Iran Diabetes Research Roadmap (IDRR) Study; Analysis of Diabetes Comorbidity Studies in Iran: A Review Article

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Abstract

Background: Most adult patients with diabetes have at least one comorbid chronic condition and approximately 40% have three or more. The purpose of this study was to investigate detailed characteristics of studies examining comorbidities of diabetes in Iran and to identify knowledge gaps in this field.

Methods: All documents published by Iranian authors in national and international journals until 2015 were evaluated. A wide search was performed in PubMed, Web of Science, SCOPUS as well as SID, IranMedex and Magiran databases using proper keywords. The obtained documents were categorized into eleven subgroups of complications, comorbidities, management, psychiatry, nutrition, prevention, physical activity, genetics, basic sciences, education and gestational diabetes mellitus (GDM). Documents were categorized based on WHO and Australian National Health and Medical Research Council (NHMRC) classification, the study methodology and topic.

Results: Overall, 311 documents were obtained. The trend of publications was ascending since 2000. About 70% of studies were about epidemiology and causes of comorbid disease and more than 90% of studies were clinical research. The design of the most studies was cross-sectional followed by case-control and randomized clinical trial. The most common subject of documents was related to endocrine (28.61%) followed by gastrointestinal (18.32%) and cardiovascular disease (14.14%).

Conclusion: Epidemiological studies are the most common type of studies about diabetes comorbidity in Iran and cross-sectional design is the most frequent methodology used while there are few cohorts. There is no study about physiopathology and shared etiology and pathogenesis of these comorbidities and diabetes.

Keyword: Diabetes mellitus, Comorbidity, Roadmap, Iran

Introduction

Diabetes Mellitus is a well-known metabolic disorder, which will bring major impacts due to its detrimental consequences (1, 2). Diabetes is a major public health concern in Iran given its high prevalence rate, increasing incidence rate, and overall economic burden (3). The International Diabetes Federation Atlas for Diabetes shows that the Middle East and North Africa (MENA)

region of the world not only has the highest prevalence of diabetes but also number of patients with diabetes with comorbidity (4, 5). Effective diabetes management often presents enormous challenges. Not surprisingly, achieving diabetes-specific treatment goals is complicated by the presence of comorbid chronic conditions (6). Comorbidity refers to the presence of more than one disorder in the same person with an index disease and often seen among patients with diabetes (7). However, diabetes-specific risk factors cannot be controlled and may miss opportunities to improve patients' quality of life, and mortality risk unless with concurrent disease treatment (8).

Presently, integrated diabetes care programs focus on diabetes-related comorbidities like cardiovascular diseases, musculoskeletal diseases, and mental diseases (9). Most adults with diabetes have at least one coexisting chronic condition and approximately 40% have three or more (10, 11). The risk of cardiovascular disease and stroke in diabetic patients is 2-4 times higher than that of nondiabetics and up to 75% of adults with diabetes either have uncontrolled hypertension or are being treated for elevated blood pressure (12). There is increasing evidence that diabetes per sec and some antidiabetic treatments may increase cancer risk (13).

The prevalence of comorbidities in patients with diabetes has been estimated by several national health surveys in Iran (4, 14-17).

However, despite the major public health impact of diabetes in our country, recent population-based data regarding its prevalence and comorbidity are sparse. Our previous study showed that diabetes research in Iran to somewhat is in line of the world diabetes research and world sanctions against Iran has not affected diabetes research as well as our diabetic patients care notably (18, 19). However, no study in Iran has systematically analyzed diabetes comorbidity so far, and there are no comprehensive data on diabetes comorbid chronic conditions and their effect on health care costs in Iran. It seems imperative to analyze the status of researches in the field of diabetes comorbidity and to identify significant research gaps

to gain insight into future health care demands of patients with diabetes.

This study was a part of Iran Diabetes Research Roadmap (IDRR) study to find the knowledge and research gap in the field of diabetes.

Methods

All publications of Iranian authors about diabetes comorbidities up to 2015 were reviewed. This study included all studies published during the study period by Iranian authors in national and international journals. Comprehensive search was performed in international databases including PubMed, Web of Science and Scopus as well as national databases including SID, IranMedex, and Magiran as described in the study protocol (20).

As the exact border of complications and comorbidities is not clear and sometimes there is overlap between these two categories, in the study protocol, these conditions were classified according to Harrison's textbook and previous studies (21, 22). Clusters of comorbidity have been shown in Table 1 and conditions other than these clusters were considered as complication. In addition, since there was no consensus about subgroup classification of hypertension (HTN) and dyslipidemia, they were considered in subgroups based on the related study's aim.

However, in this study, epidemiological studies about HTN and dyslipidemia were considered in cardiovascular and endocrine categories, respectively. Studies about management of these disorders were categorized under subgroups of diabetes management. In addition, mental comorbidities were removed from comorbidity studies and were evaluated in a separate study.

After assignment, obtained documents in each group were categorized based on the study design, subject, WHO classification (23) and Australian National Health and Medical Research Council (NHMRC) criteria (24).

WHO criteria for research classify the studies to know whether research meet health needs and improve health outcomes or not(23)? NHMRC criteria are applied for definition of research area (24).

Table 1: Classification of comorbid conditions

Cluster of chronic diseases	Disease
Heart and vascular disease	Heart valve disease
	Atrial fibrillation / flutter
	Hypertension
	Varicose veins / venous insufficiency
	Congenital heart defects
Musculoskeletal	Connective tissue disease, Rheumatic disorders
	Osteoarthritis, back pain
	Osteoporosis
Eye & Ear	Pseudoexfoliation
	Chronic otitis media†
	Meniere disease†
Kidney	Urinary calculi / urinary tract stones
	Prostatic hyperplasia / hypertrophy†
	Transplantation
Respiratory	Asthma
	COPD (chronic obstructive pulmonary disease)
	Chronic sinusitis
	Bronchiectasis
Skin	Hidradenitis†
	Atopic dermatitis†
	Psoriasis
	Lichen planus
Digestive	Irritable bowel syndrome†
	Oesophageal disease†
	Stomach and Duodenal ulcer†
	Celiac Disease
	H. Pylori infection
	NAFLD (Non-alcoholic Fatty Liver Disease)
	Crohn's disease; ulcerative colitis
	Pancreatic disease; other†
	Hepatitis
Endocrine and metabolic	Thyroid disorders†
	Obesity, dyslipidemia
	PCOD
Neurological	MS (multiple sclerosis)
	Parkinson's disease
	Myasthenia Gravis
	Epilepsy
	Migraine
Blood(forming organs) and lymphatics	Anaemia including Pernicious anaemia, Thalassemia,
General and unspecified	Down syndrome / other specified congenital abnormalities
Infectious	Pulmonary tuberculosis†
	Syphilis, UTI, vulvovagnitis, opportunistic infectious disease
Malignancies	Any type of cancer in the body

After screening according to the mentioned method, 311 documents remained. The remaining publications were categorized as described above by topic and methodology.

Statistical Analysis
Collected data was analyzed using descriptive statistics and appropriate graphs were drawn.

Results

Iranian authors up to the Jan 2015 published 311 documents about diabetes comorbidities in national and international journals. Among these

documents, 13 (4.18%) were review articles, 24 (7.71%) were case reports and others were original articles (274 articles/ 88.10%).
Trend of publications about diabetes comorbidities was ascending with a rapid growth in the study period and reached peak at 2014 (Fig. 1). However, there were small falls in growth trend in some periods and we experienced negative growth in these points that the most severe one was in 2011 that returned to normal increasing growth trend in 2012. As the number of publications before 2000 was very small, they were not included in trend analysis.
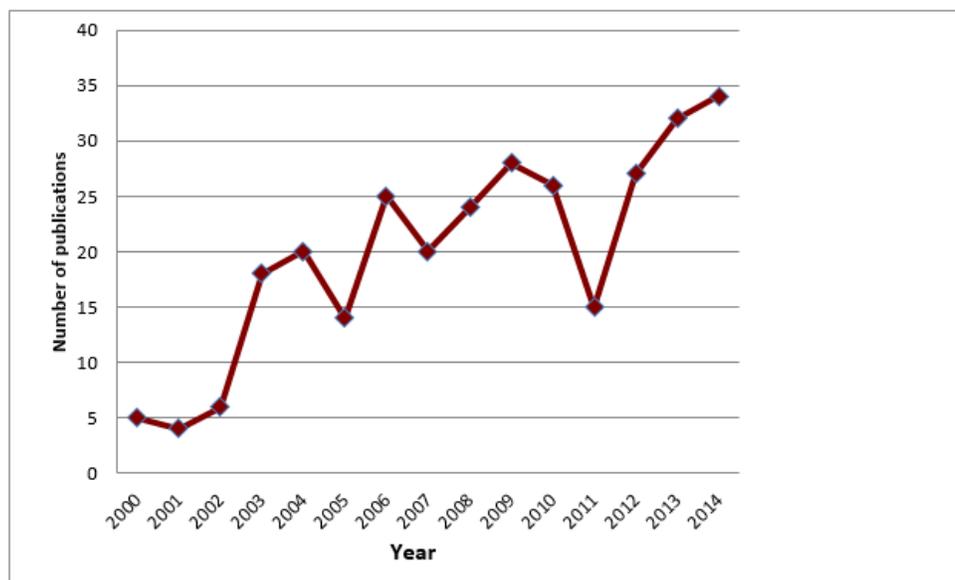

Fig. 1: Trends of publication in the field of diabetes comorbiditis from 2000 to 2015

According to WHO classification, most of studies (71%) were about epidemiology and causes of diabetes comorbidities while a small part of studies (13.50%) was about solutions and intervention and only about 2% of studies were about evaluation of interventions.
Considering NHMRC classification, clinical research was the most common type of studies (92.60%) followed by basic research (4.50%) and public health studies (0.32%). There was no health services research in the obtained studies.

Regarding the methodology, the most common design used in the obtained documents was cross-sectional followed by case-control and randomized clinical trials (RCT), respectively (Fig. 2). Only 10 cohort studies (3.21%) were found.
Comorbidities of diabetes were categorized based on the study subject (Fig. 3). Categorization of subjects has been shown in Table 1. The most common topic of obtained studies was related to endocrine (28.61%) followed by gastrointestinal (18.32%) and cardiovascular diseases (14.14%).
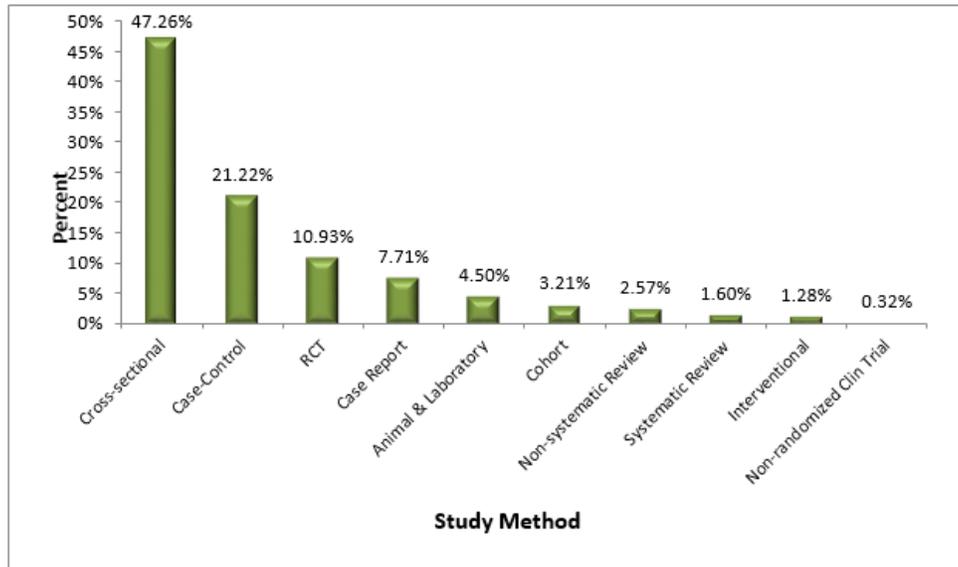
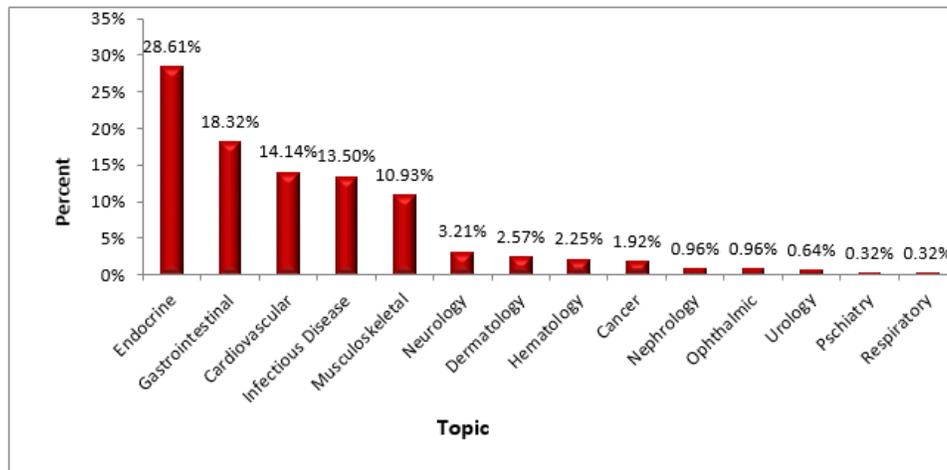**Fig. 2:** Frequency of different study design in the obtained documents

Fig. 3: Frequency of different study subjects among obtained results in diabetes comorbidity

The most frequent studies were endocrine comorbidities of diabetes including dyslipidemia, obesity, thyroid disorders and other endocrine disorders. Gastrointestinal and cardiovascular comorbidities of diabetes were in the second and third rank after endocrine comorbidities. Among endocrine comorbidities, dyslipidemia (30 documents/ 33.70%), thyroid disorders (23 studies/ 25.84%) and obesity (10 documents/ 11.23%) were the most common disorders, respectively.

The most common evaluated gastrointestinal comorbidity of diabetes was celiac disease (15 documents/ 26.31%) followed by helicobacter pylori infection (11 documents/19.28%), non-alcoholic fatty liver disease (NAFLD) (6 articles/10.52%) and hepatitis C infection (3 documents/ 5.26%).

The most common cardiovascular comorbidity studies were about hypertension (23 document/ 52.27%). Only six documents (1.92%) were

found regarding comorbid cancer incidence in diabetic patients.

Discussion

The study results showed growing trend in the number of publications about diabetes comorbidity in the study period. The most common methodology used in these studies was cross-sectional (level 4 evidence) followed by case-control (level 3 evidence) and RCT (level 1 evidence). The subject of most studies about diabetes comorbidity based on the study protocol (20) was endocrine (including dyslipidemia, thyroid disorders and obesity), gastrointestinal (including celiac disease, helicobacter pylori infection and NAFLD) and cardiovascular disease (including hypertension), respectively which among them dyslipidemia, hypertension, and celiac disease respectively were the most common disorders. Level of evidence in most of our studies in Iran is weak (level 4 and 3) and main part of studies is epidemiological studies about prevalence and incidence of diabetes comorbid conditions. In addition, more than 90% of studies were clinical research and there were few basic studies.

Any co-occurring condition with diabetes is considered as comorbidity. During more than 17 yr of follow-up, only 15.4% of the patients with diabetes had no chronic comorbidity. 70.6% of patients had at least one discordant comorbid disease at the time of diabetes diagnosis (22).

Some of these comorbid conditions are more common in diabetes. Cluster of co-existing hypertension-hyperlipidemia-obesity was the most common comorbid cluster in diabetic patients (25). The most common comorbid condition was hyperlipidemia (77%) followed by hypertension (65%) and obesity (49%). The prevalence of dyslipidemia, hypertension, and obesity have been reported 46%, 67%, and 61%, respectively in patients with diabetes in the US (26, 27).

Our study findings are to some extent compatible with the same frequency of above mentioned comorbid conditions with this difference that in our study, the frequency of studies about comorbid thyroid disorders was equal to hypertension studies and obesity was not in the next rank. Another difference is difference in categorization. In our study, comorbid conditions directly resulted from diabetes were categorized as diabetes complication (such as retinopathy) and other conditions were considered as comorbidity (such as arthritis). Hypertension (87.2%) and cardiovascular diseases (22.3%) were the most common comorbid conditions in diabetic patients (28).

Some of comobid conditions affect glycaemic control, and management of these comorbidities is required to obtain the goal of diabetes therapy.

Conclusion

There is a relatively appropriate epidemiological data about diabetes comorbidities in Iran and a proper picture of these comorbidities can be drawn. These types of studies should be limited and future studies should be more focused on other aspects of these common diabetes comorbidities by designing studies with higher level of evidence such as common pathophysiological pathways, HSR, RCTs and prospective studies.

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

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