Positive Impact of Fish Oil on Diabetic and Hypercholestrolemic Skin Disorders

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Abstract

The integumentary system is soft a highly organized structure of epidermis and dermis, which is tightly conjugated with each other. The epidermis represents the outer covering and is formed of epidermal layers, Langerhan, Merkel cell, melanocytes and immune cells travestied by hair follicles. Sweat glands are infiltrated throughout the integumentary layers, including fibroblast, and mast cells. Hair follicles with complex structure, characterized with their complicated structures and their internal structure contains immune cells during differentiation and possesses sebaceous glands for sebum production-the antibacterial components. A calcium and potassium ion in close association with lipid and cholesterol represents the main elements in epidermal permeability. Keratinocytes represent the elementary part for cholesterol and lipid formation. Cholesterol overload led to altered cell structure, hair follicle formation, integrity of blood vessels and dermal collagen. It caused deformation of hair follicles and disrupted epidermal structures and keratinocyte formation leading to impairing keratinization. Fish oil represents one of the main food additives having biomedical importance. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) represent their main components and play a great role in promoting permeability, growth and differentiation of the stratum corneum and inhibition of proinflammatory cytokines (tumor necrosis factor-α, interferon-γ, and interleukin-12 which improve the diabetic and hypercholesterolemic complications

Keywords: Skin; Diabetes; Cholesterol overload; Fish oil

Abbreviations

AGEs: Advanced Glycation End Products; BL: Basal Lamina; BMP: Bone Morphogenic Protein; CDPX2: Conradi-Hünermann-Happle Syndrome; CHILD: Congenital Hemidysplasia with Ichthyosiform erythroderma and Limb Defects; CTS: Connective Tissue Sheath; DP: Dermal Papilla; DHC-7: Dehydrocholesterol-7; ED: Epidermal Dermal junction; EPU: Epidermal Proliferative Unit; EDA: Ectodysplasin; ER: Endoplasmic Reticulum; HFs: Hair Follicles; (HMG)-CoA: Hydromethylglutaryl Coenzyme A; HDL: High Density Lipoprotein; HC: Hair Cortex; IRS: Inner Root Sheath; IF: Intermediate Filament; K: Keratinocytes; LDL: Low-Density Lipoprotein; LEF1: Lymphoid Enhancer-Binding Factor-1; MC: Mast Cells; MMPs: Matrix Metalloproteinases; ORS: Outer Root Sheath; UVR: Ultraviolet Radiation; S-CoA: Succinyl-CoA; SC: Stratum Corneum; SGl: Sebaceous Gland; SG: Stratum Germinativum; Shh: Sonic hedgehog; TRPV3: Transient Receptor Potential Channel; TA: Transit Amplifying; TGFβs: Transforming Growth Factors β; VCAM-1: Vascular Cell Adhesion Molecule

Introduction

Normal skin

Human skin cover body surfaces and protects all body organs against environmental stress (temperature, electrolyte/fluid balance, chemical) and microbial infection [1]. It is composed of epidermis, dermis, and subcutaneous tissue.

Epidermis: The epidermis is a non-vascularized multilayered stratified squamous epithelium, renewed throughout the life by the cornification and keratinization process. Leukocytes such as Langerhans cells and T cells in the epidermis and macrophage and mast cells in the dermis are the main components in mouse skin. Leukocytes are detected within or around hair follicles (HFs) which represent a reservoir of leukocyte populations in the skin [2].

The outermost Stratum corneum is a cornified layer of multilayered sheets of soft and hard keratin. The *S. granulosum*, a 3-5 sheets granular layer of keratinocytes producing keratohyalin granules involving in keratinization. Keratinocytes maintain epidermal homeostasis [3] as well as their cytoplasm is rich in keratohyalin filaments (8-15 nm) which form the cytoskeleton elements. Merkel cell and melanocytes are main elements within stratum germinativum [4]. Aged and photo-aged skin exhibited a cholesterol-dominant barrier, while atopic dermatitis is associated with ceramide-dominance and a dominance of free fatty acids is associated with psoriasis [5].

The epidermal-dermal junction is a highly dynamic and complex structure that is important in the regulation of cell adhesion, differentiation, and motility; in the transmission of extracellular signals and growth factors; and in the formation of permeability barriers. It is facilitated the proliferative capacity of the epidermis. It is composed of four components including the basal cell plasma membranes with its hemidesmosomes, electron lucent lamina lucida, basal lamina and sub-basal fibrous components [6,7]. The epidermal basement membrane is also rich in proteoglycans and other proteins that act as molecular sinks for growth factors, such as TGFβs, which restrict epidermal proliferation, and TGFα/EGFs and insulin growth factors [8].

Dermis: The dermis is located under the epidermis and is attached to it by the dermo-epidermal junction that gives skin
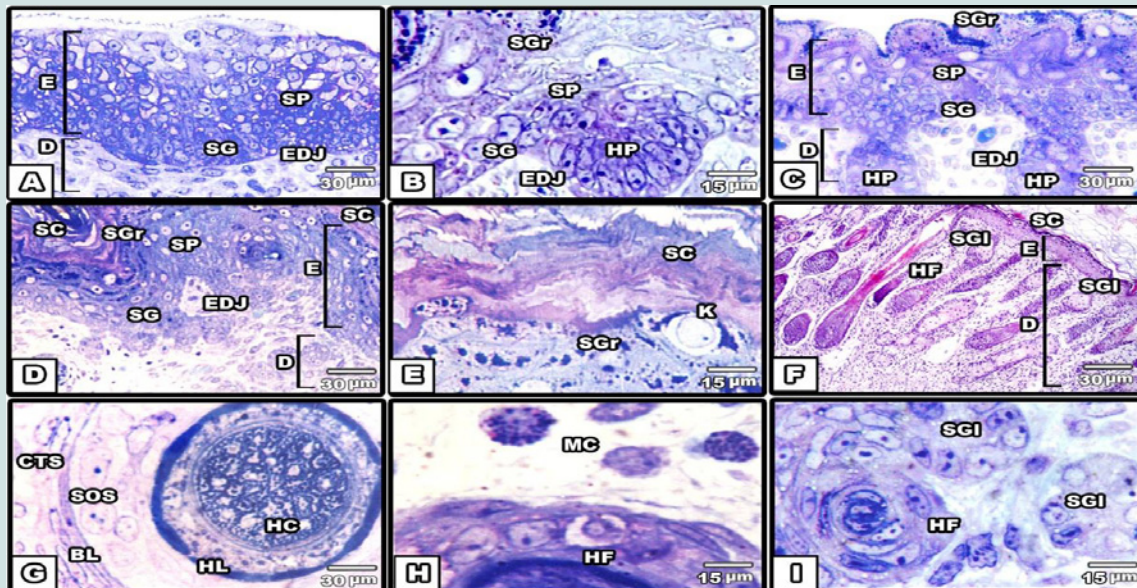
Figure 1: Photomicrographs of semi thin section of skin during prenatal development of rat. A) 13 d-old prenatal showing primitive epidermis with stratum germinativum (SG) and stratum spinosum (Sp) as well as primordium hair peg. B) and C) 15 d-old prenatal showing stages of hair follicles. Stratum granulosum (SGr) with keratohyalin granules and keratinocytes. D) 19-d-old prenatal showing development of stratum corneum (SC) and epidermal-dermal junction (EDJ). E) and F) 19-d-old prenatal showing stages of hair follicles with keratinization of inner root sheath (HF) and presence of sebaceous glands (SGl). G) 19-d-old prenatal showing stages of cross sections of hair follicles characterized by connective tissue sheath (CTS), basal lamina (BL), surface outer root sheath (SOS), Henle´s layer (HL) and keratinized inner root sheath (KZ) and hair cortex (HC). H) 19d-old prenatal showing aggregation of mast cells around hair follicle. I) 19 d-old embryo showing sebaceous gland (SGl) attached to hair follicles [9,11].

enhanced mechanical stability and form niches required for activating proliferation and differentiation of keratinocyte for healing of skin appendages (Figures 1 and 2) [9].

Dermal connective tissue composed of extracellular matrix proteins such as collagen, elastic fibers, fibronectin, glycosaminoglycans, and proteoglycans [10]. Dermal papillae are present at the base of hair follicles forming a dense extracellular matrix which undergoes extensive changes in concert the hair cycle. A presumptive papilla is one of hair follicle formation and it is probable that the component cells have an inductive effects in the genesis of hair follicles in the embryo [9,11] (Figure 1).

Hair follicle: Hair follicle morphogenesis begins early in embryonic development as dermal cells populate the skin, and signals from the epithelium induce the formation of dermal papillae (DP), the mesenchymal component of the hair follicle. Epidermal invagination form the primordium of hair placode followed by differentiation and down growth forming the hair germs (Figure 1) and then hair pegs. The follicle cells are highly proliferated especially in root region. At birth, the hairs emerged the skin surface, and the sebaceous gland (SG) cells become established in the upper segment of the root (Figure 2) [9,11].

The hair follicle undergoes cyclic changes and regeneration during life. Matrix cells proliferated rapidly during the growth (anagen) phase of the cycle but then suddenly undergo apoptosis. During anagen, the follicle regenerates, and required a reservoir of follicle stem cells [12] (Figure 3).

Sebaceous glands are present closely to the hair follicles forming a pilosebaceous unit. It is located in the upper portion of the hair follicle. Human sebum composed of cholesterol, cholesteryl esters, squalene, fatty acids, diglycerides and triglycerides, and wax esters [13]. The hair follicle (HF) and the sebaceous gland (SG) constitute two closely associated integral parts and contributed to biological and physiological function of mammalian skin [14].

Mast cells are important modulators of hair follicle cycling, specifically during anagen development. The distribution of mast cells in the skin varies in its distribution located mainly close to the blood vessels, smooth muscle cells, hair follicles, and nerve ending [15]. Mast cells are capable of the synthesis of a large number of pro- and anti-inflammatory mediators, including cytokines, growth factors and bioproducts of arachidonic acid metabolism[16,17]. The number of mast cells in the skin of the rat increases from the 17th day of the embryonic period until parturition and especially around the hair follicle pulp. The dermal area is rich in blood vessels. Heparin was found to release by mast cells at normal concentration modulate growth and differentiation of matrix metalloproteinases [18,19].

Lipid and cholesterol metabolism: Lipids play a main role in the maintenance of skin structure and function. Stratum corneum is composed mainly of ceramides, cholesterol, and free fatty acids which promote cell permeability [20]. Cholesterol is originated in the epidermal keratinocytes, and promotes cornification of stratum corneum in the late stages of epidermal differentiation [21].

Role of Diabetes & Hypercholesterolemia on Skin

Diabetes mellitus is a heterogeneous group of disorders characterized by chronic hyperglycemia and deficiency in the production and secretion or action of insulin, which leads to severe complications [22]. Obesity and diabetes are considered chronic
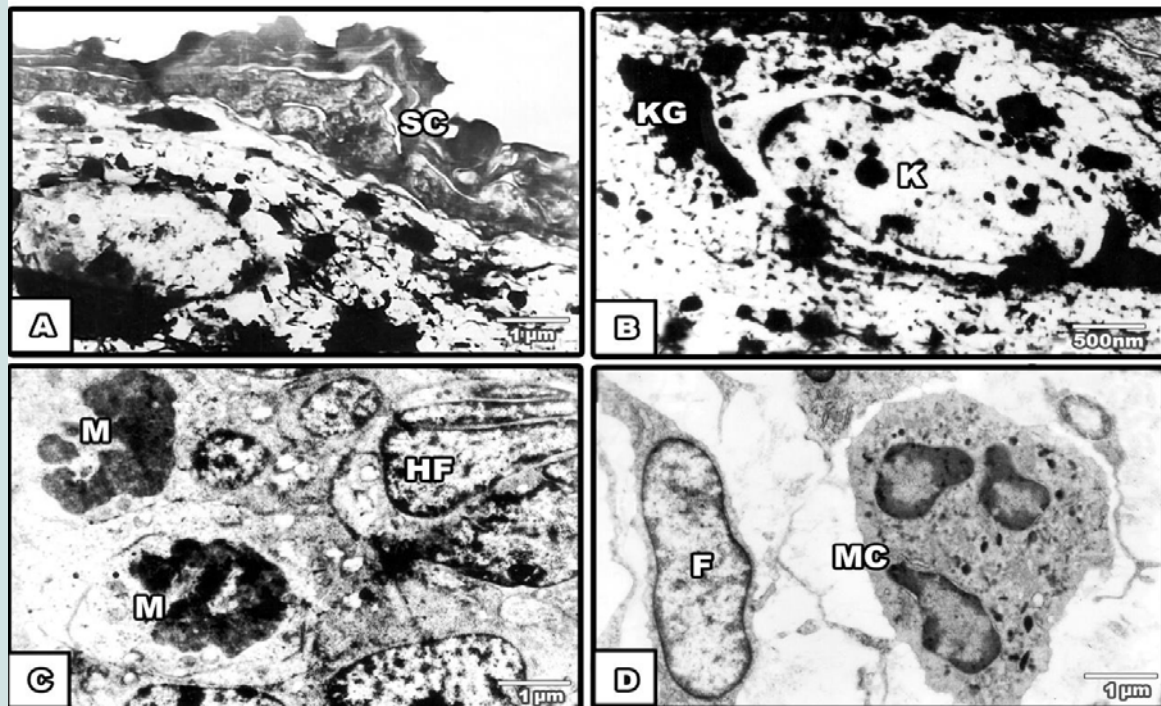
Figure 2: Transmission electron micrographs of skin of 19 d-old rat embryo. A) and B) Epidermis showing stratum granulosum and stratum corneum. Stratum granulosum showing showing keratinocytes (K) and keratohyalin granules. C) Hair follicles (HF) with grouping macrophages (M). D) showing fibroblasts (F) and mast cell (MC) [9,11].

inflammatory diseases, largely due to the inflammatory cells in white adipose tissue -including macrophages [23], B cells [24] and eosinophils [25] which promote cell-cell interaction, by releasing cell growth factors within adipose tissue. Diabetic rat showed apparent thinning of skin epidermis [26] and dermis associated with numerical reduction of mast cells [27], as well as decreased extracellular components of laminin, fibronectin and collagen [28]. There was a marked reduction of basal cell proliferation, epidermal DNA and stratum corneum turnover [29].

Perez and Kohn reported several skin disorders in diabetes mellitus such as necrobiosis lipoidica, diabetic dermopathy, diabetic bullae, yellow skin, eruptive xanthomas and perforating disorders [30]. scleredema diabeticorum is a skin complication of diabetes with deposits of collagen and aminoglycans in the dermis. Type 1 or II diabetes led to the development of scleredema in more than 50% of cases [31]. Several studies confirmed that the rates of elevated total cholesterol level and low-density lipoprotein (LDL) was reported in diabetic patients [32,33] and experimental animals [34]. Diabetic patients exhibited 2- to 6-fold increase of atherosclerosis [35] and contributed mainly to increase of cholesterol synthesis [36]. Fahien and MacDonald reported that succinate esters are potent insulin secretagogues through the generation of succinyl-CoA (S-CoA) which stimulated the formation of hydromethylglutaryl (HMG)-CoA, and mevalonate-biosynthetic precursors of cholesterol [37]. Several authors have shown that cholesterol absorption is decreased and that cholesterol biosynthesis is increased in diabetes [38,39].

Following studies the skin of diabetic mice and human patients, Bermudez et al. reported down-regulated expression of genes involved in collagen synthesis in murine diabetic skin [40]. These findings may illustrate the delay of wound healing. Both diabetes & atherosclerosis may interfere with skin microcirculation [41]. By accelerating vascular permeability [42], alterations in erythrocyte velocity [43], sequestration of leukocytes in the microcirculation [44]. These alterations are mainly described as the result of hyperglycemia and increased accumulation of advanced glycation end products [45].

Beer et al. reported that diabetes increased vascular complications such as increased levels of plasma von Willebrand factor, tissue factor pathway inhibitor and the soluble form of thrombomodulin [46,47].

Although hypercholesterolemia represents a major public health problem, yet no available studies are concerned with skin disease except recently by Pietroleonardo and Ruzicka [48] who mentioned that familial hypercholesterolemia was associated with multiple types of xanthomas occur, such as tendinous, tuberous, subperiosteal, and xanthelasma as well as multiple xanthomas skin lesions in fingers, hands, elbows, knee, and feet. The matrix metalloproteinases (MMPs) are a family of zinc-binding endopeptidases capable of degrading extracellular matrix (ECM) components including collagen and proteoglycans [49]. MMPs are also involved in modulation of growth factor and cytokine function [50]. In human skin, various MMPs are expressed in several dermal diseases or in cutaneous wound healing [51,52]. MMP-9 is produced by keratinocytes, leukocytes, macrophages, and epithelial tumoral cells [53]. MMP-9 also contributes to keratinocyte hyperproliferation and progression to invasive cancer in a mouse model of oncogene-derived skin carcinogenesis [54].
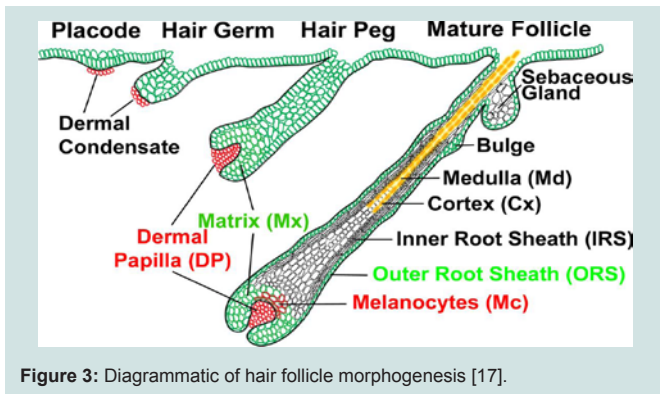
Figure 3: Diagrammatic of hair follicle morphogenesis [17].

Hypercholesterolemia exhibited a massive reduction of matrix metalloproteinases (MMPs) expression of human skin through ERK and JNK-dependent pathway [55]. Fetal skin disease of diabetic and hypercholesterolemic mother is a public health important disease as a result of widespread of both diseases with different maternal complications. The author reported that maternal diabetes or hypercholesterolemia enhanced deformations of fetal skin including retarded cornification of epidermis and differentiation of hair follicles of 15 and 19 days fetuses were following light, scanning (SEM) and transmission electron microscopy (TEM). Degeneration of stratum granulosum layer in consistent with reduction of keratinocytes was observed by reduction of cornification. Stratum germinativum and spinosum were altered and associated with massive degeneration of hair follicles. TEM illustrated deterioration of keratinocytes with apparent reduction of keratohyalin granules, the main element of stratum corneum formation as well as dramatically altered the differentiation of both stratum germinativum and spinosum cells contributed for genesis of hair follicles [56].

Ichthyosis is one of the skin disease resulted from deficiency of cholesterol in cell membranes, coupled with the accumulation of toxic sterol precursors, which impaired epidermal barrier function [57]. Cholesterol crystal embolism or atheroembolism is a disease associated with a high mortality and characterized by swelling of the venules due to obstruction of blood capillaries [58].

Mast cells (MCs) are inflammatory cells localized mainly in the dermal region where pathogens, allergens, and other environmental agents present [59].

Fish-Oil and Skin Diseases

Fish oil composed mainly of eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA; 22:6 n-3. Omega-3 and -6 PUFAs are important components promoting cell integrity, development, maintenance, and function. Docosahexaenoic acid (DHA) showed a potent anti-inflammatory properties and high significance role in improvement of Alzheimer's disease, macular degeneration, Parkinson's disease, and other brain disorders [60]. Omega-3 fatty acids inhibited arachidonic acid synthesis and incorporation into phospholipids, decreased platelet production of thromboxane A, (TXA,), a potent vasoconstrictor and inducer of platelet aggregation, and increased production by platelets of TXA. EPA is used for synthesis of prostaglandin I, (PGI,), a potent vasodilator and inhibitor of platelet aggregation [61].

Experimental dogs received 220 mg/kg of a fish oil supplement once daily for 30 days revealed increased level of serum n-3 polyunsaturated fatty acids as well as increased circulating concentration of adiponectin in healthy non-obese dogs [62].

Dietary fish oil facilitated incorporation of PUFA (Omega-3 fatty acids) in epidermal phospholipids and the epidermal levels. Epidermal phospholipids are conjugated with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) forming 15-hydroxyeicosapentaenoic acid (15-HEPE) and 17-hydroxydocosahexaenoic acid (17-HDoHE). These components caused apparent inhibition of leukotriene [63,64].

There were apparent depletion of type I tropocollagen, COL1A1 mRNA, hyaluronan, and hyaluronan synthase (rhas) 2 mRNA in Sprague-Dawley rats fed on high fat diet. These may interfere with dermal structure and function [65]. Oral administration of high level of omega-3 fatty acids significantly reduced the severity of dermatitis and the thickening of epidermis/dermis in a NC/Nga murine atopic model via decrease the production of interleukin (IL)-4, IL-5 and IL-13 in a dose-dependent manner, as well as mRNA expression of their genes, in activated MC/9 mast cells and bone marrow-derived mast cells [66].

Fish oil administrations were also associated with improvement of atopic dermatitis, psoriasis, acne vulgaris, systemic lupus erythematosus, non-melanoma skin cancer, and melanoma. Their improvements involve promoting of the permeability, maturation and differentiation of the stratum corneum and inhibition of proinflammatory cytokines (tumor necrosis factor-α, interferon-γ, and interleukin-12), inhibition of lipoxygenase and promotion of both wound healing, and apoptosis in melanoma cells [67,68].

Dietary intake of fish oil led to marked improvement of cutaneous nerve conduction velocity in diabetic rat [69]. Diabetic mice received menhaden oil or resolvin D1 (metabolite of docosahexaenoic acid) revealed neurite outgrowth of dorsal root ganglion neurons [70] and ameliorated innervation and sensitivity of the skin of diabetic rats [71]. Dietary intake of vegetable oils, poultry, and fish and seafood was associated with improvement of microvasculature of skin of healthy subjects [72].

Fish Oil and Leptin and Adiponectin

Adipose tissue secretes a large number of hormone-like peptides called adipokines such as leptin and adiponectin [73]. Both adiponectin and leptin promote various biological functions and could play an important role in lipid and glucose metabolism [74]. Leptin, is a 16 kDa anti-obesity hormone containing 167 amino acids, produced by adipocytes. Its receptor was expressed in epidermal cells of human and mouse skin. Topical administration of leptin significantly promoted wound healing, increased angiogenesis in dermis and activated proliferation and differentiation of epidermal keratinocytes [75]. Leptin protein expression was significantly higher in both diabetic and non-diabetic foot ulcers [76].

Adiponectin, recognized as a metabolic mediator of insulin sensitivity. Mice with adiponectin deficiency showed severe psoriasiform skin inflammation with enhanced infiltration of IL-17-producing dermal Vγ4+γδ-T cells [77].

Rats fed on fish oil exhibited significant increase of IL-1α and

plasma insulin [78]. Omega-3 fatty acids of marine origin exhibited strong hypolipidemic associated with a significant reduction of plasma insulin levels without changes in glucose tolerance [79].

Adiponectin is derived from adipose tissue and exhibited anti-inflammatory and antiatherogenetic effects and improve insulin secretion in rodents [80] by increasing hepatic insulin activity [81]. Its plasma concentrations are depleted in obese and insulin-resistant individuals, suggesting that these insulin-sensitizing effects may extend to humans [82]. Diet rich in fish oil improved the hyperlipidemic profiles and glucose homeostasis of rat fed on either a ketogenic diet [83] or fructose-rich diet [84] or sucrose rich diet [85].

Fish oil supplemented long-term rats fed on sucrose-rich diet for two improved the depletion of plasma leptin and adiponectin levels, insulin secretion, dyslipidemia, and adiposity [86]. Also, mice administered fish oil for 15 days possessed increase plasma adiponectin concentrations two- to threefold and their plasma level remain stable twofold higher for 7 days after replacement fish oil by the safflower oil diet [87].

Fish Oil & Reactive Oxygen Species

As we know that type I diabetes is a result of destruction of the pancreatic beta cells responsible for producing insulin. In humans, B cell destruction is apparently mediated by white cell production of active oxygen species. By the way, induced diabetes in animals by either the drugs alloxan or streptozotocin; results in the production of active oxygen species [88]. Lipid peroxidation and lipid-derived oxidized products have been reported in hypercholesterolemia. The levels of lipid- and water-soluble antioxidants were decreased comparing with increased oxidation of lipid peroxide and LDL [89].

Both obese and obese diabetic patients exhibited apparent increase of oxidative stress manifested by elevated level of plasma MDA (end product of lipid peroxidation) with increased level of plasma dicarbonyl comparing with depletion of glutathion and super oxide dismutase [90]. Obese and non-obese patients with acne vulgaris exhibited apparent increase of serum malonadialdhyde and a decrease of β-carotene, vitamins A, E and C and the activity of platelet monoamineoxidase [91]. There are several mechanisms by which obesity produces oxidative stress. One of it, the role of mitochondrial and peroxisomal oxidation of fatty acids, which involved liberation of ROS via oxidation reactions, while another is over-consumption of oxygen, which generates free radicals in the mitochondrial respiratory chain. High fat diets led to liberation of ROS through depletion of the activities of the antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [92]. ROS such as hydrogen peroxide and superoxide are generated within the mitochondrial inner membrane, by leakage of the mitochondrial electron transport chain and rapidly react with oxygen to form free radicals [93].

Fish oil is the major source of omega-3 which composes of long-chain eicosapentaenoic (EPA) and docosahexaenoic (DHA) fatty acids. FOD significantly decreased the number of Fc receptor-negative dendritic cells in cytospin-treated islets isolated from diabetic mice [94,95].

Eicosapentaenoic and docosahexaenoic acid supplementation exhibited increase of the high-density lipoprotein cholesterol and depletion of low density lipoprotein *in vitro* [96] and prevent lipid peroxidation [97,98] and increase oxidative defense glutathione reductase and glutathione peroxidase activities and blood glutathione levels in rabbits [99].

Rabbits fed a high cholesterol diet and fish oil supplementation promoted lipid peroxidation via decrease malondialdhyde and increased superoxide dismutase, which reflected a reduced free radical generation during a short-term coronary occlusion [100]. *In vitro* studies of endothelial cells revealed that Eicosapentaenoic acid decreased the glucose-mediated inhibition of nitrous oxide production [101]. Dietary omega-3 fatty acids increased SOD activity, NO levels and decreased TBARS [102].

Immuno staining of neonatal cutaneous sections revealed that antioxidant enzymes (catalase, SOD2, gluthatione peroxidase-1 (GPx)) and ROS are localized predominantly to the epidermis. Keratinocyte subpopulations showed the lowest levels of antioxidant enzymes [103].

Diabetic rats supplemented fish oil elevated arachidonic acid (omega-6) in cell membrane phospholipids resulting in a reduction in free radicals production [104].

The authors finally concluded that diabetes and or hypercholesterolemia altered skin structure and function and fish oil-supplementation scavenge the free radicals and skin structure and function of rats subjected to diabetes and or hyper cholesterolemia.

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