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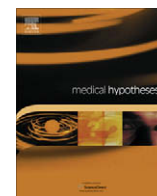
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Milk – The promoter of chronic Western diseases

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SUMMARY

Common chronic diseases of Western societies, such as coronary heart disease, diabetes mellitus, cancer, hypertension, obesity, dementia, and allergic diseases are significantly influenced by dietary habits. Cow's milk and dairy products are nutritional staples in most Western societies. Milk and dairy product consumption is recommended by most nutritional societies because of their beneficial effects for calcium uptake and bone mineralization and as a source of valuable protein. However, the adverse long-term effects of milk and milk protein consumption on human health have been neglected. A hypothesis is presented, showing for the first time that milk protein consumption is an essential adverse environmental factor promoting most chronic diseases of Western societies. Milk protein consumption induces post-prandial hyperinsulinaemia and shifts the growth hormone/insulin-like growth factor-1 (IGF-1) axis to permanently increased IGF-1 serum levels. Insulin/IGF-1 signalling is involved in the regulation of fetal growth, T-cell maturation in the thymus, linear growth, pathogenesis of acne, atherosclerosis, diabetes mellitus, obesity, cancer and neurodegenerative diseases, thus affecting most chronic diseases of Western societies. Of special concern is the possibility that milk intake during pregnancy adversely affects the early fetal programming of the IGF-1 axis which will influence health risks later in life. An accumulated body of evidence for the adverse effects of cow's milk consumption from fetal life to childhood, adolescence, adulthood and senescence will be provided which strengthens the presented hypothesis.

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Insulin and the insulin-like growth factor system

The insulin-like growth factor (IGF) system is essential for normal embryonic and postnatal growth, and plays an important role in the function of a healthy immune system, lymphopoiesis, myogenesis and bone growth among other physiological functions. Growth hormone (GH) and IGFs play an important role in growth and tissue homeostasis. GH secreted by the anterior pituitary binds to GH receptor, expressed on most peripheral cells of the body. In peripheral tissues and predominantly in the liver, GH induces the synthesis and secretion of the 7.65 kDa polypeptide hormone IGF-1, the mediator of the growth stimulating activity of GH. More than 90% of circulating IGFs are bound to IGF-binding protein-3 (IGFBP-3), the rest to IGFBP-1, -2, -4, -5, and -6, and less than 1% of IGFs circulate as free IGFs in the plasma. IGF-1 signal transduction is mediated primarily by the IGF-1-receptor (IGF1R), a tyrosine kinase receptor, which is able to form heterodimers with insulin receptor (IR). IGF-2 binds to IGF-2-receptor (IGF2R), a scavenger receptor down-regulating IGF-2. IGF-2 is also able to bind to IGF1R. Insulin primarily binds to IR-A and IR-B, but also binds with lower affinity to IGF1R. IGF-1 and IGF-2 bind to IR with lower affinity

(Fig. 1). IGF1R signal transduction is mediated primarily by the activation of the Ras-Raf-MAP kinase pathway and the phosphoinositide 3-kinase (PI3 K)/Akt pathway. IGF-1 acts a strong mitogen inducing cell growth and proliferation, but inhibits apoptosis [1]. The IR-B isoform is the form best known for the classic metabolic responses induced upon insulin binding and this isoform has low affinity for IGFs [1]. The IR-A isoform arises from alternative splicing of exon 11 encoded by the IR gene. Activation of the IR-A by insulin or IGF-2 leads to mitogenic responses similar to those described for IGF1R. Increased signalling via IR-A has been associated with the development of cancer [2]. In this regard, insulin and IGF-2 signal transduction via IR-A and IGF-1 signalling via IGF1R induce and amplify mitogenic responses (Fig. 1).

Milk and milk protein consumption increase IGF-1 serum levels

Milk is a complex, bioactive substance honed by evolution to promote growth and development of the infant mammal. Cow's milk and dairy products derived from milk are widely consumed by children and adults of Western societies well after the age of weaning. It is important to note that cow's milk contains active IGF-1 (4–50 ng/ml) and IGF-2 (40–50 ng/ml) [3,4]. IGF-signalling belongs to the canonical pathways and networks regulated by estrogen and placental GH in the bovine mammary gland. Cows treated with recombinant bovine GH to improve milk yield showed increased levels of IGF-1 in the milk [4]. High levels of IGF-1 are

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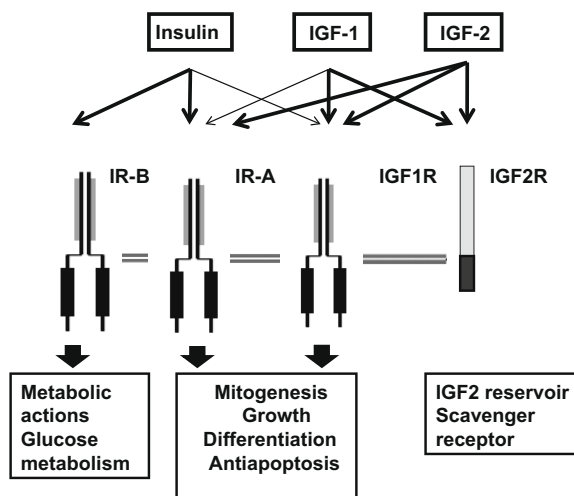


Fig. 1. IGF-1, IGF-2 and insulin signal transduction and receptor cross-reactivity.

still detectable after pasteurization and homogenization of milk [5]. Intriguingly, bovine and human IGF-1 share the same amino acid sequences and therefore bovine IGF-1 can bind to the human IGF1R [6].

Several lines of evidence indicate that IGFs in milk can survive digestion and remain bioactive in the serum of milk consumers. Studies have demonstrated intact oral absorption and plasma bioactivity of IGF-1 in neonate and adult animals, especially when IGF-1 was administered together with the protease inhibitor casein, the primary protein in milk. High milk consumption in humans is associated with a 10–20% increase in circulating IGF-1 levels among adults and a 20–30% increase among children [7–14]. Girls with a milk intake below 55 ml/day had significantly lower IGF-1 serum concentration compared to girls consuming more than 260 ml/day [15]. In 2109 European women, IGF-1 serum levels positively correlated with the intake of milk [16]. It is important to notice that dairy products increase IGF-1 levels more than any other dietary sources of protein like meat [9–16]. Moreover, milk consumption raises the ratio of IGF-1/IGFBP-3 indicating an increased bioavailability of IGF-1 [8–10,12].

The insulinotropic effect of milk and milk products

Fermented and non-fermented milk products give rise to insulinaemic responses far exceeding what could be expected from their low glycaemic indexes (GI). Despite low GIs of 15–30, milk products produce three to sixfold higher insulinaemic indexes (II) of 90–98 [17]. A large and similar dissociation of the GI and II exists for both whole milk (GI: 42 ± 5 ; II: 148 ± 14) and skim milk (GI: 37 ± 9 ; II: 140 ± 13) [18]. It has been suggested that some factor within the protein fraction of milk is responsible for milk's insulinotropic effect [18]. Skim milk has been identified as a potent insulin secretagogue in type 2 diabetic patients [19]. Except for cheese with an insulin score of 45, milk and all dairy products including yoghurt, ice cream, cottage cheese, and fermented milk products have potent insulinotropic properties [20].

In a one-week intervention study of 24 pre-pubertal eight-year-old boys the effect of daily intake of 53 g of either lean meat or skim milk (1.5 l per day) was studied with regard to insulin and IGF-1 responses. In the skim milk group insulin significantly increased by 105% (from 22 to 45 pmol/l) and IGF-1 significantly increased by 19% (from 209 to 249 ng/ml) [12]. There was no significant increase in either insulin or IGF-1 in the meat group. This study clearly showed that milk protein consumption induces

hyperinsulinaemia and increased IGF-1 serum levels. The addition of an ordinary amount of 200 ml milk to a meal with a low GI increased the insulin response by 300% to a level typically seen from a meal with a very high GI like white bread [21]. The comparison of 43 breast-fed and 43 cow's milk formula-fed one-week-old term infants showed higher insulin levels in the cow's milk formula-fed group at 90 and 150 min postprandial [22].

Differential induction of insulin and IGF-1 by milk protein fractions

The major protein fractions of cow's milk is casein (80%), the remaining 20% are whey proteins. Both, whey and casein contain specific proteins and peptides that may have growth stimulating effects. The effect of whey and casein fractions of milk on fasting concentrations of IGF-1 and insulin has been examined in 57 eight-year-old boys who received over seven days either casein or whey protein fractions with protein amounts of casein or whey similar to the content of 1.5 l skim milk. In the casein group serum IGF-1 increased by 15%, whereas there was no change in fasting insulin. In the whey group fasting insulin increased by 21%, with no change in IGF-1 [23,24]. The insulin response to a whey meal has been reported to be higher than that of a milk meal. This differential response suggests that the insulinotropic component of milk resides predominantly within the whey fraction of soluble milk proteins, whereas casein has a stronger IGF-1 stimulating effect than does whey [23,24] (Fig. 2). It is conceivable that specific whey proteins or their enzymatically cleaved peptides function as secretagogues for the release of intestinal incretins like glucagon-like peptide-1 or gastric inhibitory peptide which are known to stimulate pancreatic insulin secretion and release [25]. A typical Western combination diet composed of milk proteins and food with high glycaemic index will have potentiating effects on serum insulin and IGF-1 levels thereby promoting signalling pathways involved in mitogenesis and antiapoptosis.

Insulin induces hepatic synthesis and secretion of IGF-1

The main source of circulating IGF-1 is considered to be the liver. A study of seven insulin-dependent diabetic patients in whom insulin was withheld for 12 h received insulin infusions (1.6 mU insulin/kg/min) after an overnight fasted state. Serum IGF-1, but not IGFBP-3, significantly increased during the insulin infusion,

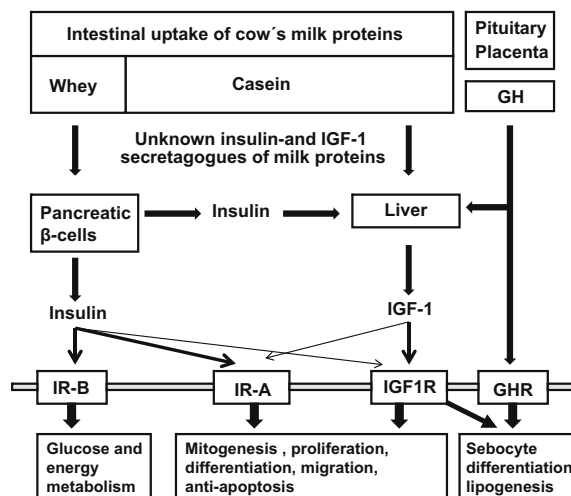


Fig. 2. Insulinotropic and IGF-1 inducing effect of milk protein and milk protein fractions.

whereas hepatic IGFBP-1 synthesis was reduced [26]. Mean serum baseline levels of IGF-1 in arterial blood (166 µg/l) and hepatic vein (160 µg/l) blood increased during the 180 min of insulin infusion to 183 µg/l and 185 µg/l, respectively [26]. Thus, insulin infusion raised serum IGF-1 levels by approximately 13%. It is conceivable that the milk protein-induced hyperinsulinaemia will stimulate hepatic IGF-1 synthesis and secretion in normal individuals as well.

The impact of milk consumption on fetal growth

Both IGF-1 and IGF-2 are expressed in fetal tissues from the earliest stage of pre-implantation to the final phase of tissue maturation before birth. IGF-2 is the primary growth factor supporting embryonic growth, with IGF-1 increasing in importance later in gestation. Concentrations of IGF-1 in the fetus are affected by nutrient supply to the fetus and nutrient-sensitive hormones [27]. Insulin positively regulates IGF-1 levels [28]. In industrialized countries, one of 10 newborns is affected with fetal macrosomia which has been associated with an increased risk of developing diabetes type 2 later in life. Milk consumption during pregnancy has been associated with a higher birth weight of the offspring [29,30]. The protein intake from dairy products but not cheese protein was associated with increase in birth weight [29]. Levels of IGF-1 and IGFBP-3 appear to be regulated by several factors, such as insulin, GH and maternal factors [31]. Levels of IGF-1 in cord sera of newborns small for gestational age (mean 48.7 ng/ml) were lower than those of newborns appropriate for gestational age (AGA) (56.4 ng/ml). Newborns large for gestational age (LGA) exhibited the highest IGF-1 cord sera levels (96.1 ng/ml) [31]. A recent study showed significantly higher insulin, leptin, IGFBP-3, and glucose concentrations in asymmetric LGA newborns than in symmetric LGA and AGA newborns [32]. Macrosomic neonates of diabetic mothers have significantly increased aortic intima-media thickness with higher serum IGF-1, IGFBP-3 and leptin concentrations than those of controls [33]. Umbilical cord serum IGF-1 levels were correlated significantly with the IGF-1 concentrations of the mothers [34]. Umbilical cord serum levels of free IGF-1, total IGF-1, IGFBP-2 and leptin have been demonstrated as predictors of birth weight [35]. Recently, normal variations in maternal glycaemia on birth size and birth outcomes has been investigated in nondiabetic mothers [36]. Each 1 mmol/l rise in mother's 60 min glucose levels after oral glucose challenge in the 28th week of gestation resulted in a 46 ± 8 g increase in offspring birth weight [36]. The mother's higher fasting glycaemia, lower insulin sensitivity, and lower insulin secretion were independently related to greater offspring adiposity at birth [36]. As high milk and milk protein consumption induces hyperinsulinaemia which favours the development of insulin resistance, substantial milk and dairy product consumption during pregnancy may contribute to the development of higher birth weight [29,30]. These data point to the important role of the insulin and the IGF-1 axis in fetal growth and the impact of milk consumption during pregnancy for the development of fetal macrosomia.

Early programming of the GH-IGF-1 axis

The GH-IGF-1 axis is closely related to feeding in the newborn [37]. More recent data point to an early programming of the IGF-1 axis within the first months of live. In early pregnancy maternal endocrine IGF-1 programs the placenta for increased functional capacity throughout gestation [38]. IGFs play a critical role in fetal and placental growth throughout gestation [27,39]. Increased maternal milk consumption during pregnancy enhances the nutrient supply for the fetus by an enlarged placenta. In the guinea pig administration of IGF-1 during early pregnancy increased placental

transport of glucose and amino acids and increased placental and fetal weights [38]. Intriguingly, an inverse association between IGF-1 at 9 months and 17 years of age has been demonstrated in humans [40]. A 1 ng/ml higher IGF-1 concentration at 9 months corresponded to 0.95 ng/ml lower IGF-1 concentration at 17 years [40]. Breast-fed infants at two months exhibited an IGF-1 serum level of 93.3 ± 23.6 ng/ml, whereas formula-fed two-months-old infants revealed increased IGF-1 levels of 129.8 ± 39.8 ng/ml [40]. At the age of 17 years, the breast-fed infants showed an increased IGF-1 level of 328 ± 78.5 in comparison to decreased IGF-1 levels of 292.9 ± 95.0 of not breast-fed adolescents of the same age [40]. These observations support the view that the IGF-1 axis is programmed early in life [40]. As milk protein consumption during pregnancy is associated with increased serum levels of IGF-1 and postprandial hyperinsulinaemia, a milk protein-mediated shift of the IGF-1 axis to higher levels has to be expected early in pregnancy. One of the first effects of milk consumption during early pregnancy might increase maternal IGF-1 levels which program the placenta for increased functional capacity throughout gestation thereby increase the risk of fetal macrosomia and other IGF-1-dependent diseases [38].

Milk consumption shifts the GH-IGF-1 axis in pre-pubertal children

After a month of drinking 710 ml of ultra-heat treated whole milk daily, 10–11-year-old Mongolian children, previously not used to milk consumption, had a higher mean plasma level of IGF-1 and higher ratio of IGF-1/IGFBP-3 [41]. The mean serum IGF-1 levels were raised in the children after 4 weeks of milk consumption by 23.4% from mean pre-treatment values of 291–358 ng/ml [41]. There is good evidence that milk consumption shifts the human intrinsic IGF-1 axis to unusual high levels.

Milk consumption and linear growth

Over the last centuries, body height significantly accelerated. Milk intake is the best source for utilization of calcium for bone growth and mineralization and is positively associated with IGF-1 serum levels [15]. Milk consumption during pregnancy is associated with increased infant size at birth [29]. During a four-week intervention with daily milk intake of 710 ml, Mongolian children experienced a rapid linear growth (the equivalent of 12 cm/year). Girls grew a mean $1.1 + 0.2$ cm and boys $1.0 + 0.2$ cm [41]. The Growing Up Today Study showed that girls drinking less than one glass milk per week had a height of 150.6 cm, while girls drinking two or more glasses per day had a height of 151.9 cm (increase of 1.3 cm) [42]. Boys with a milk intake of less than one glass per week had a height of 150.1 cm, those with more than two glasses per day had height of 152.4 cm (increase of 2.3 cm) [43]. Further evidence for the growth-promoting effect of milk comes from studies in developing countries [23]. Milk and milk protein consumption is associated with an acceleration of linear growth and body height in industrialized countries.

Effect of IGFs and insulin on adreno-gonadal maturation and onset of puberty

The GH-IGF-1 axis plays an important role for the ACTH-dependent production of dehydroepiandrosterone sulphate (DHEAS) of the human adrenal gland [44]. IGF-1 is involved in ovarian androgen synthesis and has been implicated in the pathogenesis of ovarian hyperandrogenism and polycystic ovary syndrome (PCOS) [45]. IGF-1 serum levels are increased in patients with PCOS who exhibit insulin resistance, anovulation, hyperandrogenism with acne and

hirsutism. Proliferation and differentiation of adult testicular Leydig cells is the prerequisite for the increase of circulating plasma androgens during puberty. IGF-1 is an essential local mediator of testicular steroidogenesis. In human testicular cell cultures, IGF-1 stimulated testosterone secretion and cell proliferation, whereas apoptosis was inhibited [46]. Both insulin and leptin are thought to accelerate the timing of pubertal onset and to up-regulate the tempo of pubertal progression [47,48]. The insulin sensitizing agent metformin decreases elevated serum IGF-1 levels in patients with PCOS [49]. Girls with precocious pubarche and low birth weight reveal increased IGF-1 serum levels and insulin resistance which leads to rapid progression of puberty. These girls are predisposed to develop PCOS [50]. Metformin treatment (425 mg/day) over two years of eight-year-old girls with precocious pubarche and low birth weight prevented the onset of early puberty by 0.4 years and significantly decreased serum levels of IGF-1, fasting insulin, DHEAS and testosterone [51]. In the untreated group ($n = 19$) of these girls IGF-1 increased from 215 ± 10 to 289 ± 21 ng/ml ($\Delta 0$ –24 months: 74 ± 23), whereas IGF-1 in the metformin-treated group ($n = 19$) only moderately increased from 197 ± 11 to 258 ± 22 ng/ml ($\Delta 0$ –24 months: 61 ± 24) after the 24 months intervention [51]. Fasting insulin increased in the untreated group, whereas only a moderate increase was observed in treated girls [51]. These data show that improvement of insulin resistance by metformin treatment is associated with a decrease in IGF-1 levels in girls with precocious pubarche as well as adult patients with PCOS. A recent study indicated that the GH/IGF-1 axis and insulin resistance might be involved in the mechanism of adrenarche during prepuberty in normal girls [52]. Metformin shifts the IGF-1 axis to lower levels thereby preventing an early onset of puberty. Thus, metformin treatment has the opposite effect compared to the effects of milk consumption, which shifts the IGF-1 axis and insulin to higher levels [41]. From these data it can be concluded that milk and milk protein consumption has not only an impact on the acceleration of linear growth but also on the onset of puberty.

Milk consumption, IGF-1 serum levels and acne

Acne is regarded as an androgen-dependent disease of the pilosebaceous follicle. Its course, however, corresponds less closely to plasma androgen levels than it does to GH and IGF-1 levels [53]. Significantly increased serum levels of IGF-1 have been observed in women with post-adolescent acne as well as adult acne patients [54,55]. In women, the total number of acne lesions correlated with serum IGF-1 levels. In Western societies, acne is a nearly universal disease afflicting 79–95% of the adolescent population. In men and women older than 25 years, 40–54% have some degree of facial acne, and clinical facial acne persists into middle age in 12% of women and 3% of men [56]. Epidemiologic observations point to the role of Western diet in the development or aggravation of acne [56]. Cordain et al. [56] reported on 1200 Kitavan islanders of Papua New Guinea and 115 Aché hunter-gatherers of Paraguay who do not consume dairy products and have low glycaemic diets. No case of acne has been detected in these two non-westernized populations. Prospective cohort studies (Growing Up Today Study, based 1996) in 4273 teenage boys and 6094 teenage girls in the United States demonstrated a correlation between milk consumption and acne [42,43]. In the study of boys, the strongest association has been found between intake of skim milk and acne [43]. It has been shown that high intakes of skim milk but not meat, increase serum IGF-1 and IGFBP3-levels in eight-year-old boys [57]. Sebaceous glands express IGF1R [58]. IGF-1 has been recognized as a mitogen and morphogen of sebaceous glands [58]. GH receptor has been found on the acini of sebaceous glands [59,60]. Insulin as well as IGF-1 stimulate sebocyte differentiation. However, when

insulin or IGF-1 were administered together with GH, the effect on sebocyte differentiation was potentiated compared to either hormone administered alone [60]. These data are in good agreement with the clinical association between increased IGF-1 serum levels and increased facial sebum excretion in acne patients [61]. Thus, it is conceivable that a rise in insulin and IGF-1 levels by milk consumption stimulates sebocyte proliferation and differentiation resulting in the development and progression of acne.

Endocrine disorders associated with increased IGF-1 serum levels and acne

In pre-pubertal girls with premature adrenarche significantly higher ACTH-stimulated 17-hydroxy-pregnenolone and DHEA serum levels, high IGF-1, and low IGFBP-1 have been reported [62]. It is remarkable, that premature pubarche shares many clinical characteristics with PCOS [62]. PCOS is associated with increased serum levels of IGF-1 and DHEAS, hyperinsulinemia, insulin resistance, acne and hirsutism [63]. Twofold elevated serum levels of free IGF-1 have been detected in women with PCOS [63]. Patients with acromegaly and GH hypersecretion have increased IGF-1 serum levels, exhibit greasy skin with increased sebum excretion and often develop acne. Like in PCOS, patients with acromegaly often exhibit insulin resistance and hirsutism as well as increased susceptibility for cancer. An increased risk of prostate cancer has recently been observed in patients with severe acne [64].

Milk consumption and obesity

IGF-1 is required for terminal differentiation of pre-adipocytes into adipocytes [65,66]. Milk consumption during pregnancy increased infant size and birth weight [29,30]. Data from the Danish National Birth Cohort ($n = 50,117$) demonstrate a significant association between increase in birth weight and quantified intakes of protein from dairy products [29]. Umbilical cord serum IGF-1 concentrations were higher in LGA newborns compared to AGA and SGA newborns [34]. Umbilical cord serum IGF-1 levels were correlated significantly with fat mass of the newborn [34]. Milk intake associated with a rapid early growth rate may be a risk factor for obesity [29,67]. The capacity of children's serum to stimulate differentiation of pre-adipocytes into adipocytes is correlated with IGF-1 and IGFBP3-levels [68,69]. These observations are supported by clinical data demonstrating high IGF-1 serum levels in obese children [70–72]. Obesity is a well known risk factor for the development of diabetes mellitus, arterial hypertension, cardiovascular disease and cancer. The compensatory hyperinsulinaemia that characterizes adolescent obesity chronically suppresses levels of IGFBP-1 thereby increasing the bioavailability of free IGF-1 [73]. The insulinotropic and IGF-1 rising effect of milk and milk protein consumption will have further adverse effects on obesity.

Postnatal IGF-1 axis, diabetes mellitus and hypertension

The IGF-1 axis may be programmed by diet early in infancy [40]. An inverse relation between IGF-1 levels during the first months of life and IGF-1 levels in adulthood could be observed in 109 infants of the observational Copenhagen cohort study [40]. Low levels of IGF-1 in the postnatal period are associated with high IGF-1-levels in adolescence. Low levels of IGF-1 are reported in SGA newborn infants [34]. Low birth weight is a recognized risk factor for the development of type 2 diabetes and hypertension in adulthood [74,75]. Furthermore, longitudinal and cross-sectional studies have shown that low birth weight in girls with precocious pubarche are at risk for early onset of puberty and menses and further progress

to anovulation, hyperinsulinaemic hyperandrogenism and PCOS [76]. It appears that the IGF-1 axis in SGA-low birth weight newborns is drifted to higher IGF-1 levels in adulthood promoting the development of diabetes type 2, hypertension and PCOS. Individuals who were SGA at birth may be at high risk in adulthood when consuming milk and dairy products which further increase the imbalanced IGF-1 axis to even higher levels. The potent insulinotropic properties of milk and dairy protein induces hyperinsulinaemia and reactive hypoglycaemia similar to high glycaemic load carbohydrates which have been implicated as an underlying cause of certain diseases of insulin resistance [77].

Low birth weight is associated with hypertension in adulthood. The compensatory drift of the IGF-1 axis to higher IGF-1 levels in individuals with low birth weight and low IGF-1 levels to higher IGF-1 levels in adulthood may contribute to the development of hypertension. IGF-1 receptors are up-regulated by angiotensin II [78]. In hypertensive animals there is an increased IGF-1 mRNA and protein expression and IGF-1 plasma levels in hypertensive patients have been related to pressure load [79,80].

Milk, insulin, IGF-1 and cancer

IGF-1 is a known mitogenic hormone that stimulates growth, differentiation and metabolism in a variety of cell types [81]. IGF-1 participates in the regulation of the cell cycle, inhibiting the processes of apoptosis and stimulating cell proliferation. IGF-1 is a potential tumour promoter [82]. Several studies demonstrated a link between increased IGF-1 serum levels with increased risk of breast, prostate, colorectal, and lung cancer [83]. High expression of IGF1Rs has been detected in the majority of human cancers. Several studies have confirmed that IGF-1 serum levels are related to pre-menopausal breast density, one of the strongest known breast cancer risk factors believed to represent epithelial and stromal proliferation [84–86]. A higher risk for cervical, ovarian and endometrial cancer is related to high IGF-1 levels in post- and pre-menopausal women [87]. Plasma IGF-1 levels and inherited variation in IGF-1 have been implicated to be a risk factor in prostate carcinoma [88–90]. A high intake of dairy products and calcium has been associated with an increased risk of prostate cancer in a recent meta-analysis [91]. IGF-1 and insulin act through the tyrosine kinase growth factor signalling cascade enhancing tumour cell proliferation [92].

Although, there is a large body of evidence that milk consumption increases IGF-1 serum levels which are associated with increased risk of various cancers, two recent review articles came to the conclusion that there is no support for the association between dairy product consumption and risk of breast cancer [93,94]. Parodi's [93] calculations are based on a IGF-1 content in milk of 4 ng/ml, whereas 10–50 ng/ml were reported from other sources [3]. Moreover, the role of bioactive IGF-2 in milk (40–50 ng/ml), which increases IGF-signalling by cross-reaction with the IGF1R has not been considered [93]. Most important is the fact that despite heat inactivation of growth factors, ultra-heat processed milk and fermented milk products retain the ability to raise human serum IGF-1 and insulin levels more than other sources of dietary protein. High incidence rates of cancer are common in Scandinavia where milk protein consumption is very high. A prospective study of 25,892 Norwegian women clearly showed that consumers of 750 ml or more of full-fat milk daily had a relative risk of 2.91 for breast cancer compared with those women who consumed 150 ml or less [95]. The cancer promoting effect of low-fat milk in 7,12-dimethylbenz(A)anthracene-induced mammary tumours has been demonstrated in rats [96]. Commercial milk inhibited the regression of carcinogen-induced mammary tumours in ovariectomized rats [97]. Thus, substantial evidence

supports the view that milk consumption raises IGF-1 serum levels and promotes cancer.

Milk consumption in pregnancy, birth weight and risk of breast cancer

Milk consumption during pregnancy increases maternal IGF-1 serum levels, birth weight and height of the newborn [29,42,43], all known risk factors of breast cancer [98,99]. The intrauterine environment might contribute to the predisposition of women for breast cancer in adulthood [100]. The responsible in-utero-mechanism has been linked to IGF-1 [101]. Thus, the environmental breast cancer-promoting factor of Western societies could be associated with milk-induced IGF-signalling during early pregnancy. A recent study examined the association between IGF-1 in infancy and later in life supporting the hypothesis that the IGF-1 axis can be programmed early in life [40]. An imbalance in IGF-1-dependent T-cell maturation in the fetal thymus might affect the immune system's capacity to handle anti-tumour mechanisms later in life. Thus, fetal macrosomia could have a fatal outcome later in life. Individuals affected by genetic variations in the expression of IGF-1 resulting in high IGF-1 serum levels are at increased risk for cancer. Absence of the IGF1 19-CA repeat allele has been associated with high IGF-1 levels during oral contraceptive use in nulliparous women in four different ethnic groups [102]. The IGF1 19-CA repeat allele modifies IGF-1 levels, breast volume and possibly early onset breast cancer risk after hormone exposure in young high-risk women [103,104]. Intriguingly, absence of the common IGF1 19 CA-repeat allele is more common among BRCA1 mutation carriers than among non-carriers from BRCA1 families [105]. As the IGF1 –19/–19 affects 6–13% of white women, this population subgroup may be especially vulnerable to further IGF-1 elevations by milk protein consumption.

Milk, IGF-1 and cardiovascular disease

The association between milk consumption and mortality from ischemic heart disease has been suggested in this journal 25 years ago [106]. A linear correlation between the consumption of unfermented milk proteins and male mortality of coronary heart disease has been demonstrated [107]. Animal models have shown that IGF-1 is involved in stimulating atherosclerosis [108,109]. IGF1Rs are abundant in vascular smooth muscle cells and factors that stimulate atherosclerosis, such as angiotensin II up-regulate IGF1R expression [110]. IGF-1 secreted by activated monocytes can stimulate smooth muscle cell proliferation and extracellular matrix synthesis which lead to enlargement of the developing atheroma [111]. It is conceivable, that the relative small IGF-1 polypeptide diffuses from the plasma into the early atheromatous lesions. In this regard, milk-derived IGF-1 augments local IGF-1-dependent atherogenic effects.

IGF-1 signalling and neurodegenerative diseases

The major risk factor for the development of neurodegenerative disease is aging [112]. Mechanistic links between the aging process and toxic protein aggregation, a common hallmark of neurodegenerative diseases, has been revealed. Lifespan is regulated by at least three different mechanisms, one of which is the insulin/IGF-1 signalling pathway. The insulin-IGF-1 pathway is the major candidate to link aging, proteotoxicity and late-onset neurodegenerative disease [113,114]. It has been suggested that reducing insulin-IGF-1 signalling in the brain will enable cells to maintain the activity of protein quality-control mechanisms and clearance capabilities to a later age, thereby postponing the onset of neurodegenerative

diseases [113]. Recent insights implicate the interconnection of IGF1R-signalling, regulation of lifespan, neurotrophin signalling and loss of neurogenic capacity and development of Alzheimer disease [115]. Prolonged milk-induced disturbance of the insulin-IGF-1 pathway has to be considered as a possible accelerator of neurodegenerative disorders. Intriguingly, circulating IGF-1 is able to cross the blood-brain barrier and enter into the brain. Recent research points to the possibility that the brain is the site where reduced IGF-1 signalling can consistently lead to an extended mammalian life span [114].

The IGF-axis and allergic and autoimmune disorders

The thymus is the only organ specialized in the establishment of immunological self-tolerance and stands at the crossroads between the immune and neuroendocrine systems [116]. The neuroendocrine system regulates the process of T-cell differentiation from the very early stages. T lymphocytes undergo in the thymus a complex educative process that establishes central T-cell self-tolerance of neuroendocrine principle. Neuroendocrine self-antigens correspond to peptide sequences that have been highly conserved throughout the evolution of one given family [116]. With regard to the insulin gene family, all members are expressed in the thymus network according to a precise hierarchy and topography of epithelial cells: IGF-2 (thymic cortex and thymic “nurse” cells) > IGF-1 (thymic macrophages) > insulin (medulla) [116]. The blockade of thymic IGF-mediated signalling at the level of IGF ligands or IGFs interferes with the early stages of T-cell differentiation in fetal thymic organ cultures [117]. IGF-1 stimulates thymus growth and T-cell proliferation and development. Thymocytes (pre-T-cells) express IGF1R and IGF2R. A number of data support the existence of a functional IGF-mediated signalling between stromal cells (thymic epithelial cells, macrophages) and immature T-cells during their differentiation in the thymus [117]. The majority of T-cell precursors entering the thymus are eliminated by apoptosis, ensuring that only harmless T-cells without autoimmune and allergic potential survive apoptosis in the thymus. IGF-1 activates the PI3 K-pathway, involved in the activation of cell proliferation and inhibition of apoptosis [1,82]. Consumption of boiled farm milk during pregnancy was positively associated with increased immunoglobulin E serum levels to cow’s milk and other food allergens [118]. The milk-induced maternal increase of the insulin-IGF-1 signalling might shift the insulin-IGF-1 axis in the fetal thymus,

thereby damaging proper apoptosis of allergy- and autoimmune-prone T-cells explaining the co-appearance of atopic and autoimmune diseases later in life. Intriguingly, breast-fed humans have significantly lower serum IGF-1 levels than those fed on a cow milk based formula [40]. Moreover, the consumption of milk and milk products in pregnancy would be a good explanation for the dominating maternal effect in the transmission of atopic diseases.

Discussion and hypothesis

Our “inborn belief” of the beneficial effect of cow’s milk in human nutrition is challenged. Humans are the only species on earth allowed to consume milk, an evolutionary designed sophisticated growth-signalling system, lifelong after weaning. Cow’s milk consumption and most likely other dairy products have an enormous impact on the human GH/insulin/IGF-1 axis, disturbing most sensitive hormonal regulatory signalling networks, interfering with IGF1R-signalling from fetal life to senescence (Fig. 3). The presented hypothesis elucidates that man-made manipulation of the human insulin/IGF-1 axis is involved in the development of most chronic diseases of Western societies (Table 1). For the first time, apparently unrelated aetiopathological processes in disease development could be related to disturbed insulin/IGF-1 signalling which is most critical for the early programming of various systems in the human organism. The prenatal and postnatal period may be the most sensitive periods for milk-induced disease development. This hypothesis explains most chronic diseases of Western societies on the basis of over-stimulated, proliferative responses and reduced inhibition of apoptotic mechanisms by IGF-1. Cow milk protein consumption has been identified as the basic environmental factor promoting a permanent shift of the insulin/IGF-1 axis to higher levels which are inadequate for humans. The ease of access of milk protein products and their extended distribution in Western nutrition leads to a permanent manipulation of an intrinsic and most sensitive hormonal signalling system in man. Cow milk and cow milk protein consumption with its high insulin and IGF-1 stimulatory effects has to be regarded as a violation of a physiological principal in mammalian nutrition developed during the eons of mammalian evolution. The short-sighted view on the beneficial effects of milk consumption on bone formation and bone mineralization ignores already well documented facts of harmful disease- and cancer promoting effects of milk protein

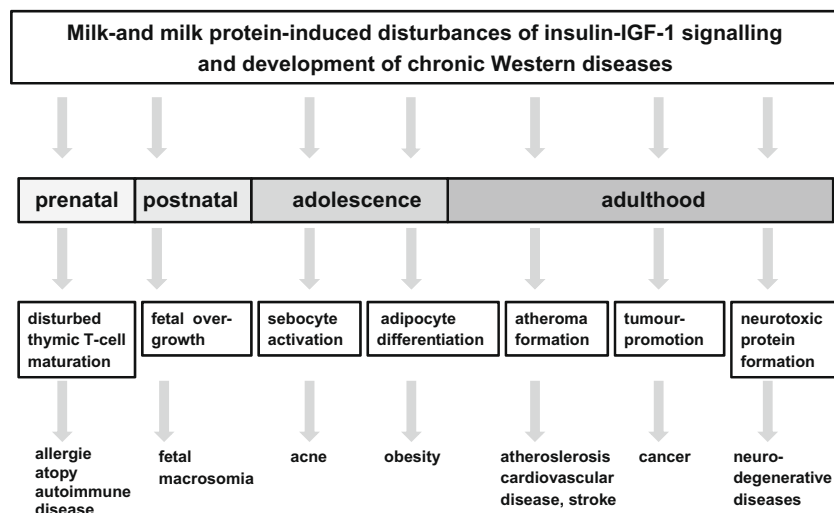


Fig. 3. Synopsis of milk and milk protein-induced disturbances of insulin/IGF-1 signalling from fetal life to senescence and associated chronic diseases of Westernized societies.

Table 1

Potential hazards of milk protein consumption due to enhanced insulin/IGF-1/IGF-2 signalling.

Thymus	Disturbance of T-cell maturation and proper T-cell apoptosis	Atopic diseases, allergies and autoimmune diseases
Placenta	Enlargement of placenta with increased flux of nutrients	Fetal macrosomia with increased risk for diabetes and cancer
Bone	Improved bone density and growth	Accelerated linear growth, height as a risk factor for breast cancer
Adrenal	Stimulation of adrenal steroidogenesis	Early puberty, increased adrenal androgen levels, early onset of acne
Ovary	Stimulation of ovarian steroidogenesis	Increased androgen synthesis, promotion of PCOS
Adipose tissue	Stimulation of adipocyte differentiation	Obesity and obesity-related diseases
Cardiovascular system	Stimulation of atherogenesis	Coronary heart disease, myocardial infarction and stroke
Glands	Tumour promoting effects, enhancement of cell proliferation, inhibition of apoptosis	Tumour promotion, induction of adenocarcinomas
Nerve system	Imbalance of protein clearance capabilities with resultant proteotoxicity	Acceleration of neurodegenerative diseases and dementia
Skin	Stimulation of sebaceous glands with increased sebaceous lipogenesis	Aggravation of acne, epidemic acne

consumption. It is a principle of science to propose a hypothesis to understand a phenomenon. The simplicity of a hypothesis and the possibility to deduce explanations for various facts increases its degree of probability. This scientific principle can be applied to insulin/IGF-1 signalling in various cell systems. According to the presented hypothesis cow milk consumption has to be regarded as a health hazard for humans which affords immediate intervention. It is of special concern, that pregnancy and the postnatal period are most sensitive programming periods in human life which should not be manipulated by an evolutionary developed growth stimulating system of another mammalian species imposed on the human IGF-1 axis. Consequently, gynaecologists should not advise pregnant women to consume milk during pregnancy. The hormonal changes during the first months of intrauterine and postnatal life may affect adult health outcomes predisposing to cancer, allergies and other diseases. Dermatologists and paediatricians should recommend to reduce milk consumption in patients with acne. In this context, persistent acne in adulthood with increased IGF-1 serum levels should be considered as an indicator disease of increased cancer risk like in PCOS and acromegaly. Paediatricians and general practitioners should consider milk restriction in patients with obesity to reduce the synergistic insulinotropic effects of milk- and hyperglycaemic carbohydrate enriched diets. Oncologists should advise their cancer patient families to refrain from milk and milk protein consumption. Especially, persons with already increased IGF-1 serum levels and those with genetic variations with elevated IGF-1/IGF1R signalling should refrain from milk consumption. Caution is also necessary in patients with a familial risk of atherosclerosis as well as neurodegenerative diseases which might be postponed in onset by a reduction of milk- and milk protein intake. It is most important to evaluate safe limits for the daily consumption of milk proteins. A better understanding of the mechanism of the insulinotropic and IGF-1 raising effects of milk proteins might lead to targeted enzymatic or biophysical destruction of these adverse mitogenic and antiapoptotic effects.

Currently, Asian populations increase their milk consumption and the Dietary Guidelines for Americans 2005 recommend that Americans should increase their intake of dairy products. An urgent global multidisciplinary approach is necessary to study the adverse effects of chronically over-stimulated insulin-IGF-1 signalling induced by milk and dairy product consumption in humans on a basis of controlled and randomized open studies. The presented epidemiological, biochemical, clinical and circumstantial evidence supports the presented hypothesis that cow's milk consumption is a major health hazard and should be recognized as a promoter of most common chronic diseases of industrialized countries (Fig. 3). Long-term reduction in milk and dairy product consumption could have an enormous impact on disease programming,

mortality, onset of chronic diseases and costs for our health care systems.

Abbreviations

ACTH	adrenocorticotrophic hormone
AGA	appropriate for gestational age
DHEAS	dehydroepiandrosterone sulphate
DHT	dihydrotestosterone
GH	growth hormone
GHR	growth hormone receptor
IGF	insulin-like growth factor
IGFBP	IGF binding protein
IGF1R	IGF-1 receptor
IGF2R	IGF-2 receptor
IR	insulin receptor
LH	luteinizing hormone
LGA	large for gestational age
MAPK	mitogen activated protein kinase
PCOS	polycystic ovary syndrome
PI3K	phosphoinositide-3-kinase
SGA	small for gestational age
SREBP	sterol response element binding protein

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