

# **Evidence for Acne-Promoting Effects of Milk and Other Insulinotropic Dairy Products**

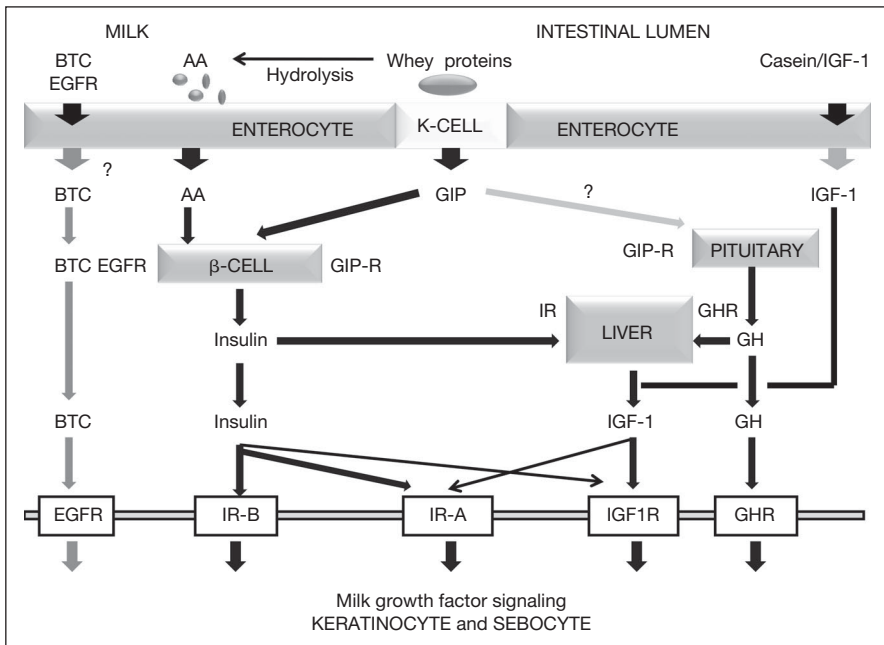
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Acne vulgaris, the most common skin disease of Western civilization, has evolved to an epidemic affecting more than 85% of adolescents and persisting in nearly 50% of young adults. Acne is not observed in non-Westernized populations without consumption of milk, dairy products and hyperglycemic carbohydrates [1]. Well-designed prospective studies published since 2005 provide evidence that components of Western diets, particularly milk and dairy products and diets enriched in carbohydrates with high glycemic index and glycemic load are associated with acne [2].

Insulinotropic food, especially refined sugars and grains, potatoes, milk and dairy products are ubiquitous elements in Western diet, and comprise nearly 50% of the per capita energy intake. The combination of milk with hyperglycemic carbohydrates potentiates hyperinsulinemic responses in comparison to the single components. Milk and whey protein-based products elevate postprandial insulin and basal IGF-1 plasma levels [3].

Increased insulin/IGF-1 signaling plays a most important role in acne pathogenesis [4]. A correlation between increased facial sebum secretion and IGF-1 serum levels has been reported in acne patients, whereas treatment with the sebum-suppressive drug isotretinoin decreases IGF-1 serum levels. Epidemiological studies confirmed the correlation between milk consumption and acne as well as milk protein consumption and increased IGF-1 plasma levels.

It is the principle of mammalian milk to promote growth and support anabolic conditions for the neonate during the nursing period. Whey proteins are most potent inducers of glucose-dependent insulinotropic polypeptide secreted by enteroendocrine K cells which in concert with hydrolyzed whey protein-derived essential amino acids stimulate insulin secretion of pancreatic  $\beta$ -cells (fig. 1). Increased

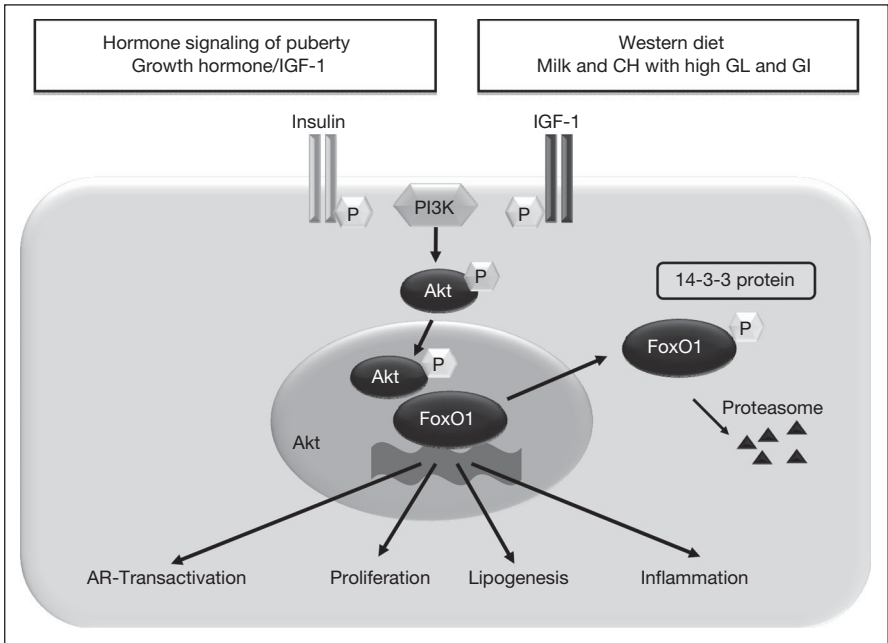


**Fig. 1.** The impact of milk protein consumption on the entero-insular-pilosebaceous signaling network. BTC =  $\beta$ -Cellulin; AA = essential amino acids; GIP = glucose-dependent insulintropic polypeptide; GH = growth hormone; IGF-1 = insulin-like growth factor-1; IR = insulin receptor; IGF1R = IGF-1 receptor; EGFR = epidermal growth factor receptor.

insulin/IGF-1 signaling activates the phosphoinositide-3 kinase (PI3K)/Akt pathway, thereby reducing the nuclear content of the transcription factor FoxO1, the key nutrigenomic regulator of acne target genes [4]. Nuclear FoxO1 deficiency has been linked to all major factors of acne pathogenesis, i.e. androgen receptor transactivation, comedogenesis, increased sebaceous lipogenesis, and follicular inflammation (fig. 2).

Acne is associated with disorders of increased growth factor signaling and insulin resistance, like polycystic ovary syndrome, acromegaly and Apert syndrome. All these diseases are associated with an increased incidence of cancer. Severe acne in males has recently been associated with an increased risk of prostate carcinoma, and a meta-analysis confirmed the relationship between high intake of dairy products and increased risk of prostate cancer.

Chronic overstimulation of humans of Western countries from the beginning of life to adulthood by a most potent postnatal growth



**Fig. 2.** Overstimulating effect of milk-derived growth factor signaling on PI3K/Akt/FoxO1 pathway. Milk protein-derived growth factor signaling is superimposed on physiological growth hormone-mediated PI3K/Akt signaling of puberty overstimulating nuclear export of FoxO1. Nuclear FoxO1 deficiency results in androgen receptor (AR) transactivation, increased follicular proliferation (comedogenesis), increased sebaceous lipogenesis and follicular inflammation. CH = Carbohydrate; GL = glycemic load; GI = glycemic index.

factor signaling system of a different mammalian species is an overlooked severe health hazard of human nutrition. The interference of the bovine milk growth factor signaling system with the human intrinsic insulin/IGF-1 axis has been proposed to be the major cause of most chronic Western diseases [5].

There are only two solutions to this problem: the restriction of milk consumption or the elimination of the insulinotropic effectors of milk. The attenuation of whey protein-based insulinotropic mechanisms will be the most important future challenge for an interdisciplinary cooperation between medicine, nutrition research and milk processing biotechnology. When the insulinemic index of milk has been adjusted to a level corresponding only to its carbohydrate moiety, we will look again into acne-free faces of less obese young people.

**Table 1.** Proposed impact of milk-induced GIP/insulin/IGF-1 oversignaling in the pathogenesis of acne and other chronic Western diseases [5]

Prenatal	Increased insulin-IGF-1 signaling in the thymus Increased placental growth and maternal glucose transport	Disturbed T cell maturation, impaired T cell apoptosis Fetal overgrowth, increased birthweight	Allergy, atopy, autoimmune diseases Fetal macrosomia, disposition for obesity
Postnatal	Increased GIP, insulin and IGF-1 plasma levels	Disturbed neonatal programming of the somatotrophic IGF-1 axis	Increased linear growth, increased risk for cancer, obesity, diabetes and arterial hypertension
Adolescence	Overstimulation of physiological growth factor signaling of puberty, nuclear FoxO1 deficiency	Promotion of acne, increased androgen signaling, increased sebogenesis, comedogenesis GIP-induced adipocyte differentiation and lipogenesis	Acne alimentaris, persistence of acne in adulthood Early onset of childhood obesity
Adulthood	Overstimulation of pancreatic $\beta$ -cells Overstimulation of endothelial and smooth muscle cells and increased lipogenesis Overstimulation of the insulin/IGF-1 signaling network Insulin/IGF-1 over stimulation of neuronal cells	Early onset of replicative $\beta$ -cell senescence Promotion of atheroma formation Stimulation of the oncogenic PI3K/Akt pathway Imbalance between protein synthesis and degradation, 'diabetes of the brain'	Diabetes mellitus type 2 Coronary heart disease, stroke Cancer promotion Early onset of neurodegenerative diseases

GIP = Glucose-dependent insulinotropic polypeptide.

The author predicts that the generation of less insulinotropic milk and milk products (insulinemic index <45) will have an enormous impact on the prevention of epidemic Western diseases like obesity, diabetes mellitus, cancer, neurodegenerative diseases and acne (table 1) [5]. Acne, the mirror of exaggerated insulinotropic Western nutrition, is a most useful clinical and epidemiological indicator of appropriate or inappropriate human nutrition. A decrease in diet-induced acne will be associated with a decline in the prevalence rates of more serious Western diseases developing with longer latency periods after the acne peak in adolescence.

## References

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