Invited Review: Pathology, Etiology, Prevention, and Treatment of Fatty Liver in Dairy Cows*

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ABSTRACT

Fatty liver (i.e., hepatic lipidosis) is a major metabolic disorder of many dairy cows in early lactation and is associated with decreased health status and reproductive performance. In severe cases, milk production and feed intake are decreased. Therefore, a practical preventative or an efficacious treatment of fatty liver could save millions of dollars yearly in treatment, replacement, and production losses for dairy farmers. Fatty liver develops when the hepatic uptake of lipids exceeds the oxidation and secretion of lipids by the liver, which usually is preceded by high concentrations of plasma NEFA mobilized from adipose tissue. Excess lipids are stored as triacylglycerol in the liver and are associated with decreased metabolic functions of the liver. Liver can be categorized into normal liver or mild, moderate, or severe fatty liver; the latter can be subdivided further into nonencephalopathic severe fatty liver and hepatic encephalopathy. Insufficient or unbalanced dietary intake, obesity, and elevated estrogen concentrations are involved in the etiology of fatty liver, which is associated with greater incidence of dystocia, diseases, infections, and inflammations. Because even mild fatty liver is associated with decreased health status and reproductive performance of dairy cows, prevention of fatty liver by supplying cows with sufficient nutrients and a clean and health-promoting environment in the periparturient period would reduce production losses of cows more than would any treatment of fatty liver. This, however, might not be enough for cows that are obese or do not eat well, had calving difficulties or twins, have metabolic or infectious diseases, or are in severe negative energy balance because of high milk production immediately after calving. Potential and commonly used preventatives, as well as treatments, are discussed in the review. Currently, detection of fatty liver is possible only by

minor surgery. Ultrasonic techniques offer a potential tool to noninvasively detect fatty liver. Future gene-array and proteomic studies may provide means to detect early molecular events in the etiology of fatty liver plus their connection with immune function and reproductive performance so that more effective treatments and preventatives of fatty liver can be developed. Such advances hopefully will make fatty liver a problem of the past.

(Key words: dairy cow, fatty liver, metabolic disorder, diseases)

Abbreviation key: HDL = high-density lipoprotein, LDL = low-density lipoprotein, TAG = triacylglycerol, TNF α = tumor necrosis factor alpha, VLDL = very-low-density lipoprotein.

INTRODUCTION

Fatty liver (i.e., hepatic lipidosis) is a major metabolic disorder of animals (Gruffat et al., 1996; Goff and Horst, 1997). It develops when the hepatic uptake of lipids exceeds the oxidation and secretion of lipids by the liver. Excess lipids are stored as triacylglycerol (TAG) in the liver and are associated with decreased metabolic functions of the liver (Grummer, 1993; Drackley, 1999). The condition is known as fatty liver or fat cow syndrome in cows (Gruffat et al., 1996). In dairy cows, fatty liver occurs primarily in the first 4 wk after calving (Grummer, 1993), when up to 50% of all cows have some accumulation of TAG in liver (Jorritsma et al., 2000, 2001). One reason is that dietary intake is insufficient to meet the increased requirements of energy for maintenance and lactation (Goff and Horst, 1997; Herdt, 2000). Thus, NEFA are mobilized from the adipose tissue, often in amounts greater than are needed by cows, and the excess is transported to the liver, especially in obese cows (McNamara, 2000). Hormonal changes and greater incidence of infections during parturition are other reasons for increased mobilization of NEFA from adipose tissue (Goff and Horst, 1997).

Fatty liver is associated with decreased health status, well-being, productivity, and reproductive performance of cows (Wensing et al., 1997). Therefore, fatty liver

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Table 1. Categories of fatty liver in dairy cows.

Liver category	Liver TAG ¹ (% wet weight)	Urinary ketones	Feed intake, milk production	Health status, reproductive performance	Liver
Normal	<1%	0 ²	0	0	Normal
Mild fatty liver	1–5%	+	0	–	Centrilobular TAG infiltration
Moderate fatty liver	5–10%	++	0	– –	TAG infiltration throughout liver
Severe fatty liver	>10%	+++	– – –	– – –	Enlarged, necrotic

¹TAG = triacylglycerol.

²The symbols + and – mean positive and negative association, respectively, and the number of symbols represents slight, moderate, or strong association; 0 means no association.

is associated with increased veterinary costs, longer calving intervals, decreased milk production, and decreased average lifetime of cows. The exact costs for fatty liver are difficult to estimate, because fatty liver currently can be diagnosed only by liver biopsy. The average costs and incidence rate of primary ketosis, a metabolic disorder that is closely associated with fatty liver (Veenhuizen et al., 1991), however, are estimated to be \$145/case (Guard, 1994) and 4.8%, respectively (Kelton et al., 1998). Assuming 9 million dairy cows in the United States, the annual costs for fatty liver in the United States can be estimated to be over \$60 million. The pathology and etiology of fatty liver and ketosis have been studied for over 20 yr by our research group and many others to help provide additional basic understanding and to find possible preventatives and treatments for fatty liver. The primary objectives of this review are to describe concisely what is known about the pathology and etiology of fatty liver, and then to summarize current and potential preventatives and treatments for fatty liver and to discuss their limitations.

CATEGORIES AND EPIDEMIOLOGY OF FATTY LIVER

Fatty liver is evaluated either by chemical or histological analysis of liver samples for liver TAG or total lipid (Woltow et al., 1991). Generally, fatty liver can be defined on the basis of percentage of liver TAG or lipid that is associated with decreased health status, well-being, productivity, or reproductive performance of cows (Wensing et al., 1997). Fatty liver can be categorized into normal liver and mild, moderate, and severe fatty liver (Table 1). The proposed beginning and end points of categories vary between reports (Reid, 1980; Gerloff et al., 1986a) because the changes associated with increasing concentrations of liver TAG or lipid are not abrupt. Additionally, cows can respond differently at the same concentration of liver TAG because concentration of liver TAG is an indirect measurement for the

effect of lipid droplets on the function of hepatocytes (Johannsen et al., 1993).

Severe or clinical fatty liver (>10% liver TAG on wet weight basis), which also is called fat cow or fat cow mobilization syndrome, often is preceded by elevated concentrations of urinary ketones, severe BW loss, and a feed intake that is depressed or much lower than required for milk production (Veenhuizen et al., 1991; Hippen et al., 1999; Jorritsma et al., 2001). Cows with severe fatty liver also can have decreased concentrations of glucocorticoids (Morrow et al., 1979). Results by Gerloff et al. (1986a) suggested that, in contrast to mild and moderate fatty liver, severe fatty liver develops prior to parturition and is associated with naturally elevated liver TAG concentrations; however, other studies could not confirm those results (van den Top et al., 1996). In extreme cases, cows develop hepatic encephalopathy, which is characterized by depressed consciousness, ataxia, somnolency, and coma (Rehage et al., 1999), and death can be caused by liver and kidney failure or cardiac arrest. The recovery rate from hepatic encephalopathy is less than 75%, because some cows remain anorexic despite intensive treatment (Morrow et al., 1979; Gerloff et al., 1986a).

Cows with moderate fatty liver (5 to 10% liver TAG) and, to a smaller extent, mild fatty liver (1 to 5% liver TAG) also have elevated concentrations of urinary ketones but not to the same extent as cows with clinical fatty liver (Hippen et al., 1999). Cows with moderate or mild fatty liver generally have a more severe negative energy balance than do cows with normal liver (<1% liver TAG; Jorritsma et al., 2001). Severe negative energy balance, fatty infiltration, and their physiological and metabolic associations are correlated positively with decreased health status and reproductive performance (Wensing et al., 1997). In the first month after calving, 5 to 10% of dairy cows have severe fatty liver and 30 to 40% have moderate fatty liver (Table 2), which indicates that up to 50% of dairy cows are at a higher risk for diseases and reproductive problems. Therefore, a better understanding of the pathology and etiology of

Table 2. Incidence of different categories of fatty liver in dairy cows.

Category of fatty liver	Incidence	Country	Breed of cows	Reference
Moderate	48%	England	Holstein	Reid, 1980
Severe	15%			
Moderate	33%	England	Guernsey	Reid, 1980
Severe	5%			
Severe	15%	Finland	Ayrshire	Gröhn et al., 1987
Moderate	65%	France	n.r. ¹	Mazur et al., 1988
Severe	5%			
Moderate	53%	Germany	n.r.	Schäfer et al., 1991
Severe	20%			
Moderate	33%	Japan	Holstein	Acorda et al., 1995
Severe	11%			
Moderate	45%	Netherlands	n.r.	Jorritsma et al., 2000
Moderate	40%	Netherlands	n.r.	Jorritsma et al., 2001
Severe	14%			
Moderate	20%	United States	n.r.	Gerloff et al., 1986a
Severe	15%			
Severe	24%	United States	n.r.	Herdt, 1991

¹n.r. = not reported.

fatty liver is important for greater profitability in the dairy industry.

PATHOLOGY OF FATTY LIVER

Gross Pathology of Fatty Liver

Excessive infiltration of lipids, or more specifically of TAG, causes gross and microscopic alterations of the liver that become more prominent with greater infiltration of lipids. The liver becomes enlarged and swollen and has round edges and a pale to yellow appearance (Kapp et al., 1979; Morrow et al., 1979). Adrenal glands, kidneys, and cardiac and skeletal muscles also can be infiltrated with excessive amounts of TAG (Kapp et al., 1979; Morrow et al., 1979; Reid and Roberts, 1982). Other gross pathological findings in cows with severe fatty liver are a) myocarditis; b) necrosis in renal, ovarian, muscle, and uterine tissues; c) necrosis and involution of the pituitary gland; d) involution of the pancreas and lymphatic system; and e) necrosis, inflammation, and ulceration of the gastrointestinal tract (Kapp et al., 1979; Morrow et al., 1979; Reid and Roberts, 1982).

Histological and Metabolic 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 volume of nuclei, rough endoplasmic reticulum, sinusoids, and other organelles; and e) decreased number of organelles (Kapp et al., 1979; Reid and Collins, 1980; Johannsen et al., 1993). Accumulation of TAG in cows with mild fatty liver is limited to the centrilobular section of the liver near

the hepatic vein, but the accumulation extends to the midzonal section and then spreads to the periportal sections in cows with moderate and severe fatty liver (Reid and Collins, 1980; Veenhuizen et al., 1991). The microscopic alterations affect cellular integrity and function of hepatocytes and, therefore, cause necrosis and cellular leakage, particularly in cows with severe fatty liver, which is demonstrated by increased concentrations of liver enzymes and bile constituents in plasma (Table 3).

Concentrations of enzymes in plasma that are in greater concentrations in liver than in other tissues are increased the most. Increased concentrations of bile constituents (bilirubin, bile acids, and cholic acid) in plasma indicate that bile flow is decreased in cows with fatty liver. Bile, therefore, accumulates in the liver, which is indicated by the effectiveness of choleretic agents in treatment of fatty liver (Fürl et al., 1993). In humans, high concentrations of bile are toxic and increase the production of free radicals in the liver, which can cause inflammation and tissue damage (Ljubuncic et al., 2000). In cattle, high concentrations of bile cause tissue damage to bovine pancreatic duct epithelial cells in culture (Alvarez et al., 1997). Increased concentrations of free radicals in the liver of cows are indicated by elevated concentrations of malondialdehyde, one of the end products of lipid peroxidation, and decreased concentrations of α -tocopherol (Mudron et al., 1999), an antioxidant, in plasma (Table 3) and to a smaller extent in the liver.

Increased concentrations of liver TAG are accompanied by decreased concentrations of structural lipids (free cholesterol, cholesteryl ester, and phospholipids), energy precursors (citrate), and energy storage mole-

Table 3. Association of fatty liver with concentrations of liver constituents in plasma of lactating dairy cows.

Constituent	Association ¹	Reference
Alkaline phosphatase	+	Staufenbiel et al., 1992; van den Top et al., 1996
Alanine aminotransferase	+	Johannsen et al., 1988
Alkaline phosphatase	+	Staufenbiel et al., 1992; van den Top et al., 1996
Aspartate aminotransferase	++	Johannsen et al., 1992; van den Top et al., 1996
Bilirubin	++	Reid et al., 1983; West, 1990
Bile acid	++	Rehage et al., 1999
Cholic acid	++	West, 1990
γ -Glutamyl transferase	++	Rehage et al., 1996
Glutamate dehydrogenase	+++	Ohtsuka et al., 2001
Lactate dehydrogenase	+	Wensing et al., 1997
Malondialdehyde	++	Mudron et al., 1999
Ornithine carbamoyl transferase	+	Gröhn et al., 1983; Reid et al., 1986
Sorbitol dehydrogenase	+	Gröhn et al., 1983
α -Tocopherol	--	Mudron et al., 1999

¹The symbols + and – mean increase and decrease, respectively, and the number of symbols represents slight, moderate, or strong association. The strength of association increases with increasing concentrations of triacylglycerol.

cules (glycogen) as shown in Table 4. Decreased concentrations of glycogen indicate an increased risk for metabolic disorders that are associated with fatty liver (Drackley et al., 1992). Therefore, they recommended using the ratio of liver TAG to liver glycogen, rather than liver TAG alone, as a diagnostic indicator for fatty liver. Fatty liver also is associated with elevated concentrations of NEFA, BHBA, and acetoacetate in blood, all of which can be cytotoxic at high concentrations.

Concentrations of proteins that are important in lipid packaging and secretion are affected by fatty liver (Table 4; Katoh, 2002) except for microsomal triacylglyceride transfer protein (Bremmer et al., 2000). Concentrations of apoprotein B, which is the major protein of very-low-density lipoproteins (VLDL) and low-density lipoproteins (LDL; Gruffat et al., 1996; Katoh, 2002), protein kinase C (Table 4), which is involved in post-

translational modification of apoprotein A-I (Katoh, 2002), and carnitine palmitoyltransferase in mitochondria, which is involved in β -oxidation and ketogenesis (Mizutani et al., 1999), are decreased in liver. Concentrations of plasma lipids, lipoproteins (apoproteins A-I, B-100, and C-III), and enzymes (lecithin-cholesterol acyltransferase) involved in lipid transport also are decreased in cows with fatty liver (Table 5), which indicates decreased secretion of lipoproteins, specifically of VLDL (Katoh, 2002). On the basis of clinical and histological findings, possible mechanisms for decreased VLDL secretion in cows with fatty liver could be a) decreased VLDL transport from endoplasmic reticulum to golgi apparatus, b) alteration of glycosylation of apoprotein B-100, c) decreased formation of secretory vesicles, and d) decreased migration of secretory vesi-

Table 4. Association of fatty liver with liver composition in lactating dairy cows.

Constituent	Association ¹	Reference
Acetoacetate	++	Mills et al., 1986
Apoprotein B	–	Gruffat et al., 1997
BHBA	++	Mills et al., 1986
Carnitine palmitoyltransferase	–	Mizutani et al., 1999
Cholesterol, total	–	van den Top et al., 1996
Cholesterol, free	–	Saarinén and Shaw, 1950; Brumby et al., 1975
Cholesteryl ester	+	Saarinén and Shaw, 1950; Brumby et al., 1975
Citrate	–	Mills et al., 1986
Glycogen	– – –	Johannsen et al., 1992; van den Top et al., 1996
Malondialdehyde	+	Mudron et al., 1999
Microsomal triacylglyceride transfer protein	0	Bremmer et al., 2000
NEFA	+	Brumby et al., 1975
Phospholipids	–	Brumby et al., 1975; van den Top et al., 1996
Protein kinase C	–	Katoh, 2002
Triacylglycerol	+++	Brumby et al., 1975; van den Top et al., 1996

¹The symbols + and – mean increase and decrease, respectively, and the number of symbols represents slight, moderate, or strong association; 0 means no association. The strength of association increases with increasing concentrations of triacylglycerol.

Table 5. Association of fatty liver with concentrations of compounds involved in lipid transport in plasma of lactating dairy cows.

Constituent	Association ¹	Reference
Apoprotein A-I	–	Bobowiec et al., 1997; Katoh, 2002
Apoprotein B-100	–	Marcos et al., 1990; Katoh, 2002
Apoprotein C-III	–	Bobowiec et al., 1997; Katoh, 2002
Cholesterol, total	–	Herd et al., 1983; Reid et al., 1983
Cholesterol, free	–	Mazur et al., 1989; Katoh, 2002
Cholesteryl ester	–	Brumby et al., 1975; Katoh, 2002
VLDL ² -cholesterol	0	Rayssiguier et al., 1988; Bobowiec et al., 1997
LDL ³ -cholesterol	–	Mazur et al., 1989; Bobowiec et al., 1997
HDL ⁴ -cholesterol	0	Mazur et al., 1989; Bobowiec et al., 1997
Lecithin-cholesterol acyltransferase	–	Katoh, 2002
Phospholipids	–	Brumby et al., 1975; Katoh, 2002
VLDL-phospholipids	0	Rayssiguier et al., 1988; Bobowiec et al., 1997
LDL-phospholipids	–	Mazur et al., 1989; Bobowiec et al., 1997
HDL-phospholipids	–	Mazur et al., 1989; Bobowiec et al., 1997
Triacylglycerol	–	Katoh, 2002
VLDL-triacylglycerol	–	Bobowiec et al., 1997
LDL-triacylglycerol	–	Mazur et al., 1989; Bobowiec et al., 1997
HDL-triacylglycerol	0	Rayssiguier et al., 1988; Bobowiec et al., 1997
VLDL-protein	–	Bobowiec et al., 1997
LDL-protein	–	Mazur et al., 1989; Bobowiec et al., 1997
HDL-protein	+	Mazur et al., 1989; Bobowiec et al., 1997

¹The symbols + and – mean increase and decrease, respectively, and the number of symbols represents slight, moderate, or strong association; 0 means no association. The strength of association increases with increasing concentrations of triacylglycerol.

²Very-low-density lipoprotein.

³Low-density lipoprotein.

⁴High-density lipoprotein.

cles from golgi apparatus to cell membrane (Gruffat et al., 1996).

Fatty liver has detrimental effects on the physiological function of lipoproteins, in particular high-density lipoproteins (**HDL**; Katoh, 2002). In cows with fatty liver, HDL particles bind more haptoglobin and serum amyloid A, which decreases concentrations of apoprotein A-I and C-III in HDL particles (Katoh, 2002). Apoprotein A-I is responsible for activation of lecithin-cholesterol acyltransferase, which esterifies free cholesterol with phosphatidylcholine to form cholesteryl

esters and lysophosphatidylcholine (Katoh, 2002). Cows with fatty liver, therefore, have decreased synthesis of cholesteryl esters, which are important precursors for the synthesis of steroids (Katoh, 2002).

Histological and compositional changes in fatty liver are associated with changes of carbohydrate, lipid, and protein metabolism in hepatocytes (Table 6). Increased infiltration of the liver by TAG is associated with decreased production of energy precursors (decreased gluconeogenesis and variable effects on ketogenesis and β -oxidation) and increased lipogenesis in the liver. Fur-

Table 6. Association of fatty liver with metabolic function in bovine hepatocytes and adipocytes.

Pathway	Association ¹	Reference
Hepatocytes:		
Gluconeogenesis	– –	Cardóniga-Valiño et al., 1997; Rukkwamsuk et al., 1999a
Insulin clearance	–	Strang et al., 1998b
Ketogenesis	±	Drackley et al., 1992
Lipogenesis	+++	Grum et al., 1996; Cardóniga-Valiño et al., 1997
β -Oxidation	±	Grum et al., 1996; Cardóniga-Valiño et al., 1997
Peroxisomal oxidation	–	Grum et al., 2002
Ureagenesis	–	Strang et al., 1998a
Adipocytes:		
Lipogenesis	0	Rukkwamsuk et al., 1999b
Lipolysis	+++	Rukkwamsuk et al., 1998

¹The symbols +, –, and ± mean increase, decrease, and variable association, respectively, and the number of symbols represents slight, moderate, or strong association; 0 means no association. The strength of association increases with increasing concentrations of triacylglycerol.

Table 7. Association of fatty liver with plasma concentrations of hormones in lactating dairy cows.

Constituent	Association ¹	Reference
Glucagon	–	de Boer et al., 1986
Glucocorticoids	–	Morrow et al., 1979
Growth hormone	+	de Boer et al., 1986
IGF-1	– –	Formigoni et al., 1996
Insulin	±	de Boer et al., 1986; Holtenius and Holtenius, 1996
Thyroxine	–	Kapp et al., 1979; Gerloff et al., 1986b
Triiodothyronine	–	Gerloff et al., 1986b

¹The symbols +, –, and ± mean increase, decrease, and variable association, respectively, and the number of symbols represents slight, moderate, or strong association. The strength of association increases with increasing concentrations of triacylglycerol.

thermore, ureagenesis and the ability of insulin to increase protein synthesis are decreased (Strang et al., 1998a), which can explain the elevated concentrations of plasma ammonia in cows with fatty liver (Rehage et al., 2001).

Fatty liver is associated with altered hormonal sensitivity of adipose tissue and the pancreas. Lipogenesis is promoted less by both insulin and glucose (Rukkwamsuk et al., 1999b). Lipolysis is inhibited less by glucose and BHBA (Rukkwamsuk et al., 1998). Clearance rates of insulin (Strang et al., 1998b), endotoxins (Breukink and Wensing, 1997), and other compounds in hepatocytes (West, 1990) and probably in other organs, and the uptake of glucose by peripheral tissues are all decreased (Ohtsuka et al., 2001).

Fatty liver is not only associated with changes in the hormonal sensitivity of tissues (Rukkwamsuk et al., 1998, 1999b) but also with changes of the concentrations of hormones themselves. Because of the decreased clearance of hormones by hepatocytes infiltrated with lipids (Strang et al., 1998b), it can be assumed that synthesis or secretion of IGF-I by liver, glucocorticoids by the adrenal glands, glucagon and insulin by the pan-

creas, and thyroxine and triiodothyronine by the thyroid glands are decreased (Table 7). Additionally, secretion of insulin by the pancreas is promoted less by glucose and glucagon (Hippen et al., 1999; She et al., 1999).

Clinical Pathology of Fatty Liver

The hormonal and pathological changes associated with fatty liver affect concentrations of metabolites and minerals in plasma (Table 8). Decreased concentrations of metabolites such as α -amino N and glucose can decrease the functions of organs in cows with fatty liver, which is true also for the ketogenic branched-chain AA (Rehage et al., 2001).

Elevated concentrations of ammonia, NEFA, BHBA, and acetoacetate can decrease the physiological functions of organs because of their toxicity at high concentrations and because of their metabolic effects. Elevated concentrations of NEFA increase lipogenesis and ketogenesis in hepatocytes (Cadórniga-Valiño et al., 1997). High concentrations of BHBA and acetoacetate decrease rates of β -oxidation, gluconeogenesis, and the citric acid cycle in hepatocytes (Table 6).

Table 8. Association of fatty liver with concentrations of plasma metabolites and minerals in lactating dairy cows.

Constituent	Association ¹	Reference
Acetoacetate	+++	de Boer et al., 1985; Staufienbiel et al., 1992
Albumin	–	Reidt et al., 1983; West, 1990
α -Amino N	–	de Boer et al., 1985
Ammonia	+	Zhu et al., 2000; Rehage et al., 2001
BHBA	+++	de Boer et al., 1985; Ohtsuka et al., 2001
Branched-chain AA	–	Rehage et al., 1999, 2001
Copper	+	Reid et al., 1986
Glucose	±	Staufienbiel et al., 1992; Ohtsuka et al., 2001
Iron	–	Reid et al., 1986
Magnesium	–	Reid et al., 1983, 1986
NEFA	+++	Gerloff et al., 1986a; Mazur et al., 1988
Protein	–	Staufienbiel et al., 1992
Urea N	–	West, 1990

¹The symbols + and – mean increase and decrease, respectively, and the number of symbols represents slight, moderate, or strong association. The strength of association increases with increasing concentrations of triacylglycerol.

Table 9. Association of fatty liver with health status in dairy cows.

Disorder	Association ¹	Reference
Displaced abomasum	+++	Wada et al., 1995; Rehage et al., 1996
Impaired immunoreactivity	++	Wentink et al., 1997; Zerbe et al., 2000
Ketosis	+++	Gröhn et al., 1987; Veenhuizen et al., 1991
Laminitis	+	Fronk et al., 1980; Rehage et al., 1996
Mastitis	++	Morrow et al., 1979
Metritis	++	Haraszti et al., 1982; Heinonen et al., 1987
Milk fever	+	Higgins and Anderson, 1983; Gröhn et al., 1987
Retained placenta	+	Haraszti et al., 1982; Heinonen et al., 1987

¹The number of + represents slight, moderate, or strong detrimental association of fatty liver. The strength of association increases with increasing concentrations of triacylglycerol.

Milk production, health status, and reproductive performance of dairy cows with fatty liver can be decreased for weeks after concentrations of liver TAG decrease back to baseline concentrations (Veenhuizen et al., 1991; Breukink and Wensing, 1997), which suggests that fatty liver is associated with long term histological, metabolic, and hormonal changes. Accumulation of TAG in liver reverses slowly (Veenhuizen et al., 1991) and probably has only minor long term negative associations with the liver itself because liver cells can regenerate within days. The detrimental associations of fatty liver with other tissues, however, are probably longer term and less reversible.

Immunological Pathology of Fatty Liver

The incidence of fatty liver is strongly associated with the incidence of other metabolic disorders, especially ketosis and displaced abomasum (Table 9) because these metabolic disorders have in common that the cows either are or will be in a severe negative energy balance. Accumulation of liver lipids in cows also is associated with increased length and severity of infectious diseases such as mastitis (Hill et al., 1985) and metritis (Haraszti et al., 1982). The incidence and severity of infectious diseases are increased somewhat in the periparturient period, even without the presence of fatty liver (Goff and Horst, 1997), because immune functions are suppressed and concentrations of proinflammatory cytokines such as tumor necrosis factor- α (TNF α) are increased (Ametaj et al., 2002).

Different aspects of the immune response are suppressed in cows with fatty liver (Breukink and Wensing, 1997; Suriyasathaporn et al., 2000). The lower cellular cytotoxicity and reactive oxygen species generation of polymorphonuclear cells in blood suggest a decreased capacity for phagocytosis by polymorphonuclear cells and macrophages in cows with fatty liver (Zerbe et al., 2000). The lower IgG concentrations after tetanus toxoid immunization (Wentink et al., 1997) and the lower interferon production in blood leukocytes (Szuster-Cie-

sielska et al., 1995) suggest that cows with fatty liver have decreased capacity to release some of the inflammatory mediators. The lower concentrations of leukocytes, lymphocytes, eosinophils, monocytes, and mature neutrophils in blood (Morrow et al., 1979; Reid et al., 1986), the decreased lymphoproliferative response after tetanus toxoid immunization (Wentink et al., 1997), and the lower number of membrane antigens on the surface of polymorphonuclear cells (Zerbe et al., 2000) suggest a decreased capacity of blood leukocytes to migrate into the infected mammary gland.

The decreased clearance of endotoxins (Breukink and Wensing, 1997) and the increased concentrations of the acute phase proteins haptoglobin and serum amyloid A, which are synthesized in the liver (Ametaj et al., 2002; Katoh, 2002), suggest that accumulation of liver lipids can affect the immune response directly by altering the ability of the liver to synthesize and degrade compounds involved in the immune response (Shi et al., 2001; Katoh, 2002). It is more likely, however, that liver lipid accumulation is associated indirectly with a decreased immune response by its association with changes in metabolic hormones, metabolites, and compounds, which affect immune functions (Breukink and Wensing, 1997; Suriyasathaporn et al., 2000). Elevated concentrations of BHBA and NEFA have compromised the immune response *in vitro* (Suriyasathaporn et al., 2000), and IGF-I stimulates neutrophil function (Zhao et al., 1993). Because lipoproteins protect various species of nonruminants against endotoxin-induced toxicity (Harris et al., 2000), it can be assumed that decreased lipoprotein concentrations in blood also are detrimental to the immune response.

Conversely, inflammatory responses could be part of the etiology of fatty liver and other periparturient disorders (Ametaj et al., 2002; Fürll and Leidel, 2002; Katoh, 2002). Liver lipid accumulation can be preceded by increased concentrations of the proinflammatory cytokine TNF α (Ametaj et al., 2002), which increase insulin resistance and plasma concentrations of haptoglobin and serum amyloid A (Katoh, 2002). Haptoglobin binds

Table 10. Association of fatty liver with reproductive performance in dairy cows.

Parameter	Association ¹	Reference
First ovarian activity	++	Reid et al., 1983; Rukkwamsuk et al., 1999c
First ovulation	+	Reid et al., 1983
First estrus	+	Paulová et al., 1990; Jorritsma et al., 2000
First insemination	+	Reid et al., 1983
Days open	++	Heinonen et al., 1987; Paulová et al., 1990
Pregnancy rate	++	Haraszti et al., 1982; Jorritsma et al., 2000
Services/cow	+	Schäfer et al., 1988; Paulová et al., 1990

¹The number of + represents slight, moderate, or strong detrimental association of fatty liver. The strength of association increases with increasing concentrations of triacylglycerol.

to apoprotein A-I, which could interfere with the functions of apoprotein A-I in HDL receptor binding and in the exchange of cholesteryl esters in steroidogenic tissues (Katoh, 2002).

Reproductive Pathology and Fatty Liver

Cows with fatty liver have decreased reproductive performance (Table 10) because follicular development starts in the early postpartal period (Breukink and Wensing, 1997). Decreased reproductive performance can be explained partly by delayed uterine involution (Higgins and Anderson, 1983). The delayed involution can be explained by an increased incidence, length, and severity of endometritis (Haraszti et al., 1982; Heinonen et al., 1987; Sheldon et al., 2002), which can be caused by a delayed and decreased immune response in the uterus (Zerbe et al., 2000). Delayed initiation of ovarian activity (Table 10) can be explained partly by decreased and delayed synthesis of steroidogenic hormones, i.e., progesterone and luteinizing hormone (Zhou et al., 1997).

Another reason for the delayed initiation of ovarian activity is a severe negative energy balance (Herdt, 1991). Additionally, decreased concentrations of IGF-I, insulin, and lipoproteins (Herdt, 1991) and elevated concentrations of ammonia, NEFA, and urea can impair normal ovarian function (Comin et al., 2002; Jorritsma et al., 2003). Decreased pregnancy rates in cows with fatty liver (Table 10) can be explained by decreased numbers of oocytes that survive during early embryonic development (Wensing et al., 1997). The much lower survival rates of oocytes collected at d 81 to 120 postpartum from cows with fatty liver (Wensing et al., 1997) suggest that the negative associations of fatty liver with reproductive performance persist until midlactation.

ETIOLOGY OF FATTY LIVER

Fatty liver develops primarily in the metabolically and physiologically challenging periparturient period because of insufficient nutrient uptake and hormonal

changes and is associated with greater incidence of diseases, infections, and inflammations. Fatty liver has been observed also in late pregnancy when cows were fed for 5 d with straw only (Gerloff and Herdt, 1984). Risk factors for fatty liver (Table 11) can be grouped into 3 categories: nutritional, managerial, and genetic.

Nutritional Risk Factors for Fatty Liver

Nutritional risk factors are related to increased lipolysis of adipose tissue or specific nutrients, hormones, or toxins that alter metabolism in the liver (Herdt, 2000). The primary nutritional risk factor for fatty liver is obesity. In obese cows (BCS ≥ 4.0), lipolysis of adipose tissue is increased more during metabolically and immunologically challenging situations, such as the peripartal period, than it is in cows with normal BCS (Rukkwamsuk et al., 1998). Obese cows have a greater decrease in feed intake in such situations and, therefore, have a more severe negative energy balance (Stockdale, 2001).

The more severe negative energy balance and decreased feed intake of obese cows in the peripartal period could be explained by the fact that increased adipose mass is associated with increased adipocyte cell size and increased adipose sensitivity to glucocorticoids and decreased sensitivity to BHBA, glucose, and insulin (Rukkwamsuk et al., 1998; Herdt, 2000). Bovine adipocytes secrete hormone-like compounds such as leptin (Chelikani et al., 2003) and most likely the proinflammatory cytokine, $\text{TNF}\alpha$ (Ohtsuka et al., 2001), although the expression of $\text{TNF}\alpha$ in bovine adipose tissue has not been confirmed. Both compounds decrease feed intake and insulin sensitivity and increase hepatic lipogenesis, catabolism, and inflammation (Drackley, 1999; Ohtsuka et al., 2001; Kushibiki et al., 2003). Obesity does not necessarily cause fatty liver, especially when cows stay healthy or adapt their feed intake to their milk production (Smith et al., 1997).

The effects of prepartal diets on the development of fatty liver are inconsistent (Hippen et al., 1999; Gerloff, 2000; Bobe et al., 2003). Possible reasons for the vari-

Table 11. Risk factors for fatty liver in lactating dairy cows.

Risk factor	Effect ¹	Reference
Prepartum:		
Obesity (BCS ≥ 4.0)	++	Wensing et al., 1997
Severe feed restriction	+++	Gerloff and Herdt, 1984
Feeding excess energy	++	Wensing et al., 1997
Long calving interval	+	Stöber and Scholz, 1991
Postpartum (especially around calving and when cows are obese):		
Diseases and infections	++	Katoh, 2002
Fasting	+++	Brumby et al., 1975; Fürll et al., 1993
Feed restriction	++	Staufenbiel et al., 1992; Drackley, 1999
Ketogenic diets	+	Stöber and Scholz, 1991
Sudden feed changes	+	Stöber and Scholz, 1991; Gerloff, 2000

¹The number of + represents slight, moderate, and strong risk factors for fatty liver.

able results are differences in BCS prior to dietary treatment, length and time of the prepartal dietary treatment period, differences in composition of the postpartal diet, and differences in other risk factors for fatty liver (Smith et al., 1997; Bobe et al., 2003). Therefore, studies that investigate the effects of BCS, prepartal diet, and postpartal diet in a factorial design are warranted.

The effects of postpartal diets on the development of fatty liver vary and are affected by similar factors, as are the effects of prepartal diets on fatty liver development (Gerloff, 2000). Sudden dietary changes and high concentrate diets increase the risk for ruminal acidosis and bacterial endotoxemia (Goff and Horst, 1997). Both of these diseases are involved in the etiology of fatty liver (Nikov et al., 1981; Fürll and Leidel, 2002). Postpartal diets containing high concentrations of protein can increase the risk for fatty liver (Murondoti et al., 2002), which could be caused by a more severe negative energy balance and increased concentrations of ammonia in blood, which are toxic at high concentrations. Further studies are needed to evaluate the effects of prepartal and postpartal diets and their interactions with each other, BCS, and health status of cows on development of fatty liver before definitive recommendations can be given.

Feed restriction by 30 to 50% and fasting for 4 to 6 d prepartum or postpartum can induce fatty liver (Table 11). The effectiveness of inducing fatty liver by feed restriction depends on the propensity of the cows to go into severe negative energy balance, which is greatest directly after calving (Drackley et al., 1992; Drackley, 1999). Feeding only straw for 5 d to decrease BCS in obese cows in late pregnancy has been observed to induce prepartal fatty liver, an abortion, and a high mortality rate (Gerloff and Herdt, 1984). Restricting feed by 20% decreased liver TAG concentration (Douglas et al., 1998; Drackley, 1999), but a follow up study by the same investigators could not confirm the results (Douglas et al., 2002).

Fatty liver can be caused by specific nutrients, hormones, or toxins that alter metabolism in the liver. To increase the likelihood of inducing fatty liver, 1,3-butanediol has been used together with feed restriction to induce experimental fatty liver and ketosis in cows, because 1,3-butanediol increases plasma BHBA concentrations (Drackley et al., 1992). The combination of 1,3-butanediol with feed restriction has a higher success rate for inducing fatty liver than does either treatment alone (Drackley et al., 1992); however, the fatty liver induction protocol is more successful in cows that are naturally susceptible to fatty liver (Smith et al., 1997; Hippen et al., 1999). Overfeeding a ration in a prolonged dry period (2 to 3 mo) and a short period of starvation (6 to 8 h) after the onset of calving has been the most promising fatty liver induction protocol (Wentink et al., 1997; Rukkwamsuk et al., 1998, 1999c). The authors, however, did not report the range of liver TAG concentrations in the control and fatty liver groups, and thus the success rate of this model cannot be determined.

Fasting for 4 to 6 d combined with injections of either estrogen or dexamethasone or administration of 2 25-mg dosages of ethionine, a methionine analog, at a 1-wk interval, have the highest success rate for consistently inducing fatty liver in cows independent of their stage of lactation (Grummer, 1993; Katoh, 2002). Feed restriction and dexamethasone increases lipolysis in adipose tissue (Katoh, 2002), and estrogen increases hepatic lipogenesis (Grummer, 1993). Ethionine inhibits ATP-dependent hepatic synthesis of proteins and phospholipids by decreasing ATP concentrations (Katoh, 2002). The BCS of cows was not reported for any of these trials (Grummer, 1993; Katoh, 2002). Therefore, it remains questionable whether thin cows (BCS ≤ 2.5) can develop fatty liver because excessive NEFA cannot be mobilized from adipose tissue.

Deficiencies of AA and water-soluble vitamins induce fatty liver in nonruminants but apparently not in dairy cows (Grummer, 1993). Bacteria present in the rumen

usually supply cows with sufficient essential AA, vitamins, and antioxidants, but deficiencies can occur during feed changes, when spoiled feed is fed, or during the periparturient periods because of the higher requirements (Stöber and Scholz, 1991). Therefore, we conclude that under certain conditions, AA and vitamin deficiencies play roles in the etiology of fatty liver. It cannot be excluded, however, that the development of fatty liver was elicited by an energy deficit rather than by an AA and vitamin deficiency, because feed changes, spoiled feed, and the periparturient period are associated closely with negative energy balance.

Management Risk Factors for Fatty Liver

Management factors that are related to nutrition and health status also can influence the incidence of fatty liver. Poor quality feeds, such as silage with elevated butyrate concentration, increase the incidence of fatty liver by increasing BHBA production and decreasing feed intake (Stöber and Scholz, 1991). Abrupt feed changes or feeding high-concentrate diets can cause rumen acidosis (Goff and Horst, 1997), which occurs frequently in the periparturient period and is involved in the etiology of fatty liver (Nikov et al., 1981), because acidosis increases ketogenesis and concentrations of endotoxins and proinflammatory cytokines (Fürll and Leidel, 2002; Kushibiki et al., 2003). Therefore, administration of rumen fluid from healthy cows often is recommended for cows with severe fatty liver to prevent rumen acidosis (Stöber and Scholz, 1991).

A greater proportion of older cows have fatty liver (Reid, 1980; Woltow et al., 1991). This increase might be related to excessive adipose tissue at calving (Jorritsma et al., 2000), higher milk production, longer calving intervals (Stöber and Scholz, 1991), weaker immune responses (Mehrzhad et al., 2002), or a lower antioxidant status (Gilbert et al., 1993), all of which are independent risk factors for fatty liver.

Other risk factors for fatty liver are inadequate space or lack of exercise for periparturient cows, poor sanitary conditions, high environmental temperatures, high humidity, and poor air circulation (Stöber and Scholz, 1991; Gerloff, 2000). All such factors can cause release of catecholamines that induce release of NEFA from adipose tissue, decrease feed intake, and increase risk for infections during the periparturient period when cows are more susceptible to infections (Goff and Horst, 1997). Diseases, particularly displaced abomasum, locomotive disorders, toxic mastitis, metritis, milk fever, and retained placenta decrease feed intake, increase nutrient requirements, and cause inflammatory responses that increase lipolysis in adipose tissue, thereby increasing lipid infiltration of the liver

(Drackley, 1999). The strength of association of a disease with fatty liver is related strongly to the degree of negative energy balance caused by the disease. Other risk factors that are associated with decreased feed intake and increased lipolysis in adipose tissue include extended pregnancy and dystocia (Herd, 2000).

Genetic Risk Factors for Fatty Liver

Genetic factors that increase the probability of fatty liver can include mutations that affect feed intake, lipid metabolism in adipose tissue, or lipid metabolism and secretion in liver. More specifically, mutations that increase lipogenesis in liver and lipolysis in adipose tissue and decrease β -oxidation and lipid packaging and secretion in the liver are very likely to cause fatty liver. To date, no specific gene has been found in cattle that increases the incidence of fatty liver in the general population.

To our knowledge, there are no heritability estimates for liver TAG or lipids. However, for ketosis and displaced abomasum, which are both associated closely with fatty liver, heritability estimates are between 0.07 and 0.32 for ketosis (Duffield, 2000) and 0.24 for displaced abomasum (Geishauser et al., 1996). Such estimates indicate a possible genetic basis for fatty liver. The variable success of inducing fatty liver by feed restriction combined with administration of 1,3 butanediol indicates also that some cows are more susceptible to fatty liver (Smith et al., 1997; Hippen et al., 1999). One problem with genetic selection against fatty liver would be that many high producing cows develop mild fatty liver in early lactation, because a severe negative energy balance and insulin resistance at the beginning of lactation enables high milk production throughout the lactation (Herd, 2000). Development of physiological tests that examine the susceptibility of cows to fatty liver could help determine the genetic basis of fatty liver independent of milk production. A similar approach has been used to examine the genetic basis of immune function (Tempelman et al., 2002).

PREVENTION OF FATTY LIVER

The goal of preventatives for fatty liver (Table 12) is to decrease or, even better, to eliminate most of the potential risk factors for fatty liver (Table 11). There are several general management practices that can help prevent fatty liver. Feeding cows a balanced ration according to their dietary requirements in the periparturient period is recommended. Treating cows immediately and aggressively in the periparturient period for infectious and metabolic disorders is recommended. A clean stall that is ventilated well with fresh air, sufficient

Table 12. Preventatives and treatments for different levels of fatty liver or ketosis in lactating dairy cows.

Preventative/treatment	Effect ¹	Reference
Preventatives of fatty liver or ketosis:		
Ammonium propionate	+	Fürll and Leidel, 2002
Calcium propionate	+	Goff et al., 1996
Choline	0	Hartwell et al., 2000; Piepenbrink and Overton, 2003; Pinotti et al., 2003
Glucagon	++	Nafikov et al., 2002
Glucocorticoids	++	Fürll et al., 1993
Glycerol	+/0	DeFrain et al., 2003
Growth hormone	0	Fetrow et al., 1999
Insulin	+/0	Hayirli et al., 2002 ²
Lysine + methionine	+/0	Bauchart et al., 1998 ³
Monensin	++	Duffield et al., 2003
Niacin	+/0	Dufva et al., 1983 ²
Propylene glycol (bolus dose)	++	Studer et al., 1993; Christensen et al., 1997; Pickett et al., 2003
Sodium borate	+	Basoglu et al., 2002
Treatment for mild and moderate fatty liver or ketosis:		
Glucagon	+/0	Bobe et al., 2003
Glucocorticoids	+	Shpigel et al., 1996; Fürll and Fürll, 1998
Glucose	+/0	Gruchy et al., 1963; Stöber and Scholz, 1991
Glucose + fructose	+/0	Kauppinen and Gröhn, 1984
Glucose + glucocorticoids	++	Shpigel et al., 1996
Glycerol	++	Gruchy et al., 1963
Magnesium propionate	+/0	Hamada et al., 1982
Nicotinic acid (bolus dose)	+/0	Waterman et al., 1972; Nurmio et al., 1974
Potassium chlorate	+	Gruchy et al., 1963
Propylene glycol	++	Schultz, 1952; Hamada et al., 1982
Sodium propionate	+	Schulz, 1952; Gruchy et al., 1963
Xylitol	+	Hamada et al., 1982; Sakai et al., 1996
Treatments for severe fatty liver or ketosis:		
Glucagon (continuous infusion)	++	Hippen et al., 1999
Glucose (continuous infusion)	++	Stöber and Scholz, 1991
Glucose + glucocorticoids	+++	Jonsgård et al., 1974; Mudron et al., 1999
Glucose + insulin	++	Stöber and Scholz, 1991; Sakai et al., 1993
Propylene glycol + glucocorticoids	+/0	Kauppinen and Gröhn, 1984

¹The number of + indicates slight, moderate, or strong effectiveness as preventative or treatment for fatty liver; 0 indicates no beneficial effect.

²Results are dosage dependent.

³Only study with positive results.

space and exercise, and fresh, high quality feed are all important to prevent diseases.

The primary approaches to prevent fatty liver are to counteract oxidative or cytotoxic damage to the liver, bacterial endotoxemia, and ruminal acidosis and, most importantly, to improve the metabolic state of cows in the peripartal period by supplying an extra source of blood glucose and by decreasing mobilization of NEFA from adipose tissue.

The glucose supply can be increased by injections of hormones. Possible options are glucagon, insulin, ACTH, glucocorticoids, and growth hormone. Subcutaneous injections of glucagon (15 mg/d for 14 d; Nafikov et al., 2002) and intramuscular injections of glucocorticoids (200 mg/d of prednisolone; Fürll et al., 1993) have been demonstrated to be successful preventatives of fatty liver. The primary beneficial effect of glucocorticoids, ACTH, and glucagon is to increase gluconeogenesis in the liver (Table 13), which increases concentrations of plasma glucose. Slow-release insulin at dosages of 0.14 IU/kg BW was also effective in preventing TAG

accumulation in the liver. Higher dosages of insulin (0.29 and 0.43 IU/kg BW), however, can result in hypoglycemic shock (Hayirli et al., 2002). Neither glucagon nor insulin are approved for use in lactating dairy cows in the United States. Growth hormone had no beneficial effect (Fetrow et al., 1999), which can be explained by the fact that growth hormone is less effective in increasing IGF-I during early lactation (Vicini et al., 1991).

Oral drenches of 1 L/d of propylene glycol for the last 10 d prepartum have been demonstrated to prevent fatty liver and ketosis by increasing plasma glucose and insulin concentrations and decreasing plasma BHBA and NEFA concentrations (Studer et al., 1993; Duffield, 2000). A recent study, however, could not confirm a preventive effect on fatty liver when oral drenches of 0.5 L/d of propylene glycol for the first 3 d postpartum were used (Pickett et al., 2003). The effectiveness of propylene glycol to increase plasma glucose concentrations depends on the dosage and the mode of administration, with stronger increases occurring in cows given higher dosages and when administered by oral

Table 13. Metabolic functions of hormones in comparison to different categories of fatty liver.¹

Metabolic function	Moderate fatty liver	Severe fatty liver	Glucagon	Insulin	ACTH/ glucocorticoids	Growth hormone
Hepatocytes:						
Gluconeogenesis	0 ²	—	+	—	+	+
Glycogenesis	—	—	—	+	+	0
Glycogenolysis	+	0	+	—	0	0
Ketogenesis	+	—	+	—	+	+
Lipogenesis	+	+	—	+	0	0
β -Oxidation	+	—	+	—	+	+
Protein synthesis	—	—	—	+	—	+
Proteolysis	$\pm$	+	$\pm$	—	0	0
VLDL3 secretion	+	—	$\pm$	$\pm$	+	+
Adipocytes:						
Glucose uptake	0	0	$\pm$	+	0	0
Lipogenesis	0	0	$\pm$	+	0	0
Lipolysis	+	+	$\pm$	—	+	+
Lipoprotein lipolysis	0	0	$\pm$	+	0	0

¹Adapted from Engelking (2000).²The symbols +, —, $\pm$, and 0 mean, respectively, increase, decrease, variable, and no effect.³Very-low-density lipoprotein.

drenches (Pehrson, 1972; Christensen et al., 1997). Oral drenches, however, are less practical for on-farm use than is administration to the diet. Differences in responses are related partly to changes in ruminal fermentation and VFA production in favor of propionate (Pehrson, 1972; Schäfer et al., 1975; Christensen et al., 1997). Propylene glycol decreases VFA concentrations in the rumen, particularly concentrations of acetate and butyrate, indicating that higher concentrations of propylene glycol might be toxic for some ruminal bacteria species (Pehrson, 1972).

Nontoxic dosages of sodium borate (Basoglu et al., 2002) have prevented fatty liver but are less researched. The improved hematological indices suggest that sodium borate either improves immune function or decreases infections (Basoglu et al., 2002).

Approaches that were mostly unsuccessful in preventing fatty liver include feeding a) supplemental fat prepartum, b) niacin or nicotinic acid, or c) compounds involved in lipid metabolism. Feeding supplemental fat prepartum prevented TAG accumulation in the liver (Grum et al., 1996); however, a follow-up study by the same investigators did not confirm the positive effect of their initial study (Douglas et al., 1998, 2002). Similarly, after encouraging results in initial studies, oral administration of niacin or nicotinic acid failed to prevent ketosis and fatty liver in more recent studies (Minor et al., 1998). The proposed mode of action was that supraphysiological concentrations of niacin decrease NEFA mobilization from adipose tissue; however, achieving supraphysiological plasma concentrations by oral administration is difficult, because niacin is degraded in the rumen (Dufva et al., 1983).

Dietary supplementation of compounds involved in lipoprotein synthesis and secretion were usually unsuccessful in preventing fatty liver and ketosis (Gerloff et al., 1986b; Bauchart et al., 1998; Piepenbrink and Overton, 2003). This approach is based on the assumption that deficiencies of compounds involved in lipoprotein synthesis and secretion, such as carnitine, choline, cyanocobalamin, inositol, lysine, and methionine, can cause fatty liver in dairy cows just as they do in nonruminants (Bauchart et al., 1998). The failure to prevent fatty liver indicates that cows are either not usually deficient in those compounds, that compounds are quickly degraded in rumen, or that lipoprotein synthesis in ruminants cannot be changed easily.

Promising alternatives to the currently reported fatty liver preventatives are dietary administration of monensin and glucose precursors such as glycerol and propionate salts. Administration of ammonium and calcium propionate orally and administration of 1 kg/d of glycerol to the diet in the periparturient period decreased plasma BHBA and NEFA concentrations, respectively (Goff et al., 1996; Fürll and Leidel, 2002; DeFrain et al., 2003). Feeding monensin during the last month before parturition has prevented ketosis (Duffield, 2000; Duffield et al., 2003). The efficacy of monensin, an antibiotic ionophore, to prevent ketosis depends on the BCS of cows; beneficial effects become evident especially in obese cows (Duffield, 2000). One advantage of monensin is that it is available in a controlled-release form and, therefore, is easy to administer. Monensin is not approved for use in lactating dairy cows in the United States but is approved in several other countries.

The primary mode of action of monensin is that it improves the glucose supply to cows by changing ruminal fermentation and VFA production in favor of propionate (Duffield et al., 2003). Monensin supplementation also has prevented bacterial infections in nonruminants (Butaye et al., 2003) but is less beneficial in ruminants. Furthermore, monensin in beef cattle that are fed high-grain diets prevents subacute ruminal acidosis, which is associated with decreased DMI; however, similar beneficial effects of monensin could not be confirmed consistently in dairy cows (Mutsvangwa et al., 2002). Dietary administration of monensin and glucose precursors such as glycerol, propionate salts, and propylene glycol would be more time and cost effective than daily oral drenches of propylene glycol and intramuscular injections of glucocorticoids and, therefore, warrant further investigation.

Overall, the effectiveness of compounds to prevent fatty liver depends on factors that differ for each compound. Therefore, the choice of preventative depends on the specific nutrition and management program of the farm. A primary target group for prevention is made up of cows that are at a higher risk of developing fatty liver in the early postparturient period such as cows that are obese or do not eat well, had calving difficulties or twins, have metabolic or infectious diseases, or quickly lose BCS.

TREATMENT OF MILD AND MODERATE FATTY LIVER

Treatment of fatty liver depends on the extent of lipid infiltration and the etiology. It is important to counteract the deficiencies that caused the initial lipid infiltration. Diagnosis of mild and moderate fatty liver is difficult and rare because affected cows often do not differ from cows with normal liver in milk production and DMI (Gerloff et al., 1986a), and the only way to correctly diagnose the categories of fatty liver is by liver biopsies, which involve minor surgery to penetrate the body cavity. Therefore, development of a noninvasive technique to categorize concentrations of liver TAG is crucial for informed treatment of mild and moderate fatty liver in the field. Ultrasonic techniques show promise for noninvasively categorizing concentrations of liver TAG (Bobe et al., 1999).

There are some general diagnostic markers, however, that can indicate an increased risk for mild or moderate fatty liver and that are related to severe negative energy balance. Cows with moderate and, to a smaller extent, mild fatty liver often have elevated concentrations of urinary ketones (Gröhn et al., 1983). Cows lose much BCS or BW in a short period before and during the time when they develop mild to moderate fatty liver

(Jorritsma et al., 2001). Their DMI is depressed or much lower than required for milk production before and during the time when cows develop mild to moderate fatty liver (Veenhuizen et al., 1991).

Treatment of mild and moderate fatty liver is important because of its association with decreased metabolic functions of the liver and other organs and decreased health status, reproductive performance, and possibly milk production for months after TAG infiltration subsides. Further, such cows have an increased risk of progressing to severe fatty liver (Gerloff et al., 1986a; Veenhuizen et al., 1991).

General management practices that can treat mild and moderate fatty liver are similar to those for prevention of fatty liver. Feed intake should be increased by offering fresh, high quality legume or grass hay (Stöber and Scholz, 1991). Moderate exercise for 1 h/d has been recommended to promote oxidation of ketone bodies in muscle (Stöber and Scholz, 1991). Their recommendation is supported by observations of Jongsård et al. (1974), who reported that ketosis treatment in Norway was least successful in winter when most cows were in tie stalls.

In comparison to preventatives, there are, to our knowledge, only 2 studies (Fürl and Fürl, 1998; Bobe et al., 2003) that determined the efficacy of potential treatments to reverse mild or moderate hepatic lipodosis. Intramuscular injections of 200 mg of prednisolone daily for 5 d decreased liver TAG concentrations (Fürl and Fürl, 1998). Subcutaneous injections of 15 mg of glucagon daily for 14 d reversed accumulation of liver TAG in cows older than 3.5 yr (Bobe et al., 2003).

Most studies focus on the treatment of ketosis without determining liver TAG concentrations. Cows with ketosis are treated primarily with multiple subcutaneous or intramuscular injections of glucocorticoids (10 to 30 mg dexamethasone, 2 to 5 mg flumethasone, or 100 to 200 mg prednisolone; Stöber and Scholz, 1991), with glucose precursors that are administered orally or intravenously, or a combination of both (Table 12). Potassium and sodium chlorates, which are modifiers of ruminal fermentation, have been used for ketosis treatment but are used rarely today (Burns, 1963; Gruchy et al., 1963).

Glucocorticoids differ in the speed and duration of their effectiveness in increasing blood glucose concentrations. Nonesterified glucocorticoids cause a faster but shorter response than do esterified glucocorticoids. Therefore, a combination of both esterified and nonesterified glucocorticoids is recommended (Stöckl et al., 1969). Glucocorticoids can be replaced by ACTH when the adrenal gland is functioning adequately (Shaw, 1956), but it is used rarely. The primary beneficial effect of glucocorticoids, ACTH, and glucagon as treatments

of fatty liver is to increase gluconeogenesis in the liver (Table 13), which increases concentrations of plasma glucose. A disadvantage of these hormones is that they have to be injected repeatedly, which is not very practical for on-farm use. Development of a subcutaneous slow-release implant of glucagon and glucocorticoids is desirable. A concern for the use of glucocorticoids and glucagon is that they might increase NEFA release from adipose tissue and thereby aggravate ketosis (Hippen et al., 1999). To prevent a potential release of NEFA, a combination of glucocorticoids, nicotinic acid, and dexamethasone-21-iso-nicotinic acid is used (Pehrson, 1972; Fürll and Leidel, 2002).

Recent research, however, questions whether glucocorticoids and glucagon are lipolytic in cows in the periparturient period and rather suggests that glucocorticoids and glucagon decrease lipogenesis in adipose tissue, which is very low during the periparturient period (Fürll and Fürll, 1998; Hippen et al., 1999). A disadvantage of glucocorticoids is that they affect the immune response; however, this was not true for all studies (Fürll and Fürll, 1998; Hoeben et al., 1999; Tempelman et al., 2002). Therefore, studies are warranted to determine how glucocorticoid treatment affects cows with infections and fatty liver that are treated with antibiotics (Stöber and Scholz, 1991). Glucocorticoids can cause hyperglycemia (Shaw, 1956; Fürll et al., 1993). Furthermore, glucocorticoids alone are less effective in treating ketosis than in combination with glucose infusions (Shpigel et al., 1996), and glucocorticoids increase blood glucose and liver glycogen concentrations slower (Burns, 1963) and are less effective in treating ketosis (Gruchy et al., 1963) than is glycerol. In comparison to glucocorticoids and ACTH, glucagon is more liver specific, less lipolytic, and more glycogenolytic, gluconeogenic, and insulinotropic (Table 13; Bassett, 1971).

Oral administrations of 1 kg/d of glycerol, 1 L/d of propylene glycol, or 100 g/d of sodium propionate have been effectively used for treatment of ketosis (Table 12). Of the 3 glucose precursors, glycerol is the most palatable and most effective in increasing glucose concentrations for an extended time; however, glucose concentrations increase slower, and greater amounts of glycerol need to be administered to achieve similar increases in plasma glucose concentrations (Johnson, 1954; Gruchy et al., 1963; Pehrson, 1972). None of the above mentioned studies compared the efficacy of glycerol, propionate salts, and propylene glycol at the same dosage on a molar or weight basis. Still, most reviews noted that propylene glycol was more beneficial for treatment of ketosis than was sodium propionate or glycerol (Schäfer et al., 1975). Therefore, there is a definite need to compare the potency of glycerol, propionate salts, and propylene glycol to prevent and treat

fatty liver before specific recommendations can be made.

A disadvantage of propylene glycol, glycerol, and sodium propionate is that they decrease VFA concentrations in the rumen, in particular concentrations of acetate and butyrate (Pehrson, 1972; Schäfer et al., 1975; Christensen et al., 1997). Additionally, propionate decreases feed intake in most but not all studies (Oba and Allen, 2003). Regarding toxicity, a 1.8-kg dose of propylene glycol via a rumen tube or 2 to 3 L of glycerol administered orally can be neurotoxic (Johnson, 1954). The dosage that causes drowsiness varies among animals, which suggests that the amount absorbed varies between animals (Johnson, 1954). Higher dosages of sodium propionate (0.5 kg) can cause diarrhea and higher water intake because sodium ions alter electrolyte concentrations in blood and increase ruminal pH, which as a positive side effect can decrease ruminal acidosis (Shaw, 1956; Pehrson, 1972; Oba and Allen, 2003). Therefore, the daily dosage of sodium propionate to treat ketosis and fatty liver should be increased slowly over days of administration (Schultz, 1952).

Combinations of sodium propionate with glycerol or propylene glycol may be more effective than either alone because sodium propionate increases blood glucose faster than does glycerol or propylene glycol. A combination of sodium propionate (300 g) with glycerol (500 g) caused hyperglycemia and severe diarrhea in ketotic cows, which can be explained by the high concentrations of glucose precursor used. A later study with a combination of 75 g of sodium propionate, 125 g of glycerol, and 100 g of propylene glycol proved to be effective for treatment of ketosis (Pehrson, 1972).

Calcium and magnesium propionate have been used for treatment of ketosis (Hamada et al., 1982; Goff et al., 1996). They are less soluble, increase blood glucose concentrations slower, and have less effect on rumen pH and concentrations of electrolytes in blood than does sodium propionate (Shaw, 1956). Other glucose precursors are ammonium lactate, calcium lactate, magnesium propionate, sodium lactate, sodium propionate, and tripropionin, which is the glycerol ester of propionic acid (Johnson, 1954; Shaw, 1956), but they are used rarely today. For soluble carbohydrates to be effective by oral administration, large dosages (3 kg/d glucose) have to be used, because they are readily fermented in the rumen to VFA, which causes smaller increases of plasma glucose concentrations (Shaw et al., 1942).

In comparison to glucocorticoids, glycerol, and sodium propionate, the efficacy of intravenous infusions of glucose to prevent ketosis is numerically lower (Gruchy et al., 1963). One reason is that blood glucose is increased for only 80 to 100 min after infusion is stopped (Shaw, 1956). Furthermore, a significant number of

cows do not react to glucose infusions, which suggests that the glucose infusions either did not induce pancreatic insulin secretion or that cows developed insulin resistance (Ohtsuka et al., 2001). Instead of glucose, intravenous administrations of 250 g of carbohydrates such as fructose, mixtures of glucose and fructose, and xylitol have been used (Table 12).

Xylitol is the most promising carbohydrate for successful treatment, because it increases insulin concentrations more and decreases concentrations of plasma ketones more than does glucose (Hamada et al., 1982; Sakai et al., 1996). Invert sugar, which is created by invertase treatment of sucrose and is a mixture of glucose and fructose, probably is the next best alternative for treatment because invert sugar is less inhibitory to gluconeogenesis and causes lower glucose losses via urine than does glucose (Kouider et al., 1978). Fructose is the least promising treatment, because intravenous administration of glucose increases concentrations of both glucose and insulin more and longer than does fructose (Kouider et al., 1978). The major disadvantage of intravenous infusions is that they are impractical for on-farm use.

In summary, the scarcity of studies that have determined the efficacy of treatments for mild and moderate fatty liver demonstrates that additional studies to confirm and compare the effectiveness of different hormones and carbohydrates alone and in combination are needed.

TREATMENT OF SEVERE FATTY LIVER

There are 2 forms of severe fatty liver. Nonencephalopathic severe fatty liver usually is characterized by low feed intake and elevated concentrations of urinary ketones. The more extreme form of severe fatty liver is hepatic encephalopathy, which is characterized additionally by depressed consciousness, ataxia, somnolency, and coma. It often is lethal despite intensive treatment. Nonencephalopathic severe fatty liver usually is not lethal; the cows, however, never regain full health and productivity. Even if they eventually become pregnant, they often develop severe fatty liver again in the following lactation and are culled early in that lactation. Many veterinarians, therefore, recommend immediate culling of cows with severe fatty liver. Effective treatment of cows with severe fatty liver has to be aggressive and long term. The recovery period can last several weeks, because these cows tend to relapse and easily go off feed again.

Cows are diagnosed rarely as having severe fatty liver, because diagnosis requires minor surgery and a liver biopsy. This requirement could explain why there is only one study to our knowledge (Hippen et al., 1999)

that specifically tested the efficacy of a treatment of severe fatty liver. Hippen et al. (1999) demonstrated that continuous intravenous infusions of glucagon for 14 d successfully treats nonencephalopathic severe fatty liver. The disadvantage is that continuous, intravenous infusions are not practical for on-farm use, and glucagon has not been approved for use in lactating cows.

Most studies have focused on testing the efficacy of treatments in severely ketotic cows and did not determine liver TAG concentrations. Typical treatments for severe ketosis are continuous intravenous infusions of glucose for 2 to 3 d at 0.5 to 1 kg/d (Stöber and Scholz, 1991) and infusions of glucose combined with glucocorticoids or insulin (Table 12). The combination treatments are preferred by most veterinarians because glucose infusion supplies glucose quickly and glucocorticoids supply longer term glucose, whereas insulin helps with the uptake of glucose by peripheral tissues (Table 13). Chloral hydrate (2,2,2-trichloro-1,1-ethanediol) is the oldest treatment of severe ketosis and was used primarily in cases of nervous ketosis because it is an anesthetic, but it is rarely used today (Shaw, 1956). Chloral hydrate is a very potent rumen modifier that is also a potent bactericide (Quaghebeur and Oyaert, 1971).

Using glucose infusions in bolus dosage is a less successful treatment of ketosis (Shaw, 1956; Gruchy et al., 1963), because blood glucose is increased only for 80 to 100 min after the infusion stops (Shaw, 1956). Injections of dexamethasone with oral administration of propylene glycol is a less effective treatment than combinations of glucose infusions and dexamethasone and dexamethasone alone (Kauppinen and Gröhn, 1984). The addition of glucose precursors to the diet is not recommended, because the DMI is often not sufficient and varies between days.

For treatment of hepatic encephalopathy, intravenous glucose administrations combined with glucocorticoid injections are used (Mudron et al., 1999). For treatment of hepatic encephalopathy in particular, the treatment should be repeated for several days (Mudron et al., 1999). Studies to evaluate the efficacy of different treatment options for severe fatty liver are needed.

CONCLUSIONS

The objective of this review was to give an overview of the pathology and etiology of fatty liver and then to describe and compare different treatments. Fatty liver is a multifactorial, multifaceted disease that develops when the hepatic uptake of lipids exceeds the oxidation and secretion of lipids by the liver and thereby causes accumulation of TAG in the liver, which is associated

with decreased metabolic function of the liver. Most of the knowledge about the pathology of fatty liver has been generated in the last 20 yr by quantifying metabolic reactions in hepatocytes and adipocytes by using *in vitro* techniques and radioactive tracer studies. Future research will probably focus additionally on gene and protein expression in hepatocytes and adipocytes and will attempt to connect data for gene and protein expression with rates of metabolic reactions.

Fatty liver can be categorized into normal liver and mild, moderate, or severe fatty liver; the latter can be further subdivided into nonencephalopathic severe fatty liver and hepatic encephalopathy. Insufficient or unbalanced dietary intake, obesity, and elevated estrogen concentrations are involved in the etiology of fatty liver, which is associated with dystocia, diseases, infections, and inflammations. The metabolic connections between these risk factors and fatty liver as well as the pathology of mild and moderate fatty liver, however, are less understood than the pathology of severe fatty liver.

One challenge is to have an animal model that consistently develops fatty liver. The most promising procedure to induce postpartum fatty liver consists of a combination of overfeeding in a prolonged dry period and a short period of starvation after the onset of calving. Future studies should focus on the development of a good model to study all aspects of the fatty liver syndrome as well as the etiology of fatty liver and identification of early steps in the development of fatty liver as well as their metabolic effects. Identification of these early steps is also important for development and use of early indicators of fatty liver. Gene-array and proteomic studies offer potential methods to detect those steps and hopefully will help in the development of strategies to prevent fatty liver.

Prevention of fatty liver by supplying cows with sufficient nutrients and a clean and health-promoting environment in the periparturient period is always better than any treatment, because fatty liver is associated with decreased health status and reproductive performance of dairy cows. Hopefully, future research will investigate metabolic links between fatty liver and health status and reproductive performance. Such studies will be very challenging, because multiple organ systems are involved, and their interactions are highly complex. Maintaining good health status and reproductive performance of high producing dairy cows, however, is and will continue to be a primary challenge for dairy research and dairy producers.

Preventatives as well as treatments for fatty liver focus on prevention of excessive lipolysis of adipose tissue, increasing hepatic gluconeogenesis or glucose supply, and increasing glucose uptake of extrahepatic tissues. Many different compounds can promote these

metabolic actions. Future research will, therefore, reveal new potential preventatives and treatments of fatty liver to the point that preventatives or treatments for specific etiologies and pathologies of fatty liver are developed. These metabolic actions need to be promoted especially in cows that are obese or do not eat well, had calving difficulties or twins, have metabolic or infectious diseases, or are in severe negative energy balance.

Potential preventatives and treatments were summarized and discussed. Successfully tested preventatives are oral drenches of propylene glycol in the periparturient period or injections of glucocorticoids, glucagon, or low dosages of slow-release insulin in the first days after calving. These choices are not very practical for on-farm use, and insulin and glucagon are not approved for use in lactating dairy cows in the United States. The addition of glucose precursors such as glycerol, propylene glycol, or propionate salts to the feed in the periparturient period is a more practical solution but has not been tested. The only successfully tested treatments of mild and moderate fatty liver are injections of glucagon or glucocorticoids for several days. Oral drenches of glucose precursors and injections of glucagon or glucocorticoids alone or in combination are promising treatments but need to be tested. Cows with severe fatty liver need a more aggressive and longer term treatment. Continuous intravenous infusions of glucose combined with glucocorticoid or insulin injections or continuous intravenous infusions of glucagon offer the most promising treatment to date. Hopefully, future research will provide new treatment options that are more practical and less labor intensive for on-farm use such as slow-release formulas of hormones. Such treatment options will reduce the problem of fatty liver and its detrimental metabolic effects.

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