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An Overview of Differential miRNA Profile of Patients with Latent Autoimmune Diabetes in Adults (LADA)

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Derleme Makalesi/ ***Review Articles***

Öz (tr)

Diabetes Mellitus (DM), pankreas beta hücre aktivitesinin bozulması, insülin sekresyonunun azalması, insülin direncinin artması ve buna bağlı olarak karbonhidrat, protein ve lipid metabolizmasının bozulması ile gelişen hiperglisemi ile karakterize metabolik ve kronik bir hastalıktır. DM; başlangıç yaşı, insülin bağımlılığı, mikro ve makrovasküler komplikasyonlar gibi karakteristik özelliklerine göre tip 1, tip 2, gestasyonel ve diğer diyabet formları olarak sınıflandırılır. Erişkinlerde latent otoimmün diyabet (LADA), tanı konulduktan sonraki en az ilk altı ayda, glisemik kontrol için insülin bağımlılığı olmaksızın yetişkinlikte başlayan otoimmün bir diyabettir. Ortak genetik, immünolojik ve metabolik özellikler nedeniyle LADA, tip 1 veya tip 2 diyabet olarak yanlış tanı alabilir. Bu nedenle LADA tanısını kolaylaştıracak biyobelirteçlere ihtiyaç vardır. MikroRNA'lar biyolojik süreçlerde yer alan küçük kodlayıcı olmayan RNA'lardır ve hedef dokuların insüline tepkisinin yanı sıra insülin üretimini, sinyallemesini, salınmasını, direncini ve glukoz homeostazını düzenler. miRNA ekspresyonundaki düzensizlik, glikoz metabolizmasının bozulmasına yol açabilir. Dolaşımdaki miRNA'lar farklı diyabet türleri ile ilişkilidir ve bunları ayırt

etme potansiyeline sahiptir. Bu nedenle, tip 1 ve tip 2 diyabetle karşılaştırıldığında LADA'da gen anlatım düzeyi değişen miRNA'ları inceledik.

Öz (en)

Diabetes mellitus (DM) is a metabolic and chronic disease characterized by hyperglycemia developing with impaired pancreatic beta cell activity, decreased insulin secretion, icreased insulin resistance, and, by extension, impaired carbohydrate, protein and lipid metabolism. DM is classified as type 1, type 2, gestational and other forms of diabetes according to the characteristic properties such as age of onset, insulin dependency, and micro- and macrovascular complications. Latent autoimmune diabetes in adults (LADA) is an autoimmune diabetes that begins in adulthood without insulin dependency for glycemic control at least in the first six months after diagnosis. Owing to the common genetic, immunologic, and metabolic features, LADA can be misdiagnosed with type 1 or type 2 diabetes. Therefore, biomarkers are needed to facilitate the diagnosis of LADA. MicroRNAs are small non-coding RNAs involved in biological processes and regulate the response of target tissues to insulin as well as insulin production, signaling, release, resistance, and glucose homeostasis. Dysregulation of miRNA expression can lead to impaired glucose metabolism. Circulating miRNAs are associated with different types of diabetes, and have a potential to determine them. Thus, we reviewed miRNAs whose gene expressions levels change in LADA when compared to type 1 and type 2 diabetes.

Keywords: LADA, autoimmune diabetes, miRNA

Pathophysiology and classification of diabetes

Diabetes mellitus (DM) is a metabolic and chronic disease characterized by hyperglycemia developing with impaired insulin secretion, insulin resistance or both, and accordingly impaired carbohydrate, protein and lipid metabolism [1-4]. DM and its associated microvascular and macrovascular complications are one of the most important causes of death [4,5]. Diabetes is a public health problem with a global prevalence of 8.5% in 2014, with the number of diabetic individuals projected to increase from 422 million to 642 million by 2040 [4]. The International Diabetes Federation (IDF) published the number of diabetic individuals as 537 million in 2021 [6]. TURDEP (Turkish Diabetes Epidemiology Study) I and II studies and the projection of the IDF Diabetes Atlas (10th edition) for 2045 indicate that rapid increase in

diabetes become an important health problem in our country and precautions should be taken [7,8].

Basically, there are two types of diabetes that differ in etiology, pathogenesis and genetics [1,9]. While type 1 diabetes is an autoimmune form of diabetes that destroys pancreatic beta cells, type 2 diabetes is a form of diabetes that causes progressive impaired glucose regulation due to insulin resistance [1]. About 5% of all diabetes types are T1D, 90% are T2D, and 5% are other types of diabetes such as gestational diabetes, adult-onset diabetes of the young (MODY) and latent autoimmune diabetes of the adult (LADA) [10,11]. MODY and LADA are the types of diabetes whose clinical diagnosis is difficult in general. These diabetes types are misdiagnosed as type 1 or type 2 diabetes because of the common pathogenetic and clinical features. Misdiagnosis leads to wrong treatment protocols and prevents the expected response [12].

Type 1 diabetes is one of the chronic diseases that often occurs in childhood and adolescence. In type 1 diabetes, an absolute deficiency of insulin is observed as a result of autoimmune destruction of pancreatic beta cells [13,14]. In addition, symptoms such as diabetic ketoacidosis (DKA), polyuria, polydipsia, polyphagia, weight loss, nausea, vomiting and glycosuria are observed in patients [15].

Type 1 diabetes has two subclasses: type 1A, which develops with a cell-mediated autoimmune attack on beta cells, and type 1B, which is less common and has no known cause. The islet inflammatory response that develops with the abnormal activation of the T cell-mediated immune system, the antibodies produced against beta cells (IAA-insulin antibodies, ICA-Islet cell antibodies, GADA/GAA- Glutamic acid decarboxylase antibodies, IA2-islet antigen 2, ZnT8A- Zinc transporter 8) and the β cell-mediated (humoral) immune response form the basis of the pathogenesis of type 1 diabetes [16-19].

GWAS and meta-analyses show that up to forty genes associated with immune function are involved in the pathogenesis of type 1 diabetes [20]. Human leukocyte antigen (HLA) gene DR3/4, DQ 0201/0302, DR 4/4 and DQ 0300/0302 alleles, insulin gene, *PTPN22*

(Protein tyrosine phosphatase, non-receptor type 22), *CTLA4* (cytotoxic T-lymphocyte associated antigen 4) and *IFIH1* (Helicase C Domain 1 induced interferon) genes are associated with susceptibility to type 1 diabetes [20-24].

Although insulin is produced in pancreatic beta cells, insulin cannot be used effectively by muscle, fat and liver cells and hyperglycemia develops in type 2 diabetes [25]. The pancreas produces more insulin to help glucose uptake, but the compensation of the beta cells is impaired, it cause to insulin resistance [26,27]. Dehydration, excessive thirst, increased susceptibility to infection, excessive urination, lethargy and blurred vision are the main symptoms of type 2 diabetes [28]. Obesity facilitates the transition to insulin resistance-based diseases such as T2D and metabolic syndrome [29].

TCF7L2 (transcription factor 7 like 2), *KCNJ11* (potassium inwardly rectifying channel subfamily J member 11), *ABCC8* (ATP binding cassette subfamily C member 8), *PPARG* (peroxisome proliferator activated receptor gamma), *FTO* (FTO alpha-ketoglutarate dependent dioxygenase), *NOTCH2* (notch receptor 2), *WFS1* (wolframin ER transmembrane glycoprotein), *CDKAL1* (CDK5 regulatory subunit associated protein 1 like 1), *IGF2BP2* (insulin like growth factor 2 mRNA binding protein 2), *SLC30A8* (solute carrier family 30 member 8), *JAZF1* (JAZF zinc finger 1) and *HHEX* (hematopoietically expressed homeobox) genes that are associated with glucose metabolism, insulin secretion, insulin receptors, post-receptor signaling and lipid metabolism play role in type 2 diabetes pathogenesis [23,30-34].

Type 2 diabetes develops in advanced ages with genetic factors and lifestyle. Increasing economic prosperity, high-calorie diet, urbanization and sedentary life have led to the spread of diabetes [32,35].

LADA at the Intersection of Type 1 and Type 2 Diabetes

Latent autoimmune diabetes in adults (LADA), defined as a subgroup of type 1 diabetes with adult onset (>30 years), slow β-cell damage

and lack of an absolute insulin requirement at diagnosis [36]. Although slow progression of β-cell destruction, insulin treatment may be required in the first 6 or 12 months following diagnosis [37]. The minimum age cut-off for LADA varies from 25 to 40 years, but 30 or 35 years is most commonly accepted [37,38]. LADA patients are not insulin resistant or obese. However, overweight is a risk factor for LADA [39].

LADA diagnosis is based on adult age of onset, presence of islet autoantibodies and insulin independence [37]. However, ketoacidosis, cardiovascular and microvascular complications, pathophysiology, autoantibodies and insulin requirements for treatment should be examined in detail to discriminate LADA from T1D and T2D. Ketoacidosis is absent at diagnosis, but may be present when patient becomes severely insulinopenic. LADA patients display increased risk for cardiovascular and microvascular complications such as in T1D and T2D [40].

The Glutamic acid decarboxylase (GAD) is the major autoantibody seen in LADA but other autoantibodies (IAA, IA2 or ZnT8A) often found in patients with type 1 diabetes can also be seen [36-38, 40]. This enzyme is found in neural and non-neural cells such as the pancreatic cells, oviduct, and testes. Although the function of GAD in the islet β-Cells is not well documented, probably it plays role in the regulation of paracrine effects in the secretion of insulin, glucagon, and somatostatin hormones [36]. It seems that autoimmunity is the major pathological symptom in LADA as such in T1D and differs LADA from T2D [37].

Studies indicate that LADA patients with multiple islet antibodies develop b-cell failure within 5 years, while those with only GAD antibodies (GADAs) or only islet cell antibodies (ICAs) mostly develop b-cell failure after 5 years. Also, impairments in the b-cell response to intravenous glucose and glucagon can be detected from the diagnosis of diabetes to up to 12 years. Then, LADA is not a latent disease, it can be defined as a slowly progressive disease [41].

LADA has been estimated to account for 3–12% of all diabetes in adults, being more frequent in Europe than in other parts of the world including Asia and North America [37]. Although LADA has a closer pathophysiology to T1D, approximately 10% of adult patients are diagnosed as T2D [12,36].

Socioeconomic, environmental, and genetic differences in populations change the prevalence of LADA. For example, in European populations, 5-12% of cases with type 2 diabetes were misdiagnosed as LADA. LADA is more common in the southern region than in the northern region of Spain or LADA is less prevalent in Northern Italy compared to throughout Italy. In epidemiological studies conducted in the African populations, 10-14% of West Africans with type 2 diabetes were misdiagnosed because of the similarity of type 2 diabetes and LADA. In East Africa, LADA is less prevalent. Type 1 diabetes and LADA have a lower prevalence than type 2 diabetes in Asia [42].

Genetics of LADA

LADA genetically resembles type 1 and type 2 diabetes [36]. Human Leukocyte Antigen (HLA) encode the major histocompatibility complex (MHC) that regulates the immune system and forms the immune background of LADA. HLA genes play role in the genetics of T1D and LADA and the highest risk is seen in carriers of the HLA haplotypes HLA-DRB1*04-DQB1*03:02 and HLADRB1* 03:01-DQB1*02:01. Also, *PTPN22*, *INS (insulin)*, and *SH2B3* (SH2B adaptor protein 3) genes related to T1D and *TCF7L2* gene linked to T2D are also associated with LADA. This common genes indicate overlapped background of T1D, T2D and LADA [37]. TCF7L2 gene distinguishes LADA from T2D and is not associated with T1D [43]. While T1D risk is associated with the HLA class II alleles DR3 and/or DR4 and DQ2 and/or DQ8 compared with the general population, recent studies showed that these phenotypes are inconsistent with LADA. The insulin-dependent diabetes mellitus 2 (IDDM2), MHC class I chain-related A

(MICA), cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and Tumor necrosis factor 2 (TNF-2) which map to a variable number of tandem repeats (VNTR) upstream of INS is associated with type 1 diabetes as well as LADA [38]

Diagnosis of LADA

LADA is diagnosed with the age spanned from 15 to 45 years, positive antibody status (GADA, ICA, IAA and ZnT8A), time to insulin dependence and other related parameters such as progressive β cell dysfunction, BMI (body mass index) and chronic complications, genetic factors and abnormal T cell function [44,45]. LADA is called 'Type 1.5 diabetes' because of the common clinical features with type 1 diabetes and type 2 diabetes (Table 1) [38]. LADA is misdiagnosed as T2D because of insulin independence in early stages and as T1D due to the presence of autoantibodies against pancreatic beta cells [44].

Table 1: Comparison of the characteristics of Type 1 Diabetes, Type 2 Diabetes, and LADA [12,37-38-46-49].

	T1D	**T2D**	**LADA**
Age at diagnosis	<35	>35	>30
C-peptide levels	Negative	Positive and high	Low and normal
Antibody presence	Positive	Negative but rare positivity*	Positive
Antibody types	IAA, ICA, GADA/ GAA, IA2, ZnT8A	GADA, IAA*	GADA, IAA, 2-IA2, ZnT8A
Insulin secretion	Low or Negative	Positive and Moderate	Positive but decreasing levels
Response to oral antiglycemic agents	Low	Moderate	Moderate
Prominent features	Autoimmunity, Lean body type	Insulin resistance, Overweight or obese body type	Autoimmunity

In addition to these diagnostic parameters, circulating microRNAs are suggested diagnostic purposes [50]. Serum and plasma miRNAs

are potential biomarkers with the predictive properties in terms of determining the risk and development of chronic complications of diabetes [14,51].

miRNAs as a diagnostic marker in LADA

MicroRNAs are small non-coding RNAs with the length of 19-24 nucleotides. MiRNAs are encoded in the genomes of mammals and involved in biological processes. MiRNAs are the negative regulators of the post-transcriptional activity and regulate the expression of target genes by degrading of mRNAs involved in protein synthesis or the suppression of transcription [14,50-52-53]. MiRNAs are involved in cell development and growth, cell proliferation, cell differentiation, apoptosis and metabolism [14,54].

MiRNAs, which have been studied in both blood and pancreatic islets, regulate the response of target tissues to insulin as well as insulin production, signaling and release, insulin resistance, and glucose homeostasis [51,55-56]. Dysregulation in miRNA expression can lead to impairment of glucose metabolism [52].

Studies have shown that circulating miRNAs are associated with different types of diabetes. Of these miRNAs, miR-375, miR-21, miR-24.1, miR-30d, miR-34a, miR-126, miR-146, and miR-148a were increased in diabetic patients compared to controls [57]. Up and down regulated expression levels of miR-152, miR-30a-5p, miR-181a, miR-24, miR-148a, miR-210, miR-27a, miR-29a, miR-27b, miR-26a, miR-25 and miR-200a were reported in newly diagnosed type 1 diabetic patients compared to controls [58]. In addition to these miRNAs, miR-103b, miR-148b, miR-223, miR-130a, miR-19a, miR-182-5p, miR-150, miR-30a-5p, miR-15a, miR-424, miR-199, and miR-486 were reported associated with T2D [51,59-60-61] whereas mir34, mir121, mir25, mir23, mir98, mir26, mir590, and hsa-miR-1-3p were found associated with T1D [62,63]. In another study, increased miR-126 levels have been reported as a biomarker for the discrimination of

prediabetic and type 2 diabetic patients [64]. In a study of Mostahfezian et al. (2019), increased miR-155 and miR-21 levels were reported in patients with T1D compared to healthy controls [65].

Seyhan et al. (2016) carried out a study in patients with T1D, T2D and LADA, prediabetics and healthy controls. They reported that increased miR-21 and miR-148a in patients with T2D and T1D compared to healthy controls, but levels of these two miRNAs were not significantly different among the type 1 and type 2 diabetic patients. Increased miR-24 and miR-375 levels only seen in patients with T1D while elevated miR-30d and miR-34a levels only seen in patients with T2D compared to healthy individuals. Decreased miR-126 and miR-146a levels were shown in prediabetic subjects. Reduced but non-significant miR-29a, miR-375, and miR-30d levels were detected in LADA. However, they couldn't find a significant change between the LADA and healthy control groups. In addition to this, miR-34a, miR-24, and miR-21 levels were found significantly for LADA patients according to the area under the curve (AUC) analysis. Elevated miR-375, miR-24, miR-21, and miR-148a levels indicate the degree and severity of β-cell injury that is found greater in T1D than T2D, than LADA and prediabetes. Also, they reported that miR-375 was a useful biomarker to distinguish subjects with T2D from those with T1D or LADA [57].

Yu et al. (2019), studying in a group of control individuals, T2D and LADA patients, were reported that up-regulated miR-93-5p and miR-555'in and down-regulated miR-507, miR-517a-3p, miR-517b-3p, miR-4691-3p, miR-370-5p, miR-448, miR-1236-3p and miR-1267 in the group of LADA patients. According to these changes, these miRNAs might be potential biomarkers discriminating LADA patients from the healthy controls and patients with T2D [14].

Similarly, there are some studies about the function of miRNAs in LADA. In a study of Liu et al. (2019) downregulated serum miR-21, miR-25, miR-146a, and miR-181a levels have been reported in the patients with autoimmune diabetes (T1D and LADA) compared

with those in patients with T2D and nondiabetic subjects [66]. Sorgjerd et al. (2022) studied on many miRNAs in patients with T1D, T2D, LADA and control subjects and reported that miR-23b-3p is a potential biomarker for differentiating LADA from type 1 diabetes [67].

In another study, miR-146a-5p, miR-223-3p and miR-21-5p were determined significantly different between the groups of patients with LADA and T2D. Analyses have shown that while the levels of mir-16-5p and mir-122-5p are decreased in LADA patients compared to type 2 diabetics, the levels of mir-21-5p, mir-146a-5p, mir-223-3p are increased [68].

As it seems in these studies summarized above, an increasing number of circulating miRNAs have been determined in diabetes mellitus pathogenesis (Table 2). However, it is seen that the investigation about the circulating miRNAs signatures in LADA patients is still limited. Therefore, further studies should be conducted in different populations to elucidate the role of miRNAs in the pathogenesis of LADA and to determine a pattern for using these miRNAs as a diagnostic biomarker.

Table 2: Changes of expression levels of LADA-related miRNAs in target tissue.

miRNA	**Expression Pattern / Regulation in LADA patients**	**P value**	**Population**	**Referance**
mir 21	Downregulated (compared with those in T2D patients and nondiabetic individuals)	$p < 0.001$	China	Liu et al. (2019)
miR-21-5p	Upregulated (compared with those in T2D patients)	$p < 0.001$	China	Fan et al. (2023)
miR-22-3p	Downregulated (compared with those in nondiabetic individuals)	-	Norway	Sørgjerd et al. (2022)
miR-23b-3p	Upregulated (compared with those in T1D patients)	-	Norway	Sørgjerd et al. (2022)

miRNA	Expression Pattern / Regulation in LADA patients	P value	Population	Referance
mir 25	Downregulated (compared with those in T2D patients and nondiabetic individuals)	$p < 0.001$	China	Liu et al. (2019)
mir 93 5p	Upregulated (compared with those in T2D patients)	$p < 0.05$	China	Yu et al. (2019)
mir 146a	Downregulated (compared with those in T2D patients and nondiabetic individuals)	$p < 0.001$	China	Liu et al. (2019)
miR-146a-5p	Upregulated (compared with those in T2D patients	$p < 0.001$	China	Fan et al. (2023)
mir 181a	Downregulated (compared with those in T2D patients and nondiabetic individuals)	$p < 0.001$	China	Liu et al. (2019)
miR-223-3p	Upregulated (compared with those in T2D patients)	$p < 0.001$	China	Fan et al. (2023)
mir 370 5p	Downregulated (compared with those in T2D patients)	$p < 0.05$	China	Yu et al. (2019)
mir 375	Downregulated (compared with those in T1D patients)	$p < 0.05$	USA	Seyhan et al. (2016)
mir 448	Downregulated (compared with those in T2D patients)	$p < 0.05$	China	Yu et al. (2019)
mir 507	Downregulated (compared with those in T2D patients)	$p < 0.05$	China	Yu et al. (2019)
mir 517a 3p	Downregulated (compared with those in T2D patients)	$p < 0.05$	China	Yu et al. (2019)
mir 517b 3p	Downregulated (compared with those in T2D patients)	$p < 0.05$	China	Yu et al. (2019)
mir 555	Upregulated (compared with those in T2D patients)	$p < 0.05$	China	Yu et al. (2019)
mir 1236 3p	Downregulated (compared with those in T2D patients)	$p < 0.05$	China	Yu et al. (2019)
mir 1267	Downregulated (compared with those in T2D patients)	$p < 0.05$	China	Yu et al. (2019)
mir 4691 3p	Downregulated (compared with those in T2D patients)	$p < 0.05$	China	Yu et al. (2019)

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