

Review: Milk and Milk Products, Insulin-like Growth Factor-1 and Cancer

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Abstract

Insulin-like growth factor-1 (IGF-1) has a structure similar to insulin. IGF-1 plays a role in growth-promoting process that is essential for normal growth and development. Physiological levels of IGF-1 in milk are ranged from 0.3 to 15 ng/ml. Milk from cows treated with recombinant bovine growth hormone (rBGH) contained higher mean IGF-1 levels as compared to milk from cows not treated with rBGH. However, this value was well within physiological limits of naturally occurring IGF-1 in milk from cows not treated with rBGH. Various studies have contradicted the intact passage of orally fed IGF-1 through the gastrointestinal tract and reaching the plasma. IGF-1 was undetectable in milk heated to temperatures (121°C for 5 minutes). Various studies have indicated association between IGF-1 and different types of cancer. However further studies are required to establish strong conclusive correlation. When it comes to association of IGF-1 from milk and milk product, we found studies indicating association between IGF-1 and different cancer as well as studies contradicting these findings. Moreover, further studies are required to establish strong conclusive correlation. The natural variation in individual's IGF-1 producing capabilities were not considered in these studies and that's an important factor to consider. FDA in their report (2009) concluded that, biologically significant levels of intact IGF-I from milk would not be absorbed in human and it presents no increased health risk to consumers.

Keywords: *Insulin-Like Growth Factor-1; rBGH; Milk; Milk Products; Dairy Processing and Cancer*

Abbreviations

IGF-1: Insulin-Like Growth Factor-1; rBGH: Recombinant Bovine Growth Hormone; IGFs: Insulin-Like Growth Factors

Introduction

Recently, there has been a rise in concern over higher level of IGF-1 in milk and milk products made from cows treated with rBGH and its link to increasing risk of cancer. In this review, we have tried to summarize the general information about IGF-1 and various scientific studies done to understand the rise in the level of IGF-1 in cows due to rBGH treatment and its level of significance to cause any increase in health risk, studies to understand the effect of various processing condition on IGF-1 level in milk, association between IGF-1 and cancer, and association between IGF-1 from milk and milk products and cancer. The objective of this review paper is to provide the comprehensive review of the overall research done in this area and identify the gaps to help future researchers come up with more conclusive evidence.

Insulin-like growth factor-1 structure and function

The Insulin-like growth factors (IGFs) are members of a family of insulin related peptides including relaxin and several peptides isolated from lower invertebrates [1]. IGFs were mentioned as humoral mediators of growth hormone action [2]. Among IGFs, Insulin like

growth factor-1 (IGF-1) is a small single chain polypeptide made up of 70 amino acids with a molecular weight of 7649 Da [3]. Similar to insulin, IGF-1 has an A and B chain and which is connected by three disulfide bonds [3]. IGF-1 has structure similar to insulin and it has an ability to bind (with low affinity) to the insulin receptor [4]. Since, IGF-1 has a structure similar to insulin, it plays an important role in cellular glucose metabolism, amino acid uptake, glycogen synthesis, mitogenesis, and lipogenesis [5]. The majority of the IGFs found in serum exist in a 150-kDa complex, which includes IGF molecule, the acid labile subunit and IGF binding protein 3. This complex enhances the half-life of serum IGFs and facilitates their endocrine actions [6].

IGF-1 is a normal constituent in blood, milk, human saliva and is a necessary part of life. IGF-1 plays a role in growth-promoting process that is essential for normal growth and development. It is involved in regulation of human development, energy balance and cell growth [7,8]. IGF-1 has a well-characterized role in protein, glucose and lipid metabolism [9]. The role of IGF-1 on glucose metabolism and growth is well demonstrated [10]. Growth hormone and IGF-1 both play an important role in growth and in homeostasis of the skin and various tissues [11]. The IGF-1 is also believed to enhances chondrocyte proliferation in the growth plate; in bone tissue, it stimulates osteoblast proliferation and differentiation and matrix formation, including the synthesis of type I collagen and other protein components [12]. IGF-1 has potent anabolic effects on growing skeletal tissue. At birth, concentrations of IGF-1 are about half adult levels; they increase gradually during childhood, reaching a peak at pubertal stages [13]. Overall IGF-1 has an important role in various growth related physiological processes.

Presence of IGF-1 in milk and milk products

Milk and milk products contains many hormones such as prolactin, steroids including estrogens, progesterone, corticoids, androgens, prostaglandins and IGF-1 [14]. Various studies have been done to determine the level of IGF-1 in milk and milk products under different conditions. IGF-1 concentration in cows' milk determined using immunoassay method and reported that the physiological levels of milk IGF-1 in cows are ranged from 0.3 to 15 ng/ml. Researcher in this study also suggested that the broad range of minimum and maximum concentrations of IGF-1 in cows' milk could be related to differences in body weight, milk composition, diet and management practice. They reported that IGF-1 concentration was higher in early lactation than mid and late lactation with concentrations in multiparous cows exceeding those in primiparous cows. They also found that IGF-1 concentration was negatively correlated to milk production on the day of sample collection ($r = -.15$) and not correlated to predicted 305-d milk yields. They also studied the samples ($n = 100$) of unprocessed bulk tank milk from a commercial processing plant and had a mean concentration of IGF-1 in milk of 4.32 ng/ml with a range of 1.27 to 8.10 ng/ml. This distribution of IGF-1 was similar to the range measured in samples from individual cows, but values were lower than those found for human milk [14].

IGF-1 level was estimated in primiparous and multiparous cows to milk, and it was reported that multiparous cows had a higher concentration (40 nmol/l) at parturition than primiparous cows (19.2 nmol/l). Researchers in this study also found that at day 2 of lactation, IGF-1 concentrations were 30 and 50% of initial estimates for multiparous and primiparous cows respectively. The final IGF-1 concentration, on day 56 of lactation, was 4.5 nmol/l for combined parity groups. At parturition in multiparous cows, the mass of IGF-1 was estimated at 183 and 157 nmol/l for blood and milk pools respectively. Milk, therefore, represents a substantial pool of IGF-1 in the cow [15]. Higher concentration of IGF-1 found in colostrum (103 ± 21 ng/mL) than in blood, however, which dropped below blood level post parturition of milk IGF-1 [15,16]. No significant relationship between IGF-1 level in milk and milk production was reported and dramatic drop in concentration of milk IGF-1 during the lactation period as 6.3 ng/ml on days 6 - 15 and 1.6 ng/ml on days 210 was observed [14].

In previous research it was found that milk from cows (34 cows) treated with recombinant bovine growth hormone (rBGH) contained higher mean IGF-1 levels (8 ng/ml) compared to (4 nm/ml) milk from cows not treated with rBGH. However, this value was well within physiological range (4 to 35 ng/ml) of naturally occurring IGF-1 in milk from cows not treated with rBGH. They also observed that 10 days after rBGH treatment IGF-1 level in milk reached to a maximum and declined in the following two weeks back to initial values. This

study included small number of cows and hence, they recommended to confirm their results with the help of larger studies including different breeds and longer periods of application time [17]. Similarly, another group of researchers in their study observed increased concentration of IGF-1 in milk obtained from rBGH treated cows (Six lactating non-pregnant Jersey cows treated with rBGH for 7 days) to 1.6 +/- 0.2 nmol/l compared to day 1 concentration of 0.44 +/- 0.04 nmol/l. They also reported that the IGF-1 in milk from cows treated with rBGH was associated predominantly with proteins ranging from 40,000 to 150,000 mol. wt., but a significant proportion (19%) of the total IGF-1 was present in the free unbound form. IGF-1 crosslinking studies revealed the presence in milk of one specifically labelled band at 31,000 mol. wt. [18]. Various other researchers also found that, the levels of IGF-1 in milk from rBGH treated cattle were within the range of inherent milk variations detected in cattle not treated with rBGH [18,19]. Furthermore, salable milk produced during the 1st week of lactation would have higher concentrations of IGF-1 than those reported in milk from rBGH treated cows. A dairy industry that is highly seasonal, such as New Zealand, might demonstrate relatively large variation in IGF-1 content of shelf milk due to this stage of lactation effect.

Effect of processing on IGF-1 level in milk, milk products and dietary intake

Concentration of IGF-1 in milk was not affected by pasteurization treatment (at 79°C for 45s) and hence it will be present in shelf milk [14]. For comparison, concentrations of IGF-1 in saliva and salivary production rate would suggest that intake of IGF-1 via saliva (2 to 4 pg/d) approximates the amount of IGF-1 present in 0.72L of milk (3.1 pg/d for bulk tank mean value of 4.3 ng/ml). Presently, no studies have been conducted evaluating the biological value of presence of IGF-I in milk or saliva [20]. IGF-1 was undetectable in milk heated to temperatures (121°C for 5 minutes) required for infant formula preparation or in commercially available infant formula. Possibly, this loss of IGF-1 is of biological significance because it is well known that neonates fed with formula or milk replacer do not thrive as well as neonates given access to maternal milk [21,22]. The research aimed at understating the effects of various dairy processes on IGF-1 concentrations in milk and IGF-1 stability during the storage period in fortified dairy products. It was reported that the IGF-1 level in raw milk determined by radioimmunoassay was significantly changed by the different levels of heat treatments. They observed that, in commercial manufacture of whole milk dry powder, IGF-1 concentration was not significantly changed. They also observed a significant reduction in IGF-1 content as the result of fermentation with a commercial starter culture. The IGF-1 content in dried powder and fortified milk displayed no significant changes over the tested storage periods of 4 week for dried milk powder and 12 days for milk, but the IGF-1 content in the yogurt decreased significantly during storage. The use of IGF-1 was varied by lactic strains and was apparent in the viable cells. The encapsulation of IGF-1 displayed that, the remaining IGF-1 content after fermentation was significantly higher compared with that of the untreated control [23].

The IGF-I in the milk of rBGH treated cows were potentially more bioactive compared to naturally occurring in milk treated without rBGH. Researcher also suggested that its bioactivity may be increased further by pasteurization [24]. The increase in serum levels (10 - 20%) of circulating IGF-1, and in children to a 20 - 30% increase was reported. This increase in serum level of circulation IGF-1 was the fact that, IGF-1 remains intact as it passes through the gastrointestinal tract and reaching the plasma in its bioactive form. Researcher also suggested that the casein is protective for IGF-1 absorption. He also reported that the girls who consume less than 55 ml of milk per day had a significantly lower IGF-1 levels than girls who consume milk in excess of 260 ml per days [25]. Similarly, study of 2,109 women showed a significant positive correlation between milk consumption and serum levels of IGF-1 [26]. Furthermore, 10% higher level of serum IGF-1 found in people who consumed 3 servings of milk daily than people who drank less than 1.5 servings [27]. Although, healthy people may absorb only limited quantities of IGF-1, the situation is likely different for people with conditions that can cause increased intestinal permeability, such as Crohn's disease, autism, celiac disease, cirrhosis, and cow's milk allergy. The use of various medications, such as aspirin and other nonsteroidal anti-inflammatory drugs, can also increase intestinal permeability. In addition, an estimated 10% to 20% of the general "healthy" population unknowingly suffers from this condition [28]. Hence, it was suggested that, it is not enough to look at healthy adults and say that the intestinal absorption of IGF-1 is negligible. Rather, the vulnerable in society need to be protected [29]. Research contrasting to aforementioned observation suggested that the data about the bioavailability of milk IGF-1 in animals and humans is lacking and it is not clear yet, how percentage of IGF-1 in consumed dairy products could be reached through the gastrointestinal tract into central compartment since it is structurally more similar to the insulin, which is rapidly degraded in gut [30].

Correlation between IGF-1 and cancer

There have been several studies done to understand the correlation between IGF-1 and Cancer. One of the study focused on this area of research mentioned about various epidemiologic studies [31] where, association of consistent high circulating levels of a potent mitogen and insulin-like growth factor (IGF-I) with increased risk for several common cancers, including those of the breast [32], prostate [33,34], lung [35] and colorectum [36] were cited. When we review these cited research papers we learn that, in the study about breast cancer it was hypothesized that high circulating IGF-I concentrations would be associated with an increased risk of breast cancer, however in their research finding they did not find any association between IGF-I concentrations and breast-cancer risk among the whole study group. In their study, they interpreted the positive relation between circulating IGF-I concentration and risk of breast cancer among premenopausal but not postmenopausal women. They suggested that Plasma IGF-I concentrations may be useful in the identification of women at high risk of breast cancer and in the development of risk reduction strategies. However, they suggested additional larger studies of this association among premenopausal women are needed to provide more precise estimates of effect. Hence, IGF-1 responsible for the high risk of breast cancer was not clearly established in this study [32,37]. In case of prostate cancer, researcher conducted a case-control study within the physician's health study on prospectively collected plasma from 152 cases and 152 controls and they suggested a strong positive association between IGF-I levels and prostate cancer risk. They suggested cancer risk reduction and treatment through identification of plasma IGF-I as a predictor of prostate cancer [33]. The association of IGF-1 and ovarian cancer is also reported [38]. Increased risk of cancer development with increased serum levels of IGFs and/or altered levels of their binding proteins are reported in various studies [39]. Data based on these studies underline the significance of IGFs system in the development of cancer risk, and a potential target for novel anticancer treatments and/or preventative strategies in high-risk groups. Elevated level of plasma IGF-1 and serum IGFBP3 in breast cancer patients is reported. Researcher also observed that, the IGF-1 did not correlate with age and nodal stage, IGF-1 and IGF binding protein 3 increased with tumor size, IGF-1 did not correlate with estrogen receptor status but did increase in progesterone-receptor-positive patients. IGF-1 levels were higher in premenopausal patients and in women with cancer recurrence. Tamoxifen reduced IGF-I levels significantly and reduced the risk of recurrence. They also suggested greater survival probability in patients with plasma IGF-1 levels < 120 ng/ml and concluded that lowering of plasma IGF-1 may reduce the risk of developing breast cancer in high-risk groups and slow the progression of breast cancer in patients at early stages of cancer [40]. Strong positive association between IGF-1 levels and prostate cancer risk was suggested in the study involving case-control study within the physicians on prospectively collected plasma from 152 cases and 152 controls [33]. The Random effects meta-analysis (Involving 5 cohort and 29 case-control studies) reported an association between dairy consumption and gastric cancer [41]. The inhibition of IGF1/IGF1 receptor as a viable therapeutic strategy to suppress the progression of Glioblastoma multiforme malignant tumor was suggested [42]. Meta-analysis results demonstrated the role of IGF1 gene rs1520220 in cancer susceptibility varies by ethnicity and cancer type and that gene rs1520220 increases cancer susceptibility in Asian populations [43]. The role of IGFs in increasing the risk of cancer and many aspects of the IGF system and its relationship to cancer were discussed [44,45]. The raised serum IGF-1 levels and its association with increased risk of prostate, breast and colorectal cancers were also discussed [46].

IGF-1 in milk and dairy products and its association with risk of developing cancer

Various researchers also tried to understand the correlation between IGF-1 and dairy products consumption, and we can see various contrasting outcome of different researches. It was suggested that the rBGH initiates the production of IGF1 to high levels in milk and presence in milk is resistant to pasteurization [14]. Consequently, the consumption of milk from rBGH treated dairy cows will likely increase the daily intake of bovine IGF-1 [47]. Human IGF-1 and bovine IGF-1 are chemically similar and allowing the bovine hormone to be biologically active in humans. They suggested that the role of IGF-1 in cancer is supported by various epidemiological studies revealing association between with increased risk of several common cancers such as prostate, breast, colon-rectum and lung and high levels

of circulating IGF-1. The combination of IGF-1 in rBGH-milk and IGF1 in the human gastrointestinal lumen would augment intraluminal concentrations of this hormone [48]. This increases the possibility of local mitogenic effects on gut tissues. The association between whole milk consumption and an increased risk of prostate cancer recurrence was suggested [49]. However, in this study, the association between whole milk and increased risk of prostate cancer recurrence was only observed among men at the upper range of overweight and obese men (BMI ≥ 27 kg/m²). They proposed mechanisms for the potential effect of dairy on risk of prostate cancer included: high calcium intake decreasing vitamin D levels [50-52] and increasing IGF-1 Levels [53,54], fluctuating phosphorus levels modifying vitamin D3 concentrations [55] and elevated saturated fat intake [56]. Their team previously reported association between saturated fat intake with an increased risk of prostate cancer-specific mortality among men with prostate cancer in the Physicians Health Study [56]. This supports the proposed hypothesis that the saturated fat content of whole milk in part contributes to the adverse association observed. Hence, this study also indicates that milk is such a complex food that IGF-1 level in milk alone cannot be considered responsible for potential agent for cancer and other constituents in milk should be considered as well. The available evidence suggests that milk increases IGF-1, and this may affect breast cancer risk. However, epidemiological studies were so far not successful in establishing a strong relationship between milk and the breast cancer risk. They also review other studies to understand the role of dairy products in the development of breast cancer risk factors and hypothesized that milk causes greater adult-attained height, early menarche, higher birth weight and delayed menopause which all can be considered as breast cancer risk factors and associated to higher levels of IGF-1. The relationship with adult weight and breast density is still not clear and inconsistent. They also hypothesized that the milk intake may influence breast cancer potentially through elevated IGF-1 level, but they were not certain about association with other dairy products. This requires more studies to examine these hypothesis [57]. Higher intakes of yogurt were associated with reduced risk of breast cancer and higher intakes of cheddar and cream cheeses were associated with a marginally significant increased risk. Associations with dairy foods were mixed and in general reflected those of overall breast cancer. However, they observed positive associations between milk intake and risk of estrogen-receptor-positive breast cancer and inverse associations between sweet dairy and estrogen-receptor-positive breast cancer. They suggested that the specific dairy foods may contribute to breast cancer risk in women although, the risk varies by source of dairy. They recommended future studies to confirm the protective potential of yogurt in this type of cancer [58]. Diet low in glycemic index and milk protein content reduces IGF-1 signaling and high IGF-1 levels may be considered as an indicator for higher risk of cancer, which may require treatment with insulin-sensitizing agents and appropriate dietary intervention [59]. Meta-analysis study concluded that there was moderate evidence that circulating IGF-1 increase with milk (and dairy protein) intake and that prostate cancer risk increased with IGF-1 level [60]. The association appears to be due to the protein content of milk [61].

Contrasting research and outcomes compared to aforementioned studies and observations are also available. It was suggested that the milk and milk product intakes were inversely associated with bladder cancer, colorectal cancer, gastric cancer, and breast cancer, and not associated with risk of ovarian cancer, pancreatic cancer, or lung cancer, while the evidence for prostate cancer risk was not consistent [62]. Dairy products are of a complex composition and also consumption varies by region, such factors makes evaluation of their association with disease risk difficult. For most cancers, association between risk of cancer and milk and dairy product consumption have been examined only in a small number of cohort studies, and data are lacking or inconsistent. Meta-analyses of cohort data available to date suggest an inverse relations between dairy product intakes and risk of colorectal and bladder cancer. They also suggested that, influence of certain cheeses and live microbes in fermented dairy products on the human gut microbiome and immune function is a growing area of study [63]. It was suggested that drinking milk before puberty reduces later risk of developing mammary cancer in rats [64]. Meta-analysis from 14 studies on milk (4879 cases) and 6 studies on dairy products (3087 cases) and involving total study population of up to 324,241 individuals reported that overall there was no significant association between milk intake and bladder cancer. However, they observed an inverse association for the United States. In addition, they reported no significant association between dairy products consumption and bladder cancer risk, but an inverse association was detected in case of the Japanese population. In their study, they concluded that, the findings of this meta-analysis were not supportive of an independent relationship between the intake of milk or dairy

products and the risk of bladder cancer. However, these findings were based on limited research and further efforts should be made to confirm these findings [65].

Conclusion

IGF-1 plays an important role in growth-promoting process that is essential for normal growth and development. Physiological levels of milk IGF-1 in cows are ranged from 0.3 to 15 ng/ml. Milk from cows treated with rBGH contained higher mean IGF-1 levels compared to milk from cows not treated with rBGH. However, this value was well within physiological limits of naturally occurring IGF-1 in milk from cows not treated with rBGH. Different studies contradicted the intact passage of orally fed IGF-1 through the gastrointestinal tract and reaching the plasma. IGF-1 in milk was not altered by pasteurization (at 79°C for 45s), whereas, IGF-1 was undetectable in milk heated to temperatures (121°C for 5 minutes) indicating that it can be destroyed by high heat treatment. Various studies indicated association between IGF-1 and different types of cancer. However, various researchers suggested requirement of further studies to establish strong conclusive correlation. Various studies supporting association between IGF-1 (from milk and milk products) and different cancer are available and on the other hand studies contradicting these findings are also available. Moreover, further studied are required to establish these strong conclusive correlation. The natural variation in individual's IGF producing capacities were not considered in these studies and that's an important factor to consider. Individuals not consuming dairy products but with abnormally high IGF-1 producing capacity are more likely to be towards higher risk of getting cancer and involvement of such individuals in these studies will have the misleading conclusion.

Food and Drug Administration (FDA) scientist reviewed the scientific literature and evaluated various studies conducted by pharmaceutical companies and based on that they reached to a conclusion, that the rBGH treatment produces an increase in the concentration of IGF-I in cow's milk. This increased level of IGF-1 was found to be within the normal physiological range observed in human breast milk. Also, IGF-I denatures under conditions used to process cow's milk for infant formula which reduces the level of native IGF-1 in final product. The oral toxicity studies in rats displayed lacking oral activity of bovine IGF-I. Considering aforementioned observations and on the basis of estimates of the amount of intact protein absorbed in humans, it is concluded that the biologically significant levels of intact IGF-I would not be absorbed in humans and hence the use of rBGH in cow presents no increased risk to the health of consumer [66]. The overall available scientific studies suggest that consumption of milk and milk products contribute to satisfy various nutrient recommendations, and may help in providing protection against various chronic diseases, on the other side very few adverse health effects have been reported very conclusively [62].

Several studies with contradicting outcomes on the association between IGF-1 from dairy products and different types of cancer are available. However, further studies are required to establish strong conclusive correlation and these studies should also consider natural variation in individual's IGF-1 producing capabilities.

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