Chapter 7
miRNA Regulation of Glucose and Lipid Metabolism in Relation to Diabetes and Non-alcoholic Fatty Liver Disease

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Abstract Glucose and lipids are important nutrients because they provide most of the energy for the cells. A pre-translational regulation by microRNAs (miRNAs) plays a pivotal role in cellular metabolism by targeting the key rate-limiting enzymes of relevant pathways to fine-tune control of metabolic homeostasis. Aberrant expression of these miRNAs can result in an over or under expression of those key enzymes, contributing to the etiology of diabetes and non-alcoholic fatty liver disease (NAFLD). Here we discuss recent studies of various miRNAs that control insulin sensitivity, hepatic glucose production and de novo lipogenesis and how aberrant expression of these miRNAs contributes to the pathophysiology of diabetes and NAFLD in animal models. We also review the current application of circulating miRNAs as biomarkers for diagnosis or disease monitoring in diabetes and NAFLD.

Keywords Diabetes · Non-alcoholic fatty liver disease · Metabolism · miRNA

7.1 Introduction

Glucose is an important energy source for most living organisms. In mammals, brain and red blood cells are dependent on glucose as the primary energy source while skeletal muscle can use both glucose and fatty acids as the energy source. In contrast, liver and adipose tissue can convert excess glucose and fatty acids to triglycerides which are important form of energy storage during a prolonged starvation period [1, 2]. Alterations of glucagon and insulin levels influence metabolism

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of these two nutrients to maintain energy homeostasis. In mammals, during fasting periods, glucagon is secreted into the plasma to maintain glucose concentrations within a narrow range, protecting the brain from hypoglycemia-induced organ damage. Glucagon achieves this by stimulating hepatic glycogen breakdown and hepatic gluconeogenesis [3]. In adipose tissue, glucagon stimulates lipolysis, generating free fatty acids and glycerol. Free fatty acids are transported to liver and skeletal muscle where β-oxidation occurs. However, during feeding periods, elevated plasma glucose stimulates insulin release, resulting in a metabolic shift from catabolic to anabolic metabolism [4]. Under this physiological condition, insulin acts on skeletal muscle and liver by promoting glycogen synthesis and stimulating de novo lipogenesis both in adipose tissue and liver, preventing overproduction of glucose during a postprandial period [5, 6].

7.2 Regulation of Glucose and Lipid Metabolism by Insulin and Deregulation

Failure of insulin action, known as insulin resistance, can perturb metabolic homeostasis in insulin responsive tissues. Insulin resistance in skeletal muscle and adipose tissue results in failure of glucose uptake, causing the retention of glucose in plasma. In contrast, hepatic insulin resistance results in the over-stimulation of hepatic glucose production, aggravating plasma glucose level [7]. In response to insulin resistance, pancreatic β-cells secrete more insulin to compensate for insulin resistance, causing elevated levels of plasma insulin known as hyperinsulinemia. Hyperinsulinemia can result in overstimulation of de novo lipogenesis and excessive fat deposition in liver, causing hepatic steatosis or non-alcoholic fatty liver disease (NAFLD) [8, 9]. Furthermore, excessive de novo lipogenesis in liver increases triglyceride secretion as the very low-density lipoprotein (VLDL) to the plasma (Fig. 7.1). Hyperlipidemia can further induce systemic insulin resistance, resulting in elevated plasma glucose due to the failure of glucose uptake by peripheral tissue and increased hepatic glucose production. The elevation of both glucose and lipid causes glucotoxicity and lipotoxicity which trigger β-cell apoptosis and lower insulin secretion [10] (Fig. 7.1).

The insulin signaling pathway plays a key role in communication with post-translational modification of the key enzymes or proteins that regulate glucose and lipid metabolism. Binding of insulin to its receptor on the target cells triggers autophosphorylation, resulting in phosphorylation of insulin receptor substrates-1 and -2 (IRS-1 and IRS-2). The phosphorylated insulin receptor substrates then bind and activate phosphoinositol-3-kinase which further converts phosphatidylinositol 4,5-bisphosphate into phosphatidylinositol 3,4,5-trisphosphate [11]. Phosphatidylinositol 3,4,5-trisphosphate then activates Akt/PKB, which in turn phosphorylates AS160 protein, an essential cytoskeleton protein that stimulates GLUT4 translocation to the plasma membrane into skeletal muscle and adipose

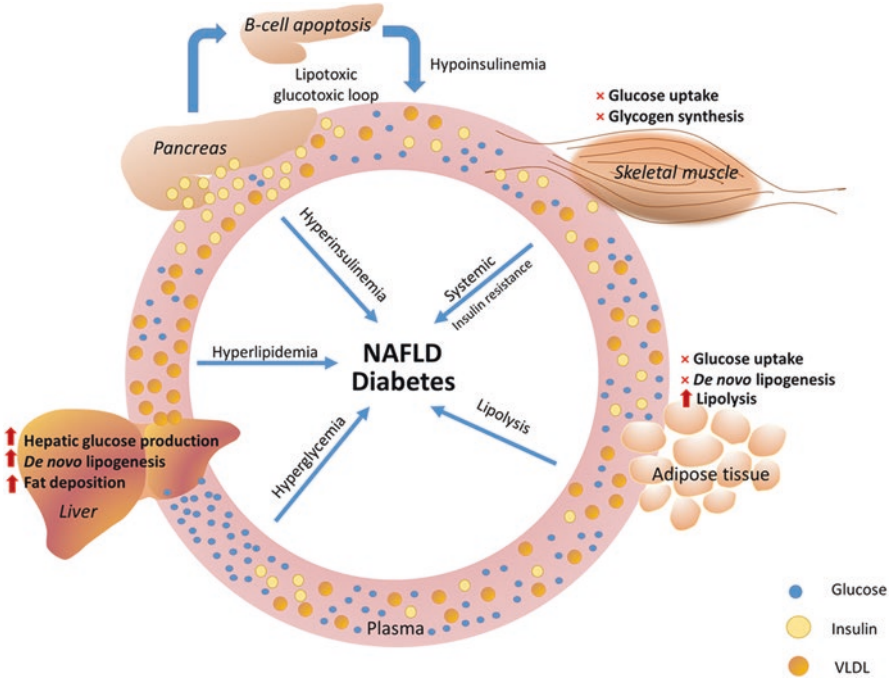

Fig. 7.1 Metabolic hallmarks of type 2 diabetes and NAFLD. Insulin resistance results in hyperinsulinemia which stimulates de novo lipogenesis and ectopic fat deposition in liver, causing NAFLD. Excessive de novo lipogenesis overspills triglyceride as VLDL in the circulation and causes systemic insulin resistance. Failure of glucose uptake in peripheral tissue and excessive hepatic glucose production result in an overt hyperglycemia. Adipose tissue insulin resistance also increased lipolysis, resulting in elevated level of non-esterified fatty acids. This situation combined with elevated levels of VLDL and glucose creates glucotoxicity and lipotoxicity which progressively deteriorate pancreatic beta cells, aggravating T2DM and NAFLD. (X = inhibit. ↑ = increase)

tissue [12, 13]. Akt/PKB phosphorylation also stimulates glycogen synthase through phosphorylation of GSK3, increasing glycogen synthesis in skeletal muscle and liver. In addition, Akt/PKB signaling activates expression of key de novo lipogenesis enzymes including acetyl-CoA carboxylase 1 (ACC1), and fatty acid synthase (FASN), resulting in increased triglyceride synthesis in liver and adipose tissue. In liver, Akt/PKB signaling inactivates FoxO1 transcription factor of the gluconeogenic enzyme genes by phosphorylation, inhibiting gluconeogenesis during postprandial periods [14]. Insulin resistance therefore prevents FoxO1 inactivation, resulting in a constitutive expression of gluconeogenic enzymes and contributes to excessive hepatic glucose production. Although deregulation of the above metabolic enzymes occurs at the transcriptional or post-translational levels, growing evidence indicates that deregulation can occur epigenetically through the microRNAs (miRNAs) [15–17].

7.3 miRNAs Mediating Abnormal Glucose and Lipid Metabolism

The miRNAs are small non-coding RNA, comprising of 20–30 nucleotides in length. They regulate expression of genes by hybridizing to their complementary sequences, located mostly at the 3′-untranslated regions (UTR) of the target mRNAs [18]. The area of base complementary between miRNA and target sequence known as "seed match" can be nearly 100% or partially complementary. This less stringent binding allows miRNAs to bind to any mRNA containing a 3'-UTR sequence partially similar to the seed match region thereby generating a variety of mRNA targets for one species of miRNA [19, 20]. Furthermore, one particular mRNA may be regulated by multiple miRNAs, adding a more complex regulatory network [19, 21]. Binding of a miRNA to its target mRNA can affect mRNA translation in two ways. If the complementary base pairing between the seed match and target sequence is perfect, this binding will result in complete degradation of mRNA target. However, if the complementarity between the seed match and target is not perfect, this would partially inhibit protein synthesis [19, 20]. Recent studies demonstrate that miRNAs can act locally within the cell or they can be transported in extracellular vesicles or exosomes that can be taken up by adjacent or remote cells or tissues [22]. Currently there are more than 2500 miRNA genes that have been identified in the human genome [23]. All of these appear to control a variety of biological and biochemical processes such as growth and development, stress response, cell death and apoptosis, and metabolism [24].

In this review, only the miRNAs that regulate key metabolic enzymes related to diabetes and NAFLD will be emphasized.

7.3.1 miRNA Regulating Insulin Sensitivity and Glucose Transport

miR-103 and miR-107 were the first two miRNAs shown to regulate insulin sensitivity in liver and adipose tissue in mice [25]. These two miRNAs were found to be elevated in leptin deficient (ob/ob) mice and in high fat diet-induced insulin resistant mice. Over-expression of miR-103 and miR-107 in the above mouse models down-regulate the expression of caveolin-1, a component of caveolae lipid raft required for insulin receptor signaling [26]. The decreased expression of caveolin-1 impairs the downstream insulin signaling cascade, disrupting glucose metabolism such as by the reduction of GLUT4 translocation in adipose tissue and increased hepatic gluconeogenesis. Inhibition of miR-103 or miR-107 expression ameliorates hyperglycemia and insulin sensitivity, demonstrating their potential roles as the therapeutic miRNAs [25]. Zhou et al. [27] reported miR-181a as a regulator of hepatic gluconeogenesis, acting through sirtuin-1, a positive regulator of hepatic insulin signaling. Mechanistically, insulin resistance induces expression of

miR-181a which down-regulates expression of sirtuin-1. The decreased sirtuin-1 level in turn causes a hepatic insulin resistance, resulting in the over-expression of two gluconeogenic enzymes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), in parallel with increased hepatic glucose production. Inhibition of miR-181a over-expression in hepatocytes of high fat-diet induced diabetic mice ameliorates hyperglycemia. In addition to the first three miRNAs, miR-802 was also reported to regulate hepatic insulin sensitivity because its expression was found to be elevated in mice bearing leptin receptor deficiency (db/db) and in high fat diet (HFD)-induced diabetic mice [28]. Mechanistically, elevated miR-802 decreases expression of HNF1β while increasing expression of the insulin suppressors, SOCS1 and SOCS3. Increased expression of both SOCS1 and SOCS2 in turn desensitizes insulin signaling, resulting in increased hepatic glucose production in these mouse models. miR-291b-3p has also been reported to regulate hepatic gluconeogenesis through the insulin signaling pathway. Over-expression of miR-291b-3p in normal mice impairs activation of Akt/PKB signalling, leading to a constitutive activation of FoxO1 transcription factor. This results in increased expression of PEPCK and G6Pase, contributing to hyperglycemia. In contrast, inhibition of miR-291b-3p expression was found to improve insulin sensitivity and ameliorate hyperglycemia [29].

7.3.2 miRNA Regulating Glucose Uptake and Glycolysis

The solute carrier family 2 facilitated glucose transporter member 4 (GLUT4) is the glucose transporter that is exclusively expressed in skeletal and cardiac muscles and adipose tissue. GLUT4 is an insulin-responsive glucose transporter which controls the overall rate of glucose uptake. Insulin signaling stimulates translocation of GLUT4 to the plasma membrane where it facilitates glucose uptake into the cells. Decreased GLUT4 expression or translocation causes elevated plasma glucose in patients with type 2 diabetes (T2DM) [30–32]. In a T2DM mouse model, re-expression of GLUT4 in skeletal muscle ameliorates insulin resistance and hyperglycemia [33]. Several miRNAs have been implicated in the direct regulation of GLUT4 expression via binding to the 3'-UTR of GLUT4 mRNA or indirectly via regulation of GLUT4. In this review we only emphasize the mRNAs that directly regulate GLUT4 expression.

miR-93 was first reported to directly regulate GLUT4 expression in adipocytes, through binding to the 3'-UTR of GLUT4 mRNA. Over-expression or inhibition of miR-93 has been shown to decrease or increase expression of GLUT4, respectively. Furthermore, miR-93 expression was elevated in women with polycystic ovary syndrome and insulin resistance [34]. miR-106b was reported to negatively regulate GLUT4 expression in L6 rat myoblasts through direct binding at the 3'-UTR of GLUT4 mRNA. The inhibitory effect of miR-93 on GLUT4 mRNA expression was accompanied by decreased glucose uptake and consumption while this inhibitory effect was lost in insulin resistant L6 myoblasts [35]. miR-29a-3p and miR-29c-3p

have been shown to regulate expression of GLUT4 in skeletal muscle. Silencing miR-29a expression increases insulin-induced glucose uptake in C1C12 mouse myocytes [36]. Over-expression of either miR-29a-3p or miR-29c-3pin primary human skeletal muscle lowers glucose uptake under both basal and insulin-stimulated conditions, and is accompanied by decreased glucose oxidation and muscle glycogen synthesis [37]. miR-29 indirectly regulates GLUT4 expression by inhibiting expression of the secreted protein acidic rich in cysteine (SPRAC) protein, a regulator of GLUT4 expression, which is often dysregulated in T2DM patients [38]. The expression levels of both miR-29a-3p and miR-29c-3p were also found to be elevated in plasma of the ob/ob mice and in humans with T2DM, reinforcing their involvement in the pathophysiology of T2DM [37]. Using miRNA-qualitative trait analysis (miQTL), Gottman et al. [39] showed that the expression of miR-31 was elevated in association with low GLUT4 expression in white adipose tissue of T2DM patients. In support of this association, ectopic expression of miR-31 in human primary preadipocyte culture lowered expression of GLUT4 in parallel with impaired adipocyte differentiation. Although the negative effect of miR-31 on GLUT4 expression was apparent in human white adipose tissue, the expression levels of this miRNA in sera of healthy and T2DM patients were found to be indistinguishable [39].

7.3.3 miRNA Regulating Hepatic Glucose Production

During a fasting period, glucagon signals the activation of several transcription factors and co-activators such as such as FoxO1, PGC-1 α and cAMP-responsive element binding protein (CREB), that drive transcription of gluconeogenic enzymes [40, 41]. Insulin signaling activates Akt/PKB which subsequently inactivates activity of the above transcription factors/coactivators, thereby inhibiting hepatic glucose production. Hepatic insulin resistance blunts the Akt/PKB signaling cascade, resulting in constitutive activation of gluconeogenesis and glycogenolysis. There appears to be the aberrant expression of miRNAs which link Akt/PKB signaling and hepatic glucose production.

miR-23a was first reported as a regulator of gluconeogenesis. Expression of miR-23a was found to be elevated in hepatocytes of hepatocellular carcinoma mice where gluconeogenesis is attenuated [42]. miR-23a inhibits gluconeogenesis through direct binding at the 3'-UTRs of both G6Pase and PGC-1α mRNAs. The latter is the transcriptional co-activator of gluconeogenic genes. Ectopic expression of miR-23a in normal primary mouse hepatocytes decreases expression of G6Pase, concomitant with reduced hepatic glucose production [42]. Liang and co-workers [43] reported miR-29a-c as a regulator of gluconeogenesis by targeting both G6Pase and PGC-1α mRNAs through the direct binding to their 3'-UTRs. Over-expression of miR-29a-c was found to reduce expression of these two genes, accompanied by attenuation of hepatic glucose production and alleviation of hyperglycemia in primary hepatocytes of both normal and db/db mice. miR-33 was reported to control

hepatic glucose production by direct targeting of the expression of PEPCK and G6Pase in human primary hepatocytes [44]. Insulin induces the expression of miR-33 in hepatocytes where it directly inhibits expression of PEPCK and G6Pase via binding to the 3'-UTRs. In addition to a direct regulation of these two gluconeogenic enzymes, miR-33 inhibits expression of CREB, and the retinoid-related orphan receptor-α (RORα) transcription factors as well as the SRC-1 transcriptional coactivator, all of which control transcription of gluconeogenic genes. In addition to gluconeogenesis, miR-33 also regulates glycogen breakdown by inhibiting expression of glycogen phosphorylase and phosphoglucomutase. Overexpression of miR-33 in human hepatocytes resulted in the inhibition of PEPCK, G6Pase, glycogen phosphorylase and phosphoglucomutase, accompanied by reduced glycogen content and hepatic glucose production [44].

miR-26a was reported as a regulator of insulin sensitivity, gluconeogenesis and lipid metabolism in mice [45]. Although miR-26a regulates gluconeogenesis by down-regulating PEPCK, fructose-1,6-bisphosphatase 1 (FBP1) and G6Pase mRNAs, only the PEPCK mRNA contains a miR-26a binding site in its 3'-UTR. Expression of miR-26a was down-regulated in livers of ob/ob mice and high fat diet (HFD)-induced insulin resistant mice. In humans, expression of miR-26a is inversely proportional to the body mass indices of overweight and obese subjects with T2DM. Over-expression of miR-26a in HFD-induced insulin resistant mice and db/db mice was found to improve insulin sensitivity while it reduced lipogenesis and hepatic glucose production [45]. Although miR-26a regulates the overall program of gluconeogenesis, only PEPCK contains a miR-26a binding site in its 3'-UTR.

In addition to miR-26a, miR-214 has been reported to control gluconeogenesis through inhibition of the ATF4 transcription factor [46]. Mechanistically, cAMP/PKA signaling or fasting down-regulates expression of miR-214, resulting in expression of ATF4 which further interacts with FoxO1 and stimulates expression of both PEPCK and G6Pase genes. Over-expression of miR-214 in primary hepatocytes of HFD-induced insulin resistant mice inhibited ATF4 expression, resulting in down-regulation of PEPCK and G6Pase, and amelioration of hyperglycemia [46].

Zhuo et al. [47] identified miR-451 as a negative regulator of hepatic glucose production in mice through inhibition of gluconeogenesis. Mechanistically, a low level of miR-45 expression in diabetic mice blocks Akt/PKB signaling and FoxO1 phosphorylation, resulting in over-expression of PEPCK and G6Pase. miR-451 also inhibits expression of glycerol kinase, an enzyme that feeds glycerol into the upper part of the gluconeogenic pathway. Ectopic expression of miR-451 in hepatocytes of diabetic mice was found to decrease expression of gluconeogenic enzymes and hepatic glucose production, ameliorating hyperglycemia. Langlet and colleagues [48] identified miR-205-5p as a regulator of Akt/PKB signaling and FoxO1. Over-expression of miR-205-5p in normal mice decreases hepatic glucose production and increases glucose tolerance while inhibition of miR-205-5p expression in high fat diet-induced insulin resistant mice improves glucose intolerance and hyperglycemia. Collectively these data indicate the protective role of miR-205-5p against hyperglycemia. The miRNAs which regulate hepatic glucose production either through gluconeogenesis or glycogenolysis are summarized in Fig. 7.2.

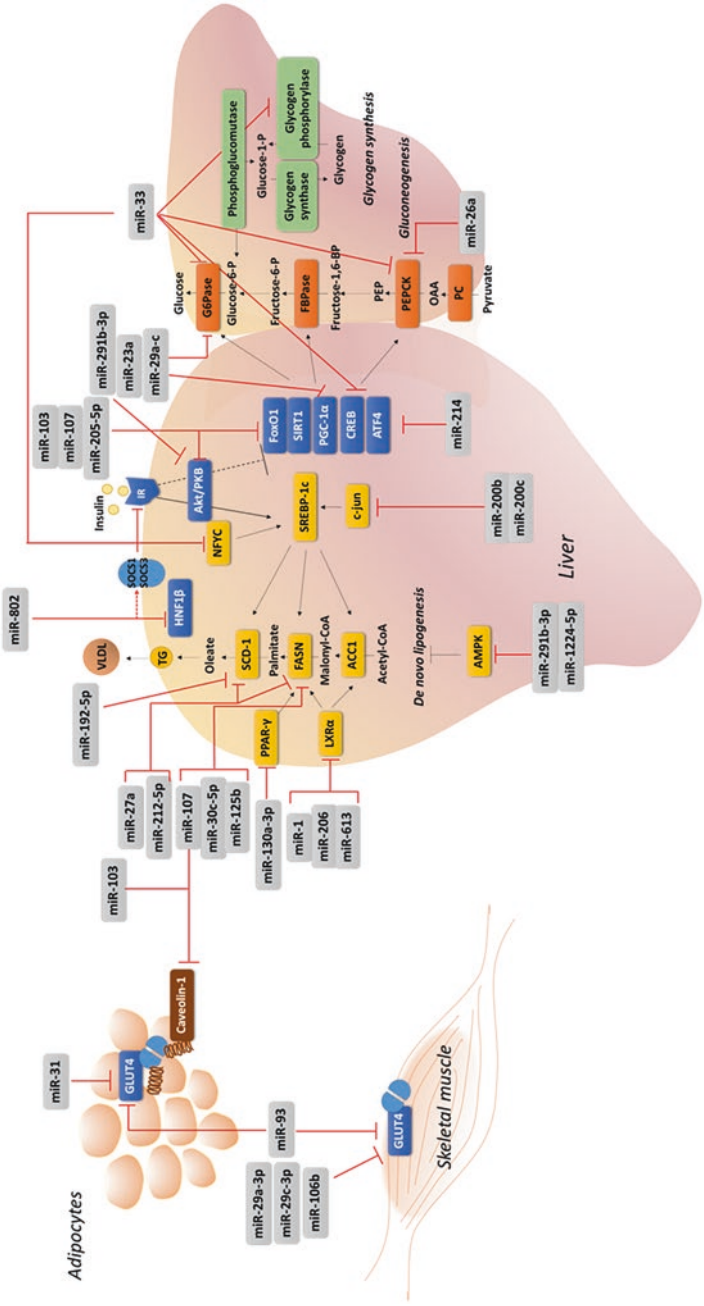

Fig. 7.2 miRNAs regulating insulin sensitivity, glucose transport, hepatic glucose production and de novo lipogenesis in mouse model. The metabolic pathways of de novo lipogenesis, gluconeogenesis and glycogen synthesis with key metabolites and enzymes (bold letters), and the pathways in liver are shown while the regulators of metabolic enzymes are boxed in blue. The miRNAs are boxed in grey and their targets are shown by a red line with a vertical bar

7.3.4 miRNA Regulating De Novo Lipogenesis

De novo lipogenesis is the synthesis of lipids from glucose and occurs in liver and adipose tissue. This process starts from the conversion of citrate-derived acetyl-CoA to long chain fatty acids, catalyzed by a series of lipogenic enzymes. Acetyl-CoA carboxylase 1 (ACC1) and fatty acid synthase (FASN) are the first two rate-limiting enzymes which regulate the overall de novo lipogenic program. ACC1 catalyzes the carboxylation of acetyl-CoA molecules to form malonyl-CoA which is then used as the carbon donor during each cycle of chain extension by FASN. Once completed, the long chain acyl-CoA is esterified with glycerol to form triglyceride which can be used as a storage nutrient or exported as the VLDL [49]. Over-stimulation of de novo lipogenesis can contribute to the pathophysiology of hepatic steatosis or NAFLD. Ectopic fat deposition in liver also causes hepatic insulin resistance and T2DM [49] (Fig. 7.1). Growing evidence indicate that deregulation of several miRNAs is associated with an aberrant expression of ACC1 and FASN in liver and adipose tissue in rodents and humans, contributing to the development of NAFLD. Some miRNAs directly regulate expression of FASN or ACC1 while some miRNAs regulate these enzymes through their transcription factors, liver X receptor (LXR), farsenoid X receptor (FXR), sterol regulatory element binding protein 1c (SREBP1c) or peroxisome proliferator-activated receptor-γ (PPAR-γ).

Bhatia and co-workers [50] first reported miR-107 as a direct regulator of FASN expression via direct interacting with 3'-UTR of FASN mRNA. Over-expression of miR-107 inhibits expression of FASN accompanied by decreased palmitate synthesis. Fang et al. [51] showed that miR-30c-5p directly binds to the 3'-UTR of FASN mRNA and represses its expression. In db/db mice, the expression of miR-30c-5p was down-regulated, resulting in an elevated level of FASN mRNA. Ectopic expression of this miRNA in these mice lowers expression of FASN, ameliorating excessive fat synthesis and deposition in their livers. Guo et al. [52] identified miR-212-5p as a negative regulator of de novo lipogenesis via binding to the 3'-UTRs of FASN mRNA. Ectopic expression of miR-212-5p in mouse hepatocytes down-regulates expression of FASN in parallel with decreased triglyceride synthesis and accumulation. Remarkably, over-expression of this miRNA in livers of mice can protect high fat diet-induced hepatic steatosis. Zhang et al. [53] found that miR-27a was a direct regulator of FASN expression. In normal mouse liver, ectopic expression of miR-27a reduced expression of FASN accompanied by reduced lipid accumulation. The expression of miR-27a was lowered in livers of ob/ob mice bearing NAFLD and administration of mimic miR-27a to their hepatocytes lowered expression of FASN concomitant with decreased triglyceride accumulation, ameliorating hepatic steatosis. Interestingly, alteration of miR-27a levels in liver was correlated with hepatic and plasma triglyceride, suggesting that miR-27a is a potential biomarker for detecting hyperlipidemia [54].

With regard to indirect regulation of FASN, some miRNAs regulate FASN expression by inhibiting expression of FASN transcription factors or other regulators. Zhong et al. [55, 56] reported that miR-1, miR-206 and miR-613 negatively regulated expression of both FASN and ACC1 in HepG2 cells by inhibiting expression of LXRα, concomitant with reduced fat accumulation. In addition to the above three miRNAs, miR-130a-3p can also down-regulate expression of FASN by inhibiting expression of PPAR-γ [57]. miR-130a-3p expression was found to be decreased in db/db mice with hepatic steatosis. Over-expression of miR-130a-3p in this mouse model inhibited FASN expression, concomitant with reduced hepatic steatosis and serum triglycerides, suggesting its role as an anti-hepatic steatotic miRNA. Goedeke and co-workers [58] identified miR-33 as an inhibitor of FASN expression by blocking expression of the nuclear transcription Y subunit gamma (NFYC), a transcription factor of SREBP1-responsive genes such as FASN and ACC1. Inhibition of miR-33 expression in primary mouse hepatocytes increases expression of FASN and ACC1, concomitant with increased hepatic lipid accumulation and circulating triglycerides. Although its direct targets are unknown, miR-185 negatively regulated expression of FASN, HMG-CoA reductase (one of rate-limiting enzymes in cholesterol biosynthetic pathway), sterol regulatory element binding proteins, SREBP2 and SREBP1c, ameliorating insulin sensitivity and hepatic steatosis [59]. miR-291b-3p is also implicated in the pathophysiology of NAFLD as its expression level was elevated in livers of high fat diet-induced hepatic steatotic mice [60]. Mechanistically, miR-291b-3p down-regulates FASN expression by inhibiting expression of the AMP-activated protein kinase (AMPK), a negative regulator of de novo lipogenesis, increasing lipogenesis and circulating triglycerides. Similar to miR-291b-3p, miR-1224-5p also inhibits expression of AMPK expression in mice. The expression of miR-1224-5p was elevated in livers of high fat diet-fed mice with hepatic steatosis and the inhibition of miR-1224-5p expression led to increased expression of AMPK and decreased expression of FASN [61].

Other miRNAs which indirectly regulate FASN expression include miR-200b and miR-200c which target c-jun, a transcription factor for SREBP1c expression. The decreased expression of c-jun in turn down-regulates expression of SREBP1c, lowering FASN expression. The expression of these two miRNAs was decreased in livers of high fat diet-induced steatotic mice while over-expression of these two miRNAs reduced FASN expression and lipid accumulation in their livers, indicating their roles in protecting against hepatic steatosis [62]. miR-125b also plays an important role in protecting high fat diet-induced hepatic steatosis in mice by inhibition of FASN expression and reduction of circulating triglycerides [63]. Interestingly miR-125b expression was induced by estrogen while this protective effect was lost in ERα-knockout or ovariectomized mice.

In addition to ACC1 and FASN, over-expression of stearoyl-CoA desaturase-1 (SCD-1), an enzyme that catalyzes the formation of monounsaturated fatty acids such as oleate and palmitoleate, hasalso been implicated in NAFLD. Deficiency of SCD-1 can protect mice from high-fat diet induced hepatic steatosis [64]. Liu et al.

[65] identified miR-192-5p as a direct regulator of SCD-1 through binding to the 3'-UTR of SCD-1 mRNA. The expression of miR-192-5p was decreased, concomitant with increased expression of SCD-1 in livers of high fat diet-induced steatotic rats. Using human Huh7 hepatocytes as a model, exposure of this cell line to a high concentration of palmitate was found to down-regulate expression of miR-192-5p, concomitant with increased SCD-1 expression and triglyceride accumulation. Moreover, over-expression of miR-192-5p decreased SCD-1 expression and alleviates triglyceride synthesis. In addition to regulating FASN expression, miR-27a and miR-212-5p were also found to regulate expression of SCD-1 via direct interaction with the 3'-UTR of SCD-1 mRNA [52, 53]. Over-expression of either of these miRNAs in ob/ob mice bearing hepatic steatosis down-regulates expression of SCD-1 concomitant with reduced lipid accumulation, alleviating liver steatosis. The miRNAs which regulate expression of FASN, ACC1 and SCD1 either directly or indirectly are summarized in Fig. 7.2.

7.4 Circulating miRNAs as Biomarkers for Diabetes and Non-alcoholic Fatty Liver Disease (NAFLD)

Circulating miRNAs are either released in the extracellular vesicles, exosomes, or bound to high density lipoprotein or argonaute protein [66–68]. The expression levels of circulating miRNAs under different pathophysiological conditions are varied, reflecting abnormal metabolism. Detecting circulating miRNA in the biological fluids also provides a non-invasive means to diagnose or monitor disease progression [17, 68]. Although the evidence above clearly indicates that aberrant expression of several miRNAs is associated with diabetes and NAFLD, not all miRNAs are released from the cells as circulating miRNAs [68]. Even if they are, their abundance or stability may be too low to be detected by the current technical means which limits their use as biomarkers [67]. Over several years, numerous efforts have been made to identify the circulating miRNAs as biomarkers for diabetes and NAFLD. As noted below, some of the above miRNAs implicated in hepatic insulin sensitivity, glucose and lipid metabolism in mouse models may not be applicable in humans.

7.4.1 miRNA Markers for Diabetes in Humans

Among various miRNAs that have been implicated in diabetes in animal models, only a few of the above miRNAs are associated with diabetes in humans. With regard to insulin sensitivity, miR-103 and miR-107, which regulate hepatic insulin resistance in mouse models, were also found to be elevated in sera of patients with

T2DM [69–71]. Of particular interest, the levels of miR-107 together with miR-33, miR-150 and miR-122 were increased in sera of patients with T2DM, suggesting that these miRNAs may act in concert, contributing to insulin resistance in humans [71]. miR-143 is another miRNA that was previously been shown to regulate insulin sensitivity in mice by targeting the oxysterol-binding-protein-related protein 8 (ORP8), a component required to initiate Akt/PKB phosphorylation [72]. Although the expression level miR-143 was high in three independent insulin resistant rodent models (i.e., high fat diet-induced insulin resistant mice, ob/ob mice or T2DM rats), its abundance in sera of normal and patients with prediabetes or T2DM was not found to be different [72–75]. This suggests that miR-143 may not be a good biomarker. The miR-23a which down-regulates gluconeogenesis by inhibiting expression of G6Pase and PGC1α in primary mouse hepatocytes was also found to be decreased in sera of patients with prediabetes and T2DM, suggesting its potential role as an early biomarker for T2DM [76].

Among other circulating miRNAs, miR-126 has been extensively studied in various cohorts of both T1DM and T2DM. Mechanistically, miR-126 promotes growth of endothelial and vascular tissues by inhibiting the expression of sprouty-related protein (SPRED1) and phosphoinositol-3 kinase regulatory subunit 2 (PIK3R2/p85-beta), both negative regulators of the vascular endothelial growth factor (VEGF) signaling pathway. In diabetic patients, loss of miR-126 expression in their plasma is attributed to the impaired vascular tissues [77–79]. Furthermore, the decrease of circulating miR-126 in serum was also associated with T1DM and gestation diabetes [80]. In addition to being a serum biomarker, miR-126 was also released in the urine which can be used as a biomarker for an early onset of T1DM in pediatric patients [81].

Glucotoxic- and lipotoxic-induced β-cell death can progressively exacerbate diabetes. Some miRNAs have been associated with the maintenance of islet β-cell mass. For example, miR-375 was recently ascribed as a biomarker for pancreatic β-cell destruction [82, 83]. Due to its high abundance, acute or profound destruction of pancreatic β-cells results in the elevated levels in sera of patients with T1DM and T2DM [84–87]. Likewise, miR-197-3p and let-7 g have also been described as biomarkers for monitoring deterioration of pancreatic β-cells in children with T1DM. The expression of these two miRNAs was found to be positively correlated with C-peptide during the progression of diabetes [88, 89].

Instead of using only one or two miRNAs as potential biomarkers, miRNA profiling has been used as an alternative approach to identify groups of miRNA that may be responsible for the onset or progression of the disease. Erener et al. [90] performed an extensive study of miRNA profiles using a large cohort of children with T1DM and identified 6 miRNAs (miR-454-3p, miR-222-3p, miR-144-5p, miR-345-5p, miR-24-3p and miR-140-5p) which were elevated in serum during the early onset of T1DM. The authors also identified two miRNAs (let-7c-5p and let-7a-5p) which were positively correlated with HbA1c in this cohort. Likewise, Yang et al. [76] performed a miRNA profiling study of sera from patients with prediabetes and T2DM compared with healthy individuals, and were able to identify a

group of miRNAs including miR-23a, let-7i, miR-486, miR-96, miR-186, miR-191, miR-192, and miR-146a which were down-regulated in both pre-diabetic and T2DM individuals.

7.4.2 miRNA Markers for NAFLD in Humans

Among other miRNAs, miR-122 which targets de novo lipogenesis [91] has been extensively studied by several investigators. Yamada et al. [92] found that the levels of miR-122 together with miR-21, miR-34a, and miR-451were elevated in sera of patients with NAFLD. Another study [93] reported that miR-122 together with miR-17, miR-20a and miR-20b were elevated in T2DM patient with NAFLD. In addition, Becker et al. [94] reported that miR-122 was increased in sera of patients with both NAFLD and the non-alcoholic steatohepatitis. Specifically, the expression level of miR-122 was found to be positively associated with total cholesterol and triglyceride levels in plasma of NAFLD patients [92, 95–97]. The level of miR-122 was also elevated in plasma of children with NAFLD in German and Italian cohorts [98]. In contrast to these reports, the expression of miR-122 was reported to be lower in sera of patients with T1DM, T2DM, maturity onset of diabetes (MODY) or mitochondrial mutation-induced diabetes [99].

The elevation of miR-21 in serum of NAFLD patients initially reported by Yamada et al. [92] was supported by two functional studies in which ablation of miR-21 expression ameliorated hepatic steatosis of high fat-diet induced fatty liver mice [100, 101]. The elevated level of miR-34a was also repeatedly demonstrated in sera of patients with NAFLD [92, 95, 102]. Mechanistically, miR-34a exerts its inhibitory effect on expression of the sirtuin 1/AMPK/PPARα axis which is a negative regulator of the de novo lipogenesis pathway [103–105]. miR-33a and miR-33b, which down-regulate expression of FASN indirectly through NFY-C, were found to be up-regulated in plasma of children with hypercholesterolemia. In addition, the expression levels of these two miRNAs were positively correlated with total cholesterol in the serum [106]. miR-181a, which controls insulin sensitivity in mouse models, was also found to be elevated in sera of patients with NAFLD. However, a larger cohort is required in further studies for conclusive data [106]. miR-103 controls insulin sensitivity and is associated with NAFLD, suggesting its potential as a non-invasive biomarker for diagnosis of NAFLD and prognosis of disease severity [68]. Geng et al. [107] showed that the expression of miR-98 may be used as a biomarker for detecting metabolic syndrome as its expression was low in patients with hypercholesterolemia. Mechanistically, miR-98 targets the SREBP2 transcription factor of enzymes involved in cholesterol biosynthesis. Animal studies showed that over-expression of miR-98 decreased total cholesterol in HepG2 cells and serum cholesterol levels in mice. Table 7.1 summarizes selected circulating miRNAs which are associated with diabetes and NAFLD.

Table 7.1 Selected circulating miRNAs which are associated with diabetes or non-alcoholic fatty liver disease

miRNA	Target	Expression level in serum of patients	Reference
DM			
miR-23a	Hepatic gluconeogenesis	Decreased	[76]
miR-103, miR-107	Insulin sensitivity	Increased	[70, 71]
miR-126	VEGF pathway	Decreased	[77]
miR-143	Insulin signaling	Not changed	[75]
miR-197-3p	Islets cell integrity	Increased	[88]
miR-375	Islets cell integrity	Increased	[85, 87]
let-7 g	Islets cell integrity	Increased	[89]
let-7c-5p and let-7a-5p	Positively associated with Hb1Ac	Increased	[90]
NAFLD			
miR-21	DNL	Increased	[92]
miR-33a, miR-33b	FASN	Increased	[105]
miR-34a	DNL	Increased	[92, 95, 102]
miR-98	SREBP2	Decreased	[107]
miR-103	Insulin sensitivity	Increased	[70, 69]
miR-122	DNL	Increased	[92–94]

7.5 Conclusions

Aberrant expression of miRNAs contributes to deregulation of glucose and lipid metabolism, contributing to the etiology of diabetes and hepatic steatosis. Using mouse and cell lines as preclinical models, many attempts have been made to identify and understand the miRNAs which regulate the key enzymes involved in glucose metabolism and de novo lipogenesis. Modulating the expression of these miRNAs may provide a means to reprogram aberrant metabolic pathways that lead to disease. From the clinical view point, serum miRNA profiling of patients with diabetes and NAFLD in different cohorts have been performed, aiming to identify circulating miRNAs which could be used as biomarkers for an early diagnosis or monitoring disease progression. This could be lead to improved outcomes of individuals suffering from metabolic disorders.

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