REVIEW ARTICLE

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Accuracy of prediction circulating miR-126 in the type 2 diabetes: a systematic review and meta-analysis

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ABSTRACT

Many studies have shown that microRNAs could play a role as predicting biomarkers. The aim of this study is investigation of predictive role of miR-126 in type 2 diabetic Mellitus (T2DM) patients. Eligible studies were selected from PubMed, MEDLINE, EMBASE, Science Direct, ProQuest databases and the information of these studies were extracted. The meta-analysis tests of standardized mean differences (SMD) with 95% confidence interval (95% CI), summary odds ratio, heterogeneity and publication bias performed using comprehensive meta-analysis version 3.0 (CMA) and STATA12 statistical analysis software. This meta-analysis included 6 studies association with circulating miR-126 in T2DM. Concentration of circulating miR-126 was lower with SMD (-0.131) (95% CI (-0.237) - (-0.025)) p-value (p= 0.016). The summary diagnostic odds ratio circulating miR-126 was (0.787) (95% CI (0.650) - (0.953)) and also which sensitivities value was (42%) with a 5% false positive rate. I2= 0.00% and p= 0.5 indicating that non-significant heterogeneity between studies. Results of this study indicated that circulating miR-126 may be as a useful marker for accurate prediction of type 2 diabetes.

Keywords: Circulating miR-126, Type 2 diabetes, Biomarker, Meta-Analysis.

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Introduction

miRNAs and diabetic pathogenesis

Type 2 diabetes is characterized by islet β-cell dysfunction in response to insulin resistance and/or relative insulin deficiency (1). Type 2 diabetes comprising 85-90% of total DM (Diabetes Mellitus) cases, and one of the biggest issues of our time, with 220 million people currently diagnosed. DM is characterized by hyperglycemia that long-term hyperglycemia in type 2 diabetes let to microvascular and macrovascular complications(2). However, understanding the role of miRNAs in physiology and pathological conditions, helping researchers to find a known target in different conditions. MicroRNAS (miRNAs) a class of the most important endogenous interfering RNAS have become a new source of interest in many fields of research in medicine. In recent years, miRNAs are known as new biomarker in diagnostic and prognosis for numerous diseases. MicroRNAs (miRNAs) are an endogenous functional class of 21-25 nucleotides small non-coding RNAs

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molecules that negatively regulate mRNA and protein expression by formation base-pairs with target mRNAs. The present of microRNAs expression in different places may play a role in commence and development of certain disease and also inhibiting target gene translation to protein. MiRNAs play a fundamental role in essential biology processes such as differentiation, proliferation and apoptosis(3). MiRNAs are involved in many processes associated with type 2 diabetes for example insulin secretion and insulin resistance, lipid metabolism and obesity(4). These are strongly associated with the onset of type 2 diabetes. MiRNAs involved in T2DM was first reported in 2004 by Poy et al(5). Hyperglycemia and hyperlipidemia resulting from T2DM lead to conditions such as fatty liver, stroke and neuropathy that in this state the expression of miRNAs is altered in target tissues in patients with diabetes. One of the target tissues is vascular endothelium, which changed in response to inflammation of diabetes. There is invers correlation between miR-126 levels and the onset diabetic vascular complications. Furthermore the many studies showed that miR-126 expression in DM inhibited endothelial progenitor cell (EPC) migration and proliferation and may induce apoptosis, as a result of leading to DM-related cardiovascular disorders(6).

History of miR-126

MiR-126 is one of the most abundant miRNAs in the endothelial cells, it promotes the pro-angiogenesis actions of VEGF and FGF and increased blood vessel formation(7). Surprisingly Zhang et al. showed that endothelial miR-126 release is decreased by athero-protective laminar shear stress(8). MiR-126 is found on chromosomes 9 within intron 7 of the epidermal growth factor (EGF)-like domain (EGFL7) gene. EGFL7 is also secreted by endothelium cells and regulates vasculogenesis (9). MiRNA-126 (also miR-126-3P) and miR-126* (also known as miR-126-5p) are highly expressed in the endothelium, however, in a study demonstrated that miR-126* (-5p) is more highly expressed than miR-126 in the endothelium. MiR-126 regulated by the binding of two transcription factor: EST1 and EST2(10). Harnprasopwat et al. showed that there is a SNP within miR-126 and also a change of the 24^{th}, base prevents the processing of the pri-miRNA in to the mature miRNA, reducing suppression of the various targets of miR-126(11). Huang et al. with study of microRNAs expression in diabetic GK (Goto-Kakizaki) and wistar rats skeletal muscle using microarray technology showed that miRNAs differentially were expressed between GK and wistar rats, so that miR-126 showed down-expression in muscle of GK rats in compared with wistar rats due to in GK rats blood glucose levels were obviously higher than wistar rats.

MiR-126 and type 2 diabetes

The human circulating-miR-126 has been studied approximately in plasma of diabetic patients because its expression is very high in endothelial cells. Therefore play a pivotal role in modulatory vascular development and homeostasis, and its secretion to plasma in diabetic patients indicates patient's condition(12). In 2010 Zampetaki et al. showed that loss of miR-126 negatively correlates with manifest artery disease and also is a good prognostic biomarker for the onset of diabetic vascular complications. This study showed that high glucose condition reduced miR-126 value in endothelial apoptotic bodies in HUVEC (Human Umbilical Vein Endothelial Cell) culture in-vitro(13). The level of

miR-126 modified in individuals with T2DM, which suggested the appropriateness of circulating miRNAs as early predictors of T2DM and its vascular complications(14).

In a study published in 2014, Wang et al., for first time describe that microRNAs are differently expressed in endothelial cells of T2DM -patients and indicated that circulating miRs raised to endothelial damage could use as prognostic biomarker in early T2DM(15). McArthur et al., investigated miRNA alteration are involved in diabetic retinopathy (DR) in a ST2-T1DM rat model, that circulating miRs shows obvious changes in early DR(16). However, miR-126 needs further studies in the diabetic patients but the discovery this microRNA as biomarker help to predict or detect the development and progression of diabetes or diabetic complications an early stage. Therefore the aim of this systematic review and meta-analysis was to identifying miR-126 as a novel biomarker in T2DM.

MiR- 126 and various cancers

Deregulation of miR-126 was reported in several solid and hematologic malignancies including lung, prostate, breast, renal cell, development and progression(17). Several studies have demonstrated that miR-126 is reduced is lung cancer tissue uninvolved adjacent lung tissue(18). A recent study examining miR-126 expression in 335 lung cancer tissues revealed that miR-126 along with VEGF were negative prognostic factors. Of note, miR-126 expression was of significant predictive value in squamous histology and in cases with lymphatic metastases(19). A separate study identified up-regulation of miR-126 in metastatic site of lung cancer(20). MiR-126 represented one of a panel of miRNA up-regulated in lung tumors from radiosensitive patients. Further investigation demonstrated that miR-126 could increase the apoptotic effects of irradiation in vitro(21). MiR-126 increase of function in vitro reduced small cell cancer cell proliferation and induced G1 arrest(22). MiR-126 was showed to regulate the PI3-kinase signaling cascade through direct targeting of the p85 beta subunit. This targeting resulted in an in vitro reduction in colon carcinoma cell growth(23). Rodriguez et al. showed that the tumor suppression intronic miRNA miR-126 is down-regulated in human cancer cell lines, bladder and prostate tumors. However, it is activated by inhibitors of DNA methylation and histone de-acetylation. These results suggesting that miR-126 could be a target of epigenetic therapy of cancer. Also, their founding indicate that by inducing expression of miR-126, epigenetic therapy not only inhibits the growth of cancer, but may also inhibit the invasiveness and metastatic potential of cancer cells as well(24). Both in vitro and in vivo studies demonstrated that miR-126 could induce proliferation of murine bone marrow progenitor cells in the presence of the AML1-ETO (AE) fusion gene(25). The association between miR-126 and AML1/ETO rearrangements was further confirmed in a separate cohort of 29 AML samples(26). Decreased expression of miR-126 as part of a miRNAs has been shown to correlate with CNS relapse in all (27). Harris et al. recently identified vascular cell adhesion molecule 1 (VCAM-1) as a target gene of miR-126(28). Zhang et al. showed that in vitro luciferase assay suggested that IRS-1 is the target gene of miR-126 and also over-expression of miR-126 bring significant decrease of IRS-1 protein, which confirmed that miR-126 negatively regulated IRS-1 at the translation level. The results of their study showed that knock-down of IRS-1 inhibited cell growth in HEK293 and MCF-7, which

regeneration the effect of miR-126(29). Recently, miR-126 was identified as a metastatic suppressing miRNA that is down-regulated in relapsing breast cancer(30).

The role of miR-126 in obesity and insulin resistance

Obesity, insulin resistance and hyperlipidemia are strongly associated with the onset of T2DM(31). Obesity usually triggers macrophage infiltration and cytokine release in adipose tissue, which lead to changes in miRNA expression and subsequently affect lipid levels and adipogenesis (32). Francisco et al. with assessed circulating miRNAs profile as cross-sectional in surgery-induced weight loss in obese patients suggested that there is no significant link between weight loss and amount of circulating miR-126. IRS-1(Insulin Receptor Substrate-1) is an important protein in insulin signaling pathway, which play a role in insulin resistance(33). Hyun et al. have shown that significantly overexpression of miR-126 in hepatocytes with mitochondrial dysfunction caused reduction in expression of IRS-1 after impairment in insulin signaling, subsequently lead to insulin resistance(34). Several studies demonstrated that decrease in IRS-1 protein in liver and skeletal muscle of animal model lead to insulin resistance and T2DM. In case of hyperlipidemia, Xiao et al. showed that the level of miR-126 was significantly decreased in patients with coronary artery disease(CAD) and high LDL cholesterol level and inversely miR-126 level was increased in patients that had risk factor but did not angiographicaly significant CAD(35).

Materials and Methods

Search Strategy

We searched online PubMed, EMBASE, Sciencedirect, ProQuest, ISI and Google Scholar for eligible studies in English Language until January 2015. The searched key words were based on (microRNA-126 or miR-126), (diabetes or T_2DM), "miR-126", "microRNA and diabetes". MiR-126, plasma and diabetes, miR-126, plasma and diabetes, circulating miR-126 and diabetes, microRNA, plasma and diabetes, microRNA, plasma and diabetes, circulating microRNA and diabetes also searched.

Study Inclusion/Exclusion Criteria

Our studies were included if they had the following inclusion criteria: i) articles published in English Language, ii)patients with type 2 diabetes disease, iii)measured the value of miR-126 in plasma or serum, iv)investigated the association between circulating miR-126 level and type 2 diabetes, and the following articles were excluded: i)studies about other microRNA, ii)review articles or letters, brief report, abstract and comments because of limited data and iii)studies with any other disease.

Data Extraction

Eligible studies were survey independently by two reviewer and disagreements were resolved by third investigator. Data extracted from these studies included: author, publication, year, sample size, country, patient age and methods to detect miR-126 on plasma or serum (table 1).

Statistical Analysis

Methods of standard recommended for diagnostic accuracy meta-analysis were used. The SMD, OR 95% CI and other related indexes across studies were calculated a statistical effect models. A test of heterogeneity was carried using Higgins I-square studies to detect statistically significant heterogeneity across studies. Heterogeneity was defined as $p<0.05$ or $I^2>50\%$. A random effects model was used in the presence of between-study heterogeneity ($p<0.05$, $I^2>50\%$) while the

fixed effect model was applied if heterogeneity was not observed ($p<0.05$, $I^2<50\%$). Publication bias is a major concern for all types of meta-analysis, therefore publication bias was evaluated using Deek's funnel plot and Begg's rank correlation, $p>0.05$ indicated that there is no potential publication bias. All analysis was performed using two statistical programs: Comprehensive Meta-Analysis (CMA) and STATA version 11 (STATA Corporation, College Station, Tx, USA). All statistical tests were two-side and significance was as $p<0.05$.

Results

Selection of Studies

One hundred and three records for miR-126 were identified from literature search in database. Of these studies, twelve articles rejected due to limited information included review, abstract and brief report. Then we screened by title, abstract and key words, 85 studies excluded because irrelevant to type 2 diabetes disease, 6 studies selected at the end and meta-analysis was carried out (figure 1). Circulating miR-126 involved in these studies was analyzed using the method of quantitative real-time PCR (qRT-PCR).

Circulating miR-126

All of these 6 selected studies reported miR-126 concentration in plasma or serum type 2 diabetic patients. In these patients, concentration of miR-126 significantly was decreased: standard mean difference (SMD) (-0.131) (95%CI (-0.237) - (-0.025)). The summary diagnostic odds ratio was (0.787) (95% CI 0.650 - 0.953) that equal to sensitivity of (0.42) or a sensitivity of (42%) for a 5% false positive rate. Heterogeneity evaluation performed using valid statistical tests include I^2-statistic and *p-value*. $I^2=0.00\%$ and $p=0.5$ indicating that non-significant heterogeneity between studies (figure 2).

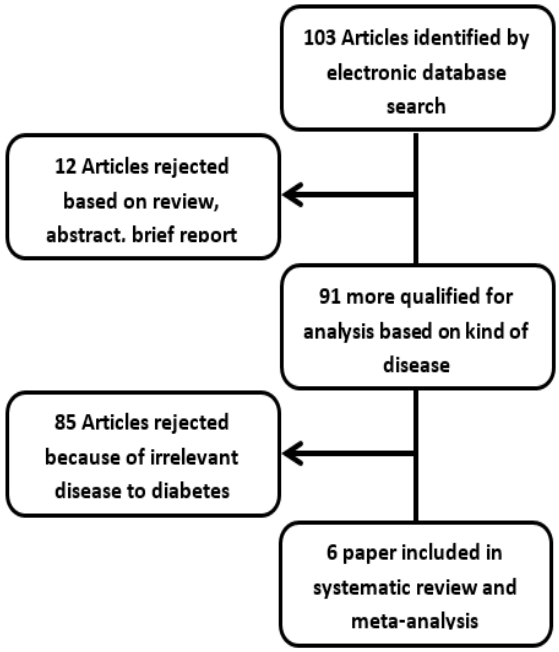


Figure1. Selection of studies

Assessment of publication bias

Publication bias was evaluated by funnel plot and Begg's test. Although the Funnel plots for

Table 1. Data extracted from these studies to detect miR-126 on plasma or serum

author	publication year	sample size Case/Control	country	patient age	methods to detect miR-126	model
Olivieri F	2014	193/136	Italy	40-80	q PCR	fixed
Liu Y	2014	317/138	China	<50<	q PCR	fixed
Wang X	2014	33/119	USA	45-65	q PCR	fixed
Zhang T	2013	30/60	USA	42-75	q PCR	fixed
Francisco J	2013	48/45	Spain	47±5	q PCR	fixed
Zampetaki A	2010	80/80	China	40-90	q PCR	fixed

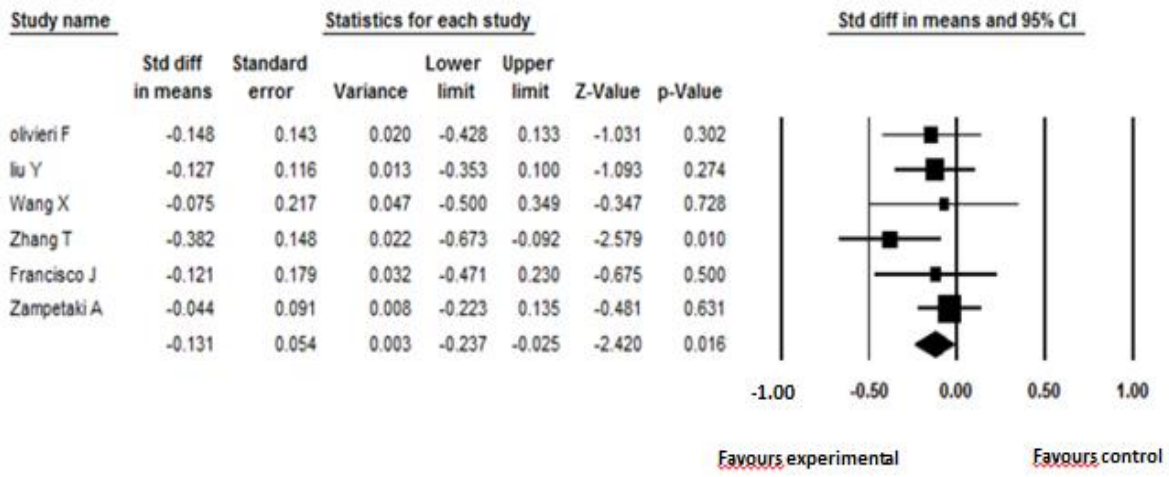


Figure 2a. Forest plot of six studies evaluating Standard Difference in means of circulating miR-126 in T_2DM. Summary Standard Difference in means (-0.131) (95% CI (-0.237) – (-0.025)) with *p-value* 0.016. Heterogeneity test I^2= 0.00%, p= 0.5.

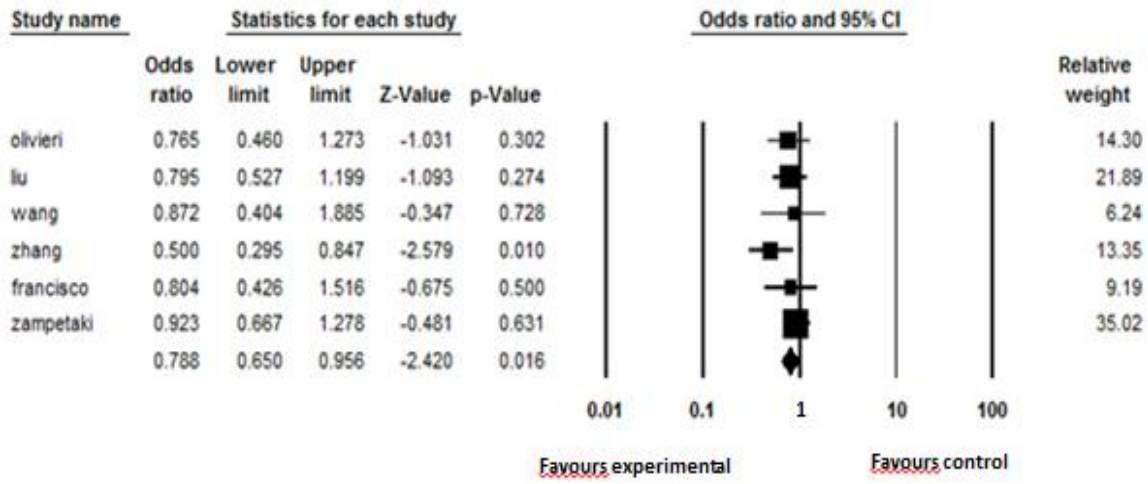
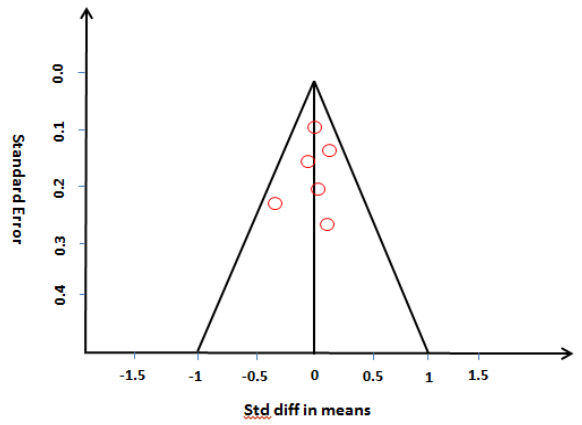


Figure 2b. Forest plot of estimate odds ratio for six studies. Summary odds ratio equal 0.788 with (95% CI 0.650 – 0.956), (*p-value* = 0.016). Total relative weight sum is 100%.

publication bias indicated some asymmetry because of few numbers of studies. The *p-value* of Begg's rank correlation was 0.850. Therefore, there are no-significant publication biases in the meta-analysis, since its *p-value* was >0.05 (figure 3).

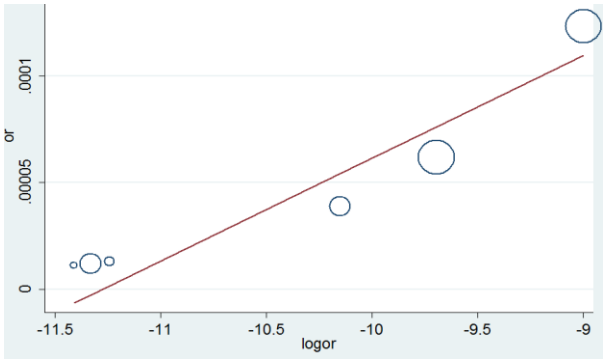
Discussion

This systematic review and meta-analysis provide information about predictive and diagnostic role of circulating miR-126 in type 2 diabetic patients.



○ Study

Figure 3a. Deek's Funnel plot the Std diff in means against the Standard Error of the Std diff in means. Red circle represent each study in the meta-analysis. Funnel plot for the of potential publication bias of the 6 included studies.



○ Study——regression line

Figure 3b. Meta- regression plot for publication bias showed that despite small number of studies, obviously heterogeneity doesn't observe. Solid circle represent each study in the meta-analysis. The line indicates the regression line.

We used studies that associated with circulating miR-126 in T2DM patients. In 6 available studies for meta-analysis, we found that mean concentration of miR-126 in peripheral blood (plasma or serum) have significantly decreased in T2DM patients. This systematic review had not clear heterogeneity; furthermore meta-analysis performed using fixed effect model. Since value<50% for I2 present non-heterogeneity, in our study I2=0.00 means loss of heterogeneity. Measurement of summary odds ratio resulted miR-126 may be as potential predictive and diagnostic biomarker in T2DM. We also investigated accuracy of miR-126 marker with sensitivity measure. Hence, the sensitivity was (42%) for a 5% false positive rate. Publication bias showed with Funnel plot. Despite small number of studies, clear publication bias not seen. Begg's rank correlation test value corresponds to 0.850 was showed loss of publication bias in this meta-analysis, suggesting that the statistics obtained approximated the actual results. Recent data suggested circulating miR-126 concentration decreased significantly early-onset T2DM. Although miR-126 marker can enable to prediction of inception T2DM, but also needs to verify with additional evaluation using effective tests. Nevertheless, small number of studies in our review is a concern; because of prediction value of miR-126 marker tend to overestimate.

Study of Zempetaki et al., indicated miRNA profile in plasma from subjects with T2D that identified low microRNA-126 in patients compare with control subjects. The results in Zempetaki study showed that loss of microRNA in hyperglycemic lepob mice primarily associated with DM complications(13). In the other study, Olivieri et al., showed that circulating miR-126 could be considered as a biomarker of physiological endothelial aging in normal glycemic subject and also exposure to high glucose levels may induce dysfunctional endothelial cells and shedding microRNA-126 in plasma in type 2 diabetes patients. Therefore, evaluated risk of developing micro and macro-vascular complications(36). Jansen et al. in

diabetic conditions showed that glucose-treated endothelial cells contains lower amounts of miR-126 and indicated reduced endothelial repair in vitro and in vivo as well as with expression analysis of miR-126 in plasma showed that diabetic mellitus is related to a significantly decreased miR-126 expression in circulating(37).

In a cohort study of 66 colorectal carcinomas, miR-126 expression is reduced in colon cancer compared to 10 adjacent non-tumor tissues(38). A recent study suggested that miR-126 may serve as a non-invasive biomarker for breast cancer. Patients with breast cancer had lower circulating levels of miR-126 when compared to normal controls. Wang et al. had been shown that further analysis for miR-126 single nucleotide polymorphism (SNP) in cohort of 6042 patients did not identify an associated breast cancer risk and also to be down-regulated in breast cancer tissues(39). In Runhua et al, study elucidate a general reduction in miR-126 expression level in gastric cancer tissues compared with matched non-tumor tissues and found that the mir-126 level was associated with clinic-pathologic parameters(40). Ectopic expression of miR-126 significantly inhibited the growth, migration and invasion of SGC-7901 gastric cancer cells in vitro and in vivo, however confirmed that miR-126 exerted these pivotal functions in gastric cancer cells by down-regulating the expression of Crk, thus miR-126 serve as tumor suppressor in human gastric cancer(41).

Since change in the levels of circulating microRNAs as biomarkers do not necessarily reflect deregulation of microRNAs expression inside cells, the functional roles and significant of microRNAs deregulated in plasma from T2DM patients still need to be determined. However, the results obtained in the present study give acceptance evidence for future analyses using circulating microRNAs to examine the pathophysiology of T2DM. Nevertheless the data presented from this systematic review and meta-analysis could show that decreased circulating miR-126 may be as predicting severity of T2DM. In addition to, our conclusion need to improve for two reasons: First, a few number studies about associated with circulating miR-126 and T2DM, Second due to small sample size, therefore the results may contain less power.

Conclusion

This meta-analysis suggested that decreased levels circulating miR-126 in T2DM patients is significantly associated with evaluated risk of progressive micro and macro vascular complications. These results should be confirmed by more studies in future.

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Conflict of Interest

The authors declared no conflict of interest.

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