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Review Article

The role of milk urea nitrogen in nutritional assessment and its relationship with phenotype of dairy cows: A review

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ABSTRACT

Urea is a small molecule that can readily cross the blood-milk barrier into milk, leading to a strong correlation between blood urea nitrogen (BUN) and milk urea nitrogen (MUN) concentrations. Although MUN is a minor component of milk, it is a valuable and cost-effective tool to flag potential nutrition-related problems in dairy herds. Many studies have suggested that intake of dietary protein and energy, as well as their synchronized release in the rumen, are major factors influencing MUN concentration. Therefore, measuring MUN can serve as a valuable indicator for improving nutritional management in dairy herds. Both excessively high and low MUN values are undesirable for dairy cows due to their negative effects on reproductive performance, health, and nitrogen use efficiency. Moreover, research indicates that MUN is a trait with low to moderate heritability and is positively correlated to nitrogen excretion. However, there are still inconsistencies regarding selecting cows with a low MUN phenotype can effectively reduce nitrogen excretion and affect other economic traits in dairy cows. This paper provides an overview of MUN's utility in nutritional assessment, presents its relationship with economically important milk traits, reproductive performance, health, and nitrogen emissions. It also describes the backgrounds of the gastrointestinal microbiota, intestine and kidney physiology in cows with different MUN concentrations, aiming to further enhance our understanding of MUN and provide a reference for optimal diets of cows.

1. Introduction

As an important source of basic nutrients and active substances, milk is considered a nearly perfect food, making significant contributions to meeting human nutritional needs and improving the quality of life. However, the dairy industry is facing increasing pressure to reduce production costs, including rising feed input and labor costs, which impact the economics of commercial dairy farms. On the other hand, fluctuating raw milk purchase prices related to imbalanced supply and demand have led to incidents of “killing cows” and “dumping milk” worldwide, highlighting the industry's vulnerabilities. In addition, the dairy industry is under pressure to decrease environmental pollution associated with dairy farming. Recent studies indicate that the livestock sector or its related supply chains contribute approximately 30% of total nitrogen emissions (Oita et al., 2016; Uwizeye et al., 2020; Yu et al., 2019). Releasing of excess nitrogen into the environment contributes to eutrophication and acidification of water and soil, leading to biodiversity loss (Yu et al., 2019). Furthermore, ammonia and nitrous oxide produced from manure also pose environmental threats, affecting both animal habitats and human health (De Vries, 2021; Wolfe and Patz, 2002). Increasing dietary protein can enhance milk protein content but also results in more nitrogen waste, as about 70% of the

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nitrogen consumed by dairy cows is excreted as urinary or fecal nitrogen, with less than 30% secreted into milk (Calsamiglia et al., 2010; Foskolos and Moorby, 2018). Consequently, reducing production costs, nitrogen emissions, and protein feed resource wastage remain primary goals for livestock farmers.

Dietary protein can be described as true protein and non-protein nitrogen (NPN), and true protein can be segmented into rumen degradable protein (RDP) and rumen undegradable protein (RUP) according to their degradability (Bach et al., 2005). Generally, RDP and NPN can be converted into ammonia in the rumen, and ammonia can then be captured by microorganisms to synthesize rumen microbial protein (MCP). Excessive ammonia is absorbed through the rumen wall into the bloodstream and transported to the liver for urea synthesis (Cholewinska et al., 2020; Morris, 2002). MCP and RUP can be transported to the retro-rumen digestive system, where they are degraded into peptides and amino acids by intestinal enzymes and microorganisms, and then absorbed by the intestine and transported to various tissues of the body through the circulatory system for utilization. Proteins that are not digested and utilized by the retro-rumen digestive system will be excreted through feces. Nitrogen absorbed into the blood of dairy cows originates from both the simple diffusion and active transport of ammonia across the rumen wall, as well as the active transport of amino acids and peptides in the small intestine (Bergen, 2021; Zhong et al., 2022). In addition, surplus amino acids and peptides absorbed by the body, which are not utilized for maintenance, milk synthesis, or fetal development, can undergo deamination in the liver to generate energy and convert nitrogen into urea. This urea will become a part of the blood urea nitrogen (BUN) pool. In general, BUN has three final destinations: secreted into milk, excreted through feces or urine, or recycled (Fig. 1). Undeniably, urea recovered by ruminants through saliva and rumen wall serves as an important nitrogen source for the synthesis of MCP (Getahun et al., 2019) which is helpful in enhancing nitrogen utilization efficiency. This feature sets ruminants apart from non-ruminant animals.

Urea, being a small neutral molecule, readily diffuses across cell membranes. Therefore, MUN exhibits a strong correlation with BUN (Broderick and Clayton, 1997; Maskaľová, 2021). MUN, as a trace component in milk, reflects the level of urea in the blood. It is not only linked to nitrogen utilization efficiency in dairy cows but also closely related to nitrogen emissions resulting from excess urea secretion, which corresponds to elevated BUN and MUN levels (Barros et al., 2019; Nousiainen et al., 2004). Because MUN is easier to measure than BUN, information on MUN is also convenient for evaluating the balance between protein and energy, with its relative level closely related to production costs (Hojman et al., 2004), since protein is typically the most costly feed nutrient. MUN is considered to be a valuable tool for evaluating protein utilization efficiency in modern dairy farming system (Barros et al., 2019; Nousiainen et al., 2004; Powell et al., 2011). This paper intends to review the role of MUN in nutritional assessment and its correlation with selected milktraits, reproductive performance, health status, and nitrogen emissions in dairy cows. We look forward to further promoting the practical application of MUN in production to improve the feeding management of dairy cows and to enhance the profitability of dairy farms while protecting the environment.

2. MUN in nutritional assessment

Usually, MUN can be used as a “signal” or “indicator” to identify potential nutrition-related problems under the current feeding conditions. Both excessively high and low MUN concentrations may indicate issues with nitrogen metabolism and partitioning, often due to an imbalance between dietary carbohydrates and nitrogen sources, if MUN is too high. Therefore, it is critical to accurately obtain MUN content information for dairy herds, and even individual cows, as incorrect information may lead managers to make incorrect decisions. Several methods are available for determining or estimating MUN concentration in milk. Among these, the enzymatic (Portnoy et al., 2021b), the diacetyl (Langenfeld et al., 2021), spectroscopy (Portnoy et al., 2021a), gas chromatography (Xie et al., 2019), and biosensors (Trivedi et al., 2009) methods have been proven effective to quantitatively determine MUN. Rapid and low-cost techniques are always in demand for quality control and other analytical purposes in the dairy industry. Mid-infrared spectroscopy is widely utilized globally, offering the opportunity to analyze numerous samples rapidly without requiring special sample pretreatments or chemical reagents; however, this type of instrumentation is sometimes unavailable in laboratories. Near-infrared spectroscopy, on the other hand, has shown promise due to its low cost and portability and has demonstrated good performance in several routine nutrient analyses (de la Roza-Delgado et al., 2017; Kalinin et al., 2013). However, this method may not be suitable for MUN analysis due to its poor detection reliability and sensitivity (Aernouts et al., 2011; Jankovská, 2018). A simplified enzymatic method coupled with portable equipment may be a

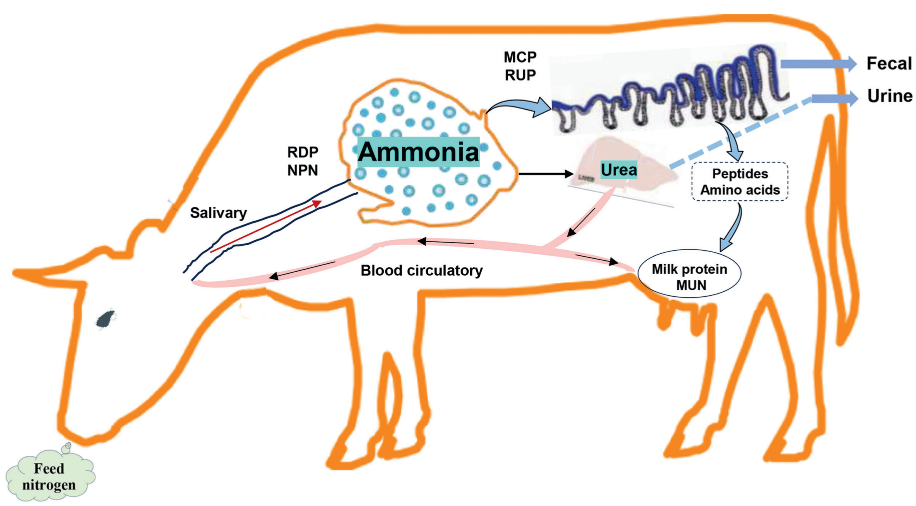

Fig. 1. The nitrogen metabolism process of bovines. RDP = rumen degradable protein; RUP = rumen undegradable protein; MCP = microbial protein; NPN = non-protein nitrogen; MUN = milk urea nitrogen.

promising option, but further investigation and development are needed in this area.

The concentration of MUN is influenced by various factors, encompassing both nutritional and non-nutritional factors. Non-nutritional factors such as breed, lactation stage, and parity can affect MUN content. Among these factors, breed is considered to be the most influential non-nutritional factor, with Holstein cows generally exhibiting lower MUN concentrations compared to other dairy animals (Bittante, 2022; Johnson and Young, 2003). The quantity and composition of dietary protein are considered the primary nutritional factors affecting MUN concentration in milk (Barros et al., 2017; Nousiainen et al., 2004; Wattiaux et al., 2011). This is because the liver's synthesis of urea depends on the ammonia nitrogen (NH_3—N) concentration produced in the rumen. Cows fed a high-crude protein (CP) diet generally absorb more NH_3—N through the rumen wall due to the production of ruminal NH_3—N exceeding the capture capacity of rumen microorganisms. A previous study revealed that an increase of one percentage unit in dietary CP led to an increase of 1.04 and 1.24 mg/dL in MUN concentration for milk yields of 40 and 30 kg/d, respectively (Aguilar et al., 2012). Moreover, an increase or decrease in the dietary RDP will also correspondingly increase or decrease MUN content, irrespective of whether a low-CP or high-CP diet is fed; however, no significant difference was observed in milk true protein concentration (Bahrami-yekdangi et al., 2016; Mutsvangwa et al., 2016). This suggests that the RDP is also an important factor that affects MUN concentration. The efficiency of rumen ammonia utilization, whether for synthesizing MCP or being absorbed by the rumen wall, largely depends on the availability of energy generated through carbohydrate fermentation. The level of synchronization between dietary energy and nitrogen release is closely associated with MUN content. A low degree of synchrony in the diet is generally related to low nitrogen utilization efficiency, as well as high MUN levels and increased nitrogen emissions (Huhtanen et al., 2015; Rius et al., 2010).

Establishing an appropriate threshold is crucial for accurately assessing the nutritional balance of the diet and the post-feeding response of dairy cows. Based on most of the previously published data, MUN should generally not exceed 18 mg/dL in most commercial farms. Researchers at Pennsylvania State University and the University of Wisconsin suggest that the appropriate range of MUN is 8 to 14 mg/dL. If the MUN levels in the herd exceed or fall below this range, it is necessary to assess the dietary protein and energy sources. For high-yielding dairy herds (annual milk production >12,000 kg), the average value of MUN can be controlled within the range of 10 to 16 mg/dL (Kohn, 2007; Wattiaux and Ranathunga, 2016). Europe and other countries in the America offer recommendations regarding MUN concentration based on their respective local production conditions but these data come from relatively old literature. For example, researchers in Canada suggest that MUN level within the range of 10 to 14 mg/dL represents an optimal nitrogen utilization efficiency (Arunvipas et al., 2004). Some countries in the European Union advocate for maintaining the herd average MUN value within the range of 10 to 16 mg/dL. The recommended MUN value in France is 11.5 to 16 mg/dL (Melendez et al., 2003), while Sweden and other Nordic countries suggest an ideal range of 10 to 15 mg/dL (Carlsson and Pehrson, 1993). In China, there is no standard range for MUN values in dairy herds. Instead, reference values are established for individual farms based on their unique production conditions. The upper limit value typically does not exceed 16 or 18 mg/dL. Monthly routine dairy herd improvement (DHI) milk testing is considered an important task in pasture management and MUN is one of the focused indicators. Furthermore, advancements in animal nutrition and genetics have led to a reduction in the average NPN (MUN) levels among herds in recent years (Hayes et al., 2023). This trend appears to be occurring across numerous countries and regions, potentially changing the establishment of MUN concentration thresholds. It is seen that the appropriate thresholds for MUN vary among countries and regions due to differences in diets, production levels, feeding management, and expected production goals. The reference value of MUN should be based on the current feeding conditions. For nutritionally well-managed dairy herds, upper threshold can range from 14 or 16 mg/dL and lower thresholds can range from 8 or 10 mg/dL. These thresholds can serve as guidelines for assessing the nutritional status of dairy herds.

3. The relationship of MUN with milk yield, milk components, and production cost

3.1. Milk yield

A balanced nutritional intake is crucial for maintaining optimal health and maximizing production performance in dairy cows. MUN serves as a valuable indicator, reflecting the synchronization of carbohydrate and nitrogen sources in the diet. Fluctuations in MUN levels may be accompanied by corresponding changes in the production performance of dairy cows. The relationship between MUN and production outcomes has been described in previous research. Some studies reported no correlation between the average milk urea (MU) level in the herd and milk yield traits (Godden et al., 2001), or only a weak correlation in Danish Holstein cows (Atashi and Hostens, 2021; Honerlagen et al., 2023), or nearly zero correlation in Danish Jersey and Red cows (Buitenhuis and Poulsen, 2023). However, strong relationships were discovered between MU concentration and milk yield in other studies. For instance, fluctuations in MUN concentrations in both Holstein and Jersey cows were observed to closely mirror milk production levels throughout the lactation period, with the timing of peak MUN concentrations aligning with variations in milk yield (Johnson and Young, 2003). Normally, high production performance requires an increased nutritional supply for animals. This heightened production performance drives dry matter and nitrogen intake, while the nitrogen utilization efficiency of dairy cows is relatively limited, potentially resulting in a disproportionately higher release of ingested nitrogen into the milk. Additionally, the low to moderate genetic correlation (0.07 to 0.35) between MUN and milk yield traits may offer another plausible explanation for this observation (Ma et al., 2023; Satola et al., 2017). Wattiaux et al. (2005) discovered a positive correlation between MUN and fat-corrected milk (FCM) yield in multiparous cows. However, they observed an inverse relationship when FCM yield exceeded 60 kg/d. Similarly, for primiparous cows, an opposite effect was observed when FCM yield surpassed 40 kg/d, and no correlation was detected when FCM yield was below 40 kg/d (Wattiaux et al., 2005). The reason for this discrepancy is not fully understood and may be attributed to variations in body metabolism and nitrogen partitioning between primiparous and multiparous cows. Further research is needed to explore this aspect in greater detail. An intriguing finding from a nearly 25-year continuous record of the Walloon Region of Belgium, encompassing data from 560,739 cows in 2356 herds, revealed a negative genetic correlation between MU and other production traits (milk yield, fat yield, and protein yield) ranging from −0.25 to −0.01. This suggests that selection for increasing milk production traits could potentially lead to decreasing MUN (Chen et al., 2021), and this finding has been corroborated by other studies (Bobbo et al., 2020; Buitenhuis and Poulsen, 2023; Miglior et al., 2007). As mentioned above, the relationship between MUN and milk yield traits remains uncertain, possibly due to differences in the physiological state, dietary intake, and dietary composition of cows, even breeds. These factors need to be considered when evaluating the relationship between MUN and milk yield traits.

3.2. Milk composition

Although MUN is a minor component of milk, any factors that cause changes in MUN may affect other components of milk. Under normal circumstances, nearly 28% of the nitrogen ingested by dairy cows can be secreted into milk, with 5% being excreted in the form of non-protein nitrogen and the remainder as true protein (Spek et al., 2013a). A previous study has shown that an increase in CP intake, accompanied by a rise in MUN concentration, does not affect milk protein yield (Bahrami-Yekdangi et al., 2014; Bahrami-yekdangi et al., 2016), suggesting that an excessively high-CP diet does not yield many benefits, whereas a low-CP diet can decrease urea excretion at a phenotypic level without adversely impacting milk protein content (Müller et al., 2021; Rius et al., 2010). A recent study has further confirmed this association and found a weak phenotypic (Jahnel et al., 2023) or genetic (Ma et al., 2023) correlation between MU and milk protein percentage throughout the lactation period. Therefore, MUN can be more easily regulated through dietary means, allowing for a reduction in nitrogen excretion by adjusting the diet nutritional composition. Interestingly, one study reported a relatively high phenotypic correlation (0.28) between MU and milk protein percentage (Honerlagen et al., 2023), but the study did not provide an explanation. Furthermore, previous research found that the genetic correlation between MU and milk fat percentage was weak or even negligible (Bobbo et al., 2020; Rzewuska and Strabel, 2013; Wood et al., 2003), while a slight negative genetic correlation (−0.25 to 0) was found in the early lactation period (Jahnel et al., 2023). At the beginning of lactation, dairy cows usually experience a period of negative energy balance, leading to an increase in milk fat percentage due to the mobilization of the cow's adipose tissue (Roche et al., 2015; Yang et al., 2019). During this period, MUN generally shows relatively low values due to insufficient feed intake compared to other lactation periods (Johnson and Young, 2003), which could explain this phenomenon. Some studies have shown a positive and moderate genetic correlation (0.26 to 0.42) between MUN and milk fat percentage (Ma et al., 2023; Miglior et al., 2007); however, the specific reasons for this correlation have not been analyzed. The relationship between MUN and somatic cell score (SCS) is also complex. For instance, previous studies found a negative phenotypic (Hojman et al., 2004) or genetic (Ma et al., 2023) relationship between MU and somatic cell count (SCC). Subsequent research found that MUN has a negative genetic correlation with SCS at the beginning of lactation, followed by a weak relationship in the middle of lactation and a tendency to have a positive correlation at the end of lactation, especially in multiparous dairy cows (Jahnel et al., 2023). Chen et al. (2021) also discovered a high negative genetic correlation between MUN and SCS at the beginning of lactation (−0.20), which decreased to zero by day 270 and then exhibited a positive relationship thereafter (0 to 0.28) (Chen et al., 2021). However, Stoop et al. (2007) found a strong positive genetic correlation between MUN and SCS (0.85) (Stoop et al., 2007). The reason for this phenomenon is unclear and may be related to the health condition of the cows, as the occurrence of mastitis can affect the concentration of MUN in milk (Stanojevic et al., 2023). Besides, the average genetic correlation between MUN and lactose is also considered low, even negligible (Ma et al., 2023; Miglior et al., 2007; Stoop et al., 2007). It seems that the correlations between MUN and milk composition are affected by parity, lactation stages and health status, and in most cases the relationships between MUN and milk component traits are weak or even negligible. This finding highlights the potential of selecting cows with low MUN phenotype to reduce nitrogen excretion without compromising production performance and milk quality. However, it is worth noting that there are some uncertain relationships between MUN and milk production. When reducing MUN traits through breeding selection, it is necessary to evaluate their correlation with other traits. At the same time, there is still a lack of research on the impact of MUN levels on the taste and flavor compounds of milk. Nevertheless, a balanced diet should be taken into consideration to effectively maintain MUN within an acceptable range.

3.3. Production cost

Over the past few years, China's dairy farming industry has encountered huge challenges: declining purchase prices for raw milk, weak overall consumption, and persistently high production costs. The profitability determines the sustainable development of the pasture, and efforts have been made to reduce production costs and enhance the profit margin. MUN appears to be closely related to feed costs, as high MUN values are typically associated with excessive protein feeding or low dietary energy availability in the diet (Godden et al., 2001). Overconsumption of dietary CP not only leads to the wastage of expensive protein feed resources and escalates feed costs (de Freitas et al., 2019) but also raises the likelihood of developing associated nutritional and metabolic disorders (Sinclair et al., 2014). Consequently, this could lead to a rise in veterinary drug usage and the potential risk of culling dairy cows. Meanwhile, low dietary energy availability may be related to decreased milk production performance, which may also have a negative effect on the profit margins of dairy farms. Interestingly, survey work revealed a strong correlation between MUN and dairy feed costs based on over 10 million DHIA records from the United States spanning from 2004 to 2015 (Hristov et al., 2018). However, the specific reasons behind this correlation have not been thoroughly explained. It is possible that the observed correlation between MUN and dairy feed costs could be attributed to the increasing price of protein feed inputs and the fluctuation of raw milk prices. Moreover, maintaining a consistently low MUN concentration in cows is not always beneficial, especially when the average MUN concentration drops below 6 to 8 mg/dL, as it comes at the cost of decreased milk production, including milk yield and protein content and yield and feed efficiency (Barros et al., 2017). When this happens, it is necessary to evaluate the dietary protein structure and carbohydrate sources to avoid unnecessary losses.

4. The relationship of MUN with reproductive performance and health status

4.1. Reproductive performance

A nutritionally balanced diet is essential not only for achieving optimal production but also for ensuring the health and well-being of the animals. Dietary proteins play a pivotal role in reproductive performance, and increased levels of dietary CP or elevated MU concentration resulting from high protein diets have been linked to reduced conception rates and pregnancy outcomes in dairy cows. For instance, a previous study found that cows with MUN concentrations between 10.0 and 12.7 mg/dL were 1.4 times more likely to be confirmed pregnant compared to cows with MUN levels exceeding 15.4 mg/dL. These findings were derived from data collected from 24 dairy herds affiliated with the Ohio Dairy Herd Improvement Cooperative Inc. in the United States (Rajala-Schutz et al., 2001). Moreover, an increase in MUN concentration from 12.5 to 13.5 mg/dL can lead to a 5% decrease in cows conception on the closet day to breeding (Kananub et al., 2020), and the unfavorable effects were more profound in high-yielding dairy herds, leading to an extension of both the calving interval and the duration between the first and successful insemination (Siatka et al., 2020). A Meta-analysis incorporating 21 papers published before 2017 revealed that the thresholds for the effects of BUN and MUN on reproductive performance in cows were 19.3 and 19.6 mg/dL, respectively. When MUN concentrations surpassed these thresholds, the likelihood of pregnancy or conception decreased by 43%, with this detrimental impact being more significant when elevated nitrogen exposure occurred prior to artificial insemination (Raboisson et al., 2017). In South Africa, another study demonstrated that both the inter-calving period and reproductive performance decrease when MUN concentrations exceed 18.1 mg/dL in Holstein Friesian cows and 13.0 mg/dL in Jersey cows, respectively (Webb and de Bruyn, 2021), which need to be verified as the local high temperature and high humidity environment may also affect reproduction performance. The varying thresholds of MUN's adverse effects on reproduction in cows across different studies reflect the influence of breed, as well as the feeding and management of cows. However, there is no doubt that high MUN concentrations have adverse effects on the reproductive performance of dairy cows. This may be due to high protein intake or elevated BUN and MUN concentrations resulting in poor embryo quality (Santos et al., 2009), and these deleterious effects are more likely to occur in early preimplantation embryos during oocyte maturation and fallopian tube transit, rather than in later embryonic stages (Rhoads et al., 2006). In addition, research has shown that a high-CP diet may lead to a reduction in the number of cells in blastocysts and an increase in the concentration of reactive oxygen species. This can cause damage by inducing oxidative stress to embryonic cells (Mitchell et al., 2009), thereby impacting reproductive ability and performance.

There are research reports indicating a negative correlation between low MUN concentration and reproductive performance. A 4-year observational study conducted in France revealed that the conception success of dairy cows can decrease by 5% to 9% when MUN concentration fall below 6.99 mg/dL after artificial insemination (Albaaj et al., 2017). This finding was also confirmed in an earlier study (Miettinen, 1991). The negative effect of low MUN concentration on reproductive performance is likely due to a deficit in energy intake or an imbalance in carbon-nitrogen balance, and this issue has been discussed in a previous study (Dunn and Moss, 1992). However, some other studies did not find a correlation between MUN and reproductive indices (Ruegg et al., 1992; Trevaskis and Fulkerson, 1999), especially between different herds (Guo et al., 2004). The absence of a correlation may be due to factors such as reproductive management practices, health conditions, heat stress, or limitations in the availability of reproductive data. In the constant pursuit of high production performance, high-CP diets (CP > 16%) are commonly employed in high-yielding herds, particularly in developing countries. However, it's important not to ignore the negative effects of such diets, as they directly impact the profitability and sustainable development of dairy farms. Low-CP diets are attracting more attention due to their economic and environmental benefits. However, it's important to note that low MUN concentrations induced by inadequate dietary CP are also undesirable. Therefore, a balanced diet is important for maintaining both reproductive performance and the overall profitability and sustainability of dairy farms. The appropriate threshold of MUN is needed to set expected production targets based on the current feeding levels, especially during the breeding season, in order to reduce its negative effects on dairy cows.

4.2. Lifespan and other diseases

In modern dairy production systems, the average productive lifespan of high-yielding dairy cows is typically around 3 to 4 years (De Vries, 2020; De Vries and Marcondes, 2020), during which 80% of the culling events are attributed to various health issues. Among those, reproduction issues, mastitis, hoof diseases, and metabolic diseases are regarded as the main reasons for culling events (Hadley et al., 2006; Pinedo and De Vries, 2010). Cow's longevity and welfare are important factors associated with the sustainability of the dairy industry. Higher longevity, achieved by avoiding culling due to related health issues, may be linked to improved economic performance on farms, reduced environmental impact of the milk industry, and enhanced welfare for the animals. Lameness is a major animal welfare issue in the dairy industry, causing pain and having a detrimental impact on cow production performance and longevity (De Vries and Marcondes, 2020). Lameness in cows is often associated with reduced activity and eating time, leading to a decrease in total feed intake amount, which subsequently impacts MUN concentration. Previous studies have demonstrated that MUN concentration is significantly lower in lame cows compared to healthy cows throughout the lactation period (Necula et al., 2022; Slovák et al., 2021). Moreover, the levels of BUN tended to decrease in lame cows, and BUN can serve as a biomarker for lameness detection (Necula et al., 2022). Ketosis is considered to be one of the most detrimental diseases during the freshening period and is a significant contributing factor to early culling in dairy cows (Probo et al., 2018; Roberts et al., 2012). The primary cause of ketosis is the imbalance of dietary nutrition, including energy deficiency or excessive protein leading to a negative energy balance, and this condition is associated with a high MUN concentration (Rius et al., 2010). Thus, MUN may have direct or indirect relationship with a cow's lifespan. For instance, a large-scale study conducted from 2001 to 2004, which included over 280,000 Holstein cows and 25,000 Ayrshire cows, found that cows with low MUN concentration are more likely to be culled compared to cows with an average herd MUN value (6.39 vs 11.11 mg/dL and 4.49 vs 12.20 mg/dL in Holstein cows and Ayrshire cows, respectively). Besides, Ayrshires cows with high concentrations of MUN (16.16 mg/dL) also tended to be culled at a higher rate compared to the average group, while high MUN concentration (>14.23 mg/dL) did not significantly affect the longevity of Holstein cows (Miglior et al., 2006) and showed a positive correlation with their longevity (Chen et al., 2021). MUN indirectly reflects the balance of dietary nutrition, and the imbalanced diet can lead to a series of health problems, including metabolic and nutritional diseases as well as reproductive failure, and affect the service life of dairy cows. However, the lifespan of cows is influenced by numerous factors, and there are only limited data directly assessing the relationship between MUN and cow longevity. Further studies are needed to confirm this relationship, including more long-term observations.

5. The relationship between MUN and nitrogen emissions

For a long time, people have mainly focused on CH_4 and CO_2 emissions, and various measures have been taken to minimize the adverse impacts of greenhouse gas emissions. Research in this area has become a hot topic. However, reducing nitrogen emissions is also urgent. According to a previous report, nitrogen emissions are expected to rise to 102% to 156% of 2010 levels in 2050; and nitrogen pollution of soil, water and atmospheric nitrogen pollution will far exceed critical environmental thresholds without effective nitrogen emission-control technologies (Bodirsky et al., 2014). This will undoubtedly create huge pressure on the human living environment. Livestock production is a significant contributor to nitrogen emissions, with previous studies indicating that livestock supply chains account for approximately 24% to 33% of current human-induced nitrogen emissions (Bodirsky et al., 2014; Uwizeye et al., 2020; Yu et al., 2019). Most nitrogen emissions originate from South Asia, East and Southeast Asia and Latin America, as a large number of livestock (such as cattle, buffalo, and pig, etc.) are raised in these places (Uwizeye et al., 2020). Synthetic nitrogen fertilizers and manure are commonly used on farmland and pastures, while nitrogen-rich products are transported globally and emitted locally after consumption. Therefore, it is not just an issue confined to one country or region; rather, nitrogen flows and emissions have evolved into a global challenge. These developments have altered the emission patterns of nitrogen in the atmosphere and affected our daily lives in various ways. For example, emissions of nitrous oxide (N_2O), ammonia, and nitrogen oxides (NOx) from manure have detrimental effects on both animal and human health (De Vries, 2021). Eutrophication and acidification of soil and water contribute to pollution and the loss of biodiversity (Yu et al., 2019). These problems of nitrogen emissions are growing concerns and require mitigation strategies.

Improving nitrogen use efficiency is recommended as a key measure to reduce both environmental burden and production costs. Less than one-third of the total ingested nitrogen is utilized by dairy cows, with over 70% of the dietary nitrogen sources being excreted through urine or feces (Calsamiglia et al., 2010; Foskolos and Moorby, 2018). Each cow can emit more than 100 kg of total nitrogen per year (Wilkerson et al., 1997). Under normal circumstances, the amount of nitrogen excreted by animals through feces is relatively stable. Dry matter intake or nitrogen intake is considered to be the best factor for predicting fecal nitrogen emissions (Huhtanen et al., 2008; Nennich et al., 2005; Yan et al., 2006); however, there is inconsistency in which factor performs best across different predictive models established by various studies. Approximately 50% of the excess nitrogen in urine is estimated to be excreted from the body, representing around 70% to 80% of the total urine volume. Measuring urinary nitrogen can be challenging in grazing systems. In such cases, MUN is considered an effective evaluation tool for predicting the emission of urea nitrogen and ammonia in dairy cows and many studies have established prediction models (Table 1). When MUN decreases by 1 mg/dL (within the range of 10 to 16 mg/dL), the emissions of urea nitrogen can be reduced by 16.6 g/d and ammonia and nitrous oxide emissions can be reduced by 7% to 12%, respectively (Powell et al., 2014). Regression analysis has shown that a decrease in MUN concentration from 14 to 10 mg/dL, within the recommended levels supported by previous literature, can lead to a reduction in relative ammonia emissions from dairy cows by 10% to 28% (Wattiaux and Ranathunga, 2016). Although the prediction models obtained varied in different studies, the emission of urine nitrogen and ammonia can be indirectly predicted by MUN or combined with body weight, which provides a tool for evaluating the impact of dairy production on the environment. Previous studies have indicated that MUN is a phenotype with low to medium heritability (Chen et al., 2021; Miglior et al., 2007), thus incorporating MUN as a targeted trait in breeding programs and reducing its value could potentially contribute to a reduction in nitrogen emissions from dairy cows. As expected, a recent study found that for every one unit decrease in MUN breeding value (MUNBV), the concentration of urinary urea nitrogen (UUN) decreased by 0.67 g/L. This led to a notable difference in UUN excretion of 165.3 g/d between grazing cows with the highest and lowest MUNBV values (Marshall et al., 2020). This variance is attributed to the reduced efficiency of nitrogen circulation in the gastrointestinal tract of dairy cows with high MUN levels (Souza et al., 2021). However, some studies have raised questions regarding the efficacy of using MUNBV as a predictor of nitrogen emission. For example, Correa-Luna et al. (2021) found that there was no significant difference in fecal nitrogen and urine nitrogen emissions between cows with low and high MUNBV values although low MUNBV grazing cows exhibited lower MUN concentration and yield (Correa-Luna et al., 2021). This discrepancy may be attributed to the absence of differences in dietary energy-protein balance and the total amount of nitrogen intake in that study. Other studies also found no significant difference in urinary nitrogen excretion between high-MUN and low-MUN cows under the same feeding conditions. However, high-MUN dairy cows were observed to have relatively lighter kidney weights (Prahl et al., 2023). In terms of urea clearance rate, high-MUN cows exhibited poor kidney performance resulting in a larger urea pool, which may allow more urea to be transferred back to the mammary glands (Müller et al., 2021). The variations in kidney function may offer an explanation for the lack of significant differences in urinary nitrogen emissions observed in the study.

Microorganisms in the digestive tract undoubtedly play a crucial role in nutrient digestion and absorption. Variations in microbial composition may further explain differences in MUN concentrations among individual cows. In terms of rumen microorganisms, a recent study showed that low-MUN dairy cows exhibit a higher relative abundance of Succinivibrionaceae_UCG002 and Ruminococcaceae_unclassified, while the relative abundance of *Butyvibrio* and Lachnospiraceae_UCG-010 were higher in high-MUN dairy cows (Honerlagen et al., 2022). Similar findings have also been reported in subsequent study where Succinivibrionaceae_UCG002 abundance was enriched in low MUNBV cows, and *Desulfovibrio* and Lachnospiraceae XPB1014 group abundance was increased in high MUNBV cows (Honerlagen et al., 2023). Succinivibrionaceae_UCG002 is the dominant urea utilization bacteria in the rumen (Jin et al., 2016), so low-MUN dairy cows may have a high urea utilization rate in the rumen. Studies have shown that the

Table 1
Prediction of the relationship between MUN and nitrogen emissions (g/d).

Item	Prediction model	R^2	Reference
Urinary nitrogen	10.09 × MUN − 17.4 + 2.26 × MUN (high NaCl level)	0.85	Spek et al. (2013a)
Urinary nitrogen	13.4 × MUN + 34	0.74	Nousiainen et al. (2004)
Urinary nitrogen	16.6 × MUN −36.4	0.84	Powell et al. (2014)
Urinary nitrogen	0.0259 × BW × MUN	0.98	Kauffman and St-Pierre (2001)
Urinary nitrogen	0.0283 × MUN × BW	0.97	Wattiaux and Karg (2004)
Urinary nitrogen	16.23 × MUN − 34.2	0.79	Wattiaux et al. (2011)
Urinary urea nitrogen	14.4 × MUN − 23.1	0.96	Burgos et al. (2007)
Urinary urea nitrogen	14.57 × MUN − 31.4		Spek et al. (2013b)
Ammonia emissions	25 + 5.03 × MUN	0.85	Burgos et al. (2010)

MUN = milk urea nitrogen; BW = body weight.

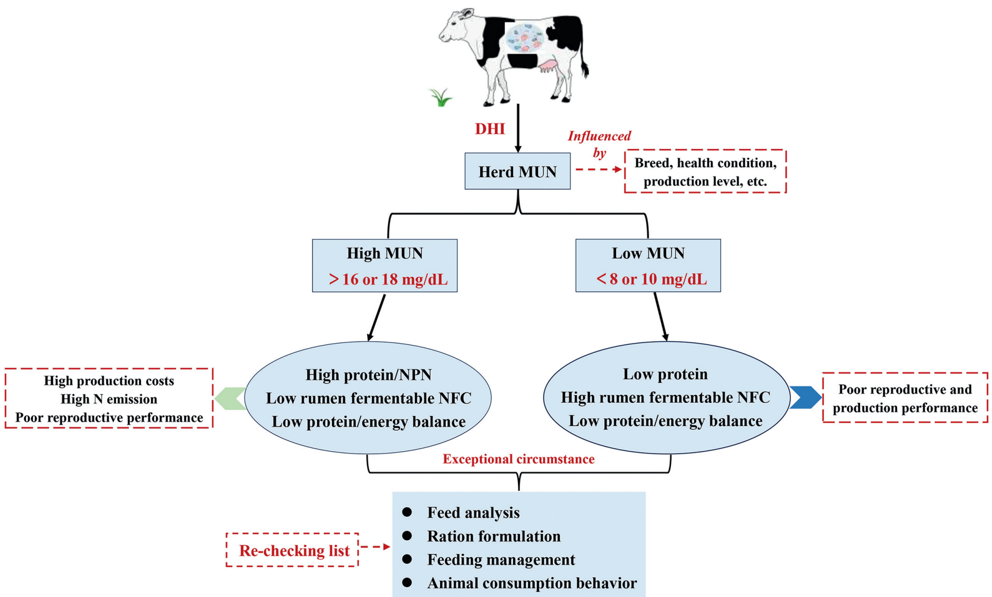

Fig. 2. The workflow for identifying the causes of high or low MUN concentrations. DHI = dairy herd improvement; MUN = milk urea nitrogen; NPN = non-protein nitrogen; NFC = non-fiber carbohydrate.

bacterial community Lachnospiraceae NK3A20 is positively correlated with the length of rumen papillae. Based on the higher incidence of the Lachnospiraceae NK3A20 in HMU phenotype dairy cows and the corresponding higher blood nitrogen pool (Müller et al., 2021), it is possible to speculate that the Lachnospiraceae NK3A20 group may enhance NH_3 and NH^{4+} absorption by stimulating rumen papillae growth. This could potentially lead to increased nitrogen effluxes into the blood and more nitrogen being secreted into milk. In addition, a recent study identified nine types of intestinal microorganisms that were highly correlated with MUN concentration by using a machine learning model. Among these, *g_Firmicutes_unclassified* exerted the most significant influence on the model, potentially being a key factor contributing to different MUN phenotypes (Yu et al., 2024). However, the mechanisms through which these intestinal microorganisms influence milk urea nitrogen require further investigation. Therefore, in addition to dietary factors, variations in host kidney reabsorption function, gut clearance rates and digestive tract microorganisms may contribute to different MUN phenotypes in cows. These factors could potentially explain the differences in nitrogen use efficiency and excretion among various MUN phenotypes. However, the role of the host gastrointestinal tract microbiota in different MUN phenotypes is not yet fully understood. Further exploration of these mechanisms could potentially provide new insights into strategies for optimizing nitrogen utilization and minimizing nitrogen emissions in dairy production systems, particularly by considering the role of rumen and retro-rumen digestive microorganisms.

6. Conclusions and perspectives

Overall, MUN can function as a practical, cost-effective, and straightforward tool for monitoring the nutritional status of dairy herds. Elevated MUN values may indicate excessive dietary crude protein or insufficient non-structural carbohydrates in the diet, while low MUN values also need to evaluate the dietary protein and carbohydrate sources. It is worth noting that before using MUN in herds daily management, the researchers or producer should pay attention to the following issues: 1) the accuracy of MUN measurement is crucially important; otherwise, it may mislead managers into making incorrect decisions; 2) the number of lactating dairy cows participating in the MUN test should be maximized, ideally over 80% of the adult herd. This testing can be integrated into the DHI program and conducted monthly; 3) it is essential to establish a baseline MUN value for the herd. As previously mentioned, the reference value of MUN can vary due to differences in dietary structure, feeding management as well as expected production goals. Therefore, it is crucial to manage MUN within an acceptable range. The upper threshold typically ranges from 16 to 18 mg/dL, while the lower value ranges from 8 to 10 mg/dL. If the herd is well managed and feeding a balanced diet that does not exceed NRC (2001) requirements for protein and has adequate energy, the reference values for MUN can be under 14 mg/dL; 4) when the MUN values of a dairy herd exceed the established thresholds, effective control measures need to be taken promptly to prevent negative impacts. These measures include re-checking the MUN concentration and production performance of the herd, evaluating the diet formulation, and assessing whether cows are selectively consuming specific parts of the ration (Fig. 2). Moreover, in the past decade, there has been a gradual increase in the genetic trend of MUN and there is a renewed interest to include MUN in breeding programs. Selecting cows with a low MUN phenotype may bring potential benefits for pasture management and reduce environmental nitrogen emissions. However, the effectiveness of reducing nitrogen excretion through selection of cows with low MUN traits and its potential impact on other economic traits remains inconsistent, and further research is needed to elucidate the role of gastrointestinal microbiota on MUN concentration. In brief, it is important to fully understand the MUN information, including its complete metabolic pathway, its relevance to dairy cow health, and its monitoring significance in terms of nitrogen use efficiency and emissions. In the future, MUN may play an increasingly important role in monitoring the nutritional status of dairy herds and minimizing nitrogen excretion into the environment.

CRediT authorship contribution statement

Xiaowei Zhao: Conceptualization, Writing – original draft. **Nan Zheng:** Writing – review & editing. **Yangdong Zhang:** Conceptualization. **Jiaqi Wang:** Conceptualization, Funding acquisition.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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