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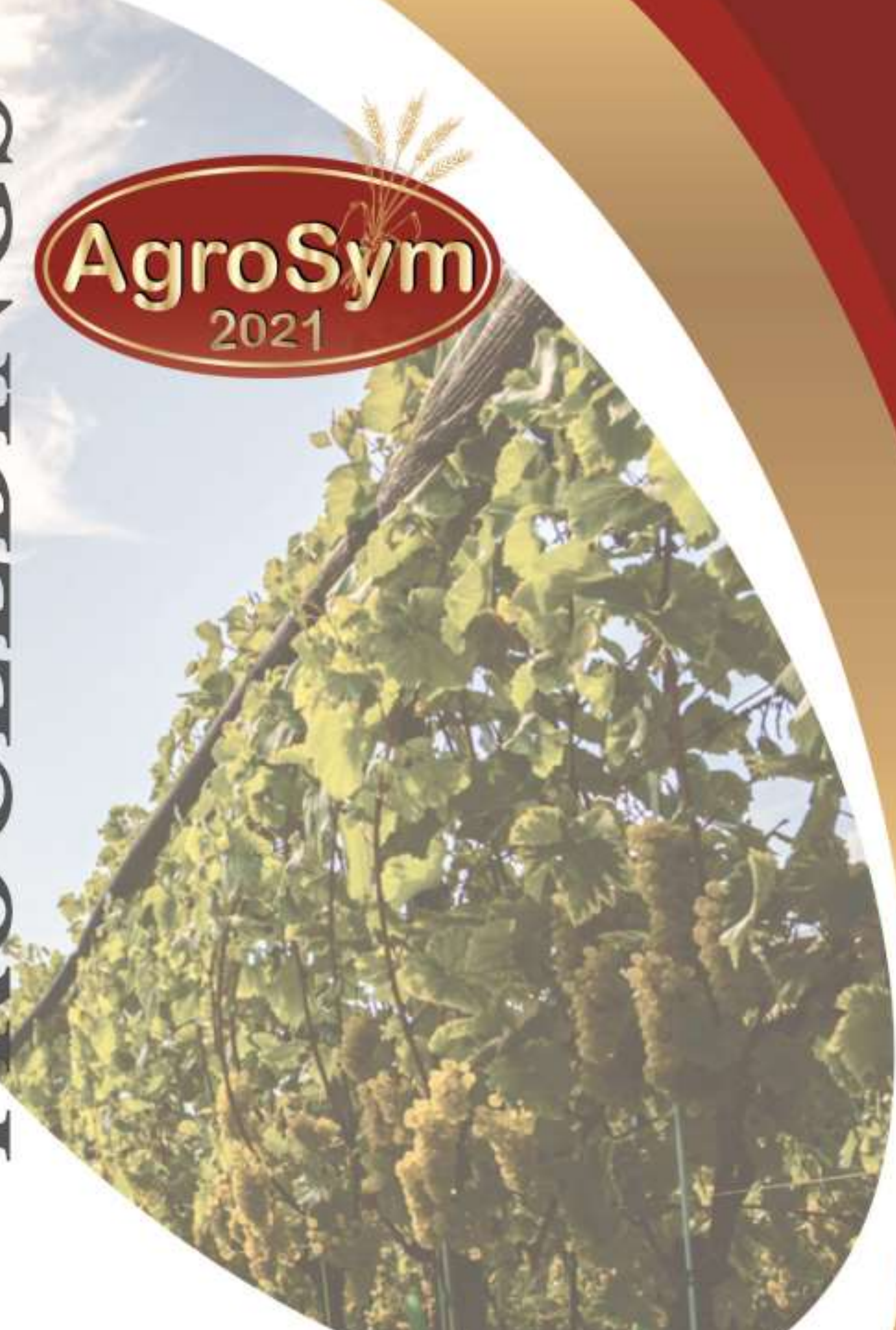

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COW MILK INSULIN LIKE GROWTH FACTOR-1: RISK OR BENEFIT FOR HUMAN HEALTH?

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Abstract

Cow milk is widely consumed by human children and adults due to its nutritional value. Besides nutrients, milk contains naturally occurring hormones, including insulin like growth factor-1 (IGF-1), that may alter their blood levels in the consumers. At the same time, the impact of IGF-1 on human health is still unclear and controversial. The aim of the study was to determine IGF-1 concentrations in cow colostrum and milk and to discuss them from the aspect of human health. Twenty Holstein cows were enrolled in the study and subjected to colostrum, milk and venous blood sampling in order to determine the IGF-1 concentration by the radioimmunoassay (RIA). Colostrum was sampled at 2, 14 and 26 hours (1st, 2nd and 3rd colostrum) after calving, while milk and venous blood were taken 10 days after calving. The concentration of IGF-1 was the highest in the 1st colostrum and decreased significantly with each subsequent sampling, so the lowest concentrations were detected in milk sampled 10 days after calving. High concentrations of IGF-1 observed in colostrum, especially in the 1st colostrum, reflect its potential for eventually use in the treatment of various intestinal diseases. However, further research should determine the conditions and limitations of its application. On the other hand, additional research is needed to determine whether IGF-1 in milk has harmful effects on human health and whether it is necessary to limit the permitted presence of this hormone in cow milk.

Keywords: *cow milk, insulin like growth factor-1 (IGF-1), human health.*

Introduction

Cow milk is considered as nutritionally valuable food in the human diet, which is consumed from birth to old age (Marangoni et al. 2019). It contains proteins of high biological value, fats, carbohydrates, minerals and vitamins, that provide beneficial effects on the overall growth of children and qualify the use of milk in the prevention and treatment of them malnutrition (Agostoni and Turck 2011; Turck 2013). In addition to nutrients, cow's milk also contains biologically active substances, including immunoglobulins, lactoferrin, enzymes, cytokines, growth factors and naturally occurring hormones. The presence of biologically active substances in cow milk is essential for the newborn (Kirovski 2015). They support the growth of the newborn calves and the development and activity of their gastrointestinal and immune functions (Kirovski et al. 2002; Georgiev 2008; Park and Nam 2015). However, when consumers ingest biologically active substances, they may also cause a wide range of biological effects in the body. For instance, milk hormones could affect hormones levels in the blood and may affect physiological and pathological processes in the organism of consumers (Malekinejad and Rezabakhsh 2015). Therefore, it has been proven that milk estrogens have harmful effects on human health (Snoj and Majdič 2018), while the impact of insulin-like growth factor-1 (IGF-1) from cow's milk has not been elucidated and attracts attention from researchers and consumers also.

Bovine IGF-1 is a polypeptide composed of 70 amino acids predominantly synthesized in the liver but can also be synthesized in other tissues and exhibit endocrine, paracrine, and autocrine effects (Fruchtman et al. 2002). This hormone is known as a strong mitogen factor, promoting cell growth and proliferation and inhibiting apoptosis (Clatici et al. 2018). In all biological fluids, IGF-1 is almost entirely (95-99%) bound to one of six structurally similar IGF binding proteins (IGFBP-1 to -6) (Forbes et al. 2012). Consequently, less than 1 % of IGF-1 circulates freely – unbound to IGFBPs (Clemmons 1993; Kirovski et al. 2008; Melnik 2009). The concentration of IGF-1 in cow milk varies widely, from approximately 1 ng/mL to 150 ng/mL, depending on the stage of lactation, milk composition, and other environmental factors (Malekinejad and Rezabakhsh 2015). Thus, the highest concentrations of IGF-1 occur immediately after parturition in colostrum and then gradually decrease until it falls to the level of 1 to 5 ng/mL (Šamanc et al. 2009; Castigliego et al. 2011).

There are several reasons why the presence of IGF-1 in cow milk is a source of human health issues. IGF-1 has a highly conserved sequence across species because bovine IGF-1 can bind with identical affinity to IGF receptors on human tissues, thus achieving physiological effects (Renaville et al. 2002; Melnik 2009). Furthermore, there are data on both beneficial and harmful effects of IGF-1 on human health in scientific literature. Ungvari and Csiszar (2012) report that low levels of circulating IGF-1 increase the risk of cardiovascular and cerebrovascular diseases in humans. At the same time, a low concentration of IGF-1 in the early phase of acute myocardial infarction predicts a worse prognosis (Conti et al. 2001). The protective effect of IGF-1 on Alzheimer's disease (O'Neill et al. 2012) and all forms of dementia, including Parkinson's disease dementia (Westwood et al. 2014), has also been documented. Typically, there are numerous estimates that IGF-1 has a positive effect on bone health; therefore, it is considered that clinical determination of IGF-1 may be useful in assessing the risk of bone fractures (Lombardi et al. 2005; Locatelli and Bianchi 2014).

On the other hand, numerous epidemiological studies have linked high levels of circulating IGF-1 to an increased risk of several cancers in humans. In this context, breast, prostate, lung and colon-rectal cancers are most commonly reported in the literature (Sutariya et al. 2018). This is important because the digestion of IGF-1 ingested through cow's milk is prevented by milk proteins, which potentially enables its intestinal absorption. Thus, higher milk consumption leads to an increase in circulating IGF-1 levels by 20-30% in children and 10-20% in adults (Melnik 2009). At the same time, homogenization and pasteurization do not significantly decrease the content and activity of IGF-1 in cow milk (Collier et al. 1991). Therefore, Tate and coworkers (2011) suggest that patients with prostate or breast cancer should be informed about the possible promotional effects of dairy products.

The study aimed to determine the concentrations of IGF-1 in cow colostrum and milk, and analyze them in the context of human health.

Materials and Methods

Animals and Housing

The experiment was conducted at the commercial dairy farm in Belgrade, Serbia. Twenty Holstein cows were assigned for the study. Cows received diets as total mixed ration (TMR) to allow ad libitum feed intake throughout the study. After calving, cows were assigned to the lactation diet (crude protein = 161 g/kg DM; crude fat = 21 g/kg DM; NEL = 7.3 MJ/kg DM; ADF = 221 g/kg DM; NDF = 358 g/kg DM). Diet was formulated to either meet or exceed the NRC (2001) requirements. The feed was offered in two equal portions at 0700 and 1600 h, and cows had free access to water. Cows were maintained under a loose housing system.

Colostrum and Blood Sampling Procedures

The primary (1^{st}), secondary (2^{nd}) and tertiary (3^{rd}) colostrum were sampled from each cow 2, 14, and 26 h after calving, respectively. The milk sample was taken 10 days after calving. The samples were collected in sterile cups and were stored at – 20 °C for the further analyses. Blood was sampled by *v. jugularis* puncture at day 10 day after calving at 1000 h. The samples were collected into serum clot activator tubes.

Sample Preparation and IGF-1 Measurement

Colostrum and Milk Samples. Thawed colostrum and milk were centrifuged (2000×*g*, 20 min) and the fatty layer was carefully removed through vacuum aspiration. Casein was precipitated by adding 175 µL of rennet to 10 mL of centrifuged colostrum supernatant. After 30 min of incubation at 37 °C, samples were centrifuged for 15 min at 3000×g, and whey (supernatant) was aliquoted and stored at − 20 °C until analysis. IGF-1 concentration in colostral and milk whey was determined using radioimmunoassay (RIA-IGF-I, INEP, Belgrade, Serbia) (Nikolić et al. 1996).

Blood Samples. On the day of sampling, blood in the serum clot activator tubes was kept at room temperature and was allowed to clot. Serum was decanted, centrifuged within 30 min at 3000×g, portioned into aliquots of 1.5 ml, and stored in polypropylene microtubes at − 20 °C until analyses. Concentrations of IGF-1 in blood were measured by radioimmunoassay (RIA-IGF-I, INEP, Belgrade, Serbia) (Nikolić et al. 1996).

Statistical analysis

The statistical analysis was performed by determination of the mean value and standard error of the mean (SEM) for each sample. The statistically significant difference between the samples was evaluated by the Student's t-test and *p* values less than 0.05 were considered to be statistically significant. The analyses were performed using Excel 2019 software (Microsoft, Redmond, WA, USA) (Vega et al. 1991).

Results and Discussion

Preliminary results of our study demonstrate that the highest concentrations of IGF-1 are present in the 1st colostrum (59.23±3.32 nmol/L) (Figure 1). At the same time, these values were statistically significantly higher compared to the 2nd colostrum (37.91±2.49 nmol/L; $p<0.001$), 3rd colostrum (22.03±1.44 nmol/L; $p<0.001$) and milk (19.16±0.77 nmol/L; $p<0.001$). Moreover, Figure 1 reveals that the concentration of IGF-1 at each subsequent colostrum sampling period, including milk sampling on the 10 days after calving, was significantly lower ($p<0.05$, respectively) than in the previous one. Consequently, the lowest concentrations of IGF-

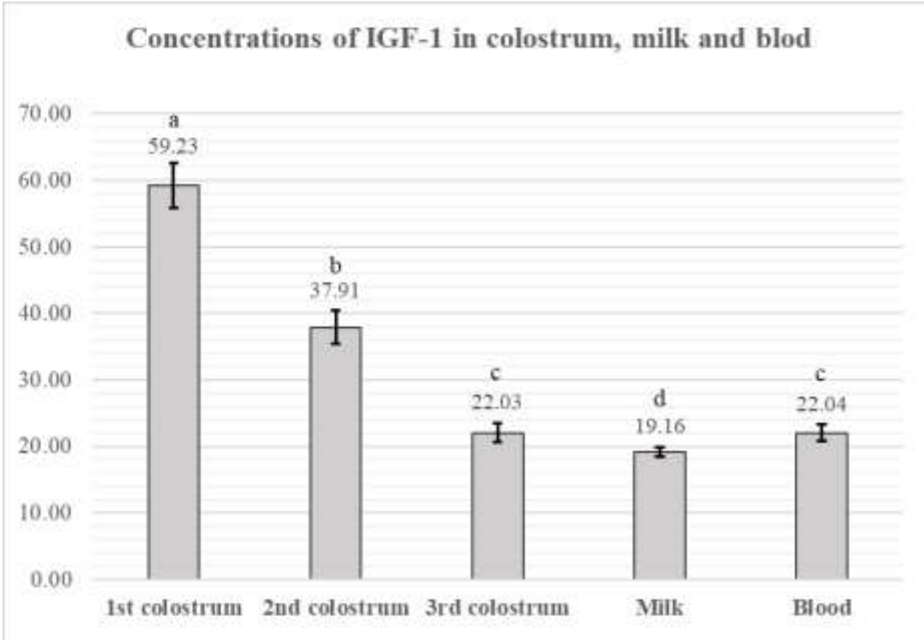

Figure 10. Mean IGF-1 concentrations (± SEM) in cow colostrum, milk and blood. 1st colostrum – sampled 2 hours after calving; 2nd colostrum – sampled 14 hours after calving; 3rd colostrum – sampled 26 hours after calving; Milk and Blood – sampled 10 days after calving. Different lowercase letters above the bars indicate a statistically significant difference ($p < 0.05$).

1 were found in milk sampled 10 days after calving, which were also significantly lower ($p<0.001$) than those determined in the blood serum (22.04±1.27 nmol/L) on the same day.

The obtained results suggest that the concentration of IGF-1 in colostrum decreases rapidly within the first day after calving, but a similar trend remains until the tenth day after calving. Analogous findings were obtained by Elfstrand and colleagues (2002), who reported that the highest concentrations of IGF-1 were present in colostrum in the first six hours after calving. Mentioned researchers also documented a rapid decrease in the concentration of IGF-1 in colostrum by 44% after 11-20 hours. This is relatively consistent with our results reflecting a 30% and 63% reduction in IGF-1 colostrum concentration after 14 and 26 hours after calving. Additionally, the further decline in IGF-1 concentration in cow's milk found in our study confirms the previously published results of Daxenberger et al. (1998), who described that IGF-1 concentrations in milk decrease gradually until 7 weeks after calving and remain low until 33 weeks of lactation. Finally, the biological importance of high IGF-1 levels in colostrum can be explained by its beneficial effect on the morphological and functional development of newborn calves (Blum and Hammon 2000; Kirovski et al. 2009).

Since colostrum is not a standard part of the human diet, the high level of IGF-1 in this mammary secretion cannot be considered a health risk for consumers. Moreover, previous literature data indicate that cow colostrum can be viewed as a functional food with health benefits for consumers. This is based on the fact that cow colostrum is a consummate source of biologically active proteins that can modulate the immunological function and improve intestinal peristalsis of consumers. Accordingly, a whole range of bovine colostrum-based products, such as various dietary supplements, drinks, and chewing gums, can be found in the markets of certain countries (Dzik et al. 2017; Mir et al. 2021). In addition, there is a growing scientific interest in the field of beneficial effects of bovine colostrum related to the physiological effects of IGF-1.

Mir and coworkers (2021) report that IGF-1 from bovine colostrum repairs intestinal morphology and function, stimulating the proliferation of intestinal crypt cells. IGF-1 also exhibits anti-inflammatory effects by several described mechanisms (Zatorski et al. 2016). Consequently, there are recommendations for using bovine colostrum or purified IGF-1 to treat inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis as the most common forms (Yadav et al. 2016; Zatorski et al. 2016). This perspective in the use of colostrum is very important because the number of diagnosed cases of IBD has increased dramatically worldwide in the last 50 years. Noteworthy, the number of new cases is growing in the population of children (Molodecky et al. 2012; Gasparetto and Guariso 2013). Furthermore, Crohn's disease and ulcerative colitis are accompanied by decreased intestinal production and circulating levels of IGF-1, which leads to other health complications. Indeed, patients with Crohn's disease or ulcerative colitis are at increased risk of developing osteopenia, osteoporosis, and osteoporotic bone fractures (Koutroubakis et al. 2011). In this context, the large amounts of IGF-1 in cow colostrum, shown by results of our previous (Kirovski et al. 2012) and presented study, only support the recommendations for the use of colostrum in the treatment of various intestinal diseases. However, subsequent research should examine the limitations of its use, because IGF-1 may have a promotional effect in patients with premalignancy conditions (Zatorski et al. 2016).

In contrast to colostrum, cow's milk and dairy products are widely used in human nutrition in our cultural sphere; therefore, consumer's interest in cow's milk safety is far greater compared to colostrum. Although it has been confirmed in various animal models (mice and rats) and cell cultures that IGF-1 promotes the growth of cancer, especially prostate (Tate et al. 2011; Cao et al. 2015) and breast cancer (Mawson et al. 2005), it is not entirely clear whether milk-borne IGF-1 can achieve a similar effect in humans. Namely, the proven increase in circulating IGF-1 in humans after milk consumption (Melnik 2009; Ventura et al. 2020) may not be the only consequence of intestinal resorption of IGF-1. There is a theory that dairy proteins are responsible for increasing IGF-1 levels after milk consumption (Giovannucci et al. 2003) because they are a source of essential amino acids that up-regulate hepatic IGF-1 gene expression (Thissen et al. 1994). If this theory is confirmed by future research, milk will be incriminated as a food independent of IGF-1 concentrations.

On the other hand, there is a theory that milk proteins, such as casein, protect IGF-1 from digestion, therefore the IGF-1 remains active in the serum after milk consumption (Melnik 2009). Accordingly, Philipps et al. (2000) suggested that radiolabeled IGF-1 could be found in the portal circulation at low concentrations. However, it is difficult to extrapolate these results to humans. Therefore, it is necessary to determine the essence of the increase in circulating IGF-1 in humans after milk consumption, as well as the critical levels of IGF-1 in cow's milk.

Conclusions

In the presented investigation, we found that IGF-1 concentrations are highest immediately after calving (first two hours) and decrease rapidly during the following 24 hours. After that, IGF-1 concentration gradually decreases, which is indicated by the measured values of IGF-1 in milk sampled on the tenth day after calving. Future research should examine the potential benefits of high concentrations of IGF-1 in colostrum, or the possible adverse effects of cow milk IGF-1 on human health.

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