role in preventing cell death in response to various stressors, including cytotoxic chemotherapy and hormonal deprivation such as androgen or estrogen reduction. This cytoprotective function is attributed to its chaperone-like activity, which helps maintain cell survival. sCLU, one of its isoforms, stabilizes the interaction between Ku70 and the proapoptotic protein Bax. By doing so, sCLU prevents Bax from binding to the mitochondrial outer membrane and exerting its proapoptotic effects. Elevated sCLU levels may enhance tumorigenesis by inhibiting Bax's proapoptotic activities. Additionally, sCLU's protective role against TNF-α-induced cell death suggests that it may also act as a suppressor of cellular immune responses, further underlining its impact on cell survival mechanisms [33].

Figure 2

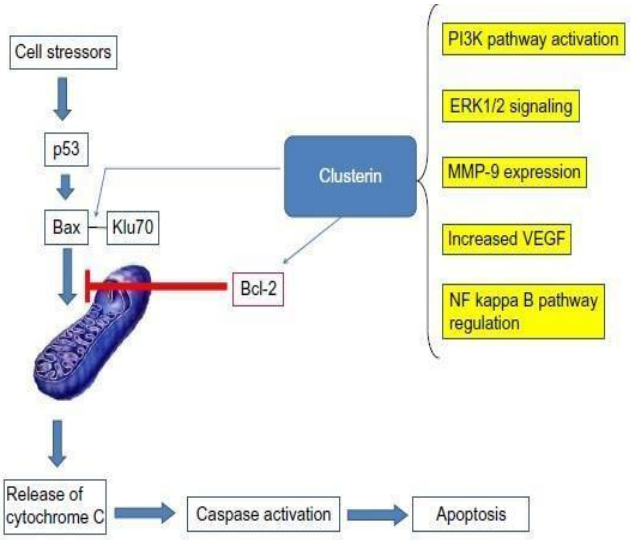

Fig.(2) Mechanisms of clusterin action [33].

Notes: On the left side, two antiapoptotic mechanisms are described (p53-dependent and p53-independent). On the right side, other protumor mechanisms are not directly related with apoptosis ***Koltai, (2014)***. Abbreviations: ERK, extracellular signal-regulated kinase; MMP, matrix metallopeptidase; NF, nuclear factor; PI3K, phosphatidylinositol 3- kinase; VEGF, vascular endothelial growth factorRole of clusterin in dermatological diseases [33].

- **Clusterin and psoriasis**

Clusterin mRNA levels were significantly lower in lesional psoriatic skin when compared to normal skin. Clusterin has an antiproliferative effect on human KCs, and clusterin gene expression is lowered in psoriatic skin that is hyperproliferative. This shows that clusterin is a negative growth signal that regulates the growth of KCs [34].

- **Clusterin and collagen diseases**

Newkirk et al. (1999) concluded that Lowered CLU levels could be involved in the pathogeneses of SLE on account of decreased protective effects [35]. ***Yanaba et al. (2012)*** suggest that the administration of CLU could be a possible treatment in patients with systemic sclerosis (SSc) who has severe digital ulcers and pulmonary arterial hypertension (PAH) [36].

- **Clusterin and chronic spontaneous urticaria**

Serum CLU levels are higher in patients who have a positive autologous serum skin test result, and it serves a variety of roles including influencing the complement system, regressing angiogenesis, and clearing bioactive cell debris. As a result, serum CLU could be used as a predictive indicator for antihistamine responsiveness in patients with choronic spontaneous urticaria [37].

Clusterin and mycosis fungoides (MF)

Clusterin (is commonly expressed in MF. CLU expression correlates with clinical stage, the histologic type of MF lesion, and greater numbers of large cells in MF. Knowledge of clusterin expression in MF specimens may be useful in the differential diagnosis of MF in large cell transformation involving skin [38].

4. Conclusions

Serum clusterin holds promise as a diagnostic and prognostic marker in post-adolescent acne. While its exact mechanisms in the pathogenesis of acne remain to be fully elucidated, its multifunctional properties suggest that it may play a pivotal role in the inflammatory and immunological processes underlying this condition. Further research is warranted to uncover the precise interactions between serum clusterin and post-adolescent acne, potentially paving the way for novel diagnostic and therapeutic strategies.

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