REVIEW ARTICLE

Iran diabetes research study; knowledge discovery in diagnosis: a scoping review

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Abstract

Introduction The rising prevalence of diabetes shows high health and socio-economic burdens. Therefore, the development and evaluation of new diagnostic methods may improve the detection of disease and its complications in the early stages. This study aimed to analyze the scope of the studies related to diabetes diagnosis.

Material and method Publications from January 2015 until December 2019 (5 years) were searched with keywords of (diabetes OR diabetic) AND (Iran) in Scopus and PubMed databases. All data were reviewed by two reviewers and the included publications were categorized based on the subjects, study design, and publication year.

Results Based on the selected criteria, 103 articles were included. The highest number of publications was observed in 2019. The trend of publication was slightly increased during the study period (2015-2019). Case-control and cross-sectional studies were the most common type of study design used in the included documents. Publications in the field of diagnostic models, biomarkers, and biosensors from 2015 to 2019 showed an increasing trend compared to others subjects.

Discussion and conclusion Studies about proper diabetes diagnostic procedures such as new diagnostic techniques, using diagnostic models, and evaluation of new diagnostic biomarkers in Iran are remarkably increased. However, more original and review studies are needed to improve scientific methods in the field of early detection of diabetes.

Keywords Diabetes mellitus · Diagnosis · Iran

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Introduction

Asia is considered the center of diabetes accounting for 60% of the world's diabetic patients [1, 2]. This global epidemic has become a major problem in most countries of Asia, especially in Iran [3, 4]. According to the World Health Organization (WHO) estimations, about 10% of people in Iran were affected by diabetes in 2016 [4, 5]. Moreover, recently, evidence has suggested that chronic and metabolic diseases such as diabetes are also highly associated with the progression and prognosis of COVID-19 [6, 7]. Considering the wide range of diabetes prevalence in Iran, there is an urgent need to develop appropriate and comprehensive methods for the early diagnosis and monitoring of the disease.

In 1997, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus reported that the diagnosis of diabetes is based on the levels of plasma glucose and its long-term complications, including nephropathy and retinopathy [8]. Later in 2009, the International Expert Committee [9] stated that measuring glycated hemoglobin

(HbA1c) is an applicable method for the diagnosis of diabetes [10]. Remarkably, the WHO and the American Diabetes Federation strengthened this reference and also suggested that both fasting blood glucose (FBG) and oral glucose tolerance test (OGTT) are gold standards for making the diagnosis of diabetes [11, 12]. Although these tests are all different in sensitivity and specificity [13].

Today, the variety of techniques and biomarkers for the diagnosis of diabetes creates a challenge for clinicians and laboratory diagnosticians [14]. In this manner, researchers should investigate these challenges and choose which test is more valid to be applied in diagnostic and clinical laboratories. Moreover, using specific diagnostic tests for each type of patient should be considered too [15].

On the other hand, the level of hyperglycemia (if any) may alter over time, relying on the degree of diabetes development. [16]. Hence, other stable tests should be regarded for diabetes diagnosis too. Interestingly, it is now well-known that different molecular pathways along with genetic factors contribute to the development of diabetes and these factors may be linked to some metabolic abnormalities which cause hyperglycemia ranged from mild to severe [16]. Consequently, an appropriate diagnosis of these involved molecules or genetic modification along with proper use of disease profile containing blood glucose-based tests and other possible factors affecting the disease process may help to have a comprehensive approach in the control and diagnosis of diabetes and subsequently prevention of diabetes complications, such as hypertension, nephropathy, and retinopathy by controlling blood glucose [17].

A scoping review is a review that analyzes the size of current studies to inform scientists regarding available evidence[18]. Hence, the present scoping review explains diagnostic procedures based on the recent studies performed in Iran. This study is a part of the "Iran Diabetes Research Roadmap Study" which is a large ongoing project focused on Iranian publications about different aspects of diabetes to suggest a plan for future diabetes researches. The outcomes of this project on previous studies (before 2015) have been published already [19, 20]. This scoping review is aimed to analyze characteristics of studies on DM and its complication diagnosis in Iran, showing the trend of studies in the last five years, to identify the most popular subjects and design of studies. We also discuss the challenges of diabetes and its complication diagnosis by comparing various methods and also introducing some responsible molecules in the disease development to be used as an accurate and reliable test in the diagnosis of diabetes. Some of these notable strategies will be fully described with their advantages and disadvantages in this study.

To our knowledge, there is no scoping review regarding the diagnosis of diabetes in Iran. Thus, we aimed to evaluate the scope of the diagnostic studies on diabetes, find out the relevant study gaps, and prioritize future research activities.

Materials and methods

To summarize the available studies related to the screen and diagnosis of diabetes performed in Iran, we conducted a scoping review based on the framework offered by Hilary Arksey & Lisa O'Malley [21]. The stages of the framework include:

Stage 1: identifying the research question: This study carried out to answer the following questions:

- What was the scope of the available studies regarding the diagnosis of diabetes?
- What was the level of evidence of the literature?
- What was the subject area of the included studies?
- What were the relevant knowledge gaps?

Stage 2: identifying relevant studies: We searched the Scopus and PubMed databases from 2015/01/01 to 2019/12/31 using the keywords such as "(diabetes OR diabetic) AND Iran". The following criteria were used to select the articles:

Inclusion criteria:

- Only original studies and reviews were included in the study.
- In original articles, the research studies associated with Iranian populations were assessed.
- Only English and Persian documents were eligible.
- Based on the topics, all studies about diabetes or complication diagnosis were included, such as accuracy-validity of test and instruments, technologies, biosensors, and molecular approaches for detection of diabetes, diagnostic models, new analytical methods about parameters related to diabetes diagnosis (Glucose, HbA_{1c}, etc.),

Exclusion criteria:

- Commentaries, letters to the editor, book, protocols, news, theses, note, short survey, and conference abstracts were removed.
- The investigations associated with non-Iranian populations were excluded.

Stage 3: study selection: All the retrieved manuscripts were imported into EndNote software to remove the duplicates. Then, the titles and abstracts of the studies were screened based on the eligibility criteria by two members of the research team.

Stage 4 and 5: charting the data and reporting the results: We used various forms to extract data related to the subjects, study design, and publication year. Obtained information presented in different tables and charts. Moreover, the search results are presented by a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

Results

Study selection The databases search resulted in 10540 articles. After the screening of the title and abstracts and removal of the duplicates, 103 articles met the inclusion criteria (Fig. 1). All of the documents were classified according to types of study design and subject area.

Study design and publication type Figure 2 shows the study design distribution in the included papers. Case-control and cross-sectional studies(43) and in-vitro/in silico studies (40) were the most common types of study design followed by cohort studies (9), narrative review/expert opinion (6), case report/case series (4) and only 1 systematic review. There were no clinical trial and animal studies among articles and this is logical because that type of study design doesn't fit with diagnostic method issues. Most of the articles were original (96) and 7 review articles were found that just one of them was a systematic review.

Subject area and trend of studies Figure 3 shows the distribution of the articles with regard to subjects and the trend of publication. The highest number of publications was observed in 2019. The trend of publication was slightly increased during the study period (2015-2019). Articles about different methods for diagnosis and prediction of diabetes had the highest number in all years (totally 43) and then analytical methods development/ validation (30), diabetic retinopathy diagnosis (13), diabetic nephropathy diagnosis (9). Among papers related to diagnosis and prediction of diabetes , there were a significant number of articles focused on diagnostic models (n=19) and new biomarkers (n=9) for diabetes diagnosis (Tables S1 and S2). In the diabetic retinopathy diagnosis group, the number of papers using diagnostic models was considerable (n=6) while in the nephropathy diagnosis group, evaluation of new biomarkers was the main subject. Figure 4 shows the trend of publications in the field of diagnostic models and biomarkers totally from 2015 to 2019.

The type of diabetes was not mentioned in most of the publications. In 30 studies that the type of diabetes was identified, 24 were performed in type 2 patients and 6 in type 1 patients.

In the field of analytical methods development/ validation, we found 11 original studies that used different types of biosensors (Table S3) and 7 studies that used other techniques such as chemiluminescence (Table S4) mostly for glucose and HbA1c

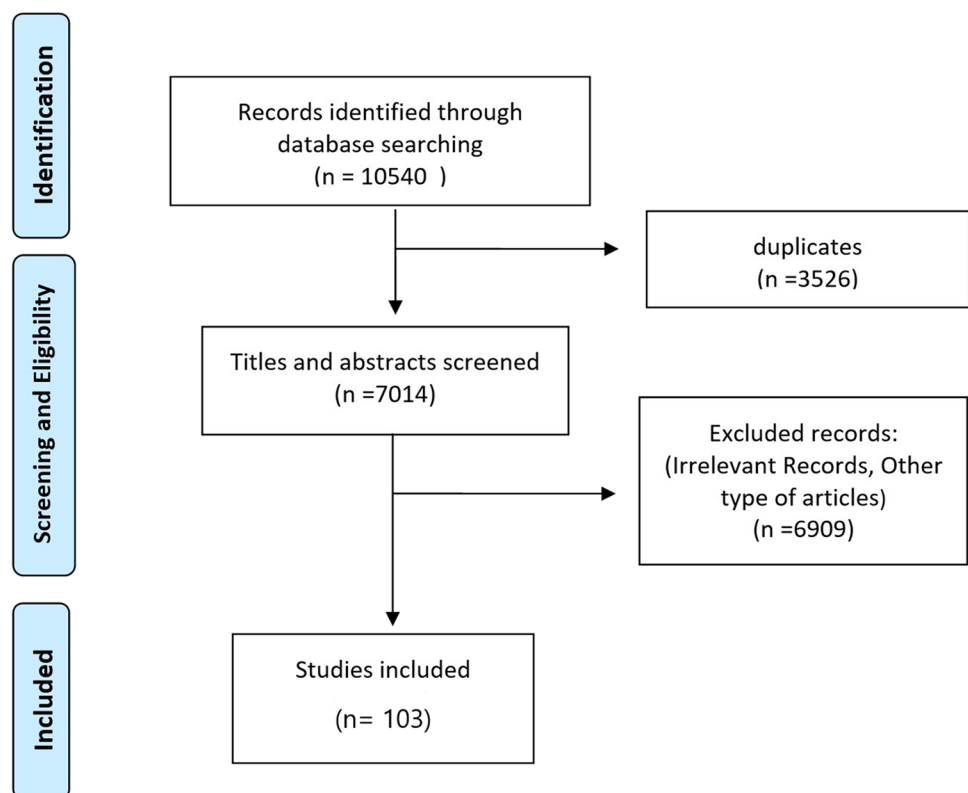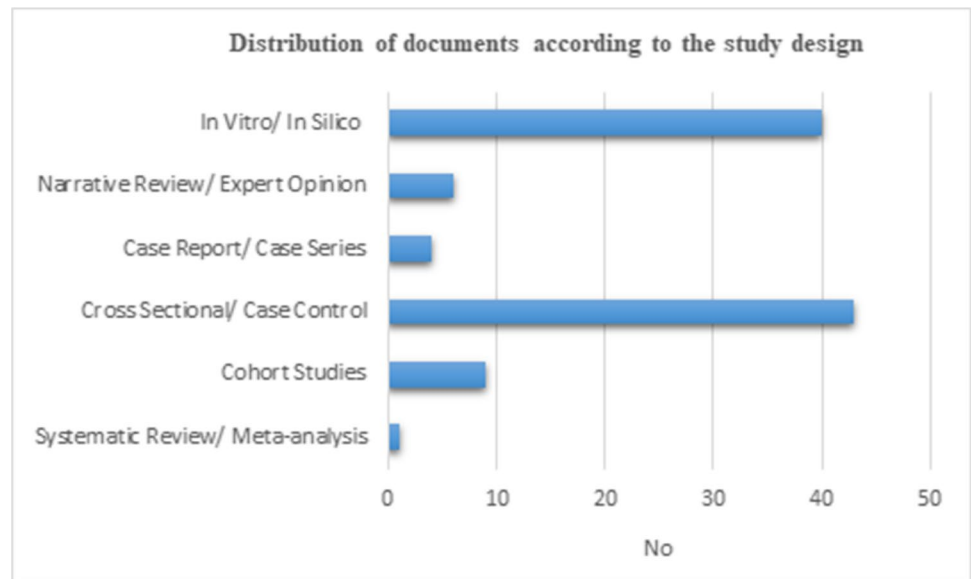**Fig. 1** Flowchart for the articles included in the scoping review

Fig. 2 The distribution of documents according to the study design

Distribution of documents according to the study design

measurement. Figure 4 reveals the trend of studies about bio-sensor-based methods in the field of diabetes diagnosis.

Discussion

It is estimated that about 4.5 million individuals had diabetes in Iran in 2011, while 25% of them were not previously diagnosed. Moreover, it is predicted that by the year 2030, 9.2 million people will have diabetes in Iran. This rising prevalence of diabetes shows high health and socio-economic burdens. However, only a few people, particularly overweight or obese individuals are screened for diabetes despite the presence of a high risk of the disease in all people regarding the current lifestyle and diet among Iranian people. These are even though current health organizations fail to detect many diabetic patients in Iran with present methods and techniques and we also need low-cost and applicable screening tools in the population [22–24].

In clinical practice, measuring fasting blood glucose is time-consuming, needing overnight fasting (which some individuals find unpleasant) and due to the variability within a person, requires to be repeated. On the other hand, although HbA1c measurement has some notable advantages including no need to fast and great stability in stress or acute

Fig. 3 The distribution of included documents with regard to the subject area

The distribution of the included publications with regard to the subject area.
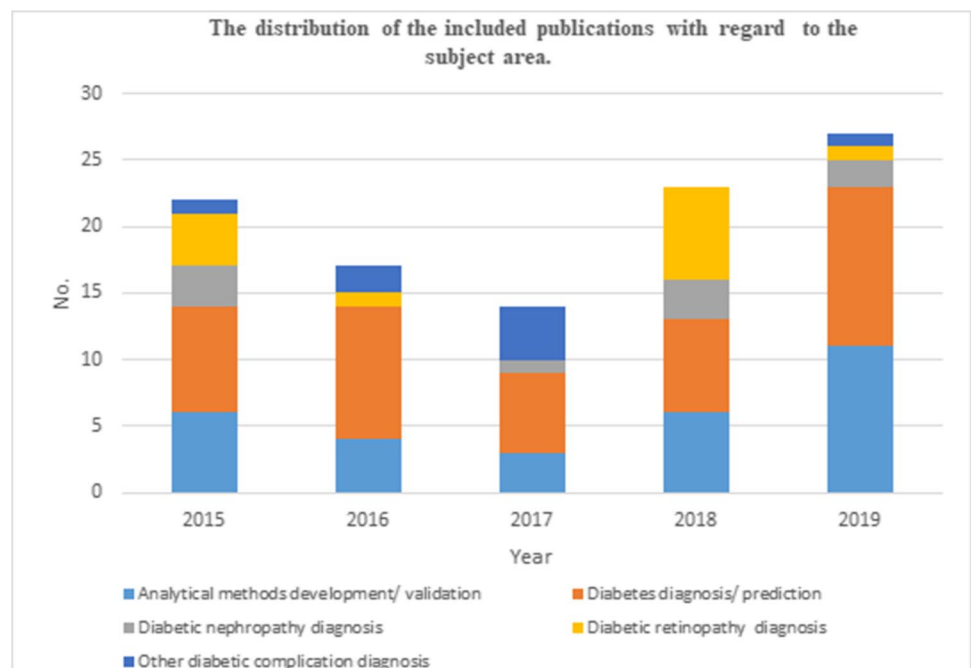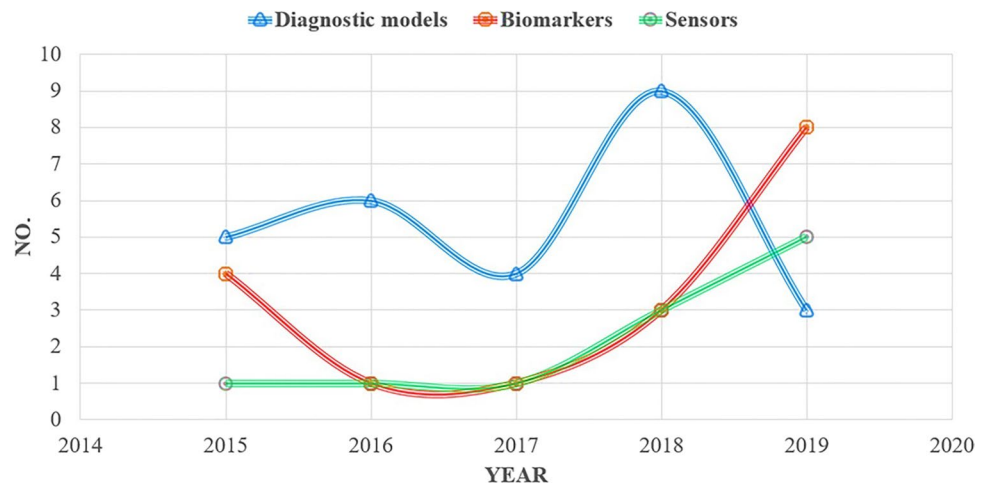
Fig. 4 Trend of publications in the field of diagnostic models, biomarkers, and biosensors from 2015 to 2019

conditions, its level differs by ethnicity and other variables, and also it could be incorrect when there is hemoglobinopathy. Moreover, HbA1c measurement is expensive with current methods [24–26]. So, some patients can be missed while healthy individuals can be identified with diabetes. These remarkably affect clinical management and services [27, 28]. Therefore, while current assays used for measuring glucose are widely accepted as diagnostic tests, there are other new methods and techniques for measuring glucose and the more simple and inexpensive way which should be reviewed for choosing the most accurate and reliable method in clinical laboratory use [24, 29].

In the present study, we reviewed the progress of studies in the field of diabetes diagnosis to provide knowledge discovery for techniques and models for detection of diabetes. Generally, the studies were increased from 2015 to 2019 in Iran (with a decline in 2016 and 2017). As expected, the most frequent studies were about diabetes diagnosis/ prediction followed by analytical methods development/ validation. The most common study design was cross-sectional/ Case-control studies. Due to the large dispersion of the studied subjects, here, we have tried to summarize some of the new diagnostic methods, including biosensor technology, diagnostic models, and biomarkers.

One of the most important technological advancements is biosensor technology which is available for accurate and cost-effective measurements. In this manner, the first biosensor for measuring glucose was introduced in 1962 by Clark and Lyons [30]. Since then, numerous developments of biosensors have been proposed for the diagnosis of diabetes. Biosensors include a biorecognition element coupled to a physicochemical transducer creating detectable signals. For measuring glucose, the biorecognition element is glucose oxidase which converts glucose to gluconic acid. Interestingly, some nonenzymatic glucose biosensors make a faster and easier process for detection [31, 32].

Almost from 2017, Iran along with other countries had made significant progress in the field of biosensors for the diagnosis of diabetes and has suggested the use of novel methods, including electrochemical biosensors in the process of early detection [33–35]. Some of these biosensors are completely non-invasive by using a microstrip bandpass filter to receive the wireless sensor data for measuring blood glucose. Remarkably, they are designed on a cost-effective substrate with a compact size which makes them practical for diabetic-care services [36]. From these findings and other similar studies, it can be inferred that the non-invasive techniques implemented on wireless sensors may propose a new procedure that can be applied at any time and any place shortly as an alternative to traditional tools for measuring blood glucose [37]. Although there is a considerable increase in the number of Iranian publications in the field of method development for glucose and HbA1c measurement, the number of reviews is limited. Along with conducting new original studies, more review articles are required to summarize the results of original articles.

Diagnostic models are also one of the most important tools using for early diagnosis and control of diabetes which has been under great consideration in the last 5 years in Iran. Remarkably the Artificial Neural Network (ANN) model has indicated the most specificity and sensitivity compared to other models in all related studies, suggesting the use of the ANN model as the most functional model for the diagnosis of diabetes [38, 39]. However, the design and training of ANN are challenging. For instance, assigning weights in the ANN model seems to be a problem that also has an important effect on the presentation of output models. Furthermore, there are some disadvantages related to the ANN model, including difficult calculations and a tendency to overfitting [40, 41]. Because of these, researchers select proper standards for parameters by merging the ANN model with other optimization procedures, including the simulated annealing or the genetic algorithm [42]. Other

diagnostic models, such as support vector machines (SVM) have been also under great consideration as a bi-objective hybrid optimization algorithm to select the least number of significant features with the most classification accuracy and to decrease noise and data dimension in diagnosis [43]. There are also some algorithms for the diagnosis of retinopathy in diabetic patients based on the Human Visual System (HVS) model or type-2 fuzzy regression model [44, 45]. It seems that performing more studies in this field can improve the capability of early diagnosis of diabetes and its complications.

Today, attention has shifted toward the role of new diagnostic biomarkers for diabetes, and almost from 2015, about 16 articles made significant progress in this field of research in Iran. Indeed, there are novel molecules recognized in the serum and urine of diabetic patients which can be considered as potential diagnostic biomarkers. For instance, osteocalcin is a plausible biomarker for screening diabetes in postmenopausal women [46]. Moreover, some studies proposed cystatin C as an applicable biomarker for the diagnosis of diabetes nephropathy, particularly in the early stages. However, cystatin C is not appropriate for monitoring the treatment of patients with diabetes [47, 48]. Some studies indicated that the serum levels of different adipokines, including adiponectin and leptin, are good indicators for following the course of diabetes [49–51]. MicroRNAs are important regulators of gene expression in many processes and are dysregulated in many pathological conditions. Among these, miR-21 and miR-155 have been suggested as possible diagnostic biomarkers for diabetes [52–55].

Putting these together, one of the most important findings of the present study is that all methods and techniques may suggest a certain strategy for the early diagnosis of diabetes and its complications. Besides, studies of this kind would help us to provide future principles for the universal control of diabetes and suggests the use of other low-cost and simple methods in addition to diagnostic gold standard tests. Importantly, recent studies also tried to improve and develop the technology of current methods, including chemiluminescence and microfluidic disc using immunoturbidimetry to evaluate glucose and HbA1c, respectively. Altogether, we may provide a better and more standard perspective for the diagnosis of people at higher risk. Moreover, it is bearing in mind that the diagnosis of diabetes is important in both terms of health and economics. In this manner, some diagnostic models can estimate the risk of diabetes using anthropometric findings even without sampling and evaluation of related analytes [38, 39]. Furthermore, new biosensors are capable of measuring blood glucose levels even without sampling, indicating that these methods are non-invasive and practical [36].

Nevertheless, in addition to all advantages of the mentioned strategies, their limitations should also be considered

and more extensive studies are required to unravel them. Moreover, any new diagnostic procedure should be available and manageable at the community level and detect people at higher risks. Likewise, any diagnostic procedure should be performed within a clinical setting due to the necessity of follow-up and treatment[56]. The present study is the first to investigate national estimates of different strategies for diabetes diagnosis in Iran. . In this study, Scopus and Pubmed databases are used because of more coverage of publications [57] and suitability for biomedical researches [58] therefore some of the related articles indexed in other databases might be missed. Despite all these data, we should note that the number of studies performed in Iran is very limited. Indeed, the present scoping review is only a roadmap that provides a new perspective for future studies to achieve a better diagnosis strategy.

Conclusion

Studies about proper diabetes diagnostic procedures such as new diagnostic techniques, using diagnostic models, and evaluation of new diagnostic biomarkers in Iran are remarkably increased. However, more studies are needed to improve these scientific methods and show their usefulness in the upgrading of diagnostic methods of diabetes and its complications in practice. Along with developing original studies, more review articles are needed to summarize the outcomes of original articles.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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