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Review Article

Prediction and Diagnosis of Fatty Liver in Dairy Cows

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Abstract

Fatty liver is defined as an accumulation of fat, mainly Triacylglycerol (TAG) in liver. Fatty liver in dairy cows is categorized into mild, moderate and severe fatty liver. Obesity in pregnant cow is crucial etiological factor for postpartal development of fatty liver. Namely, obese cows have a greater decrease in feed intake during the period around parturition and, therefore, have a more severe negative energy balance during early lactation which leads to increased lipolysis of adipose tissue. Non Esterified Fatty Acids (NEFA), released from the stored TAG in the adipose tissue, are readily taken up by liver. The excess of NEFA may be converted to TAG and deposit in liver. Liver biopsy is the only reliable method for the detection of fatty liver, especially for the determination of its severity through the estimation of total lipids and TAG. Ecography may be considered as non-invasive, on-farm method for diagnosis of fatty liver which is not commonly used do to the not widely achievable equipment. Since some metabolic and endocrine parameters are significantly correlated with fatty liver degree, they may be used as diagnostic indicators of fatty liver. The significance of those indicators for diagnosis of fatty liver is present in this review. Additionally, indicators that may be used for prediction of fatty liver are explained. Specially attention was given to glucose, NEFA, BHBA, liver enzymes, total bilirubin, total protein, albumin and urea as well as some hormones involved in lipid metabolism. Achievements of novel methods, like genomic and proteomic profiling of biological fluids of diseased cows, in providing tools for diagnosis and prognosis of this metabolic disease are presented.

Core Tip

Fatty liver is defined as an accumulation of fat, mainly Triacylglycerol (TAG) in liver. Liver biopsy is the only reliable method for the detection of fatty liver, through the estimation of total lipids and TAG. Ecography is non-invasive, on-farm method for diagnosis of fatty liver. Since some metabolic and endocrine parameters are significantly correlated with fatty liver degree, they may be used as diagnostic indicators of fatty liver. Novel methods, like genomic and proteomic profiling of biological fluids of diseased cows, provide reliable tools for diagnosis and prognosis of this metabolic disease.

Introduction

Fatty liver syndrome is one of the most important metabolic diseases in high yielding dairy cows in early lactation. Fatty liver usually develops after calving with peak incidence at about 10 days in milk [1]. It is defined as an accumulation of fat, mainly Triacylglycerol (TAG) in liver. TAG is formed when long-chain fatty acids liver of cows, the fatty acid must come primarily from those mobilized from adipose tissue and taken up subsequently by the liver.

If not cured, fatty liver leads to other metabolic diseases, infective diseases and reproductive disorders. Metabolic diseases that may arise from fatty liver are ketosis, abomasal displacement, puerperal paresis and others. There is growing evidence that the mechanisms of udder defence against mastitis are impaired in periods of negative energy balance and hyperketonemia that are usually coupled with fatty liver. The cow with fatty liver syndrome cannot sustain pregnancy due to disturbed internal signaling system which reduces fertility. Although, it is common that cows with fatty liver do not show clinical signs, the condition is usually associated with health and production problems [2] and consequently with huge economic losses on dairy farms. Despite the economic importance of this disease, it is often misidentified or overlooked due to difficulties in diagnosis [3].

Ethyopathogenesis

Nutritional factors such as obesity are crucial in fatty liver etiology [4]. Obese cows have a greater decrease in feed intake during the peripartal period (3 weeks before to 3 weeks after calving) and, therefore, have a more severe negative energy balance during early lactation [5]. That leads to increased lipolysis of adipose tissue. Nonesterified Fatty Acids (NEFA) that are released from the stored TAG in the adipose tissue are readily taken up by liver where they provide energy for liver function. If more NEFA arrive at the liver that needed for energy purposes, the excess may be oxidized incompletely and generate ketone bodies or be converted to TAG for deposition. Factors that decrease

oxidation of fatty acids generally will increase esterification [6]. Carnitin dramatically increase oxidation and decrease estarification *in vitro* [7], but the adequacy of endogenous carnitin and the effect of exogenous carnitin in vivo are not known. Liver tissue from cows at 14 days postpartum had a greater capacity for esterification of NEFA than liver from the same cows at day 50 after parturition [8]. Estrogen concentrations are one hundred times greater immediately before parturition than during estrus, and may increase TAG synthesis in liver [9]. This effect may be indirect through stimulation of lipolysis, because estrogen had little effect in TAG synthesis by isolated liver cell. Under normal conditions, TAG is secreted from the liver as Very-Low-Density Lipoproteins (VLDL). Inadequate secretion of VLDL may contributes to development of fatty liver. It should be emphases that the rate of TAG production in the liver tissue of ruminants is similar to that found in other species, but the secretion of VLDL from the liver is very limited compared with other species. Additionally, accumulation of hepatic lipids during NEB may further decrease the ability of liver to mobilaze TAG as VLDL [10]. The rate limiting step of VLDL is unknown but is probably limited by the availability of its constituents. Most often cited for limiting VLDL synthesis is the availbility of TAG, Apolipoprotein B-100 (ApoB), and phosphatidyl choline. As disscused by Bauchart et al. [11], the apperent luck of lipases for the hydrolysis of TAG from the cytosol storage pool may limit the incorporation of TAG into VLDL to those which are newly synthesized within the microsomal compartment i.e. secretory pool. However, a mechanism may exist for the transfer of TAG from the cytosolic storage pool that has yet to be identified. As known apolipoprotein B-100 is neccessary for stabilisation of the VLDL particle Interference in the synthesis or proper utilization of the ApoB molecule would than have a deppressing effect on the rate of VLDL synthesis and TAG export from the liver. Gruffat et al. [12] determined that hepatic concentrations of ApoB were lover in early lactating cows compared to pregnant, nonlactating cows. Most animals can synthesyze phosphatidylholine. Nevertheless, animals fed choline and methionine deficient diets offten develop fatty liver [13]. The mechanism of this is associated with VLDL synthesis. Yao and Vance [14] indicated that phosphatydilcholine synthesis is required for the secretion of ApoB in a hepatic cell lines.

Bobe et al [15] indicated that stressors in the animal`s environment, like heat stress, overcrowding, too frequent moves, poorly designed or maintained stalls, lack of water, or suboptimal feeding areas, contribute to development of fatty liver. Namely, those stressors decrease dry matter intake and signal breakdown of body fat around calving.

Inadequate endocrine adjustments during initiation of lactation may play a role in fatty liver pathogenesis. Namely, there is strong relation between endocrine status during the peripartal period, when the homeostatic mechanisms are under the greatest challenges, and postpartal metabolic disorders in dairy cows. It is generally observed that insulin, Insulin like Growth Factor-I (IGF-I) and Thyroid Hormone (TH) concentrations decrease immediately after calving due to the adaptation of organism to negative energy balance and initiation of lactation [16]. Contrarily, secretions of somatotropin and glucagon increase. If reductions are pronounced or not synchronized with other metabolic and endocrine adjustments, the decrease may cause a metabolic disturbance that leads to TAG accumulation in parenchymal tissue, especially the liver. Namely, decreased levels of blood insulin combined with decrease glucose

concentrations suppress fat mobilization from adipose tissue and blood NEFA reuptake and reesterification in adipose tissue, leading to increase in blood NEFA concentrations. Decreased levels of TH in blood are associated with reduced mitochondrial capacity to oxidize fatty acids which lead to diffuse lipid infiltration of hepatocytes and pronounce hepatic function impairment. When fatty liver develops, concentrations of those hormones decrease more rapidly. Anyway, the hormonal status of cows in the far-off and mid dry period and its relationship to postpartal metabolic disorders may be of great importance for prediction of fatty liver. Namely, identification of risk factors that are associated with homeorhetic mechanisms leading to metabolic disorders would provide a tool that could be used to better manage cows to prevent fatty liver or provide early warning signs that could be used to segregate cows and mark them for intensive interventional protocols after calving. This strategy requires an understanding of the point in time when adjustments of regulatory mechanisms break through physiological limits thus predisposing the cow to metabolic problems. Our results related to TH concentrations in cows affected with fatty liver showed that cows, that were affected by severe fatty liver during early lactation, were in a hypothyroid state from day 30 before calving (mid dry period) until day 12 after calving (puerperium), which means prior to development of the condition. We concluded that the hypothyroid state during the mid dry period may both be a risk factor and an early indicator of fatty liver, while, during early lactation, it is important etiopathogenetic factor of fatty liver [17]. In the same study, insulin concentrations decreased more pronounced in cows with fatty liver than in healthy cows but only after calving (unpublished data). The same trend was established for IGF-I, since its concentrations decreased more rapidly in cows affected by fatty liver, but only after calving [18].

It should be emphasizes that fatty liver is also associated with altered hormonal sensitivity of adipose tissue and the pancreas. Lipogenesis is less promoted by insulin. Additionally, clearence rates of insulin in hepatocytes and the uptake of glucose by peripheral tissues are decreased [19].

Genetic factors may increase probability of fatty liver due to mutation that affect lipid metabolism in adipose tissue, or lipid metabolism and secretion in the liver. Finally, fatty liver may develop secondary to other diseases and disorders, meaning that factors triggered by trauma or disease may contribute to development of fatty liver. These compounds (cytokines-mainly cachectin and interleukin-1) are released from white blood cells in response to injury and infection, and may increase hepatic conversion of fatty acids to TAG [20].

Categories of fatty liver

Fatty liver may be evaluated either by chemical or histological analysis of liver samples for liver TAG or total lipid [21]. Fatty liver in dairy cows is categorized into mild (liver TAG 1-5% wet weight; total lipid 5-20% of volumen), moderate (liver TAG 5-10% wet weight; total lipid 20-40 % of volumen) and severe fatty liver (liver TAG > 10% wet weight; total lipid > 40% of volume) [22].

Histological pathology of fatty liver

Histological findings in cows with fatty liver include (a) fatty cysts in liver parenchyma; (b) increased volume of individual hepatocytes; (c) mitochondrial damage; (d) compression and decreased volumen

of nuclei, rough endoplasmic reticulum, sinusoids, and other organelles; and (e) decreased number of organelles [23]. Accumulation of TAG in liver with fatty liver is limited to the centrilobular section of the liver near the hepatic vein, but the accumulation extends to the midzonal section and than spreads to the periportal sections in cows with moderate and severe fatty liver. Increased concentrations of liver TAG are accompanied with decreased concentrations of structural lipids (free cholesterol, cholesteryl ester, and phospholipids), energy precursors (citrate), and energy storage molecules (glycogen).

Accumulation of liver TAG in liver reverses slowly and probably has only minor long term negative association with the liver itself because liver cells can regenerate within days. The detrimental associations of fatty liver with other diseases, however, are probably longer and less reversible.

Diagnostic indicators of fatty liver

Liver biopsy is the only reliable method for the detection of fatty liver, especially for the determination of its severity through the estimation of total lipids and triglycerides. Biopsies obtained between 8 and 14 days postpartum are most useful in classifying cows. Liver percutaneous biopsies in dairy cows are obtained using a biopsy instruments as described by Šamanc and coworkers [17]. Namely, the biopsy is usually performed at the right 11th intercostal space, approximately 2 cm below the horizontal line through the tuber coxae. A medium-sized cannula (6 mm o.d. and 4 mm i.d; 20.5 cm long) surrounding a solid, retractable needle-pointed trocar should be inserted through the muscle and peritoneum into the liver in the direction toward the left shoulder. After boring the cannula into the liver, a sample (3 to 5 cm long and 3 to 4 mm in diameter) is obtained through creating a vacuum by drawing back the trocar and then flexing the tip of the cannula upward and gently pushing forward. The liver sample should be expelled onto a clean wipe, blotted free of blood, and placed into storage vials. Liver biopsy provides liver samples for histological measurement of liver fat content. Measurement of glycogen in liver in addition to TAG increases the usefulness of the information, as concentration of TAG and glycogen vary inversely during the early postpartum period [24]. Therefore, it is recommended using rather ratio of liver TAG to liver glycogen, rather than liver TAG alone, as a diagnostic indicator for fatty liver. Nevertheless, liver biopsy is an invasive and time-consuming process, and analytical determination of TAG and glycogen is not well-adapted to rapid testing.

Ecography may be considered as non-invasive, on-farm method for diagnosis of fatty liver in dairy cows. As there are correlations between liver TAG and ultrasound images, digital analysis of B-mode ultrasonograms has potential to classify the degree of hepatic fat infiltration and estimate liver TAG content [25]. Due to not widely achievable equipment, echography is not commonly used method for fatty liver diagnosis in dairy cows. The limit of ultrasonography is also linked to the subjective interpretation of the images. Nevertheless, recent studies based on the texture analysis of the ultrasound images show that the measurement of wavelength and the distance of the grayscale pixels may provide a high sensitivity and specificity of the test obtained for measurement of the amount of TAG in the liver [26-28].

Since some metabolic and endocrine parameters are significantly correlated with fatty liver degree, they may be used as diagnostic indicators of fatty liver [29,30]. According to our results, concentrations of puerperal NEFA, BHBA, and total bilirubin are highly positively correlated with fatty liver degree, while glucose, insulin, IGF-I, and thyroid hormone concentrations are highly negatively correlated with fatty liver degree [31]. I our study, we examined those parameters which are suitable for rapid on farm testing. Blood from those kind of testing should be performed from jugular vein [32]. It should be known that the pallet of possible indicator is much wider but the challenge is to choose reasonable number of parameters that will be reliable for diagnosis but low coasted for farmers. Most used parameters for diagnosis are presented in following section with brief explanation of its reliability for fatty liver diagnosis in dairy cows. It should be emphases that each indicator, if analyzed individually, has some deficiency. Therefore overall and combined analysis of all available parameters may lead to more precise diagnosis of fatty liver in dairy cows.

Glucose: Ruminants absorb little glucose from the intestinal tract, but absorb considerable amounts of VFA, mainly acetate, propionate, and butyrate, that are formed in the forestomach through glucose degradation [33]. Thus, circulating glucose in ruminants is derived from gluconeogenesis, primarily in the liver [34], which depends on the availability of glucogenic precursors. Cows that suffer from fatty liver had a decreased hepatic gluconeogenic capacity and consequently lower glucose concentration in blood [35]. The serum level of glucose is good indicators of hepatic functionality and decreases in its concentration may reflect fat infiltration in animals with high lipomobilization. Glucose concentration lower that 2,2 mmol/L indicate on liver imparement in postpartum dairy cows [36].

NEFA and BHBA: The concentration of NEFA is highly related to adipose tissue lipolysis, which increases in response to NEB. Concentrations of NEFA >0.7 mM after the first week postpartum indicate problems with energy balance [37]. Increased amounts of NEFA removed by the liver along with carnitin palmitoyltransferase-1 activity regulate ketogenesis and thus, BHBA production [38]. Therefore, the concentration of BHBA in blood postpartum is an effective indicator of NEB and metabolic disturbance, with concentrations > 1.2 - 1.4 mm indicating presence of subclinical ketosis which is usually associated with fatty liver disease. [39] Use of BHBA is a better indicator of energy imbalance postpartum than NEFA.

Triglycerides: Triglyceride is not adequate indicator of lipolysis in dairy cows. Nevertheless, most of the cows with high lipomobilization had trygliceride values less than 0,1 mmol/L due to accumulation of fat in the liver [40].

Liver enzymes: When fat infiltrates the liver, a lesion appears in the hepatic tissues and the levels of enzymes that indicate liver injury (AST, GGT, and GLDH) are generally augmented. Gonsales et al. [41] found that AST is more sensitive than GGT for detecting hepatic lesions. It was also reported that ornithine carbamoyltransferase (OCT) may be a very sensitive indicator of various degrees of fatty liver. Kalaitzakis et al. [42] showed that OCT increases in parallel with the severity of fatty liver and concluded that its measurement could potentially be used to differentiate animals with mild, moderate, and severe fatty liver. Namely, high serum OCT activity is probably a result of lipid accumulation in hepatocytes that cause dilatation and dysfunction of mitochondria. OCT correlate with AST activity [43].

Serum GLDH activity increased with increasing hepatic TG content, allowing the differentiation of moderate and severe fatty liver from mild cases and reference cows, but not the differentiation between moderate and severe fatty liver. Nevertheless, accoridng to meny authors, high variation of enzymes activities in healthy cows make those indicators less realaible in fatty liver diagnosis. liver Besides, enzymes plasma activities correlate with advanced tissue damage which is not usual in mild and moderate fatty liver [44].

Total bilirubin: Total bilirubin concentration may be used as indicator of fatty liver disease. It is significantly elevated in cows with moderate and severe fatty liver groups and can be used to distinguish cows with mild and moderate/severe fatty liver [45]. Nevertheless, hyperbilirubinemia is not necessarily indicative of liver dysfunction, and total bilirubin levels should always be interpreted in association with other tests for liver damage.

Total protein, albumin, urea: The serum levels of total proteins, albumin and urea are indicators of hepatic functionality and decreases in their concentration may reflect fat infiltration in animals with high lipomobilization [46].

Hormones: Changes in concentrations of hormones involved in lipid metabolisam may be used as diagnostic indicators of fatty liver. Pronounced decrease of insulin, IGF-I and thyroid hormone concentrations postpartaly indicate on fatty liver disease [47].

Acute-phase proteins: A number of acute-phase proteins induced (or suppressed) during inflammatory conditions may have merit as diagnostics of metabolic disturbance. According to study done by Imhansly et al. [48], there is the reduction of the fibrinogen serum conten in periparturient cows suffering from fatty liver. As this fibrin precursor is produced in the liver, its lower level may represent a direct consequence of hepatocyte dysfunction due to excessive lipid deposition, but may also result from coagulopathy linked to liver disease [49]. In fact, hyperfibrinolysis leading to hypofibrinogenemia is known to arise from a poor hepatic clearance of tissue plasminogen activator or from reduced hepatic production of fibrinolysis inhibitors.

The indicators for predicting fatty liver

Since overconditioned pregnant cows has lower appetite around parturition and consequentlly more pronanced NEB and lypolisis, obese dry cows has great potential to develop fatty liver postpartaly [50]. Therefore, fatty liver disease, or hepatic lipidosis, is probably the metabolic disorder most associated with excessive Body Condition Score (BCS) during the late dry period. It should be emphasys that in cows, Body Weight (BW) alone is not a good indicator of body reserves, as the relationship is affected by factors such as parity, stage of lactation, frame size, gestation, and breed [51]. In addition, because tissue mobilization in early lactation occurs as feed intake is increasing actual decreases in weight of body tissue can be masked by enhanced gastrointestinal fill, such that BW changes do not accurately reflect changes in adipose and weight of lean tissue. Body condition is defined as the ratio of body fat to nonfat components in the body of a live animal. However, large-scale direct measurements of body adiposity were (and remain) difficult and expensive. As a result, multiple systems to subjectively appraise the stored energy reserves of dairy cattle were introduced in the 1970s and 1980s, and scores were assigned to reflect the degree of apparent adiposity of

the cow; these scores were termed "body condition scores." Lowman and colleagues [52] were the first to introduce a BCS scale (0-5-point system) for dairy cows, adapting a scoring system used to rank beef cattle. BCS higher than 4.0 in late dry cows may be used as indicator for predicting fatty liver in dairy cows.

Fatty liver may be also predicted by identifying those biochemical factors that initiate changes in metabolism that lead to fatty liver. Namely, the etiology of most of the peripartal health disorders including the fatty liver is indirectly or directly provoked by NEB [53]. One research study from Michigen State University found that cows which developed severe fatty liver after calving actually had significant fat accumulation in the liver during the last 3 weeks before calving indicating that lipomobilisation was triggered at that period. According to our results and literature data, elevation of NEFA simultaneously with a decrease of glucose concentrations in the blood 5 to 7 days before calving may be indicators of development of postpartum fatty liver. Most used parameters for prediction of fatty liver are presented in following section with brief explanation of its reliability.

Glucose: Since responses to NEB largely are related to glucose supply and demand, the concentration of glucose in blood may be sensitive indicator of degree of NEB. Namely, a shortage of glucose or gluconeogenic precursors may, among other factors, cause fatty liver [54]. Our results showed that glucose concentration under 2.6 mmol/L 5 to 7 days before calving leads to fatty liver. It should have in mind that concentration of glucose in blood is regulated tightly by the cow and therefore it does not respond to NEB immediately.

NEFA and BHBA: According to many authors, lipolysis which leads to increased concentration of NEFA might be triggered few weeks before calving due to imbalanced nutrition [55,56]. Since high prepartum NEFA is associated with greater risk of postpartum fatty liver increased NEFA concentration can be used as good indicator for fatty liver prediction. Concentrations of NEFA > 0.4 mM prepartum indicate problems with energy balance [57]. Measurement of BHBA before calving is of little use because concentrations rarely begin to increase appreciably until calving. Therefore, use of NEFA is a better indicator of energy imbalance prepartum than BHBA [58].

Hormones: According to our results, hypothyroid condition during the dry period in dairy cows may predispose them to fatty liver and therefore may be used as an indicator for fatty liver prediction.

Refernce values for main blood biochemical parameters in lactating Holstein cows are presented in Table 1 [59-62].

Novel indicators of fatty liver obtained by genomic and proteomic analyses

As mantioned above, the diagnosis of fatty liver can only be confirmed by taking biopsies to determine the hepatic lipid content. Biochemical abnormalities are not usually specific for hepatic lipidosis. Thus, in view of the lack of a practically useful diagnostic tool, an alternative strategy was explored by screening for small-molecule serum biomarkers that . As indicated above, an important new paradigm in biomarker discovery research is to consider entire sets of molecular changes, instead of single parameters, that correlate with a particular disease. Imhasly et al [63] used a targeted metabolomics screen by triple quadrupole mass spectrometry to identify those

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Table 1: Reference values for main blood biochemical parameters in lactating Holstein cows.

Parameter	Referene values	
	Dry period	Early lactation
Glucose (mmol/L)	2.60-4.07	2.31-4.07
BHBA (mmol/L)	<0.60	<1.00
NEFA (mmol/L)	<0.40	<0.70
Tryglicerides (mmol/L)	0.17-0.50	0.17-0.50
AST (IU/L)	24.84-39.96	45.30-74.28
GGT (IU/L)	4.9-23.65	4.9-25.7
GLDH (IU/L)	<30.0	<30.0
Total bilirubin (nmol/L)	<8.55	<8.55
Total protein (g/L)	69.00-85.00	73.00-89.00
Albumin (g/L)	34.06-42.00	35.00-45.00
Urea (g/L)	1.90-7.80	2.78-8.78

serum biomarkers that distinguish cows with hepatic lipidosis from those affected by other peripartal disorders. This method yielded 29 metabolites. The authors concluded that metabolomic profiles, including both amino acids and lipids, distinguish hepatic lipidosis from other peripartal disorders and, hence, provide a promising new tool for the diagnosis of hepatic lipidosis.

One of the significant areas of research is the study of gene expression in liver using "microarray" techniques. These procedures allow quantification of the mRNA expression of thousands of gene sequences simultaneously on a microscope slide-sized glass plate. There are studies that confirmed that liver cellular function was impaired in cows that suffered from fatty liver disease [64]. Those impairments include: (1) down down-regulation of genes responsive to oxidative stress, but increase of potential sources of oxidants; (2) up-regulation of genes indicating enhanced DNA fragmentation and apoptosis; (3) blunted repair response to DNA damage; (4) down-regulation of components of oxidative phosphorylation, suggesting that the liver's ability to generate ATP for its functions eventually may be impaired; (5) down-regulation of enzymes in cholesterol synthesis, which may impair VLDL export and contribute to greater TG accumulation; (6) downregulation of growth hormone signaling mechanism, which may disrupt normal homeostatic and homeorhetic controls; (7) down-regulation of ubiquinone synthesis and ubiquitination activity, which are involved in targeting damaged or aberrant proteins for degradation; and (8) down-regulation of components of the immune system.

Clinical disease is triggered when accumulative cell damage in liver prevents maintenance of homeostasis. Key functions that are compromised includes mitochondrial energy status, accumulation of aberrant proteins that cannot be properly cleared, and induction of apoptosis (programmed cell death). Consequently, it may be concluded that those cell impairment may be used not only for diagnosis but also for prognosis of fatty liver disease in dairy cows.

Conclusion

In conclusion, despite the numerous published papers that analyzes possible biomarkers of fatty liver in dairy cows there is no individual metabolite that may be considered as reliable to predict fatty liver in dairy cows. Therefore, further research on molecular level are required for establishing relationships between molecular changes in damaged hepatic cells and blood biochemical changes in cows suffered from fatty liver disease.

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