

## DIFFERENCES IN CHEMICAL COMPOSITION BETWEEN COW COLOSTRUM AND MILK

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### Summary

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The aim of the present paper is to review the differences in chemical composition between colostrum and milk in cows. The concentrations of many nutrients (proteins, vitamins, minerals etc.) and biologically active substances (immunoglobulins, enzymes, hormones, growth factors etc.) are many times higher in colostrum than in milk. A special attention is given to insulin-like growth factors (IGF-1 and IGF-2) – the predominant growth factors in the colostrum of cows (especially in the first portions) unlike many other species and men. Furthermore, IGF-1 and IGF-2 are the most important factors stimulating tissue and body growth and development in newborn calves.

**Key words:** chemical composition, colostrum, cows, insulin-like growth factors, milk

### INTRODUCTION

The formation of colostrum in cow's udder occurs during the first 5–7 days after calving. Its composition is similar to that of blood and differs significantly from milk. Colostrum contains both nutrients (proteins, fats, lactose, essential fatty acids and amino acids) and non-nutrients (biologically active substances). This is the first food for neonates after the parturition that provides them with all necessary nutrients. Also, colostrum is particularly important for the passive immunization of the newborn, as the combination of its various specific (immunoglobulins, Ig) and non-specific (humoral and cellular) antibacterial factors passes in the offspring and largely supports their protection against infections during the first days after birth (Tomov, 1984; Medvezki, 1989; Iliev & Tomov, 1992; Blum & Hammon, 2000; Playford *et al.*, 2000). It

is also considered that the high concentrations of growth factors in cow colostrum (mainly insulin-like growth factors 1 and 2 – IGF-1 and IGF-2) and hormones (insulin) control the growth and development of gastrointestinal tract and contribute for the functional maturation of the organism during the first days after birth (Blum & Hammon, 2000; Blum & Baumrucker, 2002; Sauter *et al.*, 2004; Blum, 2006).

The aim of the present paper was to review and analyze the available information upon the differences in the composition between cow colostrum and milk.

### CHEMICAL COMPOSITION OF COLOSTRUM AND MILK IN COWS

Compared to milk, colostrum contains higher levels of proteins – lactalbumins,

lactoglobulins and especially immunoglobulins (IgG<sub>1</sub>, IgG<sub>2</sub>, IgM, IgA), peptides (lactoferrin, transferrin), hormones (insulin, prolactin, thyroid hormones, cortisol), growth factors, prostaglandins, enzymes, cytokines (tumor necrosis factor- $\alpha$ ), acute-phase proteins ( $\alpha_1$ -glycoprotein), nucleotides, polyamines, minerals (iron, magnesium and sodium salts), (pro)vitamins: especially  $\beta$ -carotene, vitamins A, E, D, B, cell elements – lymphocytes, monocytes, epithelial cells etc. (Gerov *et al.*, 1987; Medvezki, 1989; Blum & Hammon, 2000; Ontsouka *et al.*, 2003; Blum, 2006). The concentrations of most ingredients, especially those of immunoglobulins (Ig) and growth factors, are the highest in the first portions colostrum immediately after calving, and thereafter are rapidly decreasing (Rauprich *et al.*, 2000a; 2000b; Blum & Hammon, 2000; Playford *et al.*, 2000; Kirk, 2005; Blum, 2006). It should be noted that Ig account for more than 50% of the total amount of colostrum proteins and contain almost all antibodies, encountered in maternal blood (Tomov, 1984), about 90% of colostrum Ig being from the IgG<sub>1</sub> type. At the same time, the contents of lactose and casein in colostrum are lower than those in milk (Ontsouka *et al.*, 2003).

Many of non-nutrient e.g. biologically active substances of colostrum come directly from the blood, for instance, IgG, somatotropin, prolactin, insulin and glucagon. Other non-nutrients are locally produced in the udder from lactocytes and the stroma.

Both the nutritive and immune-related functions of colostrum are essential for newborn calves. Experimental data suggest that unlike that in women, the placenta of ruminants is not permeable to macromolecules such as Ig from the maternal blood (Medvezki, 1989). That is

why calves are born with very weak mechanisms of defense and are particularly susceptible to various infections. According to numerous data, blood serum of calves prior to suckling colostrum lacks Ig, or contains only traces of Ig, whereas the bactericidal and lysozyme activities and the alternative pathway of complement activation (APCA) are very low or absent (Tomov, 1984; Gerov *et al.*, 1987; Iliev, 1988; Tomov *et al.*, 1989; Levieux, 1999). Therefore, the intake of colostrum in the first hours after birth is extremely important for increasing the specific and non-specific resistance of calves against harmful pathogens, causing alimentary, respiratory and other disorders in the postnatal period (Kirk, 2005).

Calves obtain antibodies ready-to-use under the form of Ig, mainly from the IgG<sub>1</sub>, IgG<sub>2</sub>, IgM and IgA classes with colostrum – the so-called colostrum antibodies, bound to the globulin protein fraction (Iliev, 1988; Medvezki, 1989; Tomov *et al.*, 1989; Blum, 2006). Colostrum globulins are identical to those of maternal blood serum and during the first days of life, pass in the blood of calves through alimentary tract epithelium (Medvezki, 1989). According to Tomov *et al.* (1989), during the first hours after birth, IgM are absorbed more rapidly whereas IgG are mostly retained on the apical surface of the intestinal mucous coat, and exert there a local protective function. Also, there is a correlation between blood serum Ig of newborn calves and both peripheral blood cortisol and maternal blood cortisol, confirming the view that in physiological concentrations, glucocorticoids stimulate antibody formation (Tomov *et al.*, 1989).

The earliest colostrum intake is of primary importance for the passive immunization of calves, when colostrum's value is the most complete from biological point

of view (high titre of colostrum Ig, high lysozyme, bactericidal and APCA activities, high content of growth factors), the permeability of the epithelium of small intestine is the highest, and the acidity of abomasum content – the lowest due to the lack of hydrochloric acid (Iliev, 1988; Gueorguiev *et al.*, 1996; Kirk, 2005). Regardless of the fact that the content of biologically active substances in colostrum is preserved relatively high up for 24–36 hours, it is most appropriate that the intake of first colostrum occurs within 6 hours after calving, when Ig concentrations are the highest (Kirk, 2005). Iliev (1988) observed maximum values of IgG, vitamin A, carotene and vitamin C in the first portions of colostrum immediately after the parturition, this high level being persistent for 24 hours, and thereafter decreasing by the 5<sup>th</sup> and the 12<sup>th</sup> day.

Ig are absorbed by small intestine mucosa by pinocytosis for a relatively short time (8–12 hours after birth). Then, the permeability of intestinal mucosa in calves strongly decreased and becomes entirely impermeable after the 36<sup>th</sup> hour, in lambs – after the 3<sup>rd</sup> day (Tomov, 1984; Gerov, 1987). The absorption times of the different Ig classes are different. Thus, the absorption of IgG stops after the 27<sup>th</sup> hour, and that of IgA after the 16<sup>th</sup> hour following birth (Gerov, 1987). It is established that the strong reduction of colostrum Ig occurs simultaneously with the so-called closure period of small intestine epithelium with regard to the absorption of large macromolecules, including Ig.

The highest proportion of colostrum Ig consists of IgG, mostly IgG<sub>1</sub> that accounts for 90% of all Ig and at a lesser extent IgG<sub>2</sub> (Levieux, 1999; Ontsouka *et al.*, 2003). The content of these Ig in colostrum depends on their blood concentrations. IgG content in the first portions

varies within a very wide range in the different cattle breeds – from 18 mg/mL to 92 mg/mL (Kiddy *et al.*, 1971, McGuire *et al.*, 1983). According to Levieux (1999), the colostrum IgG level in Holstein-Friesian cattle immediately after the parturition was about 60 mg/mL, in Holstein – 50 mg/mL, and in meat-type breeds was higher – 100 mg/mL. It should be noted that IgG<sub>1</sub> concentration decreases twice in every subsequent milking and by the 7<sup>th</sup> day, is about 1 mg/mL, reaching normal milk values by the 2<sup>nd</sup>–3<sup>rd</sup> month: 0.25–0.5 mg/mL (Levieux, 1999). IgG<sub>2</sub> in colostrum varies from 1.6 mg/mL to 6.4 mg/mL, whereas in normal milk its concentration is about 0.05 mg/mL.

The class M immunoglobulins (IgM) in colostrum vary between 5 mg/mL and 8.7 mg/mL whereas in milk their concentrations are 0.04–0.05 mg/mL (Levieux, 1999). Colostrum and milk IgA levels are 1.7 and 4 mg/mL, respectively. The content of  $\beta$ -lactoglobulin and  $\alpha$ -lactoglobulin in colostrum is also higher than in milk (14 and 2 mg/mL vs 4.5 and 1.46 mg/mL, respectively). Colostrum contains relatively high amounts of lactoferrin (1.2–2.6 mg/mL), albumin (1.2–2.66 mg/mL) and transferrin (0.9–1.07 mg/mL), that decline very rapidly reaching normal values in milk of 0.15–0.30 mg/mL by the 8<sup>th</sup>–15<sup>th</sup> day (Levieux, 1999). By immunoelectrophoresis, some acute-phase proteins as  $\alpha_1$ -glycoprotein are discovered in colostrum. Its concentrations range between 1 and 1.65 mg/mL in colostrum and 0.09–0.016 mg/mL in milk (Mesa *et al.*, 1994).

Our previous data (Georgiev, 2005) demonstrate that the chemical composition of colostrum (dry matter, solid non-fat extract, lactose, milk fat and protein) changes very rapidly with time, so that by the 3<sup>rd</sup> day post partum it is already simi-

lar to that of normal milk. These results correspond to the data of Kráčmar & Zeman (2004). The lysozyme activity in the colostrum of cows with high and low milk yield changes from  $0.401 \pm 0.09$   $\mu\text{g/mL}$  and  $0.327 \pm 0.07$   $\mu\text{g/mL}$  at parturition to  $0.096 \pm 0.03$   $\mu\text{g/mL}$  and  $0.073 \pm 0.01$   $\mu\text{g/mL}$  on the 3<sup>rd</sup> post partum day, respectively (Gueorguiev *et al.*, 1996).

The most consistent changes occur in milk protein content that is reduced more than twice by the 3<sup>rd</sup> post partum day compared to initial values. This is mostly due to the sharp decrease in Ig fractions (Ontsouka *et al.*, 2003), whose concentration, as already mentioned, was the highest in the first colostrum portions (Ontsouka *et al.*, 2003). It was also found out that the differences in milk secretion rates had no significant effect upon the chemical composition of colostrum as the differences in the concentrations of fats, proteins, lactose, dry matter and the solid non-fat extract among cows with different milk yields were low and statistically insignificant. Furthermore, the differences in the milk yield of cows did not affect noticeably the levels of lysozyme in colostrum and in the blood of neonatal calves (Gueorguiev *et al.*, 1996).

Cow colostrum contains also components with concentration lower than 1 mg/mL (trace components). These are various proteins, enzymes, enzyme inhibitors, hormones, growth factors, vitamins, macro- and trace elements etc. Despite their low concentrations, trace components are physiologically important for both the local protection of the udder and the growth and development of neonates. Using cross electrophoresis, more than 30 proteins are detected in colostrum apart those already mentioned – IgG, IgA, IgM,  $\beta$ -lactoglobulin,  $\alpha$ -lactalbumin etc. (Levieux, 1999). According to data from this

author, colostrum contains some proteins of blood origin – prealbumins, C3 component of complement, haptoglobin and others, that together with lysozyme, lactoferrin, properdin, the lactoperoxidase-thiocyanate-hydrogen peroxide system, exhibit a strong antibacterial effect and are essential elements of the local non-specific resistance. The concentration of all those proteins in colostrum is considerably higher than in milk. From colostrum and milk are isolated also  $\beta_2$ -microglobulins with concentrations of 6 and 2  $\mu\text{g/mL}$ , respectively, as well as bradykinin, various kininogens etc. (Levieux, 1999).

Milk and colostrum contain about 60 enzymes, most of them being identified as endogenous: glucose-6-phosphate isomerase, phosphodiesterase,  $\alpha$ -mannosidase, galactosyltransferase (Levieux, 1999).

Of all enzymes present in milk, the highest content is that of lactoperoxidase – 0.03 mg/mL. In colostrum, the levels of this enzyme increase rapidly after birth and peak by the 4<sup>th</sup> day, and thereafter gradually decrease. The activities of alkaline phosphatase and N-acetyl- $\beta$ -glucosaminidase are 5 and 20 times higher in colostrum compared to milk, respectively (Levieux, 1999). The activity of the cell membrane-bound enzyme  $\gamma$ -glutamyl transferase in colostrum (19000 U/L) is 2.5–3 times higher than in milk and 300 times compared to serum (Vacher & Blum, 1993).

Of proteinases group, the amount of plasmin in milk is the highest. Its concentration in colostrum is about 10 times higher than that of milk, 0.49  $\mu\text{g/mL}$  and 0.04  $\mu\text{g/mL}$  (Dupont *et al.*, 1998). The presence of cathepsin D that breaks down caseins ( $\alpha$ -S1,  $\alpha$ -S2,  $\beta$ ),  $\alpha$ -lactalbumin, but not  $\beta$ -lactoglobulin is also detected (Larsen *et al.*, 1996).

Colostrum and milk contain a number of enzyme inhibitors that protect udder tissues from the proteolytic effect of leukocyte proteases. The concentration of enzyme inhibitors is the highest in the first portions of colostrum and then decreases rapidly. The  $\alpha$ -macroglobin (390  $\mu\text{g}/\text{mL}$  in colostrum and 4.5  $\mu\text{g}/\text{mL}$  in milk),  $\alpha_1$ -antitripsin (250–800  $\mu\text{g}/\text{mL}$  in colostrum, 6–20  $\mu\text{g}/\text{mL}$  in milk) belong to this group (Levieux, 1999). Other low-molecular enzyme inhibitors (12–60 kDa) are also isolated from colostrum with a not entirely obvious physiological role: serine and cysteine protease inhibitors,  $\alpha_2$ -antiplasmin, plasminogen activator inhibitor etc.

A number of hormones are detected in colostrum and milk, whose concentrations in the first colostrum are many times higher than in milk (Levieux, 1999) (Table 1).

**Table 1.** Contents of some hormones in colostrum and milk

Hormone	Concentration
Insulin	colostrum: 4.2–34.4 ng/mL milk: 0.042–0.34 ng/mL
Total cortisol	colostrum: 4.4 ng/mL milk: 0.35 ng/mL
Free cortisol	colostrum: 1.8 ng/mL milk: 0.3 ng/mL
Prolactin	colostrum: 150 ng/mL milk: 50 ng/mL
Progesterone	colostrum: 2.6 ng/mL milk: 0.8 ng/mL

The content of oestrogens (oestron, oestradiol-17 $\beta$ ) in colostrum is similar to that of plasma and almost twice higher than that of milk. The levels of somatotropin and thyroxine however are higher in milk than in colostrum (Blum & Hammon, 2000).

## GROWTH FACTORS IN COW COLOSTRUM

Many growth factors are isolated from cow colostrum. They are discovered in the beginning of the 80-ties of the last century, but are not fully investigated. At present, the physiological importance of the following main growth factors in cow colostrum is studied: IGF-1, IGF-2; colostic basic growth factor, prolin rich polypeptide etc. (Levieux, 1999). Some of them are absorbed in very low amounts and exert a local stimulating effect upon the growth and development of the gastrointestinal tract of newborn calves, whereas others, together with endogenous growth factors, are essential for the growth and development of the other organs.

The highest proportion of cow colostrum growth factors is that of insulin-like growth factors (IGFs). IGFs could originate from blood or be synthesized in the udder. There are species-related differences in the content of growth factors in colostrum. For instance, in human milk predominates the epidermal growth factor, that is not found in cow colostrum, where IGF-1 is the most abundant. Growth factors in human milk persist at relatively high levels during the entire lactation period whereas in cows, their concentrations are high only in the first portions of colostrum and then, rapidly decrease (Blum & Hammon, 2000; Rauprich *et al.*, 2000 a; 2000b).

The concentrations of IGFs and insulin are higher in colostrum than in blood unlike some hormones (somatotropin, glucagon and thyroid hormones). The levels of growth factors, insulin and other peptides is different in the various colostrum portions, being the highest in the cisternal fraction, then decreasing and rising again by the end of milking, respectively suckling. This determines the differences in the delivery of these components to

suckling calves with the different colostrum fractions (Ontsouka *et al.*, 2003).

Little is known about the physiological characteristics of IGFs. It is suggested that in neonatal calves they are essential for the regulation of growth and development of the GIT, affecting cellular proliferation and differentiation.

IGF-1 and IGF-2 are single-chain low-molecular polypeptides with proinsulin-like structure. Among the more important physiological effects of IGFs are their effects upon the transmembrane transport and metabolism of glucose, amino acids, nucleotides etc. Also, IGFs stimulate the synthesis and inhibit the breakdown of proteins, DNA, RNA and regulate cell proliferation and differentiation in tissues, at the same time inhibiting apoptosis (programmed cell death) (Disenhaus *et al.*, 1988; Bühler *et al.*, 1998; Jehle *et al.*, 1999; Breier *et al.*, 2000; Blum, 2006).

The concentration of IGF-1 in cow colostrum (383–500 µg/L) is many times higher than in women's colostrum (18 µg/L) (Baxter *et al.*, 1984; Vacher & Blum, 1993; Rauprich *et al.*, 2000a; 2000b). The lowest IGF-1 level is that of cow milk (4–10 µg/L) (Collier *et al.*, 1991; Ontsouka *et al.*, 2003). It should be noted that IGFs are not species-specific and are not destroyed during milk pasteurization at 79 °C for 45 s, as well as by gastric juice acidity (Collier *et al.*, 1991; Lowe 1991). IGF-1 is destroyed after heating milk to 121 °C for 5 min (Collier *et al.*, 1991). It was also established that at the beginning of lactation, milk IGF-1 level is higher compared to that in middle lactation and correlates negatively to milk productivity (Collier *et al.*, 1991).

About the origin of IGFs in colostrum and milk, it is proved that a part could go through from blood into milk by transport via the mammary alveolar epithelium

(Vega *et al.*, 1991). More recent data, based on polymerase-chain reaction and immunohistochemistry show that IGF-1, IGF-2 and the insulin-like growth factor binding proteins (IGF-BP) are produced locally, not in secretory cells, but in adipocytes, fibroblasts and blood vessels' smooth muscles, their expression varying during the different physiological states of the udder – mammatogenesis, lactogenesis, lactopoiesis and involution (Plath-Gabler *et al.*, 2001). It is also found out that in colostrum, IGFs could be either free or bound to IGF-BP. The free (biologically active) forms prevail during the perinatal period whereas bound forms are prevalent in milk (Schams & Einspanier, 1991; Playford *et al.*, 2000). Although the exact role of IGF-BP is not completely known, it is thought that they are important for regulation of the IGFs binding to their receptors. (Playford *et al.*, 2000). It is also demonstrated that one of IGF-BP, namely IGF-BP-3, binds also lactoferrin (Blum & Baumrucker, 2002). IGF-BP-3 and lactoferrin enter the nuclei of glandular epithelial cells and there, via yet unknown mechanisms, influence apoptosis, therefore they are important for the involution of the mammary gland (Blum & Baumrucker, 2002).

As mentioned above, IGFs concentration is the highest in the first portion of colostrum, then decreases rapidly and in milk, they are found at levels, many times lower than in colostrum (Rauprich *et al.*, 2000 a; 2000b). Therefore, the intake of colostrum during the first hours after birth is extremely important to provide the needed nutrients (proteins, carbohydrates, lipids, vitamins, minerals etc.) and for the normal growth and the morphological and functional maturation of the gastrointestinal tract of the organism, i.e. for the adequate adaptation of newborns to the new

environment, especially in the early postnatal period when the abrupt change from parenteral nutrition in the foetal period to exceptionally enteral nutrition after the birth occurs (Blum, 2006). The normal accomplishment of all these events is regulated by the high content of biologically active peptides, growth factors, hormones, cytokines etc. in colostrum (Hammon & Blum, 1997; Hadorn *et al.*, 1997; Blum & Hammon, 2000; Playford *et al.*, 2000; Blum, 2006). This view is supported by the studies of Roffler *et al.* (2003), showing that the stimulating effect of colostrum upon the growth of the gastrointestinal tract in newborn calves is due not only to IGF-1, but rather to an entire set of growth factors, as the exogenous application of first colostrum extract, where growth factors are the most abundant, stimulated to a greater extent the size of intestinal villi than the administration only of IGF-1 did.

Apart IGFs, cow colostrum and milk contain other growth factors from the group of transforming growth factors (TGF) – TGF- $\alpha$ ; TGF- $\beta$  at lower concentrations. Their levels in colostrum (20–40 mg/L) are significantly higher than in milk (1–2 mg/L) (Playford *et al.*, 2000). Although their precise physiological role is not entirely clear, it is suggested that they are involved in the proliferation of intestinal epithelial cells (Playford *et al.*, 2000). As TGF- $\alpha$  and TGF- $\beta$  are expressed at considerable amounts in cow's udder, they are believed to participate in the regulation of proliferation and reorganization of the glandular parenchyma during the mammatogenesis, lactogenesis, lactopoiesis and involution (Plath *et al.*, 1997).

By the 7<sup>th</sup> day after birth, serum levels of  $\gamma$ -globulins, glucose, albumin, essential and non-essential amino acids, triglycerides, cholesterol, insulin, IGF-1, thyroid

hormones and prolactin were statistically significantly higher in calves that suckled colostrum immediately after calving than in calves, receiving colostrum after 2–3 days (Hadorn *et al.*, 1997). The delay in colostrum intake by 24 hours results in sharp increase in the concentrations of non-esterified fatty acids, an indicator of energy deficiency in calves. Furthermore, the intake of full value colostrum increases to a large extent the absorption capacity of small intestine that is essential for the complete utilization of nutrients and immunoglobulins (Hammon & Blum, 1997; Blum & Hammon, 2000). All those data evidence the strong stimulating effect of colostrum on anabolic processes in the newborn.

In order to manifest their effect, IGF-1 and IGF-2 are bound to specific receptors, present in many tissues of neonatal calves, including the gastrointestinal tract, the liver etc. (Hammon & Blum, 2002; Ontsouka *et al.*, 2004a; 2004b). It is established that growth factors receptors are present mainly to the basolateral membrane of mucosal epithelial cells, rather than on the apical surface, that would impede the direct effect of growth factors ingested with colostrum (Playford *et al.*, 2000). During the early postnatal period however, the intestine permeability to many of colostrum ingredients, including growth factors, is considerably higher, facilitating the binding of these factors to their receptors and hence, their effect on gut growth and development (Playford *et al.*, 2000).

Factors such as the rearing technology and nutrition during the pregnancy, and especially during the dry period, the health status of cows etc. have an impact on colostrum composition and its biological value. The reduced biological value of colostrum has a rather negative effect on the status of newborn calves, with regard

to their vitality, weight gain, specific and non-specific resistance (Tomov, 1986; Iliev, 1988; Blum, 2006). Iliev (1988) established a direct correlation between the maternal blood lysozyme, complement, bactericidal and phagocytic activities and Ig content, the biological value of colostrum and blood serum concentrations of these parameters in newborn calves during the first days of life. The author has also found out that the colostrum of cows, reared in stalls, contained considerably lower levels of Ig, lysozyme, vitamins (A and C) compared to cows, reared either in stall and pasture or freely in boxes. The offspring of immobilized cows exhibited lower lysozyme and complement activities, Ig and vitamin A and C levels. This is explained by the systemic strain in immobilized cows, accompanied by increased incretion of some stress hormones – ACTH, cortisol, that in supra-physiological concentrations exert suppressive effect on antibody formation and systemic immune status (Iliev, 1988).

In conclusion, we could summarize that there are significant differences in the chemical composition between colostrum and milk. The concentration of many nutrients (proteins, vitamins, minerals etc.) and biologically active substances (Ig, enzymes, hormones, growth factors etc.) is many times higher in colostrum than in milk. Of growth factors, cow colostrum is the richest in IGF-1 and IGF-2, especially in the first portions. These factors, together with insulin, play a very crucial role in controlling the growth and development of gastrointestinal tract and the organism in newborn calves during their first days of life, when a sudden change in the mode of nutrition from entirely parenteral during the foetal stage to entirely enteral after birth does occur.

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