Review Article
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Medical Journal of the Islamic Republic of Iran (MJIRI)

Med J Islam Repub Iran. 2020(1 Apr);34.28. https://doi.org/10.47176/mjiri.34.28

Molecular biomarkers in diabetes mellitus (DM)

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Received: 12 Dec 2018 Published: 1 Apr 2020

Abstract

Background: Diabetes mellitus (DM) is a growing epidemic metabolic syndrome, which affects near 5.6% of the world's population. Almost 12% of health expenditure is dedicated to this disorder. Discovering and developing biomarkers as a practical guideline with high specificity and sensitivity for the diagnosis, prognosis, and clinical management of DM is one of the subjects of great interest among DM researchers due to the long-lasting asymptomatic clinical manifestation of DM. In this study, we described a recently identified molecular biomarker involved in DM.

Methods: This review study was done at the Diabetes Research Center affiliated to Shahid Sadoughi University of Medical Sciences. PubMed, Scopus, Google Scholar, and Web of Science were searched using the following keywords: "diabetes mellitus", "biomarker", "microRNA", "diagnostic tool" and "clinical manifestation."

Results: A total of 107 studies were finally included in this review. After evaluating numerous articles, including original, meta-analysis, and review studies, we focused on molecular biomarkers involved in DM diagnosis and management.

Conclusion: Increasing interest in biomarkers associated with DM goes back to its role in decreasing diabetes-related morbidity and mortality. This review focused on major molecular biomarkers such as proteomic and microRNA (miRNAs) as novel and interesting DM biomarkers that can help achieve timely diagnosis of DM.

Keywords: Diabetes Mellitus, Biomarkers, MicroRNAs

Conflicts of Interest: None declared
Funding: None

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Cite this article as: Aghaei Zarch SM, Dehghan Tezerjani M, Talebi M, Vahidi Mehrjardi MY. Molecular biomarkers in diabetes mellitus (DM). *Med J Islam Repub Iran.* 2020 (1 Apr);34:28. https://doi.org/10.47176/mjiri.34.28

Introduction

Diabetes mellitus (DM), as a progressive metabolic disorder, is a global epidemic that influences more than 350 million people around the world and has been identified as a contributing factor for morbidity and mortality. Type 2

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↑What is "already known" in this topic:
Diabetes mellitus (DM) is a progressive condition and can get worse without treatment. DM, especially T2DM, is predictable and preventable. Therefore, effective methods for diagnosing prediabetes are required to reduce the risk of its progression to diabetes. The current biomarkers such as glycated hemoglobin (HbA1c) have moderate sensitivity and specificity and may be inaccurate in certain clinical conditions. Therefore, combining several biomarkers may identify those at high risk for developing diabetes more accurately.

→What this article adds:
Recent studies have suggested that the expression of biomolecules, including microRNAs, proteins, and metabolites, specifically change during the progression of DM, and their signature changes with DM and its related complications. MicroRNAs (miRNAs) are autocrine and endocrine regulators of gene expression and because of their stability in body fluid, they can be used as noninvasive prediction tools in DM. In this study, our aim was to summarize biomolecules that could be potential biomarkers in DM.

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[DOI: 10.47176/mjiri.34.28]

(T2DM) and Type 1 diabetes mellitus (T1DM) are 2 major forms of DM. T1DM is characterized by self-destructive pancreatic beta cells and accounts for 5%-8% of all cases of DM. However, T2DM is the most common form of DM and occurs when the target tissue loses insulin sensitivity, including the liver, skeletal muscles, and adipose tissues (1). Among the diabetes complications, microvascular complications such as nephropathy, retinopathy, and cardiomy opathy are common in patients with T1DM and T2DM. Diabetic nephropathy (DN) as a major cause of renal failure is observed in 30% of T1DM patients and approximately 20% to 30% of T2DM individuals (2). Diabetic cardiomyopathy (DC) is characterized by cardiac remodeling and diastolic dysfunction. In addition, clinical manifestation of coronary artery and hypertension are not observed in individuals who are suffering from DM (3). Diabetic retinopathy (DR) is one of the most identified microvascular complications of diabetes mellitus (4). Approximately, one-third of diabetic individuals are suffering from diabetic retinopathy; also, proliferative diabetic retinopathy and diabetic macular edema (DME), which are vision threatening, are developed in more than 10% of the patients (5).

A biomarker mainly refers to a characteristic that is proposed as a sign of pathogenic processes, normal biological procedures, and pharmacological responses to a therapeutic involvement (6). Biomarkers are divided into 2 categories: traditional and novel biomarkers. The former such as HbA1c are those well defined in research and clinical medicine, but the latter such as miRNA and some proteomic markers are not broadly used in clinical medicine(7).

In this review, we focused on diagnostic molecular biomarkers such as proteomics and microRNAs involved in T1DM and T2DM to pinpoint new areas for further experimental studies (Tables 1 and 2).

Methods

This narrative review study focused on molecular biomarkers with a close association with DM. A thorough literature search was done on Google, Google Scholar, and Pubmed databases using the following keywords: “diabetes mellitus”, “biomarker”, “microRNA”, “diagnostic tool”, and “clinical manifestation”. Next, after evaluating numerous articles, including original, meta-analysis, and review papers, we summarized recently reported biomarkers and their roles in the onset of DM clinical manifestation.

1.Traditional proteomic biomarkers involved in T1DM

1.1. Glutamic acid decarboxylase (GAD)

Glutamic acid decarboxylase (GAD) as an enzyme converts glutamate to gamma-aminobutyric acid (GABA). This enzyme employs pyridoxal phosphate (PLP) as a cofactor for its activity. In addition, 2 isoforms of GAD can be seen in mammals, which are encoded by 2 distinct genes known as GAD1 and GAD2, but only GAD2 is expressed in the pancreas. Patients who are suffering from T1DM produce autoantibodies against GAD1 and GAD2 (8). Abnormal expression levels of the aforementioned proteins can occur in patients with T1DM and can be used as a potential biomarker for T1DM detection.

1.2. Islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP)

IGRP as a glycoprotein belongs to glucose-6-phosphatase (G6Pase) family and its expression is limited to the islet cells. G6Pase-β and G6Pase-α are well-known members of G6Pase family, among which G6Pase-β is ubiquitously expressed. Multiple helices are responsible for IGRP anchoring to endoplasmic reticulum (ER) membrane. IGRP is one of the critical factors in glycogenolysis and gluconeogenesis. Furthermore, the role of IGRP as a contributing factor in blood glucose homeostasis has also been recognized. The T1D susceptibility locus IDDM7 was mapped within the IGRP locus, which may implicate IGRP as a candidate gene in T1DM (9). According to the recent experiments in T1D, autoantibodies are produced against IGRP, so the expression levels of the autoantibodies can be used as a potential biomarker in T1D detection (10).

1.3. Tyrosine phosphatase-like protein IA-2

IA-2, with 979 residues, belongs to transmembrane protein tyrosine phosphatase family and is enzymatically inactive. It has an intracellular, transmembrane, and extracellular domains, with 379, 24, and 576 residues, respectively

Table 1. Better characterized proteomic biomarkers involved in T1DM and T2DM

Proteomic biomarker	Traditional	Novel	T1DM	T2DM	Reference
GAD	*		*		8
IGRP	*		*		10, 26
IA-2	*		*		27
ZnT8	*		*		10
Insulin	*		*		1
CCL3		*	*		18
DOC3B		*	*		20
Creatinine	*			*	1
IL-6		*		*	28, 29
CRP		*		*	29
sOB-R		*		*	30
Adipokines		*		*	1, 31
c-reactive protein (CRP)		*		*	1, 32
Ferritin		*		*	1, 33, 34
Incretins		*		*	1, 35
Cathepsin D		*		*	36, 37
NCAM.L1		*		*	36
Alpha1-antitrypsin		*		*	36, 38
Endocan		*		*	36, 39

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Table 2. The reported miRNAs in the T2DM and T1DM and its complications

Type of miRNA	Biological importance	Source	Nephropathy	Retinopathy	Cardiovascular disease	Reference
T2DM						
miR-21	Promoting fibroblast Migration and targeting SMAD7 and PTEN	Serum	*	*	*	57, 82-86
miR-29	Acting as a tumor suppressor and also engaging in apoptosis	Serum/urine	*	*	*	57, 87-90
miR-126	Playing an important role in efferocytosis by targeting ADAM-9	Plasma/urine	*	*	*	91-94
miR-200	Engaging in fibrogenesis through TGF-β signaling	Epithelial cells/	*	*	*	95-99
miR-375	Targeting 3'- phosphoinositide – dependent protein kinase – 1 and regulating Glucose – induced biological response in	Serum/blood	Need more experimental studies	*	*	100, 101
miR-7	MiR-7 plays a critical role in the proliferation of adult beta cells by targeting several components of mTOR signaling pathway.	Serum	Need more experimental studies	*	*	70, 102-104
miR-3666	By targeting adiponectin play key role in insulin secretion	Serum/peripheral blood	Need more experimental studies	Need more experimental studies	Need more experimental studies	73
miR-135a	By suppressing Rock-1 involved in insulin signaling pathway	Serum/plasma	+	Need more experimental studies	Need more experimental studies	74
T1DM						
miR-326	mediated TH-17 differentiation through translational inhibition of Ets-1	Blood	*	Need more experimental studies	Need more experimental studies	105, 106
miR-146	By targeting IRAK1 and TRAF6 modulate inflammatory response	PBMCs	*	*	*	107-110

(11). According to the recent studies, IA-2 is an essential part of secretory granules in neuroendocrine cells (12). IA-2 gene is mapped to the long arm of chromosome 2 at position 35. Also, IA-2 gene spans over 20 Kb of genomic DNA and comprises 16 exons. Moreover, it is considered as a major autoantigen in T1D. Autoantibodies to IA-2 can be used as predictive biomarkers to identify risks of developing T1D, as they appear years before the onset of T1D clinical manifestation (13).

1.4. Cation efflux transporter ZnT8

Zinc transporter 8 (ZnT8) belongs to Cation diffusion facilitator (CDF) family of proteins and its expression is restricted to the pancreatic α- and β-cells and the kidneys (14). Zinc in pancreatic β-cells is transported by ZnT8 from the cytosol into the lumens of insulin granules (15). In addition, ZnT8 is one of the major self-antigens found in T1D patients (16). Hence, autoantibodies produced against this autoantigen can be used as a potential biomarker to distinguish between individuals with T1D and healthy individuals (10).

2.Novel proteomic biomarker involved in T1DM

2.1. CCL3

Chemokines are a large family of chemoattractant cytokines for leukocytes and their receptors belong to a family of specific G-protein-coupled 7 transmembrane domain receptors. CCL3, also known as macrophage inflammatory protein-1α (MIP-1α), is a CC chemokine characterized as inducers of inflammatory process in various inflammatory autoimmune diseases. An intensive investigation done by Shehade et al disclosed that anti-CCL3 Abs were positive in nearly 87% of T1DM individuals, so anti-CCL3 Abs can be used as a powerful biomarker in T1DM (17-18).

2.2. DOC2B

DOC2 family of proteins contains 3 isoforms: designated DOC2A, DOC2B, and DOC2C. DOC2B is a calcium sensor, which positively regulates SNARE-dependent fusion of insulin vesicles with membranes in pancreatic beta cells (19). An experimental investigation conducted by Aslamy et al in 2018 revealed that human DOC2B levels were reduced over 2-fold in platelets from new-onset T1D in humans, so DOC2B abundance may serve as an early biomarker of T1D (20).

3. Traditional proteomic biomarker in T2DM

3.1. CD59

CD59 protein inhibits membrane attack complex formation; therefore, it prevents cell lysis. CD59 expression level is high in pancreatic β-cell and it plays a critical role in insulin secretion. In addition, its inactivation occurs in people with diabetes due to glycation (21). In 2013, Ghosh et al found the expression level of glycated CD59 (GCD59) as a biomarker in T2DM and revealed that this biomarker was markedly increased in DM individuals. Also, there is a positive association between this biomarker and HbA1C. This biomarker with sensitivity and specificity of 93% and 100%, respectively, can be considered as a potential biomarker to distinguish individuals with diabetes from

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healthy individuals (22).

4. Novel proteomic biomarker in T2DM

4.1. Growth-differentiation factor-15 (GDF-15)

GDF-15 belongs to TGF-β superfamily and plays a critical role in growth, differentiation, and inflammatory response (23). GDF-15 is highly expressed in macrophages, endothelial cells, and adipocyte; and its expression level markedly increases in individuals with insulin resistance and chronic kidney diseases (24). Serum GDF-15 expression levels increased in individuals with T2DM; therefore, GDF-15 as a powerful tool enables us to diagnose T2DM. In addition, the increased GDF-15 expression levels is linked with increased Ang-2 expression level in diabetic patients (25).

miRNAs are small molecules with 21 to 23 nucleotides in length that can bind to 3'-UTR region of the target molecule. MicroRNAs prevent translation by binding to their target molecules and affect approximately 30% of the coding genes (40). Furthermore, a large number of investigations have revealed that miRNAs dysregulation is linked with some clinical manifestations such as microvascular complications (nephropathy, retinopathy, and cardiomyopathy) involved in DM (Fig. 1) (41). Abundance of miRNAs in human biofluids, including urine, serum, saliva, tears, plasma, colostrum, cerebrospinal, and seminal fluids make them a valuable biomarker for numerous disease such as DM (42). In this review, we provided some better characterized miRNAs involved in T1DM and T2DM and their microvascular complications.

5. Major microRNAs involved in T2DM

5.1. miR-375

miR-375 is located on human chromosome 2 in an intergenic region between the CRYBA2 and CCDC108 genes (43). miR-375 is considered as an essential miRNA for normal glucose homeostasis, β cell proliferation, and β and α cells turnover (44). Moreover, it has been identified as a pancreatic islet cell specific miRNA that targets myotrophin mRNA. Myotrophin participates actively in the fusion of secretion granules with cell membrane; thus, miR-375 can independently inhibit glucose-induced insulin secretion (45). Also, serum expression level of miR-375 is elevated due to chronic hyperglycemia and β cell death, so miR-375 expression level is suitable for predicting β cell death (46). Furthermore, miR-375 targets PDK1 in porcine pancreatic stem cells (PSCs) and if the expression level of miR-375 increases, the inhibition of PDK1-AKT signaling cascade will occur. Therefore, pancreatic stem cells (PSCs) do not differentiate into islet-like cells (47). Recent investigations have shown that miR-375 as a contributing factor plays an important role in 3T3-L1 adipocyte differentiation via ERK-PPARγ2-ap2 signaling pathway (48). An experimental study by Karolina et al in 2012 revealed that miR-375 expression levels were increased in T2DM individuals compared to healthy controls (49).

5.2. miR-200

miR-200 family consists of 5 members whose transcripts can be seen as 2 separate polycistronic pri-miRNAs. miR200a/b and miR-429 are located in one cluster on chromosome 1, while miR-200c and miR-141 are part of another cluster on chromosome 12 (50). DM is characterized by Beta cell apoptosis. Thioredoxin-interacting protein (TXNIP) as a cellular redox regulator and a proapoptotic factor is the most upregulated gene in human pancreatic islets in response to glucose. TXNIP plays a critical role in apoptosis by inducing miR-200b. Consequently, miR-200b targets Zeb1 and blocks its activity, which results in β cell apoptosis (51). miR-200 is one of the crucial miRNAs in insulin signaling pathway that targets FOG2. miR-200 prevents disturbances in insulin signaling pathway (52). Furthermore, the loss of miR-200 transcripts promotes survival of β cell by downregulating Xiap, which is a potent inhibitor of caspase activation. As a result, human β cells can be protected against apoptosis by overexpression of Xiap (53). Therefore, miR-200 family expression alteration may be associated with T2DM (54).

5.3. miR-126

miR-126, an intronic product of an intron of the Egfl7 gene, is located on 9q34 (55). Endothelial cells are rich in miR-126, which is one of the several contributing factors in vascular integrity, wound healing, and angiogenesis (56). In addition, miR-126 plays a critical role in efferocytosis by targeting ADAM-9**.** Liu et al (2014) analyzed serum

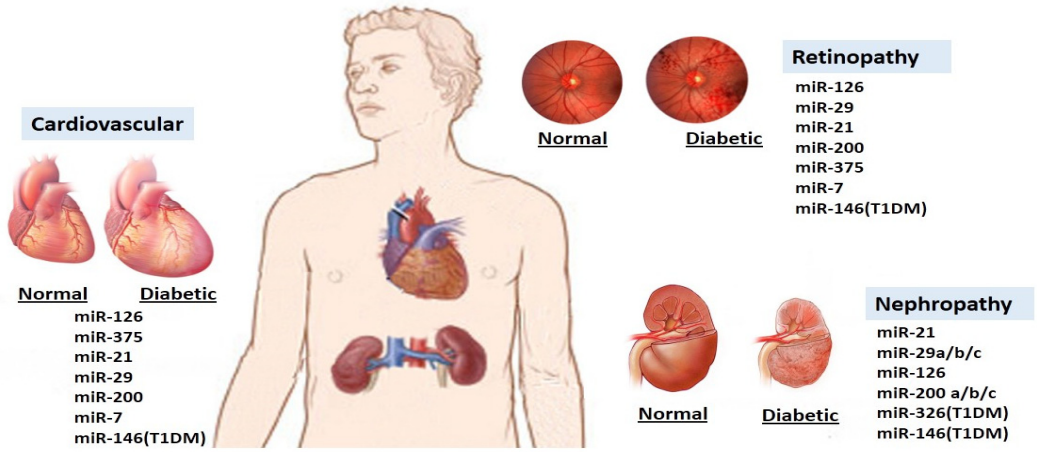

Fig. 1. Major miRNAs engaged in diabetes mellitus microvascular complications

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[DOI: 10.47176/mjiri.34.28]

miR-126 levels of diabetic's patients, prediabetics, and nondiabetic individuals as controls and found that miR-126 was significantly downregulated in diabetic patients compared with prediabetics. Their results revealed that the expression levels of miR-126 in nondiabetic controls were higher than 2 former groups. Therefore, the expression levels of miR-126 may be used as a potential distinguishing biomarker. With respect to treatment, miR-126 expression levels can also be used as a biomarker; eg, miR-126 alteration triggers T2DM clinical manifestation. Therefore, an individual with downregulated miR-126 may get diabetes within 2 years (57). Therefore, miR-126 expression levels can be applied for early T2DM diagnosis (58).

5.4. MiR-21

miR-21 is a type of miRNA which is crucial in multiple biological processes such as proliferation, development, and oncology (59). Its gene was mapped to 17q23.2, which is located on the downstream of the the gene encoding vacuole membrane protein 1 (VMP1) (60). By the analysis conducted in the promoter region of miR-21 gene, numerous binding sites for transcription factors such as SRF, activation protein1 (AP1), nuclear factor1 (NF1), signal transducer, and activator of transcription3 (STAT3), C/EBP-α, and Ets/PU-1 were identified (61). The human miR-21 promoter retains all of these elements, and their high conservation among vertebrates suggests that highly conserved transcriptional regulatory mechanisms operate on the promoter (62). It was also disclosed that TGF-β1 can increase miR-21 expression levels during renal fibrosis through a Smad3-dependent mechanism (63). According to a study done by Zampetaki and et al in 2008, it was revealed that miR-21 expression levels were downregulated in plasma of T2DM individuals than controls (64).

5.5. miR-29

The miR-29 family, with 4 mature members, miR-29a, miR-29b1, miR-29b2, and miR-29c, are encoded by 2 gene clusters. These miR-29s loci are found on 2 different chromosomes: miR-29b2/miR-29c on chromosome 1q32 and miR-29b1/miR-29a on chromosome 7q32. These miRNAs play an important role in the insulin signaling pathway by targeting these genes, including phosphoinositide 3-kinase (PI3K) regulatory subunit 1 (PIK3R1), insulin receptor substrate1 (IRS1), AKT2, and PI3K regulatory subunit 3 (PIK3R3) (65- 66). Insulin-sensitive tissues are rich in miR-29 and elevated expression levels of miR-29 were found in rodent models of diabetes or obesity (67).

5.6. miR-7

Human and mouse pancreatic islet cells are rich in miR-7 (68). miR-7 is mapped to 3 different genomic loci: 9q21, 15q26, and 19q13. The products of these 3 loci can be changed into the same mature miR-7 with 23 nucleotides (69). miR-7 plays a critical role in the proliferation of adult beta cells by targeting several components of mTOR signaling pathway, including TORC1, eukaryotic translation initiation factor 4E (eIF4E), P70S6K, MnK1, and Mnk2 (70). mTOR is an evolutionary conserved serine/threonine protein kinase that exists in 2 distinct isoforms: TORC1 and TORC2. TORC2 has a regulatory role in the cascade of insulin signaling. Wang et al indicated that miR-7 expression levels are negatively linked with beta cell proliferation; therefore, anti miR-7 oligonucleotide can be considered as a useful therapeutic tool in DM (70). In addition, Shujun et al found that expression levels of miR-7 are a useful biomarker for T2DM detection because its expression level is upregulated in T2DM with or without microvascular complications (71).

5.7. *miR-3666*

MiR-3666 as an intronic product of FOXP2 gene is located on chromosome 7 (72). J. Tan et al indicated that miR-3666 plays key role in insulin secretion by targeting adiponectin in pancreatic β-cell. They showed that transfection of miR-3666 to human pancreatic β-cell line is associated with inhibition of β-cell proliferation and inducing β-cell apoptosis. Moreover, they found that miR-3666 expression levels were increased in peripheral blood of T2DM patients but were decreased in serum samples. These results highlight the crucial role of miR-3666 in T2DM pathophysiology (73).

5.8. miR-135a

MiR-135a precursor gene (pre-miR-135a) is located within the chromosome 3 (74). Recently, it was identified that Rock-1 regulates insulin action via IRS-1 phosphorylation. Honardoost et al in a luciferase report assay identified Rock-1 as a direct target of miR-135a. Furthermore, transfection studies in C2C12 and L6 myoblast cell lines found a significantly lower insulin-resistence phenotype (75). In addition, increased expression of miR-135a in the plasma sample of newly diagnosed T2DM patients has recently been reported (76). These results suggest miR-135a as a desirable T2DM biomarker.

6. Major miRNAs involved in T1DM

6.1. MiR-326

MiR-326 precursor gene was assigned to the chromosome 11 in the intron 1 of the beta-arrestin gene (Arrb1) (77). Ets-1 is considered as an essential transcription factor for the development of natural killer (NK*)* cells. Also, Ets-1 has been identified as a negative regulator of TH-17 differentiation (78). An experimental study done by DU found that miR-326 mediated TH-17 differentiation by direct targeting of Ets-1 messenger RNA (79). In 2011, Sebastiani et al revealed that miR-326 expression levels were upregulated in T1DM and could be used as a powerful tool for detecting T1DM (77).

6.2. MiR-146

Two distinct forms of human miR-146 have been identified**:** miR-146 on chromosome 5q33 and miR-146b on chromosome 10q24 (80). An experimental study done by YANG et al in 2015 revealed that miR-146 expression levels were downregulated in the peripheral blood mononuclear cells (PBMC*)* of newly diagnosed T1DM individuals (81). Hence, miR-146 expression levels can be used as a valuable biomarker in T1DM**.**

Conclusion

DM is a metabolic disorder and the number of people suffering from this syndrome is rising very fast around the world, leading to adverse health and socioeconomic impacts. The long asymptomatic period of DM provides many

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[DOI: 10.47176/mjiri.34.28]

opportunities for disease prevention and intervention (111). Many studies have shown that the diagnosis of early-onset diabetes (eg, prediabetes) plays an important role in preventing its complications. Identification of new biomarkers can contribute to better understanding of pathogenesis events involved in DM and can be a powerful to detect DM in early stages. Among various biomarkers, miRNAs have been emerged as interesting tools for detecting DM. These molecules play a critical role in various cellular pathways involved in DM pathogenesis. Recent intensive studies confirmed that miRNAs may be a promising biomarker in identifying patients with DM.

Conflict of Interests

The authors declare that they have no competing interests.

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