



Iran Diabetes Research Roadmap (IDRR) Study; Knowledge Gap in Genetic Research on Diabetes Mellitus in Iran: A Review Article

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(Received 15 Nov 2016; accepted 15 Feb 2017)

Abstract

Background: Diabetes mellitus (DM) is the most common metabolic disorder worldwide. This study aimed to report characteristics of genetic studies in DM in Iran and to identify knowledge gap in genetics of diabetes in Iran.

Methods: All publications of Iranian authors in national and international journals up to 2015 were included. Comprehensive search was performed in PubMed, Web of Science, Scopus, SID, IranMedex and Magiran using "Diabetes mellitus" and "Iran*" keywords and their combination. This search obtained 25589 documents. The obtained documents were categorized into eleven groups of complications, comorbidity, management, psychology, nutrition, physical activity, genetics, basic sciences, prevention, education and gestational diabetes mellitus (GDM). Documents were categorized based on publication year, WHO and Australian National Health and Medical Research Council (NHMRC) classification, study design and subject area.

Results: After screening, 293 documents remained. The trend of publications was increasing and reached peak in 2013. Case-control was the most common method used in the documents. Most of the studies were association study with case-control design while there was no genome-wide association study (GWAS). Genetic risk factors for DM and its complications were the most common topics in the obtained documents followed by DM management.

Conclusion: The most of genetic studies in diabetes in Iran are association studies about genetic risk factors of diabetes while GWAS and pharmacogenetic studies are rare or absent. This may indicate low priority of personalized medicine in the field of diabetes in Iran.

Keywords: Scientific map, Scientometrics, Roadmap, Diabetes mellitus, Genetics, Iran

Introduction

Diabetes mellitus (DM) is a growing public health problem worldwide while the highest burden of diabetes is in developing countries with limited resources. According to International Diabetes Federation (IDF) reports, the number of diabetic

patients reaches to 592 million people by 2035 which most of them are in low and middle-income countries and the majority of them are under 60 (1).

Middle East and North Africa Region (MENA) has the highest prevalence of diabetes (age adjusted) in the world (1). Three countries in our region including Saudi Arabia, Kuwait, and Qatar are among the world's top 10 countries with the highest prevalence (%) of diabetes (1). In the latest IDF report, the number of people with diabetes in 2013 has been estimated 34.6 million in our region (prevalence of 10.9%) in the adult population. This rate estimated to be doubled by 2035 and reach to 11.3% (67.9 million) in the region (1). Iran is in the third place after Egypt and Pakistan in the MENA region in terms of the total number of adult population with diabetes (4396 Diabetes cases (20-79) in 1000s) (1). Diabetes imposes a high economic burden on the society and diabetic patients require higher health care resources than those without it (2).

Diabetes rate is increasing in Iran like other parts of the world due to sedentary lifestyle. The number of adult people with diabetes has increased from 1.6 million in 2000 to 4.5 million in 2012 in Iran (1, 3). This increased rate in addition to environmental factors and sedentary lifestyle may be attributed to genetic predisposing factors.

Scientists around the world are working to identify new risk factors for diabetes and its complications and new aspects of diabetes management and control. Most of studies about diabetes are investigating clinical aspects of diabetes and its complications as well as its management. In addition, to environmental and clinical factors, genetic factors may put the individuals at risk of diabetes and affect disease outcome.

In the recent two decades, scientists have begun to link genetic factors with diabetes onset and response to treatment and disease outcome. Genetic background has been approached as the predisposing factor for DM and effective factor in developing complications and in the management of diabetes that is the concept of individualized or personalized medicine introduced in recent years.

DM is a multifactorial disease and disease outcome depends on interaction of genetic and environmental factors. Multiple genes contribute to the development of diabetes that few of them

such as ACE, adiponectin, and KCNJ11 have been studied (4-6).

Up to now few scientometric studies have analyzed diabetes research output in Iran shown increasing trend of diabetes publications (7, 8). However, there is no comprehensive detail analysis about genetic studies in DM neither in Iran nor in the world. This is the first study that reports detailed characteristics of genetic research in DM in Iran. This study was a part of Iran Diabetes Roadmap study to find the knowledge gap in the field of diabetes.

The main goal of present study was to analyze and report characteristics of genetic studies in DM in Iran and to identify knowledge gap in genetics and personalized medicine in diabetes in Iran.

Methods

Analysis of genetic studies in the field of DM in Iran was performed. This is a part of Iran Diabetes Research Roadmap (IDRR) study. This study included all studies published by Iranian authors in national and international journals up to Jan 2015. International databases including PubMed, Web of Science and SCOPUS as well as national databases including SID, IranMedex, and Magiran were used as the source of information. Search in these databases was performed according to the strategy described in the study protocol in details (9). The keywords used for English database search were "Diabetes mellitus" and "Iran*" in the author affiliations. These key terms were used according to each database instructions and were combined using "AND" and "OR" operators appropriately. For search in national databases, equivalent Farsi keywords were used. This search obtained 25589 documents.

All obtained documents were categorized in eleven groups including complications, comorbidity, prevention, management, psychology, nutrition, physical activity, genetics, basic sciences, education and gestational diabetes mellitus (GDM).

In each group after removing unrelated and duplicate documents remained documents were categorized based on the study design, topic, WHO

(10) classification and Australian National Health and Medical Research Council (NHMRC) criteria (11).

NHMRC criteria define the area of research (11) and WHO criteria clarify if the research meet health needs and improve health outcomes or not (10).

Statistical Analysis

The data was analyzed by descriptive statistic and results were depicted by appropriate graphs. SPSS software version 17.00 (Chicago, IL, USA) was used for data analysis.

Results

Overall, 293 documents were classified by the publication year, topic, study design and WHO and NHMRC classifications. None of the studies

was eligible to be included in WHO classification. Among these documents, 292 were classified as Basic Sciences in NHMRC classification.

Publication Trends

Fig. 1 shows the trends of genetic publications in the field of diabetes in Iran in the recent decade. The number of documents before 2004 was few and was not included in this figure. The highest number of publications was observed in 2013, 2012 and 2011, respectively. The number of published articles reduced slightly in 2014. The trend of publication was increasing during the study period (1999 to 2015) but there was a small fall in growing trend in 2006, 2008, 2010 and 2014 compared to previous year, which returned to growing curve in the next years (Fig. 1).

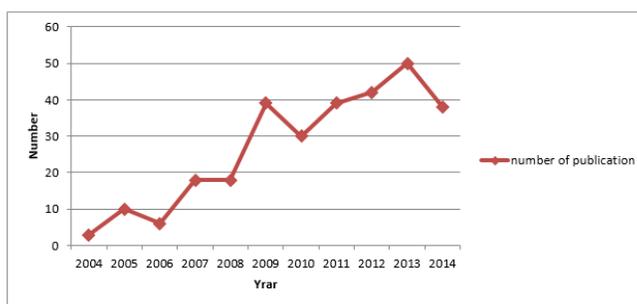


Fig. 1: Trend of publications in the field of diabetes genetics from 2000 to 2014

Methodology Classification

The frequency of different types of the study designs has been shown in Fig. 2. Case-control design was the most common type of study design used in the obtained documents followed by an-

imal and laboratory and cross-sectional study design. Most of studies were association study with case-control design while there was no genome-wide association study (GWAS). There was no cohort study among the obtained documents.

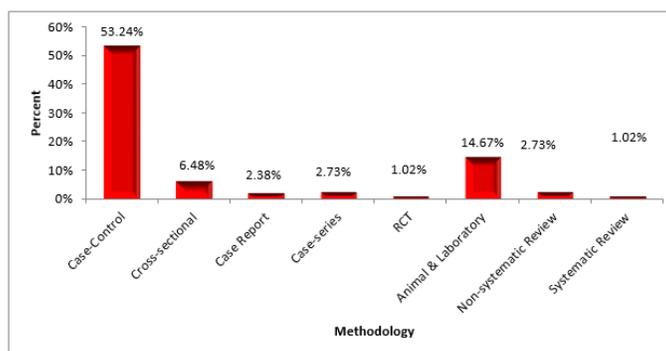


Fig. 2: Distribution of documents according to the study design

The Study Topic

The most common subject investigated in Iranian studies was genetic risk factors for DM and its complications followed by DM management (Fig. 3). The least number of studies were about pathophysiology of diabetes. Only one pharmacogenetic study was found. In addition, no study about micro RNAs in diabetes was detected.

In these studies, a few genes and variants have been assessed by different authors repeatedly in different parts of the country in different diabetic populations. The most studied genes and variants in these documents were ACE, Vit D receptor, MTHFR, KCNJ11, and TCF7L2.

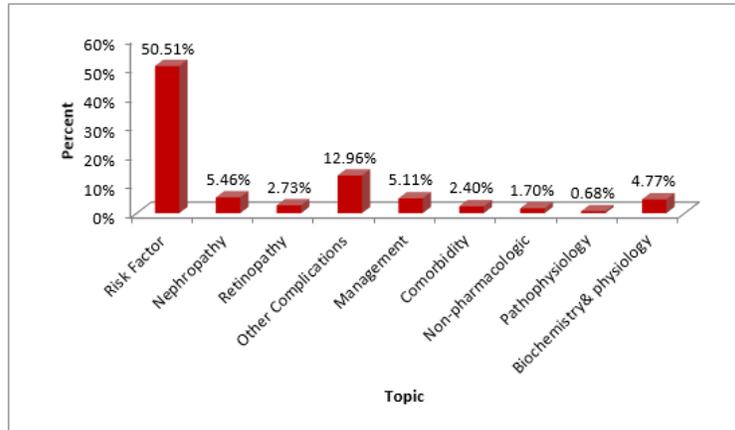


Fig. 3: Distribution of documents according to the subject area

Discussion

Studies about genetic risk factors for diabetes are the most common genetic studies performed on diabetes and most of obtained studies were association study with case-control design.

There is no comprehensive analysis of genetic studies on diabetes performed in the world and Iran as well and our study is the first one. However, scientometric studies have been conducted about diabetes research in Iran and our region.

Contribution of Iran in international publications only was 0.2% and it stood in the fourth place after Saudi Arabia, Kuwait, and Egypt among Eastern Mediterranean region countries. However, Iran had the highest growth speed among the countries in this region (12).

Turkey (30.2%), Israel (27.4%), and Iran (12.7%) produced 70% of knowledge about diabetes in our region. The growth speed of Iran was 9% during the same period. After 2011, Iran took

second place in the region by production of 22% of knowledge in diabetes (7).

Another study published recently reported a negative growth of -14.6% in Iran publications in the field of diabetes between 2013 and 2014 (13).

In addition, publications of India about diabetes were analyzed between 1999 and 2008. Diabetes research output was classified under seven broad subject areas and showed that genetics and molecular biology studies (28.6%) were the third most common subject of these studies (14).

Our study is the first one analyzing detail characteristics of genetic research in diabetes in Iran as well as the world. Our study showed growing trend of genetic research in diabetes in Iran during the study period. There were small drops in the trends of publications in some years of study. In the same time that world had the most number of diabetes research publications (2010) (15), genetic outputs in diabetes experienced a negative trend in our country, possibly due to changes in policymakers following presidential election.

Similar drops also were seen in the publication trend in our country as well as in our university in all fields of science in the same years (7). This may be explained by changes in the research budget due to changes in the strategy of policy makers or global government policy. Another factor that may be the cause of drop in genetic research trend, particularly in 2014, is world sanction against our country that reached the highest in this time. Although these sanctions had no significant effect on care of diabetic patients (16). However, they affected genetic research directly because many genetic studies require materials and higher technologies that most of them are not available in Iran and should be provided by foreign countries that sanctions limited these exchanges and resulted in decrease in genetic output during these years and limited our studies to simple and available methods.

We did not find any GWAS among the obtained results. The main cause of this finding is that GWAS studies are expensive and need high budget and availability of advanced technology. Genome-wide studies in diabetes have been conducted in other countries (17, 18) and even Meta-analysis has been reported about them (19, 20).

However, similar to other countries, most of genetic studies in Iran were association study. The genetic association studies confirm statistical associations between genetic variations and phenotypes or disease states and thus identify genetic risk factors that can be studied by methods that are more comprehensive. This genetic study type technique is usually available, inexpensive and simple to do.

In addition, among our documents, there was no study about micro RNAs in diabetes. This is because microRNA was relatively new issue at the time of our study and such studies had not begun or was running in Iran at the same time and had no publication.

We found only one pharmacogenetic study which this indicated low priority of personalized medicine in our country, previously. However, recently policymakers announced personalized medicine as the research priority of Ministry of Health. Personalized medicine and interventions

are growing in the world in recent years and they are of great interest in the management of diabetes.

Moreover, no cohort study was found among the obtained publications. By large-scale cohort studies, the effects of genetic factors in progression of diabetes and its complications are identified and how these factors affect the risk of development of specific diabetes complications.

The chance of developing the diabetes complications is greatly different among diabetic patients. Such difference may be attributed to the genetic background, gene-lifestyle interactions and ethnicity. However, few studies have investigated these factors.

The study of genetic factors effective in development of diabetes and its complications in longitudinal studies would allow researchers to develop individually tools for the prediction of diabetes outcome and its complications and to develop strategies for personalized diabetes management. DIAMAP 2010 and 2014 have highlighted lack of such studies and have recommended them in future studies (21-23).

These issues are important knowledge gap in genetics of diabetes and future diabetes research should be focused more on these issues.

Conclusion

This study shows higher rate of association studies in Iran and limited rate of GWAS and pharmacogenetic studies. This may indicate low priority of personalized medicine in the field of diabetes.

Future studies should be focused on personalized medicine including pharmacogenomics and genome-wide association studies to identify genetic factors contributing to the diabetes development, response to therapy and outcome.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

This study was supported by Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences. We wish to thank staff at Diabetes Research Center for their sincere assistance in this study. The authors declare that there is no conflict of interests.

References

1. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE (2014). Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract*, 103(2):137-49.
2. American Diabetes Association (2013). Economic costs of diabetes in the U.S. in 2012. *Diabetes care*, 36(4):1033-46.
3. Larijani B, Abolhasani F, Mohajeri-Tehrani MR, Tabatabaie O (2005). Prevalence of diabetes mellitus in Iran in 2000. *Iran J Diabetes Metab*, 4(3):75-83.
4. Rastegari A, Rabbani M, Sadeghi HM, Imani EF, Hasanzadeh A, Moazen F (2015). Association of KCNJ11 (E23K) gene polymorphism with susceptibility to type 2 diabetes in Iranian patients. *Adv Biomed Res*, 4:1.
5. Nikzamir A, Rashidi A, Esteghamati A, Nakhjavani M, Golmohammadi T, Khalilzadeh O (2010). The relationship between ACE gene insertion/deletion polymorphism and diabetic retinopathy in Iranian patients with type 2 diabetes. *Ophthalmic Genet*, 31(3):108-13.
6. Hasani-Ranjbar S, Amoli MM, Tabatabaie-Malazy O et al (2012). Effect of adiponectin gene polymorphisms on waist circumference in patients with diabetes. *J Diabetes Metab Disord*, 11:14.
7. Peykari N, Djalalinia S, Kasaeian A et al (2015). Diabetes research in Middle East countries; a scientometrics study from 1990 to 2012. *J Res Med Sci*, 20(3):253-62.
8. Nasli-Esfahani E, Farzadfar F, Kouhnavard M et al (2017). Iran Diabetes Research Roadmap (IDRR) study: A preliminary study on diabetes research in the world and Iran. *J Diabetes Metab Disord*, 16:9.
9. Shafiee G, Nasli-Esfahani E, Bandarian F, Peimani M, Yazdizadeh B, Razi F, Farzadfar F, Larijani B (2016). Iran Diabetes Research Roadmap (IDRR): The study Protocol. *J Diabetes Metab Dis*, 15:58.
10. World Health Organization (2012). World Health Report 2012: No health without research. Geneva: World Health Organization. <http://collections.plos.org/world-health-report>
11. Australian Standard Research Classifications and NHMRC Research Keywords and Phrases: Australian Government, National Health and Medical Research Council; 2008 [cited 2016]. <https://www.nhmrc.gov.au/grants-funding/policy/australian-standard-research-classifications-and-nhmrc-research-keywords-and-p>
12. Rezaei Ghale N, Mirbolouki, MR, Azizi F (2006). To trend of changes in diabetes articles between 1992 and 2002, the lack of research in developing countries. *Res Med*, 30(4): 323-7.
13. Rasolabadi M, Khaledi S, Ardalan M, Kalhor M, Penjvini S, Gharib1 (2015). Diabetes Research in Iran: a Scientometric Analysis of Publications Output. *Acat Inform Med*, 23(3):160-4.
14. Gupta BM, Kaur H, Bala A (2011). Mapping of Indian Diabetes Research during 1999-2008:A Scientometric Analysis of Publications Output. *DESIDOC J Lib Inform Technol*, 31(2):143-52.
15. Geaney F, Scutaru C, Kelly C, Glynn RW, Perry IJ (2015). Type 2 Diabetes Research Yield, 1951-2012: Bibliometrics Analysis and Density-Equalizing Mapping. *PLoS One*, 10(7):e0133009.
16. Larijani B (2016). Burden of diabetes in Iran: how will it be affected by lifting of the economic sanctions? *Lancet Diabetes Endocrinol*, 4(10):810-1.
17. Palmer ND, McDonough CW, Hicks PJ et al (2012). A genome-wide association search for type 2 diabetes genes in African Americans. *PLoS One*, 7(1):e29202..
18. Kooner JS, Saleheen D, Sim X et al (2011). Genome-wide association study in individuals of South Asian ancestry identifies six new type 2 diabetes susceptibility loci. *Nat Genet*, 43(10): 984-9.

19. Cho YS, Chen CH, Hu C et al (2012). Meta-analysis of genome-wide association studies identifies eight new loci for type 2 diabetes in east Asians. *Nat Genet*, 44(1): 67-72.
20. Ng MC, Shriver D, Chen BH et al (2014). Meta-Analysis of Genome-Wide Association Studies in African Americans Provides Insights into the Genetic Architecture of Type 2 Diabetes. *PLoS Genet*, 10(8): e1004517.
21. Hills S, Halban PA (2011). DIAMAP: a road map for diabetes research in Europe. *J Diabetes Sci Technol*, 5(3):794-7.
22. Wareham NJ, Borch-Johnsen K, Colhoun H, Groop LC, Knip Mk. Genetics and epidemiology 2010 [21 Dec 2015]. <http://www.diamap.eu/static/report/DIAMAP-Chapter-1.pdf>
23. Wareham NJ, Borch-Johnsen K, Colhoun H, Groop LC, Knip Mk , Borch-Johnsen K, Colhoun H, Groop LC, Knip M. Genetics and epidemiology 2014 [18 Dec 2014]. Available from: <http://www.diamap.eu/>.