MicroRNAs Regulation by Nutrients, the New Ray of Hope in Obesity Related Glucose and Lipid Metabolic Disorders

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Received date: July 18, 2014; Accepted date: August 20, 2014; Published date: August 25, 2014

Abstract

Glucose and lipid metabolic disorders are two most prevalent complications of obesity. Regarding increasing rates of obesity and its metabolic disorders, more effective approaches are needed for prevention or treatment of related metabolic disorders. Therefore, understanding molecular mechanisms involved in metabolic syndrome would be open new way in maintaining homeostasis in these circumstances. MicroRNAs are non-coding small RNAs with transcriptional and posttranscriptional regulatory effects on gene expression, however, any disturbance of them could be involved in the pathogenesis of obesity and its related lipid and glucose metabolic disorders. MicroRNAs are proposed as an ideal non-invasive biological markers for rapid prediction of some obesity related metabolic diseases because of their stability and measurable concentrations in body fluids. Recent evidences reported changes of some important microRNAs profile with regulatory effects on glucose and lipid metabolic pathways even years before the onset and/or diagnosis of these obesity related metabolic disorders. Nutrition and dietary components as significant epigenetic factors have an important role in posttranscriptional regulations of lipid and glucose metabolism genes by modulating of related key microRNAs. Epigenetic suggests the importance of personalized nutrition according to microRNAs profile in prevention, control and treatment of obesity and related metabolic disorders. In this review we summarize evidences regarding the influence of nutrients and food components on some important related circulating microRNAs and their signature as new diagnosis, prognosis and therapeutic agents in obesity related lipid metabolism and diabetes as dietary-derived disorders.

Keywords: MicroRNAs; Nutrition; Obesity; Metabolism

Introduction

Obesity is one of the most important risk factors for chronic diseases, such as diabetes and cardiovascular diseases. In the early twentieth century, obesity has been considered prevalent and WHO announced its epidemic prevalence in the worldwide [1-3]. Obesity is known as one of the main causes of insulin resistance, impaired insulin secretion from pancreatic beta cells and diabetes. Diabetes mellitus is a common metabolic disorder in the world and as a result of its increasing trend that accompanied with aging of the populations, the number of diabetic subjects would be doubled over two decades [4-6]. Complications of this disease, including diabetic nephropathy are also rising [7]. Despite of these increasing rates, more effective approaches to prevention and treatment of glucose and lipid disorders should be selected. Until now, only a small part of the molecular mechanisms of diabetes and the occurrence of diabetes complications have been identified in obese and overweight patients. Its molecular mechanism should be studied more. The relationship between obesity and diabetes with non-coding RNAs has recently been proposed. Some current studies have been reported specific signature of some types of non-coding RNAs in obesity related metabolic diseases such as cardiovascular disease, lipid metabolism disturbances and type 2 diabetes mellitus [8].

microRNAs (miRNAs) are non-coding small RNAs that function as post-transcriptional regulators of gene expression and modulators of the diverse biological processes and pathologies [9,10]. miRNAs are key modulator factors in response to different environmental conditions and stresses that could assist the maintenance of homeostasis in these conditions. Besides, in conditions of sever or long stress they provide a mechanism for the expression of genes to create a new scheme for adapting themselves. Any disturbance in this area would be involved in the pathogenesis of some chronic diseases such as cancer, cardiovascular diseases, type 2 diabetes and obesity [11]. In obesity and its related metabolic diseases, miRNAs are involved in several important biological processes, including adipocytes differentiation, lipid metabolism and insulin sensitivity [12]. These RNAs are stable and measurable in the body fluids such as blood and urine. Therefore, they are proposed as ideal non-invasive biological markers for rapid prediction of some diseases such as obesity and diabetes complications. It is now clear that the miRNA profile in tissues with insulin resistance, changes years before the onset and/or diagnosis of type 2 diabetes. Studies have found that its circulating level reflects an expression pattern of miRNA [13,14]. So, early detection of disease with the help of miRNA profile can significantly increase the quality of clinical management of chronic disease and improve their outcomes. Impaired expression of some types of miRNAs in obesity and diabetes opens a new window on our way to treat the problem.
It is well known that metabolic syndrome and related chronic diseases are caused by the modulating effect of the imbalanced dietary energy intake and expenditure, unhealthy nutrients and dietary components on genetic factors. Current results have shown the critical impact of nutrients as the significant epigenetic factors have an important role in the regulation of many genes. Impact of nutrition on non-coding RNAs that involved in adipogenesis, adipocytes differentiation, adipokines synthesis and secretion [15,16], insulin resistance, glucose and lipid metabolism [17,18], is the base for the Nutrigenomics science.

In this review we assessed existing valid scientific proofs and summarized evidences regarding the influence of nutrients and food components on some related circulating miRNAs and their signature as a new diagnosis tool, prognosis and therapeutic agents in obesity related lipid metabolism and diabetes as dietary-derived disorders.

History of miRNAs

Diagnosis and biogenesis

miRNAs are a class of short non-coding RNAs with about 22 nucleotides that discovered in 1993 and recognized as a class of biological regulators in the early 2000s [19]. These molecules found in prokaryotic and eukaryotic organisms such as plants, animals, and some viruses, that regulate gene expression by an effect on translation and/or stability of mRNAs through base-pairing with complementary target sequences within mRNA molecules, or in other cases, post-transcriptional regulation by changing the protein's function [8,20]. miRNA is made from stem loop regions of long primary transcriptional precursors [21,22] which are usually transcribed by RNA polymerase II (Pol II) [23,24]. The resulting transcript of polymerase is capped with a specially modified nucleotide at the 5’ end. It polyadenylated with multiple adenosines (a poly A tail), [24,25] and becomes more elongated molecules of miRNA (the primary miRNA or pri-miRNA). Under nuclear processing with the enzyme Drosha, hairpins liberated from pri-miRNA by cleaving about eleven nucleotides from hair pin base. This structure with two-nucleotide overhang at its 3’ end, with 3’ hydroxyl and 5’ phosphate groups, called as pre-miRNA (precursor-miRNA). Each hair pin loop is composed of about 70 nucleotides. Pre-miRNA hairpins exported from the nucleus to the cytoplasm where the pre-miRNA hairpin is cleaved by the RNase III enzyme Dicer, yielding an imperfect miRNA (double-stranded miRNA) with about 22 nucleotides [26]. Although each strand of the duplex may potentially act as a functional miRNA, only one strand as a mature miRNA is usually incorporated into the RNA-induced silencing complex (RISC) where the miRNA molecules bind to the 3’ UTR of free mRNA and affect the post translation gene expression (mostly inhibit). Some reports on translation silencing nuclear genes, show that the mature cytoplasmic miRNAs could return to nucleus and affect the translation by targeting mRNAs and connecting to a promoter region [27]. Recently miRNA researches have revealed multiple roles for these regulatory molecules in negative regulation (transcript degradation and sequestering, translational suppression) and possible involvement in positive regulation (activation of transcription and translation) [28-30]. Up to now the 19th Edition database miRBase (http://www.mirbase.org), identified about 25521 miRNAs in more than 193 different varieties which may target about 60% of mammalian genes and are abundant in many human cell types [31,32]. Besides, miRNAs are involved in most of biological processes.

miRNAs as Regulators of Lipid and glucose metabolism pathways

Current evidences have determined important roles for particular miRNAs in regulation of lipid and glucose metabolism pathways. Determining the miRNAs profile of abdominal fat cells and subcutaneous adipose tissue in humans has been shown the increased expression of miR-29a, miR-935, miR-100, miR-125b, miR-221 and miR-34a in obesity and decreased expression of these miRNAs in the differentiation and maturation stages of fat cells [33]. A significant positive correlation was observed between miR-143 expression, which involves in regulating of adipocytes differentiation, with body weight and visceral fat in mice under high-fat diet [33]. Respect to the recent scientific results, dyslipidemia, impaired lipolysis and impaired blood triglyceride levels are some consequences of disrupting miRNAs and involved in cholesterol metabolism, trigger of some metabolic disorders and could cause insulin resistance (IR). Some miRNAs such as miR-33 [34] and miR-122 [35] that we will discuss in the following sections are shown as the post-translational regulators of cholesterol homeostasis, fatty acid metabolism and lypogenesis (Table 1).

miR-33

In humans, the miR-33 family consists of two members named miR-33a and miR-33b, these two human intronic miRNAs are located in intron-16 within two protein-coding genes for Sterol regulatory element-binding proteins (SREBP), SREBP-2 and SREBP-1 respectively. SREBP is a key regulator of genes involved in cholesterol absorption and synthesis. Under the condition of cholesterol reduction, miR-33a and SREBF-2 are transcribed simultaneously and regulate the expression of several genes involved in cholesterol transport, fatty acid oxidation and blood lipid profile including HDL-C [36].

ATP-binding cassette transporters A1 and G1 (ABCA1, ABCG1) are the cholesterol membrane transporters and important target genes of both miR-33 [34]. The entry of miR-33 to mouse macrophages down regulates ABCA1 and ABCG1 and reduces the cholesterol efflux to protein APOA1, a protein which involved in the transport of cholesterol from tissues to the liver for excretion. In contrast, the inhibition of endogenous miR-33 simultaneously increases ABCA1 and ABCG1 protein expression (first step in the production of nascent HDL-c) and cholesterol transfer to Apoa1. ABCA1 leads to a modest but significant rise in plasma HDL-c levels. The endolysosomal transport protein, Niemann-Pick type C1 protein (NPC1), is another target gene of miR-33 [30,37]. NPC1 along with ABCA1 participates in cholesterol efflux to APOA1 [38].

Injection of anti-miR-33 to LDL-c receptor knock-out causes increased hepatic expression of ABCA1, higher levels and size of circulating HDL-c and enhanced reverse cholesterol transport. Reverse cholesterol transport results increased transport of cholesterol from extra-hepatic tissues to HDL-c and supports the impact of miR-33 target genes (ABCA1 and ABCG1) on the liver as well as other tissues [37,39]. These results are accompanied by a reduction in size and lipid content of atherosclerotic plaques, increased markers of plaque stability and decreased inflammatory gene expression. In general, it is suggested that antagonism of miR-33 could protect the cardiovascular system [40]. Injection of anti-miR-33 oligonucleotide increased the hepatic expression of ABCA1 in African green monkeys. It was also induced a sustained increase in plasma HDL-c and reduced plasma...
levels of very-low-density lipoprotein (VLDL), it’s also accompanied by the reduction in triglycerides levels [34].

The decreased expression of miR-33 a/b target various genes in fatty acid oxidation pathways, including Peroxisomal carnitine O-octanoyltransferase (CROT), Mitochondrial carnitine palmitoyltransferase 1a (CPT1A), hydroxacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase β-subunit (HADHB) and Protein kinase AMP-activated alpha 1 catalytic subunit (PRKAA1). The decreased expression of miR-33 a/b also, regulate certain genes that involved in the synthesis of fatty acids such as Fatty acid synthase (FASN), ATP citrate lyase (ACLX), Acetyl-CoA carboxylase a (ACACA), hepatocellular Siruin-6 (SIRT6) and the expression of insulin receptor substrates 2 (IRS2), one critical component of the insulin signal transduction pathway in the liver [34,41].

miR-33b in cooperation with SREBF1 inversely affects on glucose metabolism in hepatocytes, through pyruvate carboxy kinase (PKC1) and glucose-6 - phosphate (G6PC) pathways. It is a key regulatory enzyme of hepatic gluconeogenesis pathways. miR-33b also contributes to the regulation of cholesterol and fatty acid homeostasis by targeting key transcriptional regulators of lipid metabolism, including steroid receptor co-activator 1 (SRC1), steroid receptor co-activator 3 (SRC3), nuclear transcription factor Y, gamma, (NFYC), and nuclear receptor-interacting protein 1 (RIP140) [42,43]. These results show regulation of various lipid and glucose metabolic pathways by miR-33, including cholesterol efflux, fatty acid metabolism and insulin signaling. Also, the key transcriptional regulators of glucose and lipid metabolism also targeted, indicating to the clinical significance and manipulation of miR-33a/b as a new therapeutic target in metabolic diseases.

miR-122

Besides of miR-33, miR-122 is another important miRNA that conserved between vertebrate specie. Approximately 70% of total liver miRNA expression belongs to MiR-122 that is most abundant miRNAs in the liver, and is prominently involved in the regulation of lipid and glucose metabolism [44,45]. miR-122 has a key role in hepatitis C infection and its down-regulation has been found in hepatocellular carcinoma (HCC) [45,46]. In patients with non-alcoholic fatty liver disease (NAFLD) the hepatic and serum miR-122 levels associates with hepatic steatosis and fibrosis, suggesting serum miR-122 level as a useful predictive marker of liver fibrosis in patients with NAFLD [47].

In vivo experiments suggest the miR-122 importance in maintenance of liver function through down-regulation of several genes involved in liver lipid and glucose metabolism and increasing the expression of some other related genes that are normally repressed in hepatocytes [45,46]. Hepatic miR-122 inhibition down-regulates hepatic expression of several genes involved in regulation of lipid biosynthesis and oxidation such as acetyl-CoA carboxylase a and β (ACC1, ACC2), stearoyl-CoA desaturase (SCD1), ATP citrate lyase (ACLX) and Fatty acid synthase (FAS) and therefore, caused sustain reduction of total plasma cholesterol levels by 30% (in dose dependent manner), decreased HDL-c, apolipoprotein AI, LDL-c and apolipoprotein B, increased hepatic fatty acid oxidation, decreased hepatic fatty acid and cholesterol synthesis rates. Although the mechanisms are not clearly known, probably some large part of them is related to the impact of miR-122 on AMP-activated protein kinase (AMPK), miR-122 directly suppresses AMPK, the important regulator of metabolism that promotes ATP-generating pathways like fatty acid oxidation and inhibits energy storage through fatty acid synthesis. Hepatic miR-122 inhibition increases AMPK activation that inhibits ACC2 and induce energy usage from fatty acids [45,46]. Also, recent evidences show connections of miR-122 to the PPAR family, a family of nuclear receptors with regulating effect on metabolism. Up-regulation of PPARβ/δ has been reported upon hepatic miR-122 inactivation [48]. Although hepatic functions of PPARβ/δ have not yet been clearly studied, an interaction between the PPARβ/δ and AMPK pathways was shown recently in muscle. Therefore, it is hypothesized that liver miR-122 depletion increased hepatic fatty acid oxidation probably indirectly activating by AMPK through higher PPARβ/δ protein levels [44,49].

Besides, miR-122 reduces lactate production and increases oxygen consumption, by targeting many of glycolytic genes, especially by the reduced pyruvate kinase (PK) gene expression (Isform M2 (PKM2) in human hepatocellular carcinoma. PK level is significantly associated with poor clinical outcomes of HCC patients [50]. These evidences demonstrated the regulatory role of miR-122 in lipid and glucose metabolism, having an implication of therapeutic intervention targeting in metabolic syndrome.

miR-375

miRNAs have an important role in the development and secretory function of pancreas [36,37], but their accurate functional pathways except for miR-375 is not completely clear [38]. miR-375 is one most abundant pancreatic miRNA and involved in the development of the endocrine pancreas. miR-375 targets two key transcriptional factors, Pdx-1 (Pancreatic and duodenal homeobox 1) and Neuro D1, 2 (Neuronal differentiation 1,2) [39]. Key target genes of Pdx1 are involved in glucose-stimulated insulin transcription and secretion including Glut2 (Glucose transporter2), glucokinase, MafA, insulin and GLP1 (glucagon-like peptide 1) [51]. Previous studies have shown that Pdx1, MafA and NeuroD1 synergistically activate the insulin promoter [52]. Pdx-1 and Neuro D1, 2 mediate pancreas development , differentiation of β-cell and non-β-cells into insulin-producing cells, insulin gene transcription in β-cells and this cells maintenance [52,53]. Therefore, miR-375 inhibition results in pancreas development disorders, impaired β-cell function, glucose-induced insulin secretion and increased blood glucose levels [30,37,38]. In diabetic mice, inhibition of miR- 375 leads to increased blood glucose levels through increased glucagon and reduced the number of pancreatic β and a cell [54]. Genetic deletion of miR-375 in obese mice (375/ob) significantly reduced adaptive β-cell expansion in response to increasing insulin demand in insulin resistance tissues and resulted in a severely diabetic state [55].

Recently, Ling et al. showed increased expression of miR-375 and some evidences of 3T3-L1 adipocyte differentiation such as increased PPARγ (Peroxisome proliferator-activated receptor γ) and aP2 (Adipocyte Protein 2) mRNA levels and suppressed phosphorylation of ERK1/2 (Extracellular-signal-regulated kinases). In contrast, anti-miR-375 increased ERK1/2 phosphorylation levels in pre-adipocytes after stimulation of adipogenic differentiation [56]. Also, in some previous evidences have been reported the effects of ERK-PPARγ pathway on adipocyte differentiation and adipogenesis, by activating mitogen-activated protein kinases (MAPKs), an essential kinase in adipocyte differentiation pathway [57-59]. Therefore this study reported the effect of miR-375 in the differentiation of pre-adipocytes and adipocytes with targeting ERK, PPARγ and aP2 pathways [56] and...
suggested the probable importance of miR-375 in obesity induced peripheral insulin resistance by targeting ERK 1/2 phosphorylation.

In general, miR-375 targets β-cells from multiple pathways such as insulin gene expression and secretion, beta cell proliferation and dealing with insulin resistance; so that the blood levels of this miRNA could be used as a biomarker of beta cell death and diabetes [60].

miR-29

The important mammalian target organs for miR-29 family (a, b and c) are muscle, adipose and liver tissues that strongly deregulated by hyperglycaemia and hyperinsulinemia [61]. Plasma signatures of some miRNAs including miR-29b, can accurately differentiate patients with a high risk of developing diabetes from healthy controls [62]. In diabetic mice and humans [13,63,64] elevated circulating and cellular levels of miR-29a have been reported in β-cells that exposed to high levels of glucose. The effects of increased levels of glucose in human INS-1E β-cells on miR-29a gene expression, β-cells proliferation and glucose induced insulin secretion, introduced miR-29a as a causing factors of the β-cell dysfunction in glucose-induced insulin secretion [65]. In β-cells treated with high glucose levels, the over-expression of miR-29a reduced Syntaxin1A (Stx-1a) expression ,one of two t-SNAREs involved in insulin exocytose from the β cell, suggests mediatary role of miR-29a in glucose-induced down-regulation of Stx-1a in β-cells [66]. In contrast in obese diabetic rat, miR-29 family (a-c) gene expression increases in hepatocytes exposed with reduced blood glucose through inhibition of hepatic gluconeogenesis pathways including Glucose 6-phosphatase (G6Pase) and Peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α) [66].

Obesity-induced molecular changes and environmental signals strongly deregulate miRNAs in adipose tissue. miR-29a and miR-29b gene expression increases in the in vitro incubation of 3T3-L1 adipocytes with high glucose and insulin. Their increased expression with reduced insulin-dependent glucose uptake in these cells, indicate the role of miR-29 in the development of adipocytes insulin resistance and inhibition of insulin signal transduction through Akt (Protein Kinase B (phosphorylation pathway [67,68].

Adiponectin is an insulin sensitizing cytokines. Recent findings demonstrate a significant inverse association of adiponectin with insulin resistance and inflammation status in diabetic patients [69-71]. Activating transcription factor 3 (ATF3), a member of the ATF/cAMP-responsive element-binding protein family of transcription factors and a stress-inducible transcriptional repressor, suppress adiponectin gene expression. In genetically predisposed mice to type 2 diabetes, high fat diet significantly increased AFT3, serum IL-6, TNF-α and miR-29a levels and decrease serum adiponectin levels. This study shows a significant relation between miR-29a over-expression and decreased serum adiponectin [72]. Also, a restricted information exist about the effect of miR-29 on the expression of adiponectin, this study suggests that in obesity induced insulin resistance, miR-29a could be believed to be a selective repressor of adiponectin gene.

Down-regulation of miR-29b in diabetic mice in response to advanced glycation end (AGE) product is associated with progressive diabetic kidney injury, micro-albuminuria, renal fibrosis, and inflammation [73]. High glucose-induced cell apoptosis was prevented in db/db mice with knockdown of miR-29c. In a recent study, over-expression of miR-29c targeted Spry1 protein, activated Rho kinase and induction of podocyte apoptosis. Anti-miR-29c significantly reduced albuminuria and kidney mesangial matrix accumulation [74]. These findings identify miR-29b/c not only as novel targets in glucose and lipid metabolic disorder, but also as key mediators in diabetic complications specially nephropathy.

miR-103 & miR-107

miR-103 and miR-107 are another important miRNAs target multiple mRNA involve in human cellular acetyl-CoA pathways and lipid metabolism. miR-103 and miR-107 exist within introns of the pantothenate kinase (PANK) genes in vertebrate genomes. PANK enzymes also affect cellular acetyl-CoA and lipid metabolic pathways. Therefore, the miR-103 and miR-107 act synergistically with ‘host’ gene [75]. Genome-wide miRNA profiling studies, identify that in pre-adipocytes ectopic expression of the miR-103 increases speed of adipogenesis by up-regulation of many adipogenesis involved markers specially Peroxisome proliferators-activated receptor gamma (PPARγ) and Fatty Acid Binding Protein 4 (FABP4). It also, increases triglyceride accumulation at an early stage of adipogenesis [76]. Several anti-adipogenic factors such as Aryl hydrocarbon receptor nuclear translocator (ARNT), Frizzled homolog 1 (FZD1), and Runt-related transcription factor 1 (RUNX1T/ETO/MTG8) may be involved in adipogenesis as targets of miR-103 and miR-107 [76]. These results showed the importance of miR-103 and miR-107 in adipose biology. Hepatic miR-103 up-regulation in hyperglycemic rats suggests its role in the pathophysiology of type 2 diabetes [68]. Silencing the up-regulation of miR-103 and miR-107 in obese mice improve glucose homeostasis and their up-regulation act on the contrary in adipose and liver tissues. So, subsequently they have a key role in insulin sensitivity and glucose homeostasis.

Another target gene of miR-103/107 is Caveolin-1, a critical regulator of insulin receptor. Up-regulated Caveolin in adipocytes upon inhibition of miR-103/107 is simultaneous with insulin receptor stabilization, enhanced insulin signaling, decreased adipocyte size and enhanced insulin-stimulated glucose uptake [77]. Recently miRNAs microarray in ob/ob streptozotocin (STZ)-induced type 1 diabetic mice with NAFLD, showed the up-regulation of eight miRNAs including miR-103 and miR-107 and down-regulation of four miRNAs such as miR-29c, and miR-122 in comparison to normal C57Bl/6 mice [78].

In general, these evidences lead to a suggestion that miR-103 and miR-107 represent potential targets for the regulation of lipid and glucose metabolism, hepatic energy, adipogenesis, insulin sensitivity and associate with the pathophysiological processes of Type 2 diabetes and NAFLD. Table 1 has been summarized discussed key metabolic miRNAs together with their targets in lipid and glucose metabolism.

**Effect of nutrition on miRNA expression**

Differences of tissue and circulating miRNAs profile in subjects with metabolic syndrome from healthy subjects and various gene expression between diet induced obese and non-obese mice [54,79,80] and humans [33,81] have proposed involvement of diet-dependent epigenetic mechanisms in regulation of gene expression. Dietary components including macro nutrients (proteins and amino acids, carbohydrates and fatty acids) and micro nutrients (vitamins and minerals) can exert some of their epigenetic effects through affecting miRNAs expression and functions. The scientific evidences that have demonstrated these relations would be discussed in the following parts.
miRANs | Target genes | Target pathway | References
---|---|---|---
miR-33 | ABCA1, ABCG1, NPC1, CROT, CPT1A, HADHB, PRKAA1, FASN, ACLY, ACACA, SIRT6, IRS2, PKC1, G6PC, SRC1, SRC3, NFYC, RIP140 | Cholesterol membrane transporters, Cholesterol efflux, Fatty acids oxidation, Fatty acids synthesis, Insulin signal transduction, Hepatic gluconeogenesis, Lipid metabolism (Transcriptional regulation) | 35, 31, 38, 35, 42, 35, 42, 43, 44, 43, 44 |
miR-122 | ACC1, ACC2, SCD1, ACLY, FAS, AMPK, PK | Lipid biosynthesis, Lipid oxidation, ATP-generating pathways, Glycolytic pathways | 46, 46, 47, 46, 47 |
miR-375 | Pdx-1, Neuro D1, 2, ERK, PPARγ, aP2, Pancreatic β-cells and α cell | Transcriptional pathway in pancreas, Pre-adipocytes and adipocytes differentiation, Insulin and glucagon production, Cells development and proliferation | 40, 52, 50-53 |
miR-29 | Stx-1a, AKT, Adiponectin, Spry1 protein and Rho kinase, G6Pase, PGC-1α | Insulin exocytose, Insulin signal transduction, Insulin resistance, Podocyte apoptosis, Glucose metabolism | 59, 60, 61, 65, 67, 59 |
miR-103 | PPARγ, FABP4 | Adipogenesis | 69 |
miR-103/107 | ARNT, FZD1, RUNX1/ETO/MTG8, Caveolin-1 | Adipogenesis, Regulation of insulin receptor | 69, 70 |

Table 1: miRNAs with regulatory effects on glucose and lipid metabolic pathways

The impact of macronutrients on microRNA

Phytochemicals

Dietary polyphenols are found to improve dyslipidemia [82,83] and insulin resistance [84-86] in rodents with metabolic syndrome. Each polyphenol targets specific hepatic miRNAs [87-89]. Proanthocyanidins are most abundant polyphenol class in the human diets. In hepatocytes of obese rat treated with grape seed proanthocyanidins (GSP), hepatic cholesterol efflux increased by repressing miR-33 and its target gene (ABCA1) to produce new HDL-c particles and lipogenesis is reduced by silencing miR-122 [90]. In T2DM hypertensive patients long-term supplementation with grape seed proanthocyanidins (GSP) increases hepatic cholesterol efflux and decreases miR-33 expression. In this study RES and epigallocatechin gallate (EGCG) repressed miR-33a and miR-122 [92]. Chronic treatment of GSPE in healthy rats, in a dose-dependent manner can improve tolerance to lipid overload and postprandial lipemia through repressing liver miR-33a and miR-122 and decreasing their target genes even in population with normal-dose intake [93]. In diet-induced hyperlipidemic mice plant-derived polyphenols prevented fatty liver disease by regulating expression of miR-103/107 and miR-122 and changes in lipid and glucose metabolism [94]. The nature of binding polyphenols such as green tea catechins to miRNAs and proteins have shown in some recent studies [95,96]. In general, considering these significant effects of polyphenolic compound on the expression of some essential miRNAs involved in metabolic pathways, introduce polyphenols as new posttranscriptional modulators of metabolic pathways including lipid and glucose metabolism.

Fatty acids

Fatty acids are other dietary components with impact on miRNA expression levels that have been demonstrated in various cell lines. Increased butyrate, a short-chain fatty acid produced in the mammalian colon by colonizing bacteria with effect on cell differentiation, in human colonic cells and stem cells enhances the expression of miR-375 [97]. This finding suggests that at least some parts of butyrate impact on cell differentiation can be related to its modulator effect on miRNA expression.
Over-expressions of miR-375 and miR-107 have been reported with increased PUFA n-3 in the early stages of mice colon cancer [98]. High fat diet is supposed as an important agent in pathogenesis of obesity and obesity related metabolic diseases that could change the expression of miRNAs. Down-regulation of hepatic miR-122 has been reported in murine [99] and rat [100] fed with high fat diet, but there are conflicting results for miR-103 and miR-107. In murine models high fat diet resulted in miR-103 and miR-107 up-regulation [101] while, some other evidences showed down-regulation of these miRNAs [77].

The expression of miR-33 increased in response to reduced sterols in human macrophages, whereas in rats with both normal and high-fat diet, dietary cholesterol intake caused miR-33 over-expression in peritoneal and peripheral macrophages [34].

Maternal consumption of a high-fat diet during pregnancy and lactation lead to hepatic lipid metabolism disturbances in offspring and their adulthood, by modulating various related genes in offspring including increased hepatic IκB kinase and β-oxidation-related gene and down-regulation of miR-122 [102]. Moreover, maternal high-fat diet consumption before conception down-expressed some miRNAs including miR-122 during pregnancy and lactation. Early miRNAs disturbances can result metabolic disorders in adult life. These evidences suggest an epigenetic mechanism of diet that can explain how dietary induced early changes in gene expression is maintained until adulthood [103].

Dietary supplementation with Conjugated linoleic acid (CLA) in many mammalian species is considered for reducing body fat stores particularly abdominal white adipose tissue and increasing lean body mass. CLA works with the mechanism of enhancing lipolysis in adipose tissue, increasing fat oxidation in muscle cells, reducing the uptake and storage of fatty acids in adipose tissue, fat cell apoptosis, reducing the size of fat cells, inhibition of enzymes involved in lipid metabolism, increasing energy metabolism and changing gene expression of proteins involved in lipid metabolism [104,105]. Therefore, it reduces insulin resistance and increase insulin sensitivity in adipose tissue and muscle cells. An animal study was performed to investigate the impacts of CLA supplementation on mice adipose tissue gene expressions. Results showed the effects of CLA on miR-103 and miR-107 down-regulation in mice fed standard fat-diet [99]. In general dietary fatty acids are considered as important modulator factor in regulations of miRNAs involved in lipid and glucose metabolism pathways.

Amino acids

miRNAs expression is significantly responsive to nitrogen (N) and amino acids starvations. Recently, miRNAs were shown to act in plant nutrient metabolism. Sequencing technology in plants showed that in response to N deficiency, members of same miRNA families have different expressions. Upon these conditions the expression of some miRNAs was repressed and that of some others was induced [106]. Consumption of methionine-choline-deficient diet in mice as experimental animal, lead to diet-induced NAFLD, liver steatosis and over-expression of some miRNAs in liver metabolic pathways [107]. Also, amino acid deficient diets stimulate the expression of proteins that compete with miRNAs for binding to their target miRNAs. miR-122 represses the expression of cationic amino acid transporter 1 (CAT-1) mRNA in human hepatocytes, but evidences demonstrated that in various stressful conditions for cells, such as amino acid deprivation, oxidative stresses and reticulum stress, miR-122 is inhibited and this repression is relieved. Binding of HuR, an AU-rich element binding protein, to the 3'UTR of CAT-1 mRNA results down-regulation of CAT-1 and suggesting that proteins interacting with the 3'UTR act as modulators of miRNAs potential to repress gene expression [108].

Rapidly up- or down-regulation of specific genes in human skeletal muscle during insulin infusion [109], fasting [110] or a high-glycemic meal [110,111] lead to this concept that essential amino acids (EAA) ingestion alters the expression of miRNAs and genes associated with muscle growth. It is suggested that some miRNAs levels increased after administration of essential amino acids including histidine, isoleucine, leucine, methionine, phenylalanine, threonine and valine [112]. Therefore both quality and quantity of dietary amino acids can alter miRNAs expression in various metabolic pathways, also further studies needed for identifying dietary protein effects on the expression of key regulatory miRNAs involved in lipid and glucose metabolism.

Carbohydrates

Circulating levels or availability of glucose has been recognized as the modulating factor of miRNA expression [113]. As mentioned before, hyperglycemia reported as a factor that increase some miRNAs involved in glucose metabolism and insulin resistances such as miR-375 and miR-33 [55,63]. However, different miR-122 and miR-375 profile between healthy and glucose intolerant subject’s indicates the effect of hyperglycemia and insulin sensitivity on the expression of miRNA involved in glucose metabolisms [114].

A maternal low protein-high carbohydrate diet during pregnancy causes over-expression of hepatic G6Pc and alters some related miRNAs expression in male piglets, which suggests epigenetic effects of high carbohydrate diet on early onset of hyperglycemia in adulthood [115].

High carbohydrate diet consumption for just 6 days in healthy subjects significantly reduced circulating levels of some miRNAs including miR-29 [116]. miR-29b down-regulation have previously been demonstrated as a predictor of type 2 diabetes development and its complications such as nephropathy [73]. In conflict with miR-29 b, hyperglycemic conditions enhance the expression of miR29c and reduce the expression of its target Sprouty Homolog 1 (Spry1). This condition induces cell apoptosis and fibronectin synthesis, which are characteristics of diabetic nephropathy [74]. It was concluded that the dietary macronutrients composition and serum glucose levels involve in the regulation of the level of serum miRNAs, and consequently may lead to regulate insulin signaling, glucose uptake and cause the development and complications of type 2 diabetes.

Micronutrients which found their impact on miRNA expression

Only a few studies have investigated the effects of vitamins, mineral and their derivatives on the expression of miRNAs that involved in glucose and lipid metabolisms in different experimental models. Vitamin A is one of these micro nutrients. Vitamin A is a lipophilic micronutrient (VA, Retinol) that has long been implicated as an essential nutritional factor in human health for its roles in the development and maturation of various cells (growth), anti-infective and immunity booster activities. Retinoid acid (RA) is active metabolite of vitamin A and is in attention due to its numerous effects on immunity, cell differentiations and regulation of gene expressions.
Adipose tissue is a place for vitamin A storage and retinol conversion to its active metabolite RA. The importance of vitamin A in adipose tissue biology, obesity and type II diabetes has been shown in recent years [117,118].

| Dietary components | Target miRNAs | Change | Subjects or type of cells | References |
|--------------------|---------------|--------|---------------------------|------------|
| Polyphenols        |               |        |                           |            |
| GSP                | miR-33a, miR-122 | Down-regulation | Rats hepatocyte | 83         |
| GPE                | miR-33a, miR-122 | Up-regulation-Down-regulation | Rats and humans hepatocyte | 85         |
| GSPE               | miR-33a, miR-122 | Down-regulation | Rats and humans hepatocyte | 85         |
| GSPE               | miR-33a, miR-122 | Down-regulation | Healthy rats | 86         |
| RES                | miR-33a, miR-122 | Down-regulation | Rats and humans hepatocyte | 85         |
| EGCG               | miR-33a, miR-122 | Down-regulation | Rats and humans hepatocyte | 85         |
| Polypenoics        | miR-103/107, miR-122 | Up-regulation-Down-regulation | Hyperlipidemic mice | 87         |
| Fatty acids        |               |        |                           |            |
| Butyrate           | miR-375       | Up-regulation | Human colon and stem cells | 90         |
| PUFA n-3           | miR-375, miR-107 | Up-regulation | Mice colon cancer cells | 91         |
| High fat diet      | miR-122       | Down-regulation | Murine and rats, Humans | 92, 96     |
|                   | miR-103/107   | Up or down-regulation | Murine and rats | 92, 70     |
| Cholesterol        | miR-33        | Up-regulation | Rats | 35         |
| CLA                | miR-103/107   | Down-regulation | Mice | 92         |
| Protein            |               |        |                           |            |
| Protein deficiency | miR-122       | Up-regulation | Human hepatoma cells | 101        |
| Carbohydrates      |               |        |                           |            |
| Hyperglycemia      | miR-375, miR-33, miR-122 | Up-regulation | Mice, human islets of Langerhans | 51, 56, 107 |
| High carbohydrate diet | miR-29, miR-29b, miR-29c | Down-regulation-Up-regulation | Humans | 109        |
| Vitamins           |               |        |                           |            |
| RA                 | miR-103       | Up-regulation | Human neuroblastoma cells | 121, 122   |
| 1, 25- dihydroxyvitamin D3 | miR-29a, miR-29b | Up-regulation | human prostate cancer cells | 126        |
| Vitamin E deficiency | miR-122a     | Down-regulation | Rats and humans hepatocytes | 133        |

Table 2: Dietary polyphenols and nutrients effects on miRNAs involved in glucose and lipid metabolic pathways

There are multiple isomeric forms of RA, such as all-trans RA and 9-cis RA [119] that modulates gene expression through the activation of two families of nuclear receptors and RA receptors by all-trans RA and RXRs through 9-cis RA [120,121].

Srebp-1c expression, transcription, maturation and saturation are induced by synergistic effect of Retinal and vitamin A with insulin in primary hepatocytes that is followed by regulation of the Srebp-1c target gene, FASN. This up-regulation is done via binding of the general transcription factors and the diet-associated transcription factors like SREBP-1c to proximal promoter of FASN. Also, Retinoids and retinal can regulate hepatic Srebp-1c expression through activation of RXR [122,123]. These evidences show the importance of vitamin A in regulation of genes targets in glucose metabolic pathway and lipogenesis.

Trans-RA acts as a potent anti-tumor retinoid derivative by inhibiting of cell proliferation, cell differentiation and apoptosis [124,125]. Inadequate supply of all trans-RA (atRA) leads to the repressed transcriptional expression of retinoic acid-responsive genes and in reverse manner adequate pharmacological atRA can reverse this effect with targeting miRNAs involvement pathways [126,127]. miR-103 is one of these genes that is up-regulated by retinoic acid (RA) in human neuroblastoma cells [128]. Besides some other evidences demonstrated the impact of atRA on neuronal cells differentiation by up-regulation of miR-9 and miR-103 [129] suggests that some of RA effects on cell differentiation could be mediated by their impact on miRNAs profile expressions.

Altered vitamin D metabolism in type 2 diabetic mice, suggests the protective effects of vitamin D metabolites against diabetic
complications specially diabetic nephropathy [130]. It is appeared that vitamin D enhances the intracellular mechanisms of insulin action. It is mediated by vitamin D receptor (VDR) and Insulin receptor substrate (IRS-1). In vitamin D treated mice under high fat diet significant weight loss, muscle VDR down-regulation, liver VDR up-regulation, increased muscle IRS-1 transcriptional levels and down-regulation of hepatic IRS-1 have been reported in compared to control group [131]. The physiologically active form of vitamin D3, 1,25-Dihydroxyvitamin D3, plays a key role in cell differentiation and inhibits porcine pre-adipocyte differentiation in a dose-dependent manner through down-regulating the expression of adipogenesis-related genes [132]. Therefore, vitamin D could regulate post translational expression of genes involved in metabolic syndrome, lipid and glucose metabolism. Co-administration of 1,25-dihydroxy vitamin D3 with testosterone modulate lipid metabolism in human prostate cancer cells through up-regulation of the miRNAs that target peroxisome proliferators-activated receptor alpha (PPAR-α) such as miR-29a, miR-29b and increased lipogenesis [133]. Plasma levels of 25(OH) vitamin D in early pregnancy are significantly associated with some maternal peripheral blood gene expression and post-transcription regulation of miRNAs [134].

Vitamin E, its main congeners α-tocopherol (αT) consists of two classes of compounds: tocopherols and tocotrienols. Synthetic ligands of PPAR-α and PPAR-γ are currently used for treating hyperlipidemia and diabetes. Tocotrienol-enriched palm oil as PPAR modulator increases insulin sensitivity reduces blood glucose levels and improves whole body glucose utilization in patients and preclinical animal diabetic db/db mice [135,136]. Vitamin E regulates gene expression by modulating of mRNA concentrations in various tissues of mammals [137-139]. Vitamin E deficiency caused a reduced concentration of hepatic miRNA-122a, suggesting vitamin E as an important regulator of lipid metabolism with up-regulation of miR-122 as the most abundant miRNA in rat and human liver [140]. Other evidences confirmed that the increased dietary Vitamin E decreases the activity of superoxide dismutase (SOD) and increases the expression of hepatic miRNAs such as miR-122 in Nile tilapia [141]. There aren’t any reported evidences about other micro nutrients including minerals and gene expression of miRNAs involved in glucose and lipid metabolism pathways.

In general, despite recent evidences reported in this review, so far little studies have been conducted about the effects of nutrients and nutritional factors on the miRNA involved in glucose and lipid metabolism. So, further studies are necessary recommended for identifying more miRNAs’ probable influence by nutrients.

**Conclusion**

Emerging evidences suggest that miRNAs play important roles in the development or treatment of obesity related glucose and lipid metabolism. Expression profiling studies have revealed that some miRNAs are deregulated in obesity and metabolic syndrome possibly involved in the pathogenesis of various these metabolic disorders. miRNAs are stable in body biological fluids and measurable as ideal biomarkers for non-invasive and rapid diseases prediction and diagnosis. Early detection significantly increases the quality of clinical nutrition management and improves complications of chronic diseases. Investigation of miRNAs in obesity and related metabolic disorders, genetic targets of miRNAs and their influence by dietary modulators can potentially identify novel pathways involved in metabolic disorders and influence future therapeutic approaches. In recent years, nutrition, dietary modulators and phytochemicals have been interested as important epigenetic factors involved in post-transcriptional regulations of adipogenesis, lipid and glucose metabolism genes. We can use of miRNA profiling as a useful aid for designing therapeutic approaches, assessment of the nutritional status and planning the suitable diet in obesity related metabolic diseases.

In a context of epigenetic effects of nutritional factors on miRNAs and their host gene expression, the personalized nutrition is in its infancy. Up to now, only few nutritional factors and phytochemicals have been demonstrated in this field, but can discuss them in the field of personalized nutrition, as a good way to predict and treat metabolic complications of obesity. Also multi-faceted mechanism of action is likely for effects of nutrition and nutritional components on involved miRNAs in metabolic disorders.

With further researches on principal that involved miRNAs expression and nutritional factors, in complement with the absorption of food derived exogenous miRNAs [142] and breast milk miRNAs with immune-modulator activities [143] in humans, we can reach the famous phrase that “you are what you eat”.

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