Milk consumption: aggravating factor of acne and promoter of chronic diseases of Western societies

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Introduction
Many chronic diseases that are common in Western societies including coronary heart disease, diabetes, arterial hypertension, obesity, dementia, and atopic diseases are strongly influenced by dietary factors. In countries with Western lifestyles, acne, for instance, is epidemic among young people, affecting 79–95% of adolescents, which suggests that an environmental factor may be the cause [1]. Consumption of cow’s milk and dairy products containing cow’s milk is one of the pillars of the Western diet. Results from the American Growing Up Today study with 4,273 boys and 6,094 girls aged 9–15 years, showed a significant correlation between the consumption of milk and acne [2, 3]; the correlation was particularly strong in boys who drank low-fat milk [3]. In contrast, another study reported that not a single case of acne was found among the 1,200 Kivavan inhabitants of Papua New Guinea or the 115 Aché hunters and gatherers of Paraguay who do not drink milk or consume dairy products [1]. These results suggest that milk consumption is a contributing factor in the acne seen in Western industrialized nations.

Milk is a complex fluid that developed over the course of mammalian evolution. Its primary function is to support growth and cell proliferation. The following describes the biochemical effects of milk consumption on physiological insulin and IGF-1-mediated signal transduction in human beings. Milk not only negatively influences growth, atherosclerosis, carcinogenesis and neurodegenerative diseases. Observations of molecular biology are supported by epidemiologic data and unmask milk consumption as a promoter of chronic diseases of Western societies.

Keywords
Affects the homeostasis of the pilosebaceous unit; it also induces unwanted mitogenic effects in various glandular tissues and organ systems.

Growth hormone/IGF-1 axis

Growth hormone (syn.: somatotropin, GH) and insulin-like growth factor 1 (somatomedin C, IGF-1) both play a central role in growth and in homeostasis of the skin and various tissues [4]. During puberty, there is increased secretion of GH from the anterior pituitary. Growth hormone binds to GH receptors of most peripheral cells. In the liver, growth hormone induces the synthesis and secretion of the polypeptide hormone IGF-1, which is the actual mediator of growth. More than 90% of IGFs circulating in the plasma are bound to IGF binding protein-3 (IGFBP-3) and the rest to IGFBPs 1, 2, 4, 6. Less than 1% of IGFs circulate as free IGFs in plasma. IGF-1 signal transduction occurs via the IGF-1 receptor (IGF1R), a tyrosine kinase receptor that can form heterodimers with the insulin receptor.

IGF-2 binds to the IGF-2 receptor which functions as a scavenger receptor. Insulin binds primarily to the insulin receptor, but it can also bind with low affinity to IGF1R. IGF-1 and IGF-2 can also bind with low affinity to the insulin receptor, so that overlap between signal transduction of IGF-1 and insulin is possible (Figure 1) [5]. IGF1R signal transduction primarily activates the Ras/Raf/MAP/kinase signalling cascade as well as the phosphoinositol-3-kinase (PI3K) signalling cascade, which promotes cell proliferation, lipogenesis, and growth, but inhibit apoptosis [4].

Relationship between IGF-1 signal transduction and acne

Acne has traditionally been viewed as primarily an androgen-dependent disorder affecting the pilosebaceous unit; this, despite the fact that it usually subsides after puberty while androgen levels remain consistent [6]. Indeed, the presence of IGF1R mRNA and SREBP-1 protein has been found even distributed in large amounts in all portions of the sebaceous gland [11]. This pattern of expression underscores the role of IGF-1 as a morphogen and mitigates in the hair follicle [11].

IGF-1 stimulates lipogenesis of the sebaceous glands

Both IGF-1 and insulin stimulate sebogenesis [6]. In sebaceous glands grown in organ cultures, IGF-1 has been shown to induce dose-dependent lipogenesis [12]. In SEB-1 sebocytes in humans, IGF-1 causes an increase in lipogenesis which is associated with the induction of sterol response element-binding protein-1 (SREBP-1) mRNA and SREBP-1 protein [13]. SREBPs are the main regulators of lipogenesis, controlling cellular lipid homeostasis and cellular cholesterol levels [14]. In human SEB-1 sebocytes, IGF-1 activates PI3K/Akt and MAPK/ERK signal transduction pathways, along with the induction of SREBP-1 mRNA and SREBP-1 protein [15]. Administration of a PI3K inhibitor has been shown to inhibit IGF-1-induced SREBP-1 expression and lipogenesis [15]. This underscores the close regulatory relationship between IGF-1 and sebocytic lipogenesis.

IGF-1 stimulates adrenal and gonadal androgen synthesis

The GH/IGF-1 axis plays a key role in ACTH-dependent synthesis of DHEAS in the adrenal gland [16-18]. IGF-1 and IGF1R occur in the zona reticularis of the adrenal gland [16]. In adults, a positive association has been found between IGF-1 and serum DHEAS [17]. IGF-1 increases the sensitivity of the adrenal gland to ACTH and promotes the expression of androgen-synthesizing enzymes [19, 20]. In healthy prepubescent girls, as well as in prepubescent girls with premature adrenarche, a positive correlation has
been found between IGF-1 and DHEAS in serum [21, 22]. DHEAS is believed to induce comedonic acne.

The IGF-1 system plays a central role in ovarian androgen synthesis. There is evidence of a correlation between IGF-1 concentrations in the follicular fluid of developing follicles and serum levels of IGF-1 [23]. IGF-1 has been found to increase significantly after LH increases in the dominant follicle [23]. IGF-1 stimulates estrogen synthesis by the granulosa cells [24–26]. It also increases the efficiency of LH in thecal interstitial cells in conjunction with increased androgen synthesis by the ovaries [27]. Thus IGF-1 is key to ovarian steroidogenesis and has also been associated with the pathogenesis of ovarian hyperandrogenism in polycystic ovary syndrome (PCOS) [27, 28].

Patients with PCOS often have elevated levels of IGF-1 and insulin as well as insulin resistance, elevated levels of DHEAS, hirsutism, irregular menstrual cycles, and acne [29–31]. The expression of IGF1R in the ovarian stroma and the number of IGF1R on erythrocytes in women with PCOS is significantly higher than in controls [32, 33].

IGF-1 also plays a central role in androgen production in the testes. IGF-1 and IGF1R have been found in higher concentrations in the androgen-synthesizing Leydig cells [34–39]. Studies have shown that in rodents, IGF-1 induces testosterone production in the testes during puberty [40, 41]. LH and HCG stimulate IGF-1 secretion and IGF1R gene expression in the Leydig cells in rodents [41–44]. Along with LH, IGF-1 stimulates the proliferation of Leydig cell precursors and testosterone synthesis. In human testicular cells, IGF-1 induces testosterone secretion and cell proliferation, but inhibits apoptosis [45]. Administration of IGF-1 and IGF-2 to briefly stimulate the Leydig cells in rats has been shown to increase HCG-stimulated testosterone secretion for a considerable length of time afterward [46]. IGF-1 plays a central role in the differentiation of Leydig cells and in testicular androgen synthesis [44, 47, 48].

IGF-1 stimulates peripheral androgen signal transduction

IGF-1 also influences intracrine androgen regulation in the skin. A dose-dependent increase in the activity of 5α-reductase has been observed after administering IGF-1 to skin fibroblasts [49]. IGF-1 is thus an important stimulator of peripheral androgen receptor (AR)-mediated signal transduction. IGF-1 also activates the androgen receptor. The AR is associated with the inhibitory protein FOXO1 in the cell nucleus, which suppresses AR-mediated signal transduction. IGF-1 and insulin bring about phosphorylation of FOXO1, which reverses inhibition of AR [50]. Thus IGF-1 stimulates the synthesis of potent androgens and activates AR. Both mechanisms increase androgen-dependent signal transduction. The expression of IGF-1 is itself AR-dependent [51]. Retinoids, which are successfully used in the treatment of acne, suppress not only signal transduction via fibroblast growth factor receptor-2b (FGFR2b), but also IGF1R signal transduction. Thus all-trans retinoic acid in dermal papilla induces IGFBP-3, causing a decrease in the bioavailability of IGF-1 [52]. Isotretinoin inhibits the expression of 5α-reductase, which is activated by IGF-1 [53].

Interactions between IGF1R and FGFR2b signal transduction in acne

The significance of androgen-dependent FGFR2b-mediated signal transduction in acne vulgaris, acne in Apert syndrome, and unilateral aceneform nevi has recently been described [54, 55]. FGFR2b and IGF1R are tyrosine kinase receptors that together activate the MAPK and PI3K signal pathway. The recruitment profiles of IGF1R, FGFR1, and EGFR overlap [56]. Figure 2 shows the interaction between IGF1R/FGFR2b signal transduction and relevant hormones.

Increased serum levels of IGF-1 as a result of milk consumption

Milk is a complex bioactive secretion that plays an important role in enhancing growth and in the development of newborn mammals. Human beings are the only mammals that have access to milk, drank 710 ml of ultra-heat treated milk a day for four weeks, which led to a 23.4% increase in serum levels of IGF-1 [71]. The ratio of IGF-1 to IGFBP-3 and GH also rose due to milk consumption [71]. Milk consumption thus alters the GH/IGF-1 axis in prepubescent children.

In one study, 46 children aged 10 to 11 years from Mongolia (Ulaanbaatar), who were not accustomed to consuming milk, drank 710 ml of ultra-heat treated milk a day for four weeks, which led to a 23.4% increase in serum levels of IGF-1 [71]. The ratio of IGF-1 to IGFBP-3 and GH also rose due to milk consumption [71]. Milk consumption thus alters the GH/IGF-1 axis in prepubescent children to the higher levels seen during puberty. In other words, it leads to a non-physiological increase in IGF-1 levels, which are already elevated physiologically during puberty. This may be one explanation for the acne “epidemic” in Western societies in which milk is consumed. Yet consumption of cow’s milk affects not only the sebaceous glands, but also affects other organ systems as well.

The effect of milk consumption on fetal development

The incidence of fetal macrosomia (birthweight > 4000 g) is on the rise in industrialized nations (8–10%). In umbilical
Perspectives

Milk consumption and obesity

The rise in childhood obesity is a serious problem in Western industrialized nations. Not only sebocytes, but also adipocytes are IGF-1-dependent. IGF-1 induces terminal differentiation of pre-adipocytes into adipocytes [87, 88]. The ability of serum in children to stimulate pre-adipocytes to differentiate into mature adipocytes correlates with serum levels of IGFBP-3 and IGF-1 [89, 90]. High levels of IGF-1 have been measured in obese children [91–93]. Alteration of the IGF-1 axis during fetal development with subsequent fetal macrosomia could pave the (metabolic) way to obesity. IGF-1 levels in umbilical cord blood have been shown to correlate significantly with the thickness of the triceps skin fold as a measure of fatty tissue [72].

Acne in endocrine disorders with elevated IGF-1 levels

Elevated serum levels of ACTH-stimulated 17-hydroxyprogrenolon, DHEAS, and IGF-1 have been reported in pubescent girls with premature adrenarche [79]. Premature pubarche shares some features with PCOS [79], which in turn is associated with elevated serum levels of IGF-1, DHEAS, hyperinsulinemia, insulin resistance, acne, and hirsutism [80]. A two-fold increase in serum levels of free IGF-1 have been reported in patients with PCOS. In patients with acromegaly, elevated serum levels of IGF-1, oily skin, increased sebum secretion, and acne have also been observed [81–85]. PCOS and acromegaly patients also have an increased risk of developing cancer. A recent study reported an increased risk of prostate cancer in patients with a long history of severe acne [86]. Acne in patients with PCOS, and persistent acne in adults, may be viewed as indicators of an increased risk of tumorous disease due to elevated IGF-1 levels.

Milk consumption and acne

Milk is the most important source of calcium and promoter of bone growth and bone mineralization, which is positively associated with the serum level of IGF-1 [69]. Milk consumption during pregnancy leads to increased size and weight of the newborn [74]. During a four-week-long intervention study on children in Mongolia, consumption of milk led to an acceleration of linear growth (12 cm/year) [71]. Results from the Growing Up Today Study conducted in the United States, and from studies done in developing nations, have also confirmed a correlation between milk consumption and linear growth [2, 3, 68]. The activation of bone growth, which occurs at a time when pubescent children are experiencing a growth spurt, as well as increased androgen synthesis and hyperproliferative effects on the pilosebaceous unit, are all induced by IGF-1.

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Milk consumption, IGF-1, and carcinogenesis

IGF-1 is a mitogen that stimulates growth, differentiation, and inhibits apoptosis, and thus IGF-1 has the characteristics of a tumor promoter [5, 94]. Various studies have demonstrated a correlation between elevated serum levels of IGF-1 and an increased incidence of
breast, prostate, colorectal, and lung cancer [95]. Most cancers have a high expression of IGF1R. IGF-1 also correlates with premenopausal mammographic density of breast tissue, which is the most significant risk factor in the development of breast cancer [37–39]. Mammographic measurement of breast density represents epithelial and stromal proliferation. Thus, the clinical presentation of breast cancer, seen by the unaided eye of the dermatologist as a clinical manifestation of IGF-1-stimulated sebaceous gland proliferation, could have a radiological counterpart in increased breast tissue density also stimulated by IGF-1. Not only breast cancer, but also cervical, ovarian, and endometrial carcinomas in premenopausal and postmenopausal women have been associated with increased serum IGF-1 [96]. In addition, elevated plasma levels of IGF-1 and hereditary variations in IGF1 gene expression have been identified as risk factors in prostate cancer [97–99]. Persistently high levels of IGF-1 could thus explain the correlation between acne and prostate cancer in men as well as the increased risk of tumor disease in acne patients with PCOS and in acromegaly. One meta-analysis showed an association between increased milk consumption and an increased risk of prostate cancer [100].

IGF-1 and insulin both promote tumor cell proliferation [101]. Despite growing evidence of the role of milk and IGF-1 in promoting carcinogenesis, two review articles have reported no association between milk consumption and a risk of breast cancer [102, 103]. It should be noted that the findings from this article by Parodi [102] are based on an IGF-1 contents in milk of only 4 ng/ml although current concentrations of IGF-1 range between 10–50 ng/ml [57]. Furthermore, IGF-2 in cow’s milk (40–50 ng/ml) was not addressed. IGF-2 binds to IGF1R and thus also induces IGF-1-dependent signal transduction (Figure 1) [58]. There was no mention of the crucial fact that milk protein consumption per se - unlike meat consumption - causes a rise in IGF-1 and insulin levels. The high level of consumption of milk and milk protein in Scandinavian countries is well known. Results from a prospective study of 25,892 Norwegian women clearly showed that consumption in excess of 750 ml of whole milk a day leads to a relative risk of breast cancer of 2.91 compared with consumption of less than 150 ml [104]. Data from molecular biological and epidemiological studies thus support the notion that excessive consumption of milk promotes carcinogenesis.

Milk consumption during pregnancy, increased birth weight, and risk of breast cancer

In pregnant women, milk consumption increases serum levels of IGF-1, birth weight, and neonatal size [74–76]. Increased birth weight and body size have already been identified as epidemiological risk factors in breast cancer [105–106]. It is thought that the intrauterine milieu increases the predisposition for breast cancer in adulthood [107]. Presumably, IGF-1 is the crucial factor in this in-utero mechanism [108]. Associations between IGF-1 levels in early childhood and late adolescence support the notion that the IGF-1 axis is established early on [109]. It is possible that consumption of cow’s milk during pregnancy interferes in the long term with the intrinsic adjustment of the IGF-1 axis in human beings.

Milk, IGF-1, atherosclerosis, and cardiovascular disease

The relationship between milk consumption and mortality from coronary heart disease was shown 25 years ago [110]. In men, a highly significant linear correlation was found between consumption of unfermented milk protein and mortality from coronary heart disease [111]. Animal experiments have demonstrated the atherogenic effect of IGF-1 [112, 113]. IGF-1 receptors are expressed in abundance by smooth muscle cells of the vessels and their expression is upregulated by angiotensin II [114]. IGF-1 secreted by activated monocytes stimulates the proliferation of smooth muscle cells and synthesis of extracellular matrix, which contribute to growth of atheromatous lesions [115]. It is conceivable that at higher concentrations, the IGF-1 in plasma passes the endothelial barriers of vessels and stimulates the cells in atheromatous plaques. The origins of atherosclerosis are already found during childhood. Serum levels of IGF-1, IGFBP-3, and leptin in macrosomic newborns have been shown to correlate significantly with a greater thickness of the intimal/media of the aorta [116]. Early IGF-1-induced vascular changes could thus lay the foundation for later atherosclerosis. A rise in IGF-1 levels due to milk consumption could accelerate the development of atherosclerosis.

IGF-1 and neurodegenerative diseases

The main risk factor for developing neurodegenerative disease is age [117]. There is a relationship between aging of the cell and an accumulation of toxic proteins, which is the common feature in all neurodegenerative diseases. The insulin/IGF-1 signalling cascade plays a central role in regulating life span. It is the connecting element between cellular aging, proteotoxicity, and the development of neurodegenerative disease [118, 119]. Reduced insulin-IGF-1 signal transduction in the brain could maintain homeostasis of protein metabolism longer, thereby delaying the development of neurodegenerative diseases [118]. Similar ideas have been discussed especially with regard to the pathogenesis of Alzheimer’s disease [120]. Overstimulation of IGF-1-signaling pathways in the brain due to milk consumption could thus accelerate the onset of neurodegenerative disease. IGF-1 passes the blood-brain barrier and reaches the neurons in the brain.

IGF-1, atopy, and autoimmunity

The incidence of atopic disease is increasing in Western nations. In Europe, the incidence of atopic dermatitis is the highest in Scandinavia where there is also a high incidence of cardiovascular disease and cancer as well as the greatest consumption of cow’s milk protein. The thymus is the only organ that establishes immunological “self” tolerance. It is thus the junction between the neuroendocrine and immune systems [121]. The neuroendocrine system regulates early steps in T-cell differentiation. T cells in the thymus undergo a complex learning and differentiation process, which ultimately eliminates T cells with autoimmune potential by means of apoptosis. Insulin, IGF-1, and IGF-2 are expressed in the network of the thymus according to a strict hierarchy. IGF-2 is formed by the epithelial cells of the cortex and by nurse cells. IGF-1 is secreted by macrophages in the thymus, and insulin is secreted by the medulla of the thymus [121]. Thymocytes (pre-T cells) express IGF1R and IGF2R. There have been
There is mounting evidence that milk consumption during pregnancy may have negative effects on normal maturation of the immune system. Newborns who were breast-fed have lower serum concentrations of IGF-1 than newborns who have been fed formula containing cow's milk [109], which suggests that the physiological IGF-1 axis in humans is lower and that as a result of ingestion of cow's milk during pregnancy and during the postnatal period it is unphysiologically shifted.

**Future directions**

Our deeply-rooted beliefs about the wholesomeness of milk and dairy products should be reconsidered under careful, scientific evaluation. We are just beginning to reassess the biological effects of milk and dairy products as foodstuffs. Human beings are the only species on earth that from the beginning of the perinatal period into adulthood are subjected to external hormonal manipulation of IGF-1-dependent maturation and differentiation processes in various cell and organ systems. Milk developed over the course of mammalian evolution as a highly complex, biologically active carrier of signals which was intended only to be consumed during infancy. The consumption of cow's milk interferes with the sensitive endocrine regulatory network from the fetal period into old age. It is time to look beyond milk as merely a positive stimulant of bone growth and instead to take all organ systems into account. Milk consumption during pregnancy, in particular, should be carefully evaluated; intrauterine changes in the regulatory axes can negatively impact later life, predisposing a person to chronic diseases. Persistent acne in adulthood, especially in PCOS, should be cause for assessing IGF-1 levels and should raise the possibility of an increased risk of cancer. Given the tumor promoter effect of IGF-1, patients with tumorous disease should restrict consumption of milk and milk protein. The same applies to patients with coronary heart disease and with a family history of neurodegenerative disease. Milk consumption has already been identified as an aggravating factor in the acne “epidemic” among adolescents, and preliminary successes have been reported with reduced milk consumption. It is even more important that excessive milk consumption can promote diseases commonly associated with a Western lifestyle (Table 1).

**Table 1: Potential risks of cow's milk consumption.**

<table>
<thead>
<tr>
<th>Organ/system</th>
<th>Effects of Milk Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymus</td>
<td>Disrupted T-cell maturation and abnormal T-cell apoptosis</td>
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<tr>
<td>Placenta</td>
<td>Placental enlargement with increased flow of nutrients</td>
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<tr>
<td>Bones</td>
<td>Accelerated bone growth and density</td>
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<tr>
<td>Adrenal gland</td>
<td>Stimulation of androgen synthesis</td>
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<tr>
<td>Ovary</td>
<td>Stimulation of androgen synthesis</td>
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<tr>
<td>Adipose tissue</td>
<td>Stimulation of adipocyte differentiation</td>
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<tr>
<td>Cardiovascular system</td>
<td>Stimulation of atherogenesis</td>
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<tr>
<td>Glands</td>
<td>Tumor promotion, accelerated cell proliferation, inhibition of apoptosis</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Protein synthesis and protein degradation are imbalanced with resulting proteotoxicity</td>
</tr>
<tr>
<td>Skin</td>
<td>Stimulation of sebaceous glands with increased sebogenesis</td>
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<tr>
<td></td>
<td>Stimulation of keratinocyte proliferation</td>
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</tbody>
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Conflict of interest
None.

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children and adolescents: relationship to gender, pubertal development, growth, insulin, and nutritional status. 


