BMJ Open

Low utilization despite affordability of diabetes medicines in Iran (2000-2012): a time-series and benchmarking study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005859
Article Type:	Research
Date Submitted by the Author:	04-Jun-2014
Complete List of Authors:	Sarayani, Amir; Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Rashidian, Arash; Tehran University of Medical Sciences, Gholami, Kheirollah; Research Center for Rational Use of Drugs and Faculty of Pharmacy, Tehran University of Medical Sciences,
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Diabetes and endocrinology, Health policy, Pharmacology and therapeutics
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, General diabetes < DIABETES & ENDOCRINOLOGY

Title:

Low utilization despite affordability of diabetes medicines in Iran (2000-2012): a time-series and benchmarking study

Authors:

Amir Sarayani PharmD, MPH

Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran

Arash Rashidian MD, PhD

Department of Health Management and Economics and Knowledge Utilization Research Center, Tehran University of Medical Sciences, Tehran, Iran

Kheirollah Gholami M.Sc., PharmD

Research Center for Rational Use of Drugs and Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Word Count: 3312

Abstract:

Objectives:

Diabetes is a major public health concern worldwide particularly in low- and middle-income countries (LMICs). Limited data exists on the status of access to diabetes medicines in LMICs. We assessed the utilization and affordability of diabetes medicines in Iran as a middle-income country.

Design:

We used a retrospective time-series design (2000-2012) and assessed national diabetes medicines utilization using pharmaceuticals wholesale data.

Methods:

We calculated defined daily dose consumptions per population days (DDDs/1000 inhabitants/day; DIDs) indicator. Findings were benchmarked with data from OECD countries. We also employed Drug Utilization-90% (DU-90) method to compare DU-90s with the World Health Organization recommendations. We measured affordability using numbers of daily wage required to purchase a monthly use of medicines.

Results:

Diabetes medicines' consumption increased from 4.47 to 33.54 DIDs. The benchmarking showed that medicines' utilization in Iran in 2011 were only 54% of the median DIDs of 22 OECD countries. Oral hypoglycemic agents consisted over 80% of use throughout the study period. Regular and NPH insulin, glibenclamide, metformin and gliclazide were the DU-90 drugs in 2012. Metformin, glibenclamide, and regular/NPH insulin combination therapy were affordable throughout the study period (~0.4, ~0.1, ~0.3 of daily wage, respectively). While the affordability of novel insulin preparations improved overtime, they were still unaffordable in 2012.

Conclusions:

The utilization of diabetes medicines was low, perhaps due to under-diagnosis and inadequate management of diabetic patients. This had occurred despite affordability of

essential diabetes medicines in Iran. Appropriate policies are required to address the under-utilization of diabetes medicines in Iran.

Keywords:

Drug utilization, diabetes, affordability, pharmaceutical policy, defined daily dose, access to medicines, essential medicines

Article Summary:

Strength and Limitations of this study:

- This is the first study to evaluate the pattern of utilization and affordability of diabetes drugs in a low or middle income country using WHO methodology.
- We used data from OECD countries to benchmark the inadequacy of diabetes medicines utilization in Iran, noting the differences in diabetes prevalence in the countries.
- Although the affordability of essential diabetes medicines is achieved in Iran, and despite the gradual increase in diabetes medicines usage, it remains substantially lower than what is needed for the estimated diabetic population.
- National wholesale data was used to estimate drug utilization. However, as a limitation, this data may not reflect the real drug consumption by the patients.

INTRODUCTION:

Diabetes is a major public health concern worldwide with an estimated global prevalence of 8.3% in 2011[1, 2], while approximately 80% of diabetic patients reside in low-income and middle-income countries.[2] Proper management of diabetes consists of interventions targeting patient's diet, exercise status, and prescribing medicines (insulin and oral hypoglycemic agents).[3] Currently, medicines are an essential part of diabetes management guidelines for most patients. Insulin would be commenced readily after diagnosis of type-1 diabetes and would be added to the therapeutic regimen of type-2 diabetes as required. In addition, oral hypoglycemic agents, e.g. metformin, are usually initiated alongside life-style modifications at diagnosis of type-2 diabetes.[4] Thus, appropriate utilization of diabetes medicines should be high on agenda for health policy makers.[5]

Previous studies have reported different utilization patterns of diabetes medicines in different countries.[6-8] For example, Melander et al (2004) analyzed data from ten European countries (1994-2003) and identified an increasing trend in diabetes medicines consumption.[6] They also observed large differences in utilization patterns among the countries, and concluded that these might have occurred due to the differences in diabetes screening and management patterns in those countries.[6] Few reports exist on affordability of medicines and the utilization patterns of diabetes medicines in low-income and middle-income countries where the burden of diabetes is believed to be more significant than high-income countries.[2, 9] Iran is an upper-middle-income country with a diabetes prevalence of 8.7% among adult population in 2007, of which over 45% were undiagnosed cases.[10] Still, very few reports exist on the utilization patterns of diabetes medicines in order to show the current situation of diabetes pharmacotherapy in the country.

Health and pharmaceutical system in Iran

Health care system in Iran is primarily based on a government funded primary health care system and social health insurance plans that facilitate access to secondary and tertiary care. Private sector is the main provider of ambulatory care in urban areas.[11] In 2010 social health care insurance covered 84% of the population.[12] Insurance organizations reimbursement policies for medicines follow a general rule: covering 90% of inpatient and 70% of outpatient costs if the provider has a contract with the insurance organization.[13] Almost all community and hospital pharmacies have contracts with major insurance organizations and the lowest-priced generic product is usually set for reimbursement purposes. This means that the users might pay more than the 10% (inpatient care) or 30% (outpatient care) expected copayments at the time of use. Hence, major concerns exist among health policy makers regarding out of pocket expenditures for health services[14]. Still, it has been argued that adequate affordability of medicines has been achieved in Iran.[15, 16] Implementation of a generic-based pharmaceutical policy including a highly-regulated National Drug List and medicines pricing systems may have contributed to the assumed adequacy of access to medicines in Iran.[17, 18] Since 2001, international companies (brand or generic products) become more involved in the local pharmaceutical market and the market size expanded from 661 million USD in 2003 (of which 20.5% were imported products) to over 2.3 billion USD in 2008 (of which 33.6% were imported products).[17] It is estimated that the pharmaceutical market size in Iran would be 3.65 billion USD in 2013.[19]

Objectives

In the present study, we evaluated the trends of diabetes medicines utilization in Iran during 2000-2012 using national pharmaceuticals wholesale data. We benchmarked our findings with available international data on diabetes medicines use. Finally, the trend of diabetes medicines affordability in Iran was evaluated as a potential determinant of medicines utilization.

METHODS:

Design:

A retrospective time-series design was used to investigate the trends of utilization and affordability for diabetes medicines in Iran (2000-2012). We benchmarked the rate of drug utilization with the most recent available data from 22 countries in 2011.

National data sources:

Annual wholesale data was obtained from Iran's Food and Drug Organization. The data is produced based on the sales' reports of wholesale companies to community and inpatient pharmacies all over the country and is available as an electronic medium from 2000 onwards. Each pharmaceutical product (medicinal dosage forms) is identified with a generic name and a unique code in the database and can be linked to the manufacturer or import company, the wholesale company, the number of sold items, and their total retail price. Diabetes medicines available on the market during the study period were identified based on the National Drug List and consultation with experts. Several examinations were carried out to assess quality of the data. Generic codes were set as the main standard for accuracy examination. We looked for discrepancies in recorded generic - or brand-generic codes, dosage forms, producer/importer and wholesale companies' data. To standardize pharmaceutical consumption data per inhabitant, we obtained annual population figures from the Statistics Center of Iran.

International data source:

We collected data on diabetes medicines utilization in 22 countries of the Organization for Economic Co-operation and Development-(OECD) via the Health Data: Pharmaceutical market database.

Evaluating Utilization Pattern in Iran:

The Anatomical Therapeutic Classification/Defined Daily Dose (ATC/DDD) methodology was used to standardize the raw sales data. The latest version of the ATC/DDD guideline (2013) was retrieved from the website of WHO Collaborating Centre for Drug Statistics Methodology.[20] In the present study, the ATC codes of A10 group were used to standardize diabetes medicines. We used 2nd (all diabetes medicines), 3rd (insulin or oral hypoglycemic agents) and 5th (individual pharmaceutical substance) level of ATC classification for each data line recorded in the dataset and the DDD quantities were entered respectively. To calculate the number of DDDs per 1000 inhabitants per day (DID), the following formula was used: (Number of DDDs*1000) / (Number of Population*365).[6] We summarized the annual drug utilization data for different ATC levels and calculated the utilization growth rates. Annual share of utilization for oral hypoglycemic agents and insulin were calculated. Regression models were used to confirm the trend of utilization over time.

Drug Utilization-90% (DU-90) methodology was used to compare national A10 utilization with the recommendations of World Health Organization (WHO).[21] ATC codes which consisted 90% of total consumed DDDs in oral anti-diabetic agents (A10B) and insulin preparations (A10A) categories were identified. The DU-90 list was compared with the WHO Essential Medicines List (18th edition, 2013). [22]

Benchmarking utilization patterns:

We compared the A10 consumption data for 22 OECD countries in 2011 with Iran's corresponding figures. We then selected a subgroup of OCED countries that has a diabetes

prevalence of 8-10% (according to the International Diabetes Federation 2012 report [23]), which is comparable to Iran. These countries were Australia, Finland, Estonia, Germany and Spain. We compared 2000-2011 trends of A10 utilization in Iran with these countries.

Evaluating Affordability:

Affordability was operationalized as the number of daily wage to cover the monthly cost of each medicine or a treatment protocol.[24]

We calculated the affordability of each oral hypoglycemic agent separately using the cost of a hypothetical monthly treatment (30 DDDs).

For insulins, we calculated affordability for a hypothetical monthly treatment (30 DDDs) of commonly used insulin therapy combinations (NPH and regular, premixed NPH and regular, aspart and glargine, and premixed aspart). Different insulins had different prices and their prices were varied in different years. Hence we calculated the price of each insulin combination therapy DDD (40 IU) in each year based on the proportions of annual insulin consumption in that year. As an example, for NPH and regular therapy combination, if NPH and regular insulin consumption accounted for 65 and 35 per cent of the total consumption of NPH and regular in a defined year, one DDD cost of this therapy combination was calculated as 0.65 of one DDD of NPH plus 0.35 of one DDD of regular insulin for that year.

We used the minimum daily wage defined by the Social Security Organization of Iran in each year to calculate the affordability indicators. If the monthly cost of a medicine or therapy combination was less than one daily wage, it was considered as affordable.[16]

Results:

Diabetes medicines (A10) consumption increased during the study period from 4.47 to 33.54 DID. However, the margin of annual growth varied widely from 34.6% in 2001 to 3.7% in 2012 and we observed a single negative growth rate of 15.4% in 2002. The increasing trend was detected for both A10A (insulins and analogues) and A10B (blood glucose lowering drugs, excl. insulins) categories. Nevertheless, A10B share of total A10 utilization in DDDs was consistently over 80% throughout the study period. Fig. 1 illustrates the trends of A10, A10A, and A10B utilizations.

During the first seven years, the only available drugs from A10A subgroup were NPH (A10AB02 and A10AB02), regular (A10AC01 and A10AC02) and mixed insulin (A10AD01) products. The beef-origin products were removed from the market in 2005. Novel insulin analogues were introduced to the market after 2007: insulin aspart (A10AB05) and insulin glargine (A10AE04) in 2007 and mixed aspart (A10AD05) in 2009. In the final year of study (2012), total utilization of the novel preparations was less than 0.3 DID while 5.73 DID of NPH and regular insulins were consumed. Table 1 illustrates a summary of utilization figures for A10A drugs.

In A10B subgroup, total amount of utilization increased from 6.32 to 27.5 DID and a relatively consistent growth was observed during the 12-years period. There were only three medicines available on the market during the first three years: glibenclamide (A10BB02), chlorpropamide (A10BB02) and metformin (A10BA02) while over 90% of A10B utilization was due to glibenclamide use. Utilization of metformin raised dramatically from 0.34 to 9.35 DID (27.5-fold) while glibenclamide use increased by 2.7-fold throughout the study period. In 2012, metformin comprised 33.9% of A10B utilization while glibenclamide

share had decreased to 55.2%. New oral hypoglycemic agents gradually entered the market, starting with gliclazide (A10BB09) and acarbose (A10BF01) in 2003 while chlorpropamide was removed from the market in 2004. Gliclazide, repaglinide (A10BX02) and pioglitazone (A10BG03) (that entered the market in 2006) were among new oral agents to show the highest rates of utilization growth. However, a dramatic decline in gliclazide utilization was observed in 2012. Table 2 shows a summary of utilization figures for A10B drugs.

Over the study period, DU-90 drugs were identified for A10A and A10B subgroups. Regular and NPH insulin (beef or human origin) were in the list for A10A. Glibenclamide and metformin constituted the list for A10B until 2010 and gliclazide appeared in the list in the last two years. The WHO list of Essential Medicines (2013) includes regular and NPH insulins, glibenclamide, gliclazide, and metformin from A10 group, all appearing on Iran's DU-90 lists (Fig. 2).

Benchmarking with OECD countries showed that Iran had a low A10 utilization in 2011 (Fig. 3). The prevalence of diabetes in Australia, Finland, Germany, Spain and Estonia were similar to Iran in 2011 (8-10%). The utilization of A10 medicines increased in all of these countries from 2000 to 2011 but the magnitude of growth was highest in Iran (430.7%). Nevertheless, the annual A10 utilization in Iran was consistently and substantially lower than those five countries during the benchmarking period (Fig. 4).

Treatment with metformin, glibenclamide or even the combination therapy has been consistently affordable over the study period and the combination therapy cost approximately half a daily wage in 2012. Newer A10B agents became relatively more affordable after their initial introduction into the market and the cost of treatment with

gliclazide, repaglinide or pioglitazone was affordable in 2012 (0.1, 0.5, and 0.6 of daily wage, respectively).

Treatment with regular and NPH insulin was consistently affordable during the study period (0.1-0.6 daily wage) but premixed insulins only became affordable during the last three years. Treatment with novel insulin preparations including premixed aspart insulin and aspart/glargine combination has never been affordable since their presence on the market. In 2012, treatment with premixed aspart insulin cost 4.8 daily wages and combination therapy with aspart and glargine insulins required 5.8 daily wage. Fig. 5 and 6 illustrate the pattern of diabetes medicines affordability over the study period.

Discussion:

Our findings showed that A10 utilization increased approximately 7-fold over a 13-years period (2000-2012) from 4.47 to 33.54 DID. The growth of diabetes prevalence may explain the rise of A10 utilization to some extent. A longitudinal study on the prevalence of diabetes in Iran reported that diabetes rate among Iranian adults increased approximately by twofold during 1999-2007 period.[25] In addition to the rise of diabetes prevalence, the evidence on the efficiency of diabetes intensive management and the essential role of metformin should be considered as important underlying factors in the upsurge of A10 utilization during the last decade.[5, 26]

Insulin preparations (A10A) seem to be under-utilized in comparison to the oral hypoglycemic agents (A10B) during the study period. In 2012, insulin utilization only comprised 17% of total A10 consumption. A report from 10 European countries showed that share of insulin utilization in 2003 was over 30% in nine countries and the data from Sweden, Norway, Germany, Denmark, and England revealed similar figures at above 40%.[6] It should be noted that some guidelines recommend early use of insulin for the management of type-2 diabetes.[3] Thus, we consider under-utilization of insulins a salient signal of irrational A10 use in Iran. A few studies have reported inadequacy of physicians' knowledge about clinical guidelines and also patients' concerns about insulin injection in Iran.[27-29] Although further research is required to expand our knowledge of insulin under-utilization factors, effective educational interventions could be recommended to improve health care professionals' and patients' attitudes and behavior toward appropriate and timely use of insulin for diabetes management.[30, 31]

Pattern of A10B utilization revealed a few important issues. Glibenclamide has been used for several decades in Iran and comprised the highest share of utilization during the study period. This medication was recommended by WHO as an essential medicine until 2013; however, the latest WHO list of essential medicines recommends gliclazide particularly for elderly patients to avoid hypoglycemia side effect.[22] Despite a rapid growth in gliclazide utilization and its appearance on the DU-90 list from 2011, policies and educational intervention are necessary to modify local pharmaceuticals production and also physicians' prescribing behavior. The negative growth rate for gliclazide utilization in 2012 requires further elaboration. During this year, drug shortages were quite common in the country due to sanctions on Iran financial and trading system which significantly affected drug import and local production.[32, 33] Metformin use increased significantly during the study period; however, off-label uses including weight loss or polycystic ovary syndrome may result in overestimation of diabetes-related utilization but their contribution seems to be small.

In comparison to the OECD countries, A10 utilization appears to be inadequate in Iran. One of the main reasons might be the high rate of undiagnosed diabetes.[10] OECD data is based on information provided by the authorities in each country. Some countries provide use wholesale data while others use prescription databases. They may also differ in collecting over-the-counter, hospital and non-reimbursed drug use data. However, drug utilization data from Czech Republic, Denmark, Estonia, Finland, Slovak Republic, and Sweden reported wholesale data which was similar to our data source from Iran in the present study.[34]

As expected, the analyses demonstrated that most A10 medicines were affordable during the study period. It seems that the main factor on the affordability of the medicines, were the pricing system in Iran for generic medicines. Medicines prices are highly regulated in

Iran by the Pricing Committee, Food and Drug Organization. The decline pattern in the "number of days' wages" for some of the newer A10 drugs can be justified by the fact that local production usually begins some years after a pharmaceutical entity is registered and imported. New products (oral agents or insulin) remained unaffordable until their retail price dramatically reduced.

It should be noted that we did not consider the effect of insurance coverage on the treatment cost and also did not included cost of syringes required for insulin injections. Still gradual increases in the population coverage of the insurance organizations from 74% in 2002 to 83% in 2010 may have contributed to better access.[12] As our findings showed, little concern may exist regarding the affordability of conventional insulin preparations; however, use of novel preparations and pen injectors may be limited by the treatment cost. In 2013 the new glargine and aspart insulins were added to the insurers benefit package, albeit with a higher copayment rate due to a reference pricing approach, which may result in better access to these medicines in future. Future studies should evaluate the share of insurance plans in providing access to A10 medicines in Iran.

Limitations: We used "consumption" and "utilization" terms interchangeably throughout the article. Nevertheless, it should be emphasized that our study was conducted based on wholesale data and our findings must be interpreted according to data limitations, e.g. expired medicines in pharmacies or uncertainty about drug taking behavior of patients. In a recent review, we reported that 62-87% of Iranian diabetic patients were adherent to their diabetes medicines.[35] Thus, the real A10 consumption might be lower than the findings based on wholesale data; however, insufficient adherence to diabetes medication is

reported to be a global problem[36] and may not introduce a major bias in benchmarking studies.

In conclusion, use of diabetes medicines has increased during a thirteen-year period in Iran as a middle-income country; nevertheless, the utilization does not seem to be adequate due to high rate of undiagnosed patients and inappropriate management of diagnosed cases. Although the affordability of essential diabetes medicines is achieved, optimizing the pattern of medicines use, e.g. underutilization of insulin and overutilization of glibenclamide, should be on agenda for health policy makers. Improving better access to effective novel products (such gliclazide and pen insulins) should be a major consideration for decision makers.

Funding:

This study was supported by a research grant from Deputy of Research, Tehran University of Medical Science and the Research Center for Rational Use of Drugs. (Grant number: 92-01-156-22298)

Competing Interests:

We have no conflict of interests to declare.

Contributorship Statement

AS developed the research proposal, extracted and analyzed the data. He contributed to interpretation of findings and drafted the manuscript.

AR contributed to proposal development, data analysis, results interpretation and major revision of the draft.

KG contributed to proposal development, data acquisition and extraction, results interpretation, and minor revision of the manuscript.

Data Sharing Statement:

Data might be available to the interested researchers upon request from the authors

Reference:

1. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. The Lancet 2011;**378**(9785):31-40
2. Whiting DR, Guariguata L, Weil C, et al. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;**94**(3):311-21
3. Alldredge BK, Corelli RL, Ernst ME, et al. *Koda-Kimble & Young's Applied Therapeutics; The Clinical use of Drug*. 10 ed: Lippincott Williams & Wilkins, 2012.
4. Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;**32**(1):193-203 [doi: 10.2337/dc08-9025published Online First: Epub Date].
5. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;**321**(7258):405-12
6. Melander A, Folino-Gallo P, Walley T, et al. Utilisation of antihyperglycaemic drugs in ten European countries: different developments and different levels. Diabetologia 2006;**49**(9):2024-29 [doi: 10.1007/s00125-006-0331-3published Online First: Epub Date].
7. Doró P, Benkő R, Kosik E, et al. Utilization of oral antihyperglycemic drugs over a 7–year period (1998–2004) in a Hungarian population and adherence to drug therapy. Eur J Clin Pharmacol 2005;**61**(12):893-97 [doi: 10.1007/s00228-005-0031-9published Online First: Epub Date].
8. Baviera M, Monesi L, Marzona I, et al. Trends in drug prescriptions to diabetic patients from 2000 to 2008 in Italy's Lombardy Region: A large population-based study. Diabetes Res Clin Pract 2011;**93**(1):123-30 [doi: http://dx.doi.org/10.1016/j.diabres.2011.05.004published Online First: Epub Date].
9. Rashidian A, Jahanmehr N, Jabbour S, et al. Bibliographic review of research publications on access to and use of medicines in low-income and middle-income countries in the Eastern Mediterranean Region: identifying the research gaps. BMJ open 2013;**3**(10):e003332
10. Esteghamati A, Meysamie A, Khalilzadeh O, et al. Third national surveillance of risk factors of non-communicable diseases (SuRFNCD-2007) in Iran: methods and results on prevalence of diabetes, hypertension, obesity, central obesity, and dyslipidemia. BMC Public Health 2009;**9**(1):167 [doi: 10.1186/1471-2458-9-167published Online First: Epub Date].
11. Oliaimanesh A, Abolhallaj M, Zangeneh M, et al. National Health Accounts Islamic Republic of Iran-2008. Tehran: National Institue of Health Research, Ministry of Health and Medical Education, 2013.
12. Rashidian A, Khosravi A, Khabiri R, et al. Islamic Republic of Iran's Multiple Indicator Demographic and Health Survey (IrMIDHS)-2010. Tehran: National Institue of Health Research, Ministry of Health and Medical Education, 2012.
13. Davari M, Haycox A, Walley T. The Iranian Health Insurance System; Past Experiences, Present Challenges And Future Strategies. Iranian J Publ Health 2012;**41**(9):1-9

14. Kavosi Z, Rashidian A, Pourreza A, et al. Inequality in household catastrophic health care expenditure in a low-income society of Iran. Health Policy Plan 2012;**27**(7):613-23 [doi: 10.1093/heapol/czs001published Online First: Epub Date].
15. Cheraghali AM, Nikfar S, Behmanesh Y, et al. Evaluation of availability, accessibility and prescribing pattern of medicines in the Islamic Republic of Iran. Eastern Mediterranean health journal 2004;**10**(3):406-15
16. Abdollahiasl A. Medicine prices, availability, affordability and price components-Iran. Medicine prices and access to medicines in the Eastern Mediterranean Region. Cairo, Egypt: Essential Medicines and Pharmaceutical Policies Unit, World Health Organization, Regional Office for the Eastern Mediterranean, 2010.
17. Dinarvand R. New National Drug Policy in Iran leading to Expanded Pharmaceutical Market and Extended Access of Public to Medicines. Iranian journal of public health 2009;**38**(Suppl. 1):158-61
18. Davari M, Walley T, Haycox A. Pharmaceutical Policy and Market in Iran: past experiences and future challenges. Journal of Pharmaceutical Health Services Research 2011;**2**(1):47-52
19. Iran Pharmaceuticals & Healthcare Report Q2 2009. London, UK: BUSINESS MONITOR INTERNATIONAL.
20. Guidelines for ATC classification and DDD assignment. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, 2013.
21. Wettermark B, Pehrsson Å, Jinnerot D, et al. Drug utilisation 90% profiles—a useful tool for quality assessment of prescribing in primary health care in Stockholm. Pharmacoepidemiol Drug Saf 2003;**12**(6):499-510
22. WHO Model List of Essential Medicines: World Health Organization, 2013.
23. International Diabetes Federation-DIABETES ATLAS UPDATE 2012. Secondary International Diabetes Federation-DIABETES ATLAS UPDATE 2012 2012. http://www.idf.org/diabetesatlas/5e/Update2012.
24. Cameron A, Ewen M, Ross-Degnan D, et al. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. The Lancet;**373**(9659):240-49 [doi: http://dx.doi.org/10.1016/S0140-6736(08)61762-6published Online First: Epub Date].
25. Esteghamati A, Ashraf H, Khalilzadeh O, et al. Trends of diabetes according to body mass index levels in Iran: results of the national Surveys of Risk Factors of Non-Communicable Diseases (1999–2007). Diabet Med 2010;**27**(11):1233-40 [doi: 10.1111/j.1464-5491.2010.03103.xpublished Online First: Epub Date].
26. UKPDS. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ: British Medical Journal 1998:703-13
27. Peimani M, Tabatabaei-Malazy O, Heshmat R, et al. Knowledge, attitude and practice of physicians in the field of diabetes and its complications: A pilot study. Iran J Diabetes and Lipid Disord 2010;**9**:1-7
28. Shakibazadeh E, Larijani B, Shojaeezadeh D, et al. Patients' Perspectives on Factors that Influence Diabetes Self-Care. Iranian journal of public health 2011;**40**(4):146-58
29. Mounesan L, Nedjat S, Majdzadeh R, et al. Only One Third of Tehran's Physicians are Familiar with 'Evidence-Based Clinical Guidelines'. Int J Prev Med 2013;**4**(3):349-57
30. Sarayani A, Rashidian A, Gholami K, et al. Efficacy of continuing education in improving pharmacists' competencies for providing weight management service: Three-arm

randomized controlled trial. J Contin Educ Health Prof 2012;**32**(3):163-73 [doi: 10.1002/chp.21141published Online First: Epub Date].
31. Forsetlund L, Bjørndal A, Rashidian A, et al. Continuing education meetings and workshops: effects on professional practice and health care outcomes. Cochrane Database Syst Rev 2009;**2**(2)
32. Cheraghali AM. Impacts of international sanctions on Iranian pharmaceutical market. Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences 2013;**21**(1):64 [doi: 10.1186/2008-2231-21-64published Online First: Epub Date].
33. Butler D. Iran hit by drug shortage. Nature 2013;**504**(7478):15-6 [doi: 10.1038/504015apublished Online First: Epub Date].
34. OECD Health Data 2013 Definitions, Sources and Methods: Pharmaceutical consumption by DDDs: OECD Health Data 2013; http://www.oecd.org/health/healthdata.
35. Sarayani A, Jahangard-Rafsanjani Z, Hadjibabaie M, et al. A comprehensive review of adherence to diabetes and cardiovascular medications in Iran; implications for practice and research. Journal of Diabetes & Metabolic Disorders 2013;**12**(1):57
36. Cramer JA. A Systematic Review of Adherence With Medications for Diabetes. Diabetes Care 2004;**27**(5):1218-24 [doi: 10.2337/diacare.27.5.1218published Online First: Epub Date].

Table 1- Number of DDDs per 1000 inhabitants per day (DID) for A10A (Insulins and analogues) medicines

ATC code	2000/ 2001	2001/ 2002	2002/ 2003	2003/ 2004	2004/ 2005	2005/ 2006	2006/ 2007	2007/ 2008	2008/ 2009	2009/ 2010	2010/ 2011	2011/ 2012	2012/ 2013
A10AC01 (insulin (human))	0.64	0.93	1.10	1.36	1.48	1.77	1.87	2.49	2.22	2.79	3.09	3.36	3.52
A10AB01 (insulin (human))	0.16	0.20	0.31	0.42	0.50	0.63	0.72	0.93	1.00	1.15	1.32	1.80	1.91
A10AD01 (insulin (human))	<0.01	<0.01	<0.01	<0.01	<0.01	-	-	-	0.04	0.03	0.16	0.26	0.30
A10AE04 (insulin glargine)	-	-	-	-	-	-	-	<0.01	0.02	0.02	0.01	0.03	0.13
A10AD05 (insulin aspart)	-	-	-	-	-	-	-	-	-	0.03	0.07	0.09	0.11
A10AB05 (insulin aspart)	-	-	-	-	-	-	-	<0.01	0.01	0.00	0.01	0.03	0.05
A10AB04 (insulin lispro)	-	-	-	-	-	-	-	-	-	-	-	-	<0.01
A10AB02 (insulin (beef))	0.07	0.05	0.05	0.03	0.01	-	-	-	-	-	-	-	-
A10AC02 (insulin (beef))	0.29	0.14	0.21	0.09	0.03	-	-	-	-	-	-	-	-

Table 2- Number of DDDs per 1000 inhabitants per day (DID) for A10B (Blood glucose lowering drugs, excl. insulins) medicines

	2000/ 2001	2001/ 2002	2002/ 2003	2003/ 2004	2004/ 2005	2005/ 2006	2006/ 2007	2007/ 2008	2008/ 2009	2009/ 2010	2010/ 2011	2011/ 2012	2012/ 2013
A10BB01 (glibenclamide)	5.69	8.01	5.86	7.31	8.69	9.55	11.33	10.88	12.68	12.06	13.29	15.40	15.18
A10BA02 (metformin)	0.34	0.62	0.88	1.31	1.63	2.19	3.01	3.46	4.41	5.52	5.94	8.58	9.35
A10BB09 (gliclazide)	-	-	-	<0.01	0.06	0.14	0.23	0.44	0.59	0.74	0.88	1.31	1.13
A10BG0 (pioglitazone)	-	-	-	-	-	-	0.01	0.11	0.27	0.45	0.68	0.94	1.10
A10BX02 (repaglinide)	-	-	-	-	-	-	0.02	0.03	0.04	0.06	0.15	0.31	0.48
A10BF01 (acarbose)	-	-	-	<0.01	<0.01	<0.01	0.03	0.07	0.13	0.14	0.16	0.24	0.26
A10BD02 (metformin and sulfonamides)	-	-	-	-	-	-	-	-	-	-	-	0.01	0.03
A10BD05 (metformin and pioglitazone)	-	-	-	-	-	-	-	-	-	-	-	-	<0.01
A10BD07 (metformin and sitagliptin)	-	-	-	-	-	-	-	-	-	-	-	<0.01	<0.01
A10BB02 (chlorpropamide)	0.29	0.12	0.11	0.09	<0.01	-	-	-	-	-	-	-	-

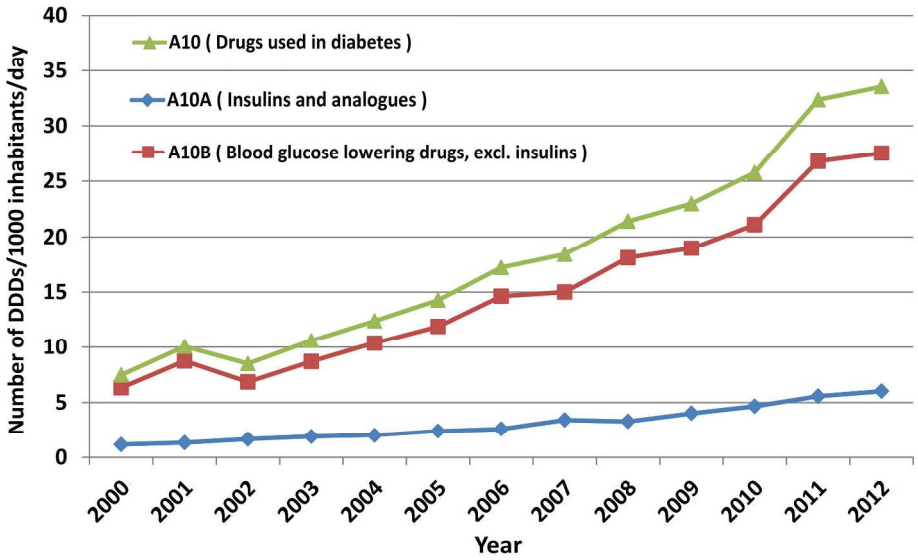

Figure 1- Utilization Pattern of Diabetes Medicines (A10) in Iran

256x166mm (300 x 300 DPI)

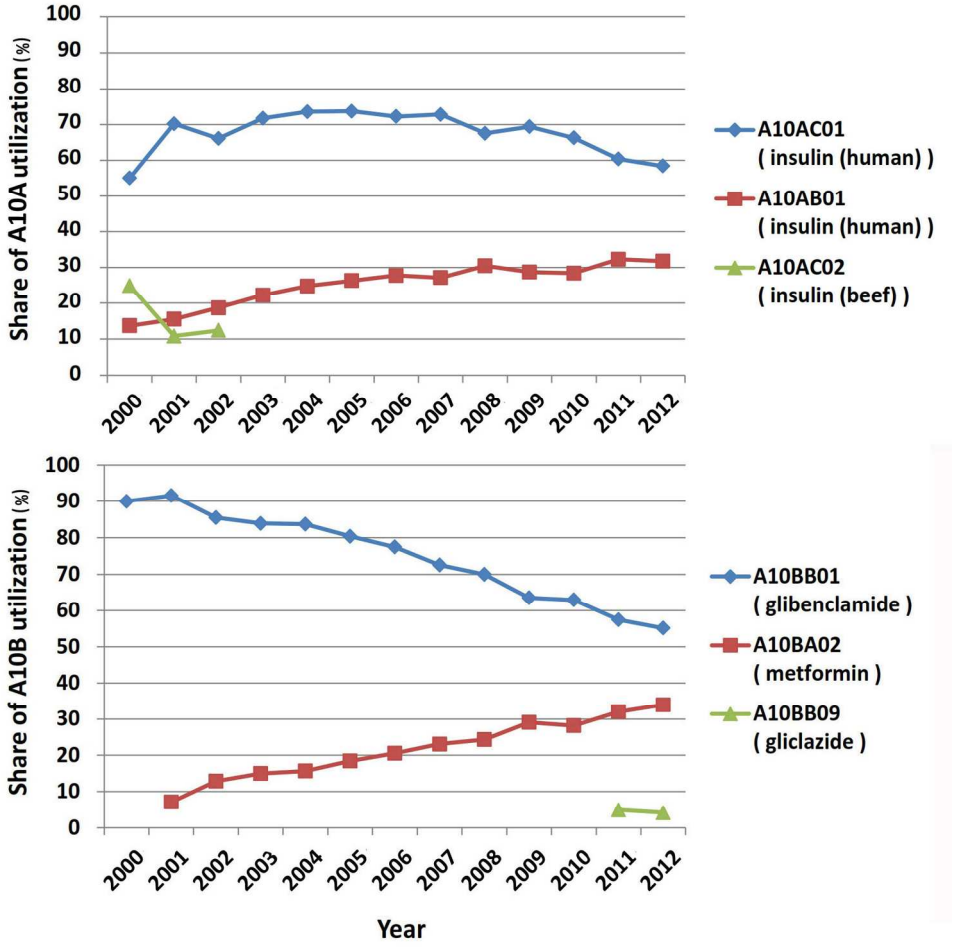

Figure 2- Pattern of Drug Utilization-90% for Diabetes medicines in Iran

154x158mm (300 x 300 DPI)

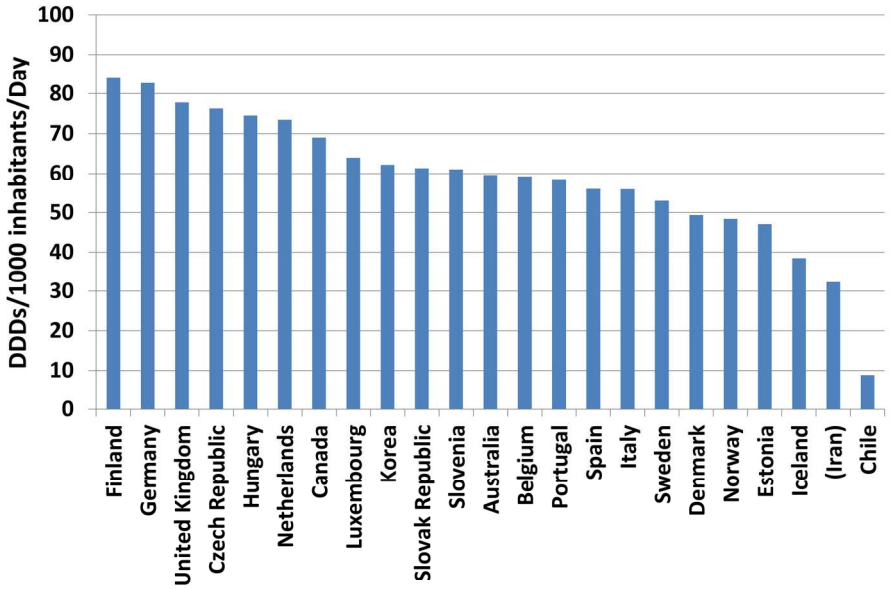

Figure 3- Benchmarking Diabetes Drugs Utilization in Iran with OECD Countries (2011)

170x119mm (300 x 300 DPI)

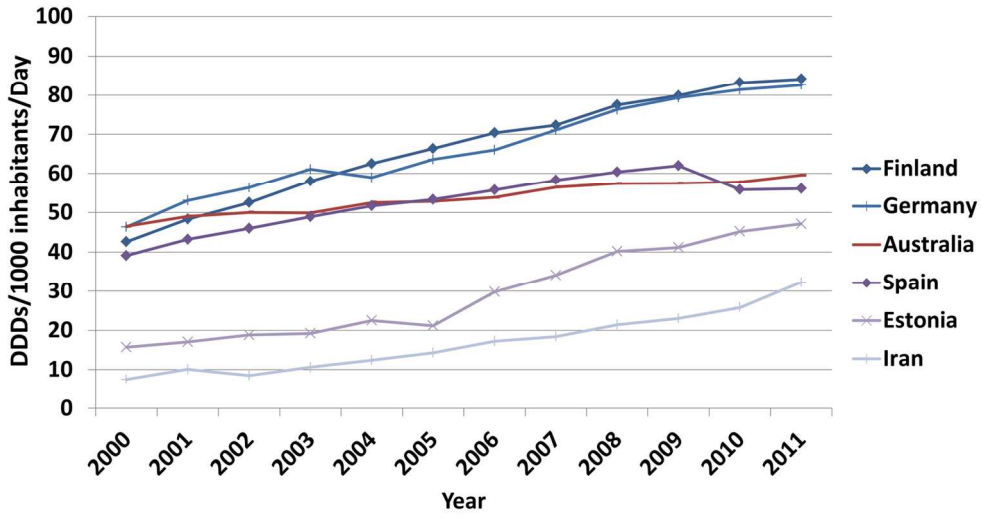

Figure 4- Benchmarking the Trend of Diabetes Drugs Utilization
(Iran and OECD countries with comparable diabetes prevalence according to IDF statistics)

144x86mm (300 x 300 DPI)

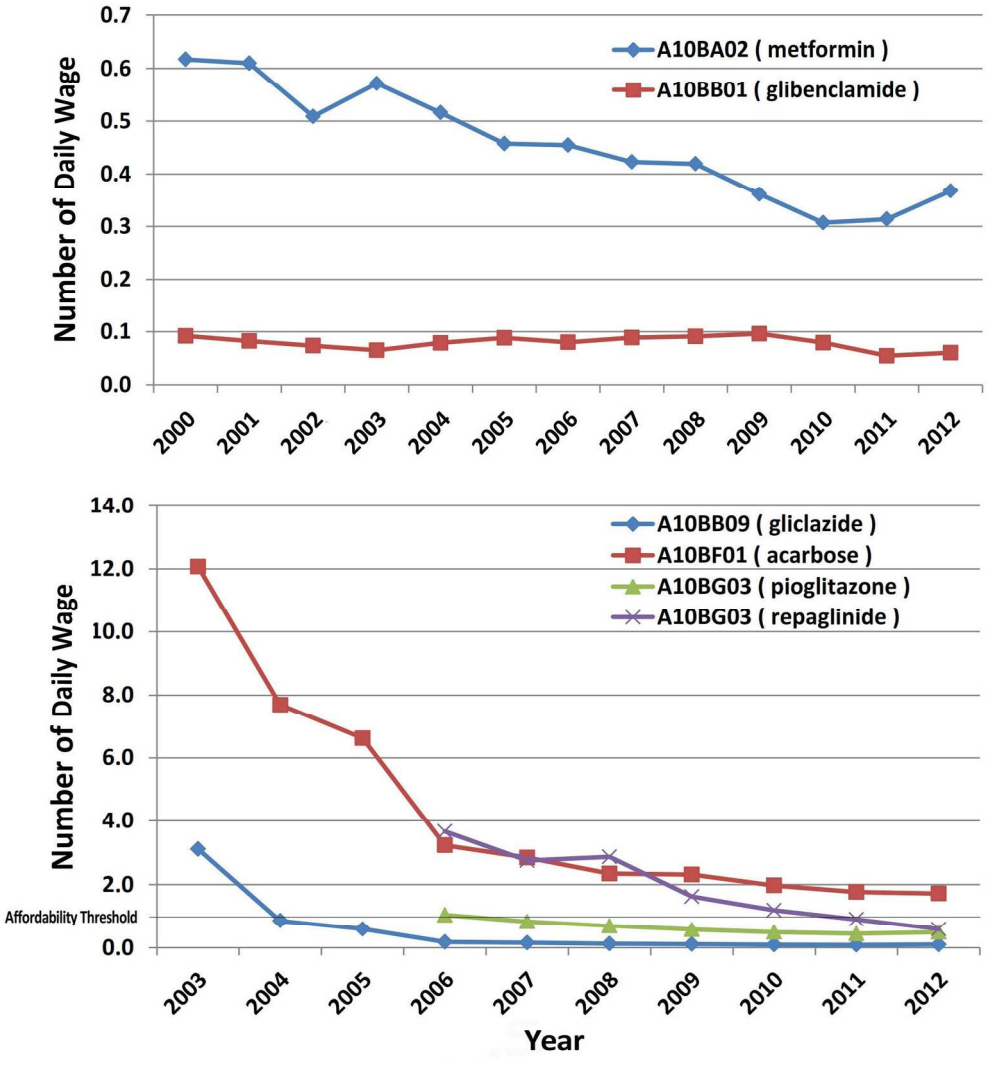

Figure 5- Affordability of Oral Hypoglycemic Agents in Iran

171x198mm (300 x 300 DPI)

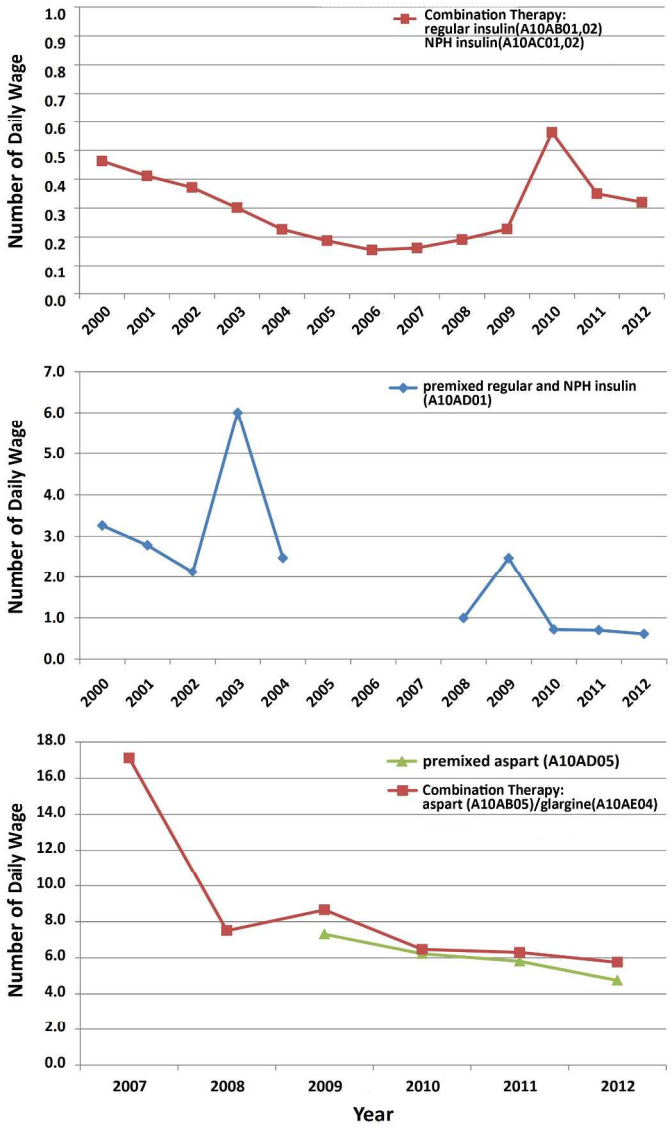

Figure 6- Affordability of Insulin preparations in Iran

178x304mm (300 x 300 DPI)

BMJ Open

Low utilization of diabetes medicines in Iran, despite their affordability (2000-2012): a time-series and benchmarking study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005859.R1
Article Type:	Research
Date Submitted by the Author:	19-Aug-2014
Complete List of Authors:	Sarayani, Amir; Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Rashidian, Arash; Tehran University of Medical Sciences, Gholami, Kheirollah; Research Center for Rational Use of Drugs and Faculty of Pharmacy, Tehran University of Medical Sciences,
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Diabetes and endocrinology, Health policy, Pharmacology and therapeutics
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, General diabetes < DIABETES & ENDOCRINOLOGY

Title:

Low utilization of diabetes medicines in Iran, despite their affordability (2000-2012): a time-series and benchmarking study

Authors:

Amir Sarayani PharmD, MPH

Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran

Arash Rashidian MD, PhD*

Department of Health Management and Economics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

Knowledge Utilization Research Center, Tehran University of Medical Sciences, Tehran, Iran

Kheirollah Gholami M.Sc., PharmD

Research Center for Rational Use of Drugs and Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

* Corresponding author.

Word Count: 3086

Keywords:

Drug utilization, diabetes, affordability, pharmaceutical policy, defined daily dose, access to medicines, essential medicines

Abstract:

Objectives:

Diabetes is a major public health concern worldwide, particularly in low- and middle-income countries (LMICs). Limited data exists on the status of access to diabetes medicines in LMICs. We assessed the utilization and affordability of diabetes medicines in Iran as a middle-income country.

Design:

We used a retrospective time-series design (2000-2012) and assessed national diabetes medicines' utilization using pharmaceuticals wholesale data.

Methods:

We calculated defined daily dose consumptions per population days (DDDs/1000 inhabitants/day; DIDs) indicator. Findings were benchmarked with data from OECD countries. We also employed Drug Utilization-90% (DU-90) method to compare DU-90s with the Essential Medicines list published by the World Health Organization. We measured affordability using number of minimum daily wage required to purchase a treatment course for one month.

Results:

Diabetes medicines' consumption increased from 4.47 to 33.54 DIDs. The benchmarking showed that medicines' utilization in Iran in 2011 was only 54% of the median DIDs of 22 OECD countries. Oral hypoglycemic agents consisted over 80% of use throughout the study period. Regular and NPH insulin, glibenclamide, metformin and gliclazide were the DU-90 drugs in 2012. Metformin, glibenclamide, and regular/NPH insulin combination therapy were affordable throughout the study period (~0.4, ~0.1, ~0.3 of minimum daily wage, respectively). While the affordability of novel insulin preparations improved over time, they were still unaffordable in 2012.

Conclusions:

The utilization of diabetes medicines was relatively low, perhaps due to under-diagnosis and inadequate management of diabetic patients. This had occurred despite affordability of essential diabetes medicines in Iran. Appropriate policies are required to address the under-utilization of diabetes medicines in Iran.

Article Summary:

Strength and Limitations of this study:

- To the best of our knowledge, this is the first study to evaluate the pattern of utilization and affordability of diabetes drugs in a low or middle income country over a period of time.
- We used data from OECD countries to assess the adequacy of utilization in Iran.
- Our findings showed that utilization of diabetes drugs does not seem to be adequate. Although the affordability of essential diabetes medicines is achieved, optimizing the pattern of use requires screening for undiagnosed patients and improving management of diagnosed cases.
- National wholesale data was used to estimate drug utilization; however, this data may not reflect the real drug consumption by patients.

INTRODUCTION:

Diabetes is a major public health concern worldwide, with an estimated global prevalence of 8.3% in 2011[1, 2], while approximately 80% of diabetic patients reside in low-income and middle-income countries.[2] Proper management of diabetes consists of interventions targeting the patient's diet, exercise status, and prescribing medicines (insulin and oral hypoglycemic agents).[3] Currently, medicines are an essential part of diabetes management guidelines for most patients. Insulin would be commenced readily after diagnosis of type-1 diabetes and would be added to the therapeutic regimen of type-2 diabetes as required. In addition, oral hypoglycemic agents, e.g. metformin, are usually initiated alongside life-style modifications at diagnosis of type-2 diabetes.[4] Thus, appropriate utilization of diabetes medicines should be high on the agenda for health policy makers.[5]

Previous studies have reported different utilization patterns of diabetes medicines in different countries.[6-8] For example, Melander et al (2004) analyzed data from ten European countries (1994-2003) and identified an increasing trend in diabetes medicine's consumption.[6] They also observed large differences in utilization patterns among these countries, and concluded that these might have occurred due to the differences in diabetes screening and management patterns in those countries.[6] Few reports exist on the affordability of medicines and the utilization patterns of diabetes medicines in low-income and middle-income countries where the burden of diabetes is believed to be more significant than high-income countries.[2, 9] National studies in Iran, an upper-middle-income country, have estimated a significant prevalence of diabetes in the country (7.7% in 2005 and 8.7% in 2007), of which over 45% were undiagnosed cases.[10, 11] Moreover, a meta-analysis reported that the prevalence of diabetes in Iran is increasing by 0.4%

annually.[12] Still, very few reports exist on the utilization patterns of diabetes medicines in order to show the current situation of diabetes pharmacotherapy in the country.

Health and pharmaceutical system in Iran

The health care system in Iran is primarily based on a government funded primary health care system and social health insurance plans that facilitate access to secondary and tertiary care. The private sector is the main provider of ambulatory care in urban areas.[13] In 2010 social health care insurance covered 84% of the population.[14] Insurance organizations' reimbursement policies for medicines follow a general rule: covering 90% of inpatient and 70% of outpatient costs if the provider has a contract with the insurance organization.[15] Almost all community and hospital pharmacies have contracts with major insurance organizations and the lowest-priced generic product is usually set for reimbursement purposes. This means that the users might pay more than the 10% (inpatient care) or 30% (outpatient care) expected copayments at the time of use. Hence, major concerns exist among health policy makers regarding out of pocket expenditures for health services[16]. Still, it has been argued that adequate affordability of medicines has been achieved in Iran.[17, 18] Implementation of a generic-based pharmaceutical policy including a highly-regulated National Drug List and medicines pricing systems may have contributed to the assumed adequacy of access to medicines in Iran.[19, 20] Since 2001, international companies (brand or generic products) became more involved in the local pharmaceutical market and the market size expanded from 661 million USD in 2003 (of which 20.5% were imported products) to over 2.3 billion USD in 2008 (of which 33.6% were imported products).[19] It is estimated that the pharmaceutical market size in Iran would be 3.65

billion USD in 2013.[21]

Objectives

In the present study, we evaluated the trends of diabetes medicines' utilization in Iran during 2000-2012 using national pharmaceuticals wholesale data. We benchmarked our findings with available international data on diabetes medicines' use. Finally, the trend of diabetes medicines affordability in Iran was evaluated as a potential determinant of medicines' utilization.

METHODS:

Design:

A retrospective time-series design was used to investigate the trends of utilization and affordability for diabetes medicines in Iran (2000-2012). We benchmarked the rate of drug utilization with the most recent available data from 22 countries in 2011.

National data sources:

Annual wholesale data was obtained from Iran's Food and Drug Organization. The data is produced based on the sales' reports of wholesale companies to community and inpatient pharmacies all over the country and has been available as an electronic medium since 2000. Each pharmaceutical product (medicinal dosage forms) is identified with a generic name and a unique code in the database and can be linked to the manufacturer or import company, the wholesale company, the number of sold items, and their total retail price. Diabetes medicines available on the market during the study period were identified based on consultation with experts and the National Drug List. Several examinations were carried out to assess the quality of the data. Generic codes were set as the main standard for accuracy examination. We looked for discrepancies in recorded generic - or brand-generic codes, dosage forms, producer/importer and wholesale companies' data. To standardize pharmaceutical consumption data per inhabitant, we obtained annual population figures from the Statistics Center of Iran.

International data source:

We collected data on diabetes medicines utilization in 22 countries of the Organization for Economic Co-operation and Development-(OECD) via the Health Data: Pharmaceutical market database.[22]

Evaluating Utilization Patterns in Iran:

The Anatomical Therapeutic Classification/Defined Daily Dose (ATC/DDD) methodology was used to standardize the raw sales data. The latest version of the ATC/DDD guideline (2013) was retrieved from the website of the World Health Organization Collaborating Centre for Drug Statistics Methodology.[23] In the present study, the ATC codes of A10 group were used to standardize diabetes medicines. We used 2nd (all diabetes medicines), 3rd (insulin or oral hypoglycemic agents) and 5th (individual pharmaceutical substance) level of ATC classification for each data line recorded in the dataset and the DDD quantities were entered respectively. To calculate the number of DDDs per 1000 inhabitants per day (DID), the following formula was used: (Number of DDDs*1000) / (Number of Population*365).[6] We summarized the annual drug utilization data for different ATC levels and calculated the utilization growth rates. The annual share of utilization for oral hypoglycemic agents and insulin were calculated. The trend lines of utilization over time were developed using the "add trend line" command in the Microsoft Excel computer software.

We used the 'Drug Utilization-90% (DU-90)' methodology to compare the pattern of A10 utilization with the Essential Medicines List (18th edition, 2013) published by the WHO.[24, 25] ATC codes which consisted 90% of total consumed DDDs in oral anti-diabetic agents (A10B) and insulin preparations (A10A) categories were identified.

Benchmarking utilization patterns:

We compared the A10 consumption data for 22 OECD countries in 2011 with Iran's corresponding figures. We then selected a subgroup of OCED countries that has a diabetes prevalence of 8-10% (according to the International Diabetes Federation 2012 report [26]),

which is comparable to Iran. These countries were Australia, Finland, Estonia, Germany and Spain. We compared 2000-2011 trends of A10 utilization in Iran with these countries.

Evaluating Affordability:

Affordability was operationalized as the number of minimum daily wage for covering the monthly cost of each medicine or a treatment protocol.[27] We used the minimum daily wage defined by the Social Security Organization of Iran to calculate the affordability indicators. This official figure is announced each year and is closely comparable to the salary of the lowest paid government workers. If the monthly cost of a medicine or therapy combination was less than one minimum daily wage, it was considered as affordable.[18]

We calculated the affordability of each oral hypoglycemic agent separately using the cost of a hypothetical monthly treatment (30 DDDs). For insulins, we calculated affordability for a hypothetical monthly treatment (30 DDDs) of commonly used insulin therapy combinations (NPH and regular, premixed NPH and regular, aspart and glargine, and premixed aspart). Insulins preparations had different prices and their prices varied during the period of study. Hence we calculated the price of each insulin combination therapy DDD (40 IU) in each year based on the proportions of annual insulin consumption in that year. As an example, for NPH and regular therapy combination, if NPH and regular insulin consumption accounted for 65 and 35 per cent of the total consumption of NPH and regular in a defined year, one DDD cost of this therapy combination was calculated as 0.65 of one DDD of NPH plus 0.35 of one DDD of regular insulin for that year. The cost of syringes or needles required for conventional insulin or pen injectors were not included in the affordability model.

Results:

Diabetes medicines' (A10) consumption increased during the study period from 4.47 to 33.54 DID. However, the margin of annual growth varied widely from 34.6% in 2001 to 3.7% in 2012 and we observed a single negative growth rate of 15.4% in 2002. The increasing trend was detected for both A10A (insulins and analogues) and A10B (blood glucose lowering drugs, excl. insulins) categories. Nevertheless, A10B share of total A10 utilization in DDDs was consistently over 80% throughout the study period. Fig. 1 illustrates the trends of A10, A10A, and A10B utilizations. A linear trend line provided a high correlation coefficient (R^2) equal to 0.94.

During the first seven years, the only available drugs from A10A subgroup were NPH (A10AB02 and A10AB02), regular (A10AC01 and A10AC02) and mixed insulin (A10AD01) products. The beef-origin products were removed from the market in 2005. Novel insulin analogues were introduced to the market after 2007: insulin aspart (A10AB05) and insulin glargine (A10AE04) in 2007 and mixed aspart (A10AD05) in 2009. In the final year of study (2012), total utilization of the novel preparations was less than 0.3 DID while 5.73 DID of NPH and regular insulins were consumed. Table 1 illustrates a summary of the utilization figures for A10A drugs. The correlation coefficient of a linear trend line for A10A utilization was 0.94.

In the A10B subgroup, the total amount of utilization increased from 6.32 to 27.5 DID and a relatively consistent growth was observed during the 12-year period (R^2 of a linear trend line=0.94). There were only three medicines available on the market during the first three years: glibenclamide (A10BB02), chlorpropamide (A10BB02) and metformin (A10BA02) while over 90% of A10B utilization was due to glibenclamide use. Utilization of metformin

raised dramatically from 0.34 to 9.35 DID (27.5-fold) while glibenclamide use increased by 2.7-fold throughout the study period. In 2012, metformin comprised 33.9% of A10B utilization while glibenclamide's share had decreased to 55.2%. New oral hypoglycemic agents gradually entered the market, starting with gliclazide (A10BB09) and acarbose (A10BF01) in 2003 while chlorpropamide was removed from the market in 2004. Gliclazide, repaglinide (A10BX02) and pioglitazone (A10BG03) (that entered the market in 2006) were among new oral agents that showed the highest rates of utilization growth. However, a dramatic decline in gliclazide utilization was observed in 2012. Table 2 shows a summary of the utilization figures for A10B drugs.

Over the study period, DU-90 drugs were identified for A10A and A10B subgroups. Regular and NPH insulin (beef or human origin) were on the list for A10A. Glibenclamide and metformin constituted the list for A10B until 2010 and gliclazide appeared in the list in the last two years. The WHO list of Essential Medicines (2013) includes regular and NPH insulins, glibenclamide, gliclazide, and metformin from A10 group, all appearing on Iran's DU-90 lists (Fig. 2).

Benchmarking with OECD countries showed that Iran had a low A10 utilization in 2011 (Fig. 3). The prevalence of diabetes in Australia, Finland, Germany, Spain and Estonia were similar to Iran in 2011 (8-10%). The utilization of A10 medicines increased in all of these countries from 2000 to 2011 but the magnitude of growth was highest in Iran (430.7%). Nevertheless, the annual per capita A10 utilization in Iran was consistently and substantially lower than those five countries during the benchmarking period (Fig. 4).

Treatment with metformin, glibenclamide or even the combination therapy has been consistently affordable over the study period and the combination therapy cost was

approximately half a minimum daily wage in 2012. Newer A10B agents became relatively more affordable after their initial introduction into the market and the cost of treatment with gliclazide, repaglinide or pioglitazone was affordable in 2012 (0.1, 0.5, and 0.6 of minimum daily wage, respectively).

Treatment with regular and NPH insulin was consistently affordable during the study period (0.1-0.6 minimum daily wage) but premixed insulins only became affordable during the last three years. Treatment with novel insulin preparations including premixed aspart insulin and aspart/glargine combination has never been affordable since their presence on the market. In 2012, treatment with premixed aspart insulin cost 4.8 minimum daily wages and combination therapy with aspart and glargine insulins required 5.8 minimum daily wages. Fig. 5 and 6 illustrate the pattern of diabetes medicines affordability over the study period.

Discussion:

Our findings showed that A10 utilization increased approximately 7-fold over a 13-yearperiod (2000-2012) from 4.47 to 33.54 DID. The growth of diabetes prevalence may explain the rise of A10 utilization to some extent. A longitudinal study on the prevalence of diabetes in Iran reported that diabetes rate among Iranian adults increased approximately twofold during 1999-2007 period.[28] In addition to the rise in diabetes prevalence, the evidence on the efficiency of diabetes intensive management and the essential role of metformin should be considered as important underlying factors in the upsurge of A10 utilization during the last decade.[5, 29]

Insulin preparations (A10A) seem to be under-utilized in comparison with oral hypoglycemic agents (A10B) during the study period. In 2012, insulin utilization only comprised 17% of total A10 consumption. A report from 10 European countries showed that the share of insulin utilization in 2003 was over 30% in nine countries and the data from Sweden, Norway, Germany, Denmark, and England revealed similar figures at above 40%.[6] It should be noted that some guidelines recommend early use of insulin for the management of type-2 diabetes.[3] Thus, we consider under-utilization of insulins a salient signal of irrational A10 use in Iran. A few studies have reported inadequacy of physicians' knowledge about clinical guidelines and also patients' concerns about insulin injection in Iran.[30-32] Although further research is required to expand our knowledge of insulin under-utilization factors, effective educational interventions could be recommended to improve health care professionals' and patients' attitudes and behavior toward appropriate and timely use of insulin for diabetes management.[33, 34] Other barriers to insulin use include the availability and affordability of syringes/needles for insulin injection or the blood glucose

monitoring tests required for tight glucose control.[35] Such barriers have been highlighted by Beran et al in a series of reports which necessitates further studies to evaluate the affordability of diabetes care rather than diabetes medicines alone.[35, 36]

The pattern of A10B utilization revealed a few important issues. Glibenclamide has been used for several decades in Iran and comprised the highest share of utilization during the study period. This medication was recommended by WHO as an essential medicine until 2013; however, the latest WHO list of essential medicines recommends gliclazide particularly for elderly patients to avoid hypoglycemia side effects.[25] Despite a rapid growth in gliclazide utilization and its appearance on the DU-90 list from 2011, policies and educational intervention are necessary to modify local pharmaceuticals production and also physicians' prescribing behavior. The negative growth rate for gliclazide utilization in 2012 requires further elaboration. During this year, drug shortages were quite common in the country due to sanctions on the Iranian financial and trading system which significantly affected drug import and local production.[37, 38]

In comparison with the OECD countries, A10 utilization appears to be inadequate in Iran. One of the main reasons may be the high rate of undiagnosed diabetes.[10] OECD data is based on information provided by the authorities in each country. Some countries provide use of wholesale data while others use prescription databases. They may also differ in collecting over-the-counter, hospital and non-reimbursed drug use data. However, drug utilization data from Czech Republic, Denmark, Estonia, Finland, Slovak Republic, and Sweden reported wholesale data which was similar to our data source from Iran in the present study.[39]

As expected, the analyses demonstrated that most A10 medicines were affordable during the study period. It seems that the main factor in the affordability of the medicines was the pricing system in Iran for generic medicines. Medicines prices are highly regulated in Iran by the Pricing Committee, Food and Drug Organization. The decline pattern in the "number of daily wage" for some of the newer A10 drugs can be justified by the fact that local production usually begins some years after a pharmaceutical entity is registered and imported. New products (oral agents or insulin) remained unaffordable until their retail price is dramatically reduced.

It should be noted that we did not consider the effect of insurance coverage on the treatment cost and also did not include cost of syringes required for insulin injections. Still gradual increases in the population coverage of the insurance organizations from 74% in 2002 to 83% in 2010 may have contributed to better access.[14] As our findings showed, little concern may exist regarding the affordability of conventional insulin preparations; however, use of novel preparations and pen injectors may be limited by the treatment cost. In 2013 the new glargine and aspart insulins were added to the insurers benefit package, albeit with a higher copayment rate due to a reference pricing approach, which may result in better access to these medicines in future. Future studies should evaluate the share of insurance plans in providing access to A10 medicines in Iran.

Limitations: We used "consumption" and "utilization" terms interchangeably throughout the article. Nevertheless, it should be emphasized that our study was conducted based on wholesale data and our findings must be interpreted according to data limitations, e.g. expired medicines in pharmacies or uncertainty about drug taking behaviors of patients. In a recent review, we reported that 62-87% of Iranian diabetic patients were adherent to their

diabetes medicines.[40] Thus, the real A10 consumption might be lower than the findings based on wholesale data; however, insufficient adherence to diabetes medication is reported to be a global problem[41] and may not introduce a major bias in benchmarking studies.

In conclusion, use of diabetes medicines has increased during a thirteen-year period in Iran as a middle-income country; nevertheless, the utilization does not seem to be adequate due to the high rate of undiagnosed patients and inappropriate management of diagnosed cases. Although the affordability of essential diabetes medicines has been achieved, optimizing the pattern of medicines use, e.g. underutilization of insulin and overutilization of glibenclamide, should be on the agenda for health policy makers. Improving better access to effective novel products (such as gliclazide and pen insulins) should be a major consideration for decision makers.

Funding:

This study was supported by a research grant from the Deputy of Research, Tehran University of Medical Sciences and the Research Center for Rational Use of Drugs. (Grant number: 92-01-156-22298)

Competing Interests:

We have no conflict of interests to declare.

Contributorship Statement:

AS developed the research proposal, extracted and analyzed the data. He contributed to interpretation of findings and drafted the manuscript.

AR contributed to proposal development, data analysis, results interpretation and major revision of the draft.

KG contributed to proposal development, data acquisition and extraction, results interpretation, and minor revision of the manuscript.

Data Sharing Statement:

Dataset might be available to the interested researchers upon request from the authors.

Figure Legends:

Figure 1- Utilization pattern of diabetes medicines (A10) in Iran

Figure 2- Pattern of drug utilization-90% for diabetes medicines in Iran

Figure 3- Benchmarking diabetes drugs utilization in Iran with OECD countries (2011)

Figure 4- Benchmarking the trend of diabetes drugs utilization (Iran and OECD countries with comparable diabetes prevalence according to IDF statistics)

Figure 5- Affordability of oral hypoglycemic agents in Iran

Figure 6- Affordability of insulin preparations in Iran

Reference:

1. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. The Lancet 2011;**378**(9785):31-40
2. Whiting DR, Guariguata L, Weil C, et al. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes research and clinical practice 2011;**94**(3):311-21
3. Alldredge BK, Corelli RL, Ernst ME, et al. *Koda-Kimble & Young's Applied Therapeutics; The Clinical use of Drug*. 10 ed: Lippincott Williams & Wilkins, 2012.
4. Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;**32**(1):193-203 [doi: 10.2337/dc08-9025published Online First: Epub Date].
5. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;**321**(7258):405-12
6. Melander A, Folino-Gallo P, Walley T, et al. Utilisation of antihyperglycaemic drugs in ten European countries: different developments and different levels. Diabetologia 2006;**49**(9):2024-29 [doi: 10.1007/s00125-006-0331-3published Online First: Epub Date].
7. Doró P, Benkő R, Kosik E, et al. Utilization of oral antihyperglycemic drugs over a 7–year period (1998–2004) in a Hungarian population and adherence to drug therapy. Eur J Clin Pharmacol 2005;**61**(12):893-97 [doi: 10.1007/s00228-005-0031-9published Online First: Epub Date].
8. Baviera M, Monesi L, Marzona I, et al. Trends in drug prescriptions to diabetic patients from 2000 to 2008 in Italy's Lombardy Region: A large population-based study. Diabetes Res Clin Pract 2011;**93**(1):123-30 [doi: http://dx.doi.org/10.1016/j.diabres.2011.05.004published Online First: Epub Date].
9. Rashidian A, Jahanmehr N, Jabbour S, et al. Bibliographic review of research publications on access to and use of medicines in low-income and middle-income countries in the Eastern Mediterranean Region: identifying the research gaps. BMJ open 2013;**3**(10):e003332
10. Esteghamati A, Meysamie A, Khalilzadeh O, et al. Third national surveillance of risk factors of non-communicable diseases (SuRFNCD-2007) in Iran: methods and results on prevalence of diabetes, hypertension, obesity, central obesity, and dyslipidemia. BMC Public Health 2009;**9**(1):167 [doi: 10.1186/1471-2458-9-167published Online First: Epub Date].
11. Esteghamati A, Gouya MM, Abbasi M, et al. Prevalence of Diabetes and Impaired Fasting Glucose in the Adult Population of Iran: National Survey of Risk Factors for Non-Communicable Diseases of Iran. Diabetes Care 2008;**31**(1):96-98 [doi: 10.2337/dc07-0959published Online First: Epub Date].
12. Haghdoost A, Rezazadeh-Kermani M, Sadghirad B, et al. Prevalence of type 2 diabetes in the Islamic Republic of Iran: systematic review and meta-analysis. Eastern

Mediterranean health journal= La revue de santé de la Méditerranée orientale= al-Majallah al-ṣiḥḥīyah li-sharq al-mutawassiṭ 2009;**15**(3):591-99
13. Oliaimanesh A, Abolhallaj M, Zangeneh M, et al. National Health Accounts Islamic Republic of Iran-2008. Tehran: National Institue of Health Research, Ministry of Health and Medical Education, 2013.
14. Rashidian A, Khosravi A, Khabiri R, et al. Islamic Republic of Iran's Multiple Indicator Demographic and Health Survey (IrMIDHS)-2010. Tehran: National Institue of Health Research, Ministry of Health and Medical Education, 2012.
15. Davari M, Haycox A, Walley T. The Iranian Health Insurance System; Past Experiences, Present Challenges And Future Strategies. Iranian J Publ Health 2012;**41**(9):1-9
16. Kavosi Z, Rashidian A, Pourreza A, et al. Inequality in household catastrophic health care expenditure in a low-income society of Iran. Health Policy Plan 2012;**27**(7):613-23 [doi: 10.1093/heapol/czs001published Online First: Epub Date].
17. Cheraghali AM, Nikfar S, Behmanesh Y, et al. Evaluation of availability, accessibility and prescribing pattern of medicines in the Islamic Republic of Iran. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit 2004;**10**(3):406-15
18. Abdollahiasl A. Medicine prices, availability, affordability and price components-Iran. Medicine prices and access to medicines in the Eastern Mediterranean Region. Cairo, Egypt: Essential Medicines and Pharmaceutical Policies Unit, World Health Organization, Regional Office for the Eastern Mediterranean, 2010.
19. Dinarvand R. New National Drug Policy in Iran leading to Expanded Pharmaceutical Market and Extended Access of Public to Medicines. Iranian journal of public health 2009;**38**(Suppl. 1):158-61
20. Davari M, Walley T, Haycox A. Pharmaceutical Policy and Market in Iran: past experiences and future challenges. Journal of Pharmaceutical Health Services Research 2011;**2**(1):47-52
21. Iran Pharmaceuticals & Healthcare Report Q2 2009. London, UK: Business Monitor International.
22. OECD. OECD Health Data: Pharmaceutical market. http://dx.doi.org/10.1787/data-00545-en.
23. Guidelines for ATC classification and DDD assignment. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, 2013.
24. Wettermark B, Pehrsson Å, Jinnerot D, et al. Drug utilisation 90% profiles—a useful tool for quality assessment of prescribing in primary health care in Stockholm. Pharmacoepidemiol Drug Saf 2003;**12**(6):499-510
25. WHO Model List of Essential Medicines: World Health Organization, 2013.
26. International Diabetes Federation-DIABETES ATLAS UPDATE 2012. http://www.idf.org/diabetesatlas/5e/Update2012.
27. Cameron A, Ewen M, Ross-Degnan D, et al. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. The Lancet;**373**(9659):240-49 [doi: http://dx.doi.org/10.1016/S0140-6736(08)61762-6published Online First: Epub Date].
28. Esteghamati A, Ashraf H, Khalilzadeh O, et al. Trends of diabetes according to body mass index levels in Iran: results of the national Surveys of Risk Factors of Non-Communicable Diseases (1999–2007). Diabet Med 2010;**27**(11):1233-40 [doi: 10.1111/j.1464-5491.2010.03103.xpublished Online First: Epub Date].

29. UKPDS. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ: British Medical Journal 1998:703-13
30. Peimani M, Tabatabaei-Malazy O, Heshmat R, et al. Knowledge, attitude and practice of physicians in the field of diabetes and its complications: A pilot study. Iran J Diabetes and Lipid Disord 2010;**9**:1-7
31. Shakibazadeh E, Larijani B, Shojaeezadeh D, et al. Patients' Perspectives on Factors that Influence Diabetes Self-Care. Iranian journal of public health 2011;**40**(4):146-58
32. Mounesan L, Nedjat S, Majdzadeh R, et al. Only One Third of Tehran's Physicians are Familiar with 'Evidence-Based Clinical Guidelines'. Int J Prev Med 2013;**4**(3):349-57
33. Sarayani A, Rashidian A, Gholami K, et al. Efficacy of continuing education in improving pharmacists' competencies for providing weight management service: Three-arm randomized controlled trial. J Contin Educ Health Prof 2012;**32**(3):163-73 [doi: 10.1002/chp.21141published Online First: Epub Date].
34. Forsetlund L, Bjørndal A, Rashidian A, et al. Continuing education meetings and workshops: effects on professional practice and health care outcomes. Cochrane Database Syst Rev 2009;**2**(2)
35. Beran D, McCabe A, Yudkin JS. Access to medicines versus access to treatment: the case of type 1 diabetes. Bull World Health Organ 2008;**86**(8):648-9 [doi: 10.2471/blt.07.048710published Online First: Epub Date].
36. Beran D, Yudkin JS. Looking beyond the issue of access to insulin: what is needed for proper diabetes care in resource poor settings. Diabetes Res Clin Pract 2010;**88**(3):217-21 [doi: 10.1016/j.diabres.2010.03.029published Online First: Epub Date].
37. Cheraghali AM. Impacts of international sanctions on Iranian pharmaceutical market. Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences 2013;**21**(1):64 [doi: 10.1186/2008-2231-21-64published Online First: Epub Date].
38. Butler D. Iran hit by drug shortage. Nature 2013;**504**(7478):15-6 [doi: 10.1038/504015apublished Online First: Epub Date].
39. OECD Health Data 2013 Definitions, Sources and Methods: Pharmaceutical consumption by DDDs: OECD Health Data 2013; http://www.oecd.org/health/healthdata.
40. Sarayani A, Jahangard-Rafsanjani Z, Hadjibabaie M, et al. A comprehensive review of adherence to diabetes and cardiovascular medications in Iran; implications for practice and research. Journal of Diabetes & Metabolic Disorders 2013;**12**(1):57
41. Cramer JA. A Systematic Review of Adherence With Medications for Diabetes. Diabetes Care 2004;**27**(5):1218-24 [doi: 10.2337/diacare.27.5.1218published Online First: Epub Date].

Table 1- Number of DDDs per 1000 inhabitants per day (DID) for A10A (Insulins and analogues) medicines

ATC code	2000/ 2001	2001/ 2002	2002/ 2003	2003/ 2004	2004/ 2005	2005/ 2006	2006/ 2007	2007/ 2008	2008/ 2009	2009/ 2010	2010/ 2011	2011/ 2012	2012/ 2013
A10AC01 (insulin (human))	0.64	0.93	1.10	1.36	1.48	1.77	1.87	2.49	2.22	2.79	3.09	3.36	3.52
A10AB01 (insulin (human))	0.16	0.20	0.31	0.42	0.50	0.63	0.72	0.93	1.00	1.15	1.32	1.80	1.91
A10AD01 (insulin (human))	<0.01	<0.01	<0.01	<0.01	<0.01	-	-	-	0.04	0.03	0.16	0.26	0.30
A10AE04 (insulin glargine)	-	-	-	-	-	-	-	<0.01	0.02	0.02	0.01	0.03	0.13
A10AD05 (insulin aspart)	-	-	-	-	-	-	-	-	-	0.03	0.07	0.09	0.11
A10AB05 (insulin aspart)	-	-	-	-	-	-	-	<0.01	0.01	0.00	0.01	0.03	0.05
A10AB04 (insulin lispro)	-	-	-	-	-	-	-	-	-	-	-	-	<0.01
A10AB02 (insulin (beef))	0.07	0.05	0.05	0.03	0.01	-	-	-	-	-	-	-	-
A10AC02 (insulin (beef))	0.29	0.14	0.21	0.09	0.03	-	-	-	-	-	-	-	-

Table 2- Number of DDDs per 1000 inhabitants per day (DID) for A10B (Blood glucose lowering drugs, excl. insulins) medicines

	2000/ 2001	2001/ 2002	2002/ 2003	2003/ 2004	2004/ 2005	2005/ 2006	2006/ 2007	2007/ 2008	2008/ 2009	2009/ 2010	2010/ 2011	2011/ 2012	2012/ 2013
A10BB01 (glibenclamide)	5.69	8.01	5.86	7.31	8.69	9.55	11.33	10.88	12.68	12.06	13.29	15.40	15.18
A10BA02 (metformin)	0.34	0.62	0.88	1.31	1.63	2.19	3.01	3.46	4.41	5.52	5.94	8.58	9.35
A10BB09 (gliclazide)	-	-	-	<0.01	0.06	0.14	0.23	0.44	0.59	0.74	0.88	1.31	1.13
A10BG0 (pioglitazone)	-	-	-	-	-	-	0.01	0.11	0.27	0.45	0.68	0.94	1.10
A10BX02 (repaglinide)	-	-	-	-	-	-	0.02	0.03	0.04	0.06	0.15	0.31	0.48
A10BF01 (acarbose)	-	-	-	<0.01	<0.01	<0.01	0.03	0.07	0.13	0.14	0.16	0.24	0.26
A10BD02 (metformin and sulfonamides)	-	-	-	-	-	-	-	-	-	-	-	0.01	0.03
A10BD05 (metformin and pioglitazone)	-	-	-	-	-	-	-	-	-	-	-	-	<0.01
A10BD07 (metformin and sitagliptin)	-	-	-	-	-	-	-	-	-	-	-	<0.01	<0.01
A10BB02 (chlorpropamide)	0.29	0.12	0.11	0.09	<0.01	-	-	-	-	-	-	-	-

Title:

Low utilization ~~despite affordability~~ of diabetes medicines in Iran, despite their affordability (2000-2012): a time-series and benchmarking study

Authors:

Amir Sarayani PharmD, MPH

Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran

Arash Rashidian MD, PhD*

Department of Health Management and Economics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

Knowledge Utilization Research Center, Tehran University of Medical Sciences, Tehran, Iran

Kheirollah Gholami M.Sc., PharmD

Research Center for Rational Use of Drugs and Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

* Corresponding author.

Word Count: 3065~~5~~86

Abstract:

Objectives:

Diabetes is a major public health concern worldwide, particularly in low- and middle-income countries (LMICs). Limited data exists on the status of access to diabetes medicines in LMICs. We assessed the utilization and affordability of diabetes medicines in Iran as a middle-income country.

Design:

We used a retrospective time-series design (2000-2012) and assessed national diabetes medicines' utilization using pharmaceuticals wholesale data.

Methods:

We calculated defined daily dose consumptions per population days (DDDs/1000 inhabitants/day; DIDs) indicator. Findings were benchmarked with data from OECD countries. We also employed Drug Utilization-90% (DU-90) method to compare DU-90s with the Essential Medicines list published by the World Health Organization. We measured affordability using number of minimum daily wage required to purchase a treatment course for one month.

Results:

Diabetes medicines' consumption increased from 4.47 to 33.54 DIDs. The benchmarking showed that medicines' utilization in Iran in 2011 ~~were~~ was only 54% of the median DIDs of 22 OECD countries. Oral hypoglycemic agents consisted over 80% of use throughout the study period. Regular and NPH insulin, glibenclamide, metformin and gliclazide were the DU-90 drugs in 2012. Metformin, glibenclamide, and regular/NPH insulin combination therapy were affordable throughout the study period (~0.4, ~0.1, ~0.3 of minimum daily wage, respectively). While the affordability of novel insulin preparations improved over time, they were still unaffordable in 2012.

Conclusions:

The utilization of diabetes medicines was relatively low, perhaps due to under-diagnosis and inadequate management of diabetic patients. This had occurred despite affordability of essential diabetes medicines in Iran. Appropriate policies are required to address the under-utilization of diabetes medicines in Iran.

Keywords:

Drug utilization, diabetes, affordability, pharmaceutical policy, defined daily dose, access to medicines, essential medicines

Article Summary:

Strength and Limitations of this study:

- To the best of our knowledge, this is the first study to evaluate the pattern of utilization and affordability of diabetes drugs in a low or middle income country over a period of time.
- We used data from OECD countries to assess the adequacy of utilization in Iran.
- Our findings showed that utilization of diabetes drugs does not seem to be adequate. Although the affordability of essential diabetes medicines is achieved, optimizing the pattern of use requires screening for undiagnosed patients and improving management of diagnosed cases.
- National wholesale data was used to estimate drug utilization; however, this data may not reflect the real drug consumption by patients.

INTRODUCTION:

Diabetes is a major public health concern worldwide, with an estimated global prevalence of 8.3% in 2011[1, 2], while approximately 80% of diabetic patients reside in low-income and middle-income countries.[2] Proper management of diabetes consists of interventions targeting the patient's diet, exercise status, and prescribing medicines (insulin and oral hypoglycemic agents).[3] Currently, medicines are an essential part of diabetes management guidelines for most patients. Insulin would be commenced readily after diagnosis of type-1 diabetes and would be added to the therapeutic regimen of type-2 diabetes as required. In addition, oral hypoglycemic agents, e.g. metformin, are usually initiated alongside life-style modifications at diagnosis of type-2 diabetes.[4] Thus, appropriate utilization of diabetes medicines should be high on the agenda for health policy makers.[5]

Previous studies have reported different utilization patterns of diabetes medicines in different countries.[6-8] For example, Melander et al (2004) analyzed data from ten European countries (1994-2003) and identified an increasing trend in diabetes medicine's consumption.[6] They also observed large differences in utilization patterns among these countries, and concluded that these might have occurred due to the differences in diabetes screening and management patterns in those countries.[6] Few reports exist on the affordability of medicines and the utilization patterns of diabetes medicines in low-income and middle-income countries where the burden of diabetes is believed to be more significant than high-income countries.[2, 9] National studies in Iran, an upper-middle-income country, have estimated a significant prevalence of diabetes in the country (7.7% in 2005 and 8.7% in 2007), of which over 45% were undiagnosed cases.[10, 11] Moreover, a meta-analysis reported that the prevalence of diabetes in Iran is increasing by 0.4%

annually.[12] Still, very few reports exist on the utilization patterns of diabetes medicines in order to show the current situation of diabetes pharmacotherapy in the country.

Health and pharmaceutical system in Iran

The ~~Health~~ health care system in Iran is primarily based on a government funded primary health care system and social health insurance plans that facilitate access to secondary and tertiary care. ~~Private~~The private sector is the main provider of ambulatory care in urban areas.[13] In 2010 social health care insurance covered 84% of the population.[14] Insurance organizations' reimbursement policies for medicines follow a general rule: covering 90% of inpatient and 70% of outpatient costs if the provider has a contract with the insurance organization.[15] Almost all community and hospital pharmacies have contracts with major insurance organizations and the lowest-priced generic product is usually set for reimbursement purposes. This means that the users might pay more than the 10% (inpatient care) or 30% (outpatient care) expected copayments at the time of use. Hence, major concerns exist among health policy makers regarding out of pocket expenditures for health services[16]. Still, it has been argued that adequate affordability of medicines has been achieved in Iran.[17, 18] Implementation of a generic-based pharmaceutical policy including a highly-regulated National Drug List and medicines pricing systems may have contributed to the assumed adequacy of access to medicines in Iran.[19, 20] Since 2001, international companies (brand or generic products) ~~become~~ became more involved in the local pharmaceutical market and the market size expanded from 661 million USD in 2003 (of which 20.5% were imported products) to over 2.3 billion USD in 2008 (of which 33.6% were imported products).[19] It is estimated that the pharmaceutical market size in Iran would be

3.65 billion USD in 2013.[21]

Objectives

In the present study, we evaluated the trends of diabetes medicines' utilization in Iran during 2000-2012 using national pharmaceuticals wholesale data. We benchmarked our findings with available international data on diabetes medicines' use. Finally, the trend of diabetes medicines affordability in Iran was evaluated as a potential determinant of medicines' utilization.

METHODS:

Design:

A retrospective time-series design was used to investigate the trends of utilization and affordability for diabetes medicines in Iran (2000-2012). We benchmarked the rate of drug utilization with the most recent available data from 22 countries in 2011.

National data sources:

Annual wholesale data was obtained from Iran's Food and Drug Organization. The data is produced based on the sales' reports of wholesale companies to community and inpatient pharmacies all over the country and ~~is~~ has been available as an electronic medium ~~from~~ since 2000 ~~onwards~~. Each pharmaceutical product (medicinal dosage forms) is identified with a generic name and a unique code in the database and can be linked to the manufacturer or import company, the wholesale company, the number of sold items, and their total retail price. Diabetes medicines available on the market during the study period were identified based on ~~the National Drug List and consultation with experts~~consultation with experts and the National Drug List. Several examinations were carried out to assess the quality of the data. Generic codes were set as the main standard for accuracy examination. We looked for discrepancies in recorded generic - or brand-generic codes, dosage forms, producer/importer and wholesale companies' data. To standardize pharmaceutical consumption data per inhabitant, we obtained annual population figures from the Statistics Center of Iran.

International data source:

We collected data on diabetes medicines utilization in 22 countries of the Organization for

Economic Co-operation and Development-(OECD) via the Health Data: Pharmaceutical market database.[22]

Evaluating Utilization Patterns in Iran:

The Anatomical Therapeutic Classification/Defined Daily Dose (ATC/DDD) methodology was used to standardize the raw sales data. The latest version of the ATC/DDD guideline (2013) was retrieved from the website of the ~~WHO~~ World Health Organization Collaborating Centre for Drug Statistics Methodology.[23] In the present study, the ATC codes of A10 group were used to standardize diabetes medicines. We used 2nd (all diabetes medicines), 3rd (insulin or oral hypoglycemic agents) and 5th (individual pharmaceutical substance) level of ATC classification for each data line recorded in the dataset and the DDD quantities were entered respectively. To calculate the number of DDDs per 1000 inhabitants per day (DID), the following formula was used: (Number of DDDs*1000) / (Number of Population*365).[6] We summarized the annual drug utilization data for different ATC levels and calculated the utilization growth rates. The ~~Annual~~ annual share of utilization for oral hypoglycemic agents and insulin were calculated. The trend lines of utilization over time were developed using the "add trend line" command in the Microsoft Excel computer software.

We used the 'Drug Utilization-90% (DU-90)' methodology to compare the pattern of A10 utilization with the Essential Medicines List (18th edition, 2013) published by the ~~WHO~~World ~~Health Organization~~.[24, 25] ATC codes which consisted 90% of total consumed DDDs in oral anti-diabetic agents (A10B) and insulin preparations (A10A) categories were identified.

Benchmarking utilization patterns:

We compared the A10 consumption data for 22 OECD countries in 2011 with Iran's corresponding figures. We then selected a subgroup of OCED countries that has a diabetes prevalence of 8-10% (according to the International Diabetes Federation 2012 report [26]), which is comparable to Iran. These countries were Australia, Finland, Estonia, Germany and Spain. We compared 2000-2011 trends of A10 utilization in Iran with these countries.

Evaluating Affordability:

Affordability was operationalized as the number of minimum daily wage ~~to cover~~ for covering the monthly cost of each medicine or a treatment protocol.[27] We used the minimum daily wage defined by the Social Security Organization of Iran to calculate the affordability indicators. This official figure is announced each year and is closely comparable to the salary of the lowest paid government workers. If the monthly cost of a medicine or therapy combination was less than one minimum daily wage, it was considered as affordable.[18]

We calculated the affordability of each oral hypoglycemic agent separately using the cost of a hypothetical monthly treatment (30 DDDs). For insulins, we calculated affordability for a hypothetical monthly treatment (30 DDDs) of commonly used insulin therapy combinations (NPH and regular, premixed NPH and regular, aspart and glargine, and premixed aspart). ~~Different i~~Insulins preparations had different prices and their prices ~~were~~ varied ~~in~~ during the period of study~~different years~~. Hence we calculated the price of each insulin combination therapy DDD (40 IU) in each year based on the proportions of annual insulin consumption in that year. As an example, for NPH and regular therapy combination, if NPH and regular insulin consumption accounted for 65 and 35 per cent of the total consumption of NPH and regular in a defined year, one DDD cost of this therapy combination was

calculated as 0.65 of one DDD of NPH plus 0.35 of one DDD of regular insulin for that year.

The cost of syringes or needles required for conventional insulin or pen injectors were not included in the affordability model.

Results:

Diabetes medicines' (A10) consumption increased during the study period from 4.47 to 33.54 DID. However, the margin of annual growth varied widely from 34.6% in 2001 to 3.7% in 2012 and we observed a single negative growth rate of 15.4% in 2002. The increasing trend was detected for both A10A (insulins and analogues) and A10B (blood glucose lowering drugs, excl. insulins) categories. Nevertheless, A10B share of total A10 utilization in DDDs was consistently over 80% throughout the study period. Fig. 1 illustrates the trends of A10, A10A, and A10B utilizations. A linear trend line provided a high correlation coefficient (R^2) equal to 0.94.

During the first seven years, the only available drugs from A10A subgroup were NPH (A10AB02 and A10AB02), regular (A10AC01 and A10AC02) and mixed insulin (A10AD01) products. The beef-origin products were removed from the market in 2005. Novel insulin analogues were introduced to the market after 2007: insulin aspart (A10AB05) and insulin glargine (A10AE04) in 2007 and mixed aspart (A10AD05) in 2009. In the final year of study (2012), total utilization of the novel preparations was less than 0.3 DID while 5.73 DID of NPH and regular insulins were consumed. Table 1 illustrates a summary of the utilization figures for A10A drugs. The correlation coefficient of a linear trend line for A10A utilization was 0.94.

In the A10B subgroup, the total amount of utilization increased from 6.32 to 27.5 DID and a relatively consistent growth was observed during the 12-years period (R^2 of a linear trend line=0.94). There were only three medicines available on the market during the first three years: glibenclamide (A10BB02), chlorpropamide (A10BB02) and metformin (A10BA02) while over 90% of A10B utilization was due to glibenclamide use. Utilization of metformin

raised dramatically from 0.34 to 9.35 DID (27.5-fold) while glibenclamide use increased by 2.7-fold throughout the study period. In 2012, metformin comprised 33.9% of A10B utilization while glibenclamide's share had decreased to 55.2%. New oral hypoglycemic agents gradually entered the market, starting with gliclazide (A10BB09) and acarbose (A10BF01) in 2003 while chlorpropamide was removed from the market in 2004. Gliclazide, repaglinide (A10BX02) and pioglitazone (A10BG03) (that entered the market in 2006) were among new oral agents ~~to show~~that showed the highest rates of utilization growth. However, a dramatic decline in gliclazide utilization was observed in 2012. Table 2 shows a summary of the ~~-~~utilization figures for A10B drugs.

Over the study period, DU-90 drugs were identified for A10A and A10B subgroups. Regular and NPH insulin (beef or human origin) were ~~in~~ on the list for A10A. Glibenclamide and metformin constituted the list for A10B until 2010 and gliclazide appeared in the list in the last two years. The WHO list of Essential Medicines (2013) includes regular and NPH insulins, glibenclamide, gliclazide, and metformin from A10 group, all appearing on Iran's DU-90 lists (Fig. 2).

Benchmarking with OECD countries showed that Iran had a low A10 utilization in 2011 (Fig. 3). The prevalence of diabetes in Australia, Finland, Germany, Spain and Estonia were similar to Iran in 2011 (8-10%). The utilization of A10 medicines increased in all of these countries from 2000 to 2011 but the magnitude of growth was highest in Iran (430.7%). Nevertheless, the annual per capita A10 utilization in Iran was consistently and substantially lower than those five countries during the benchmarking period (Fig. 4).

Treatment with metformin, glibenclamide or even the combination therapy has been consistently affordable over the study period and the combination therapy cost was

approximately half a minimum daily wage in 2012. Newer A10B agents became relatively more affordable after their initial introduction into the market and the cost of treatment with gliclazide, repaglinide or pioglitazone was affordable in 2012 (0.1, 0.5, and 0.6 of minimum daily wage, respectively).

Treatment with regular and NPH insulin was consistently affordable during the study period (0.1-0.6 minimum daily wage) but premixed insulins only became affordable during the last three years. Treatment with novel insulin preparations including premixed aspart insulin and aspart/glargine combination has never been affordable since their presence on the market. In 2012, treatment with premixed aspart insulin cost 4.8 minimum daily wages and combination therapy with aspart and glargine insulins required 5.8 minimum daily wages. Fig. 5 and 6 illustrate the pattern of diabetes medicines affordability over the study period.

Discussion:

Our findings showed that A10 utilization increased approximately 7-fold over a 13-years period (2000-2012) from 4.47 to 33.54 DID. The growth of diabetes prevalence may explain the rise of A10 utilization to some extent. A longitudinal study on the prevalence of diabetes in Iran reported that diabetes rate among Iranian adults increased approximately by twofold during 1999-2007 period.[28] In addition to the rise of in diabetes prevalence, the evidence on the efficiency of diabetes intensive management and the essential role of metformin should be considered as important underlying factors in the upsurge of A10 utilization during the last decade.[5, 29]

Insulin preparations (A10A) seem to be under-utilized in comparison to with the oral hypoglycemic agents (A10B) during the study period. In 2012, insulin utilization only comprised 17% of total A10 consumption. A report from 10 European countries showed that the share of insulin utilization in 2003 was over 30% in nine countries and the data from Sweden, Norway, Germany, Denmark, and England revealed similar figures at above 40%.[6] It should be noted that some guidelines recommend early use of insulin for the management of type-2 diabetes.[3] Thus, we consider under-utilization of insulins a salient signal of irrational A10 use in Iran. A few studies have reported inadequacy of physicians' knowledge about clinical guidelines and also patients' concerns about insulin injection in Iran.[30-32] Although further research is required to expand our knowledge of insulin under-utilization factors, effective educational interventions could be recommended to improve health care professionals' and patients' attitudes and behavior toward appropriate and timely use of insulin for diabetes management.[33, 34] Other barriers to insulin use include the availability and affordability of syringes/needles for insulin injection or the blood

glucose monitoring tests required for tight glucose control.[35] Such barriers have been highlighted by Beran et al in a series of reports which necessitates further studies to evaluate the affordability of diabetes care rather than diabetes medicines alone.[35, 36]

~~Pattern~~ The pattern of A10B utilization revealed a few important issues. Glibenclamide has been used for several decades in Iran and comprised the highest share of utilization during the study period. This medication was recommended by WHO as an essential medicine until 2013; however, the latest WHO list of essential medicines recommends gliclazide particularly for elderly patients to avoid hypoglycemia side effects.[25] Despite a rapid growth in gliclazide utilization and its appearance on the DU-90 list from 2011, policies and educational intervention are necessary to modify local pharmaceuticals production and also physicians' prescribing behavior. The negative growth rate for gliclazide utilization in 2012 requires further elaboration. During this year, drug shortages were quite common in the country due to sanctions on the Iranian financial and trading system which significantly affected drug import and local production.[37, 38]

In comparison ~~to~~ with the OECD countries, A10 utilization appears to be inadequate in Iran. One of the main reasons ~~might~~ may be the high rate of undiagnosed diabetes.[10] OECD data is based on information provided by the authorities in each country. Some countries provide use of wholesale data while others use prescription databases. They may also differ in collecting over-the-counter, hospital and non-reimbursed drug use data. However, drug utilization data from Czech Republic, Denmark, Estonia, Finland, Slovak Republic, and Sweden reported wholesale data which was similar to our data source from Iran in the present study.[39]

As expected, the analyses demonstrated that most A10 medicines were affordable during the study period. It seems that the main factor ~~on~~ in the affordability of the medicines~~, were~~ was the pricing system in Iran for generic medicines. Medicines prices are highly regulated in Iran by the Pricing Committee, Food and Drug Organization. The decline pattern in the "number of da~~ys'~~ily wage~~s~~" for some of the newer A10 drugs can be justified by the fact that local production usually begins some years after a pharmaceutical entity is registered and imported. New products (oral agents or insulin) remained unaffordable until their retail price is dramatically reduced.

It should be noted that we did not consider the effect of insurance coverage on the treatment cost and also did not include~~d~~ cost of syringes required for insulin injections. Still gradual increases in the population coverage of the insurance organizations from 74% in 2002 to 83% in 2010 may have contributed to better access.[14] As our findings showed, little concern may exist regarding the affordability of conventional insulin preparations; however, use of novel preparations and pen injectors may be limited by the treatment cost. In 2013 the new glargine and aspart insulins were added to the insurers benefit package, albeit with a higher copayment rate due to a reference pricing approach, which may result in better access to these medicines in future. Future studies should evaluate the share of insurance plans in providing access to A10 medicines in Iran.

Limitations: We used "consumption" and "utilization" terms interchangeably throughout the article. Nevertheless, it should be emphasized that our study was conducted based on wholesale data and our findings must be interpreted according to data limitations, e.g. expired medicines in pharmacies or uncertainty about drug taking behavior~~s~~ of patients. In a recent review, we reported that 62-87% of Iranian diabetic patients were adherent to their

diabetes medicines.[40] Thus, the real A10 consumption might be lower than the findings based on wholesale data; however, insufficient adherence to diabetes medication is reported to be a global problem[41] and may not introduce a major bias in benchmarking studies.

In conclusion, use of diabetes medicines has increased during a thirteen-year period in Iran as a middle-income country; nevertheless, the utilization does not seem to be adequate due to the high rate of undiagnosed patients and inappropriate management of diagnosed cases. Although the affordability of essential diabetes medicines ~~is~~ has been achieved, optimizing the pattern of medicines use, e.g. underutilization of insulin and overutilization of glibenclamide, should be on the agenda for health policy makers. Improving better access to effective novel products (such as gliclazide and pen insulins) should be a major consideration for decision makers.

Funding:

This study was supported by a research grant from the Deputy of Research, Tehran University of Medical Sciences and the Research Center for Rational Use of Drugs. (Grant number: 92-01-156-22298)

Competing Interests:

We have no conflict of interests to declare.

Contributorship Statement:

AS developed the research proposal, extracted and analyzed the data. He contributed to interpretation of findings and drafted the manuscript.

AR contributed to proposal development, data analysis, results interpretation and major revision of the draft.

KG contributed to proposal development, data acquisition and extraction, results interpretation, and minor revision of the manuscript.

Data Sharing Statement:

Dataset might be available to the interested researchers upon request from the authors.

Figure Legends:

Figure 1- Utilization pattern of diabetes medicines (A10) in Iran

Figure 2- Pattern of drug utilization-90% for diabetes medicines in Iran

Figure 3- Benchmarking diabetes drugs utilization in Iran with OECD countries (2011)

Figure 4- Benchmarking the trend of diabetes drugs utilization (Iran and OECD countries with comparable diabetes prevalence according to IDF statistics)

Figure 5- Affordability of oral hypoglycemic agents in Iran

Figure 6- Affordability of insulin preparations in Iran

Reference:

1. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. The Lancet 2011;**378**(9785):31-40
2. Whiting DR, Guariguata L, Weil C, et al. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes research and clinical practice 2011;**94**(3):311-21
3. Alldredge BK, Corelli RL, Ernst ME, et al. *Koda-Kimble & Young's Applied Therapeutics; The Clinical use of Drug*. 10 ed: Lippincott Williams & Wilkins, 2012.
4. Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;**32**(1):193-203 [doi: 10.2337/dc08-9025published Online First: Epub Date].
5. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;**321**(7258):405-12
6. Melander A, Folino-Gallo P, Walley T, et al. Utilisation of antihyperglycaemic drugs in ten European countries: different developments and different levels. Diabetologia 2006;**49**(9):2024-29 [doi: 10.1007/s00125-006-0331-3published Online First: Epub Date].
7. Doró P, Benkő R, Kosik E, et al. Utilization of oral antihyperglycemic drugs over a 7–year period (1998–2004) in a Hungarian population and adherence to drug therapy. Eur J Clin Pharmacol 2005;**61**(12):893-97 [doi: 10.1007/s00228-005-0031-9published Online First: Epub Date].
8. Baviera M, Monesi L, Marzona I, et al. Trends in drug prescriptions to diabetic patients from 2000 to 2008 in Italy's Lombardy Region: A large population-based study. Diabetes Res Clin Pract 2011;**93**(1):123-30 [doi: http://dx.doi.org/10.1016/j.diabres.2011.05.004published Online First: Epub Date].
9. Rashidian A, Jahanmehr N, Jabbour S, et al. Bibliographic review of research publications on access to and use of medicines in low-income and middle-income countries in the Eastern Mediterranean Region: identifying the research gaps. BMJ open 2013;**3**(10):e003332
10. Esteghamati A, Meysamie A, Khalilzadeh O, et al. Third national surveillance of risk factors of non-communicable diseases (SuRFNCD-2007) in Iran: methods and results on prevalence of diabetes, hypertension, obesity, central obesity, and dyslipidemia. BMC Public Health 2009;**9**(1):167 [doi: 10.1186/1471-2458-9-167published Online First: Epub Date].
11. Esteghamati A, Gouya MM, Abbasi M, et al. Prevalence of Diabetes and Impaired Fasting Glucose in the Adult Population of Iran: National Survey of Risk Factors for Non-Communicable Diseases of Iran. Diabetes Care 2008;**31**(1):96-98 [doi: 10.2337/dc07-0959published Online First: Epub Date].
12. Haghdoost A, Rezazadeh-Kermani M, Sadghirad B, et al. Prevalence of type 2 diabetes in the Islamic Republic of Iran: systematic review and meta-analysis. Eastern

Mediterranean health journal= La revue de santé de la Méditerranée orientale= al-Majallah al-ṣiḥḥīyah li-sharq al-mutawassiṭ 2009;**15**(3):591-99
13. Oliaimanesh A, Abolhallaj M, Zangeneh M, et al. National Health Accounts Islamic Republic of Iran-2008. Tehran: National Institue of Health Research, Ministry of Health and Medical Education, 2013.
14. Rashidian A, Khosravi A, Khabiri R, et al. Islamic Republic of Iran's Multiple Indicator Demographic and Health Survey (IrMIDHS)-2010. Tehran: National Institue of Health Research, Ministry of Health and Medical Education, 2012.
15. Davari M, Haycox A, Walley T. The Iranian Health Insurance System; Past Experiences, Present Challenges And Future Strategies. Iranian J Publ Health 2012;**41**(9):1-9
16. Kavosi Z, Rashidian A, Pourreza A, et al. Inequality in household catastrophic health care expenditure in a low-income society of Iran. Health Policy Plan 2012;**27**(7):613-23 [doi: 10.1093/heapol/czs001published Online First: Epub Date].
17. Cheraghali AM, Nikfar S, Behmanesh Y, et al. Evaluation of availability, accessibility and prescribing pattern of medicines in the Islamic Republic of Iran. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit 2004;**10**(3):406-15
18. Abdollahiasl A. Medicine prices, availability, affordability and price components-Iran. Medicine prices and access to medicines in the Eastern Mediterranean Region. Cairo, Egypt: Essential Medicines and Pharmaceutical Policies Unit, World Health Organization, Regional Office for the Eastern Mediterranean, 2010.
19. Dinarvand R. New National Drug Policy in Iran leading to Expanded Pharmaceutical Market and Extended Access of Public to Medicines. Iranian journal of public health 2009;**38**(Suppl. 1):158-61
20. Davari M, Walley T, Haycox A. Pharmaceutical Policy and Market in Iran: past experiences and future challenges. Journal of Pharmaceutical Health Services Research 2011;**2**(1):47-52
21. Iran Pharmaceuticals & Healthcare Report Q2 2009. London, UK: Business Monitor International.
22. OECD. OECD Health Data: Pharmaceutical market. http://dx.doi.org/10.1787/data-00545-en.
23. Guidelines for ATC classification and DDD assignment. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, 2013.
24. Wettermark B, Pehrsson Å, Jinnerot D, et al. Drug utilisation 90% profiles—a useful tool for quality assessment of prescribing in primary health care in Stockholm. Pharmacoepidemiol Drug Saf 2003;**12**(6):499-510
25. WHO Model List of Essential Medicines: World Health Organization, 2013.
26. International Diabetes Federation-DIABETES ATLAS UPDATE 2012. http://www.idf.org/diabetesatlas/5e/Update2012.
27. Cameron A, Ewen M, Ross-Degnan D, et al. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. The Lancet;**373**(9659):240-49 [doi: http://dx.doi.org/10.1016/S0140-6736(08)61762-6published Online First: Epub Date].
28. Esteghamati A, Ashraf H, Khalilzadeh O, et al. Trends of diabetes according to body mass index levels in Iran: results of the national Surveys of Risk Factors of Non-Communicable Diseases (1999–2007). Diabet Med 2010;**27**(11):1233-40 [doi: 10.1111/j.1464-5491.2010.03103.xpublished Online First: Epub Date].

29. UKPDS. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ: British Medical Journal 1998:703-13
30. Peimani M, Tabatabaei-Malazy O, Heshmat R, et al. Knowledge, attitude and practice of physicians in the field of diabetes and its complications: A pilot study. Iran J Diabetes and Lipid Disord 2010;**9**:1-7
31. Shakibazadeh E, Larijani B, Shojaeezadeh D, et al. Patients' Perspectives on Factors that Influence Diabetes Self-Care. Iranian journal of public health 2011;**40**(4):146-58
32. Mounesan L, Nedjat S, Majdzadeh R, et al. Only One Third of Tehran's Physicians are Familiar with 'Evidence-Based Clinical Guidelines'. Int J Prev Med 2013;**4**(3):349-57
33. Sarayani A, Rashidian A, Gholami K, et al. Efficacy of continuing education in improving pharmacists' competencies for providing weight management service: Three-arm randomized controlled trial. J Contin Educ Health Prof 2012;**32**(3):163-73 [doi: 10.1002/chp.21141published Online First: Epub Date].
34. Forsetlund L, Bjørndal A, Rashidian A, et al. Continuing education meetings and workshops: effects on professional practice and health care outcomes. Cochrane Database Syst Rev 2009;**2**(2)
35. Beran D, McCabe A, Yudkin JS. Access to medicines versus access to treatment: the case of type 1 diabetes. Bull World Health Organ 2008;**86**(8):648-9 [doi: 10.2471/blt.07.048710published Online First: Epub Date].
36. Beran D, Yudkin JS. Looking beyond the issue of access to insulin: what is needed for proper diabetes care in resource poor settings. Diabetes Res Clin Pract 2010;**88**(3):217-21 [doi: 10.1016/j.diabres.2010.03.029published Online First: Epub Date].
37. Cheraghali AM. Impacts of international sanctions on Iranian pharmaceutical market. Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences 2013;**21**(1):64 [doi: 10.1186/2008-2231-21-64published Online First: Epub Date].
38. Butler D. Iran hit by drug shortage. Nature 2013;**504**(7478):15-6 [doi: 10.1038/504015apublished Online First: Epub Date].
39. OECD Health Data 2013 Definitions, Sources and Methods: Pharmaceutical consumption by DDDs: OECD Health Data 2013; http://www.oecd.org/health/healthdata.
40. Sarayani A, Jahangard-Rafsanjani Z, Hadjibabaie M, et al. A comprehensive review of adherence to diabetes and cardiovascular medications in Iran; implications for practice and research. Journal of Diabetes & Metabolic Disorders 2013;**12**(1):57
41. Cramer JA. A Systematic Review of Adherence With Medications for Diabetes. Diabetes Care 2004;**27**(5):1218-24 [doi: 10.2337/diacare.27.5.1218published Online First: Epub Date].

Table 1- Number of DDDs per 1000 inhabitants per day (DID) for A10A (Insulins and analogues) medicines

ATC code	2000/ 2001	2001/ 2002	2002/ 2003	2003/ 2004	2004/ 2005	2005/ 2006	2006/ 2007	2007/ 2008	2008/ 2009	2009/ 2010	2010/ 2011	2011/ 2012	2012/ 2013
A10AC01 (insulin (human))	0.64	0.93	1.10	1.36	1.48	1.77	1.87	2.49	2.22	2.79	3.09	3.36	3.52
A10AB01 (insulin (human))	0.16	0.20	0.31	0.42	0.50	0.63	0.72	0.93	1.00	1.15	1.32	1.80	1.91
A10AD01 (insulin (human))	<0.01	<0.01	<0.01	<0.01	<0.01	-	-	-	0.04	0.03	0.16	0.26	0.30
A10AE04 (insulin glargine)	-	-	-	-	-	-	-	<0.01	0.02	0.02	0.01	0.03	0.13
A10AD05 (insulin aspart)	-	-	-	-	-	-	-	-	-	0.03	0.07	0.09	0.11
A10AB05 (insulin aspart)	-	-	-	-	-	-	-	<0.01	0.01	0.00	0.01	0.03	0.05
A10AB04 (insulin lispro)	-	-	-	-	-	-	-	-	-	-	-	-	<0.01
A10AB02 (insulin (beef))	0.07	0.05	0.05	0.03	0.01	-	-	-	-	-	-	-	-
A10AC02 (insulin (beef))	0.29	0.14	0.21	0.09	0.03	-	-	-	-	-	-	-	-

Table 2- Number of DDDs per 1000 inhabitants per day (DID) for A10B (Blood glucose lowering drugs, excl. insulins) medicines

	2000/ 2001	2001/ 2002	2002/ 2003	2003/ 2004	2004/ 2005	2005/ 2006	2006/ 2007	2007/ 2008	2008/ 2009	2009/ 2010	2010/ 2011	2011/ 2012	2012/ 2013
A10BB01 (glibenclamide)	5.69	8.01	5.86	7.31	8.69	9.55	11.33	10.88	12.68	12.06	13.29	15.40	15.18
A10BA02 (metformin)	0.34	0.62	0.88	1.31	1.63	2.19	3.01	3.46	4.41	5.52	5.94	8.58	9.35
A10BB09 (gliclazide)	-	-	-	<0.01	0.06	0.14	0.23	0.44	0.59	0.74	0.88	1.31	1.13
A10BG0 (pioglitazone)	-	-	-	-	-	-	0.01	0.11	0.27	0.45	0.68	0.94	1.10
A10BX02 (repaglinide)	-	-	-	-	-	-	0.02	0.03	0.04	0.06	0.15	0.31	0.48
A10BF01 (acarbose)	-	-	-	<0.01	<0.01	<0.01	0.03	0.07	0.13	0.14	0.16	0.24	0.26
A10BD02 (metformin and sulfonamides)	-	-	-	-	-	-	-	-	-	-	-	0.01	0.03
A10BD05 (metformin and pioglitazone)	-	-	-	-	-	-	-	-	-	-	-	-	<0.01
A10BD07 (metformin and sitagliptin)	-	-	-	-	-	-	-	-	-	-	-	<0.01	<0.01
A10BB02 (chlorpropamide)	0.29	0.12	0.11	0.09	<0.01	-	-	-	-	-	-	-	-

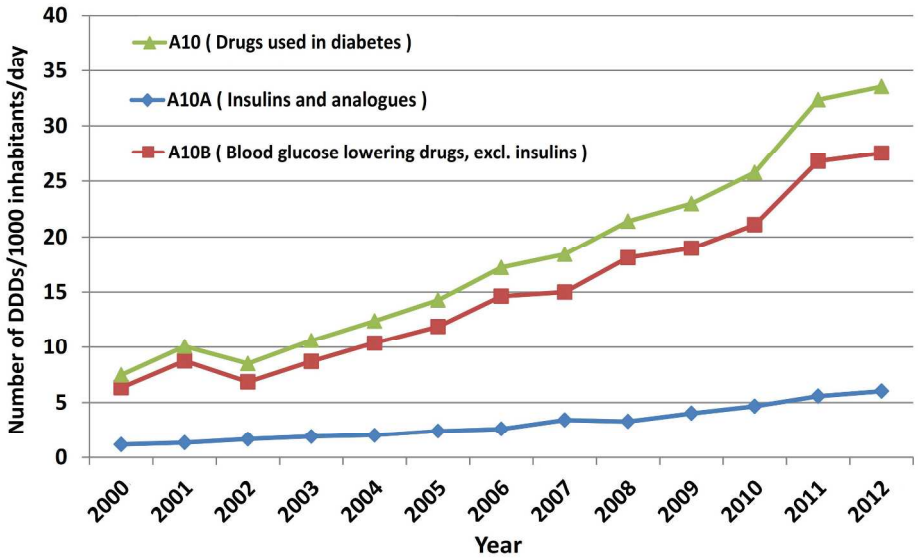

Figure 1- Utilization Pattern of Diabetes Medicines (A10) in Iran

256x166mm (300 x 300 DPI)

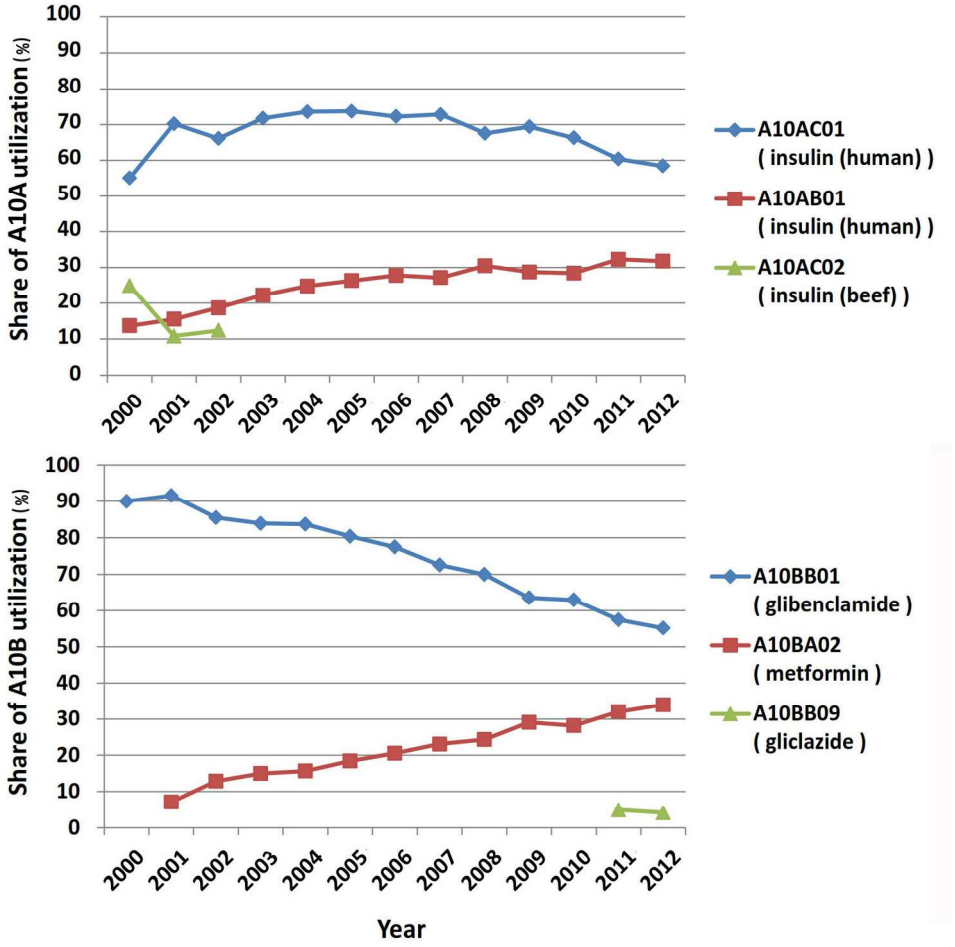

Figure 2- Pattern of Drug Utilization-90% for Diabetes medicines in Iran

154x158mm (300 x 300 DPI)

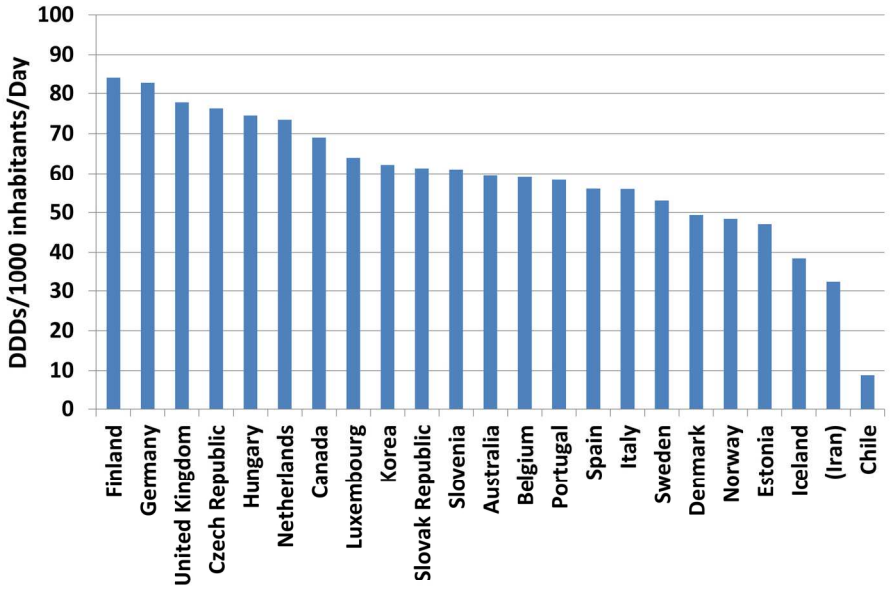

Figure 3- Benchmarking Diabetes Drugs Utilization in Iran with OECD Countries (2011)

170x119mm (300 x 300 DPI)

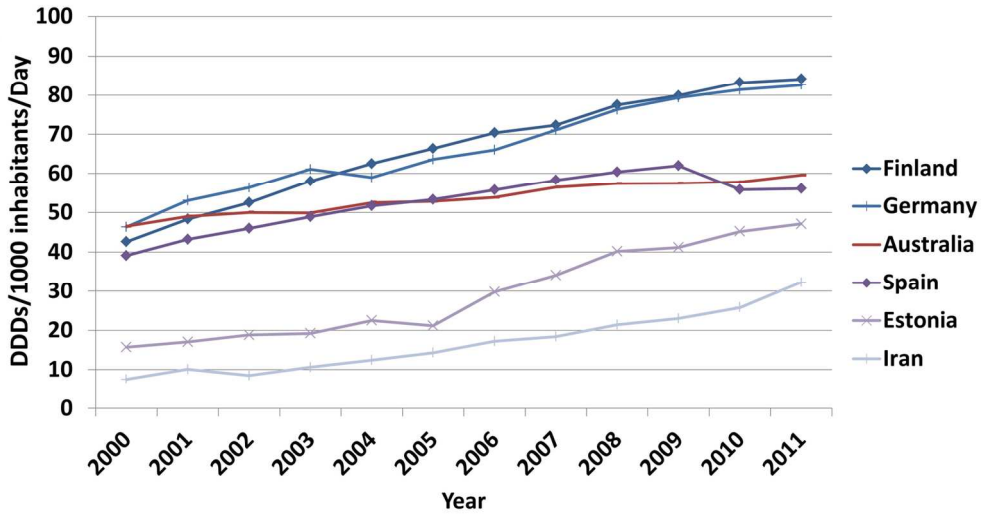

Figure 4- Benchmarking the Trend of Diabetes Drugs Utilization
(Iran and OECD countries with comparable diabetes prevalence according to IDF statistics)

144x86mm (300 x 300 DPI)

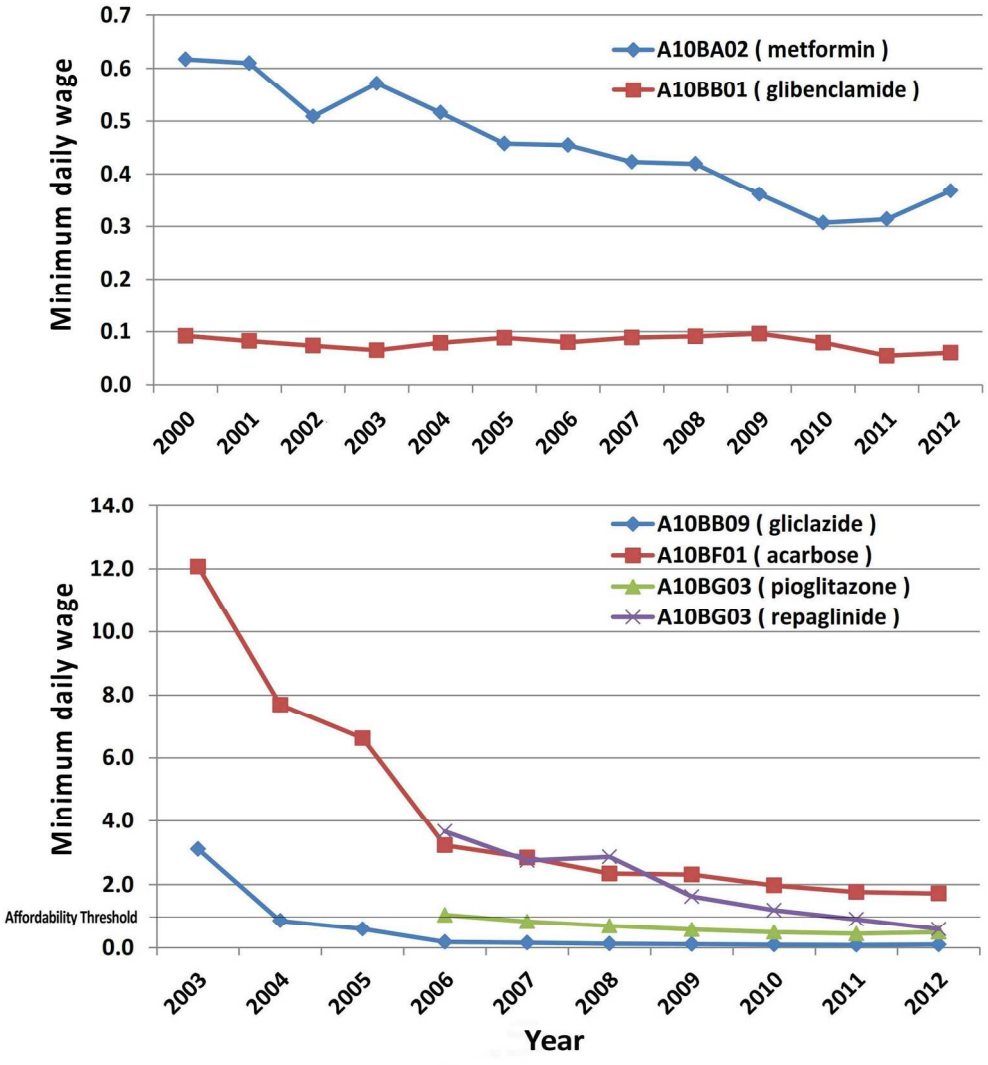

Figure 5- Affordability of Oral Hypoglycemic Agents in Iran

171x198mm (300 x 300 DPI)

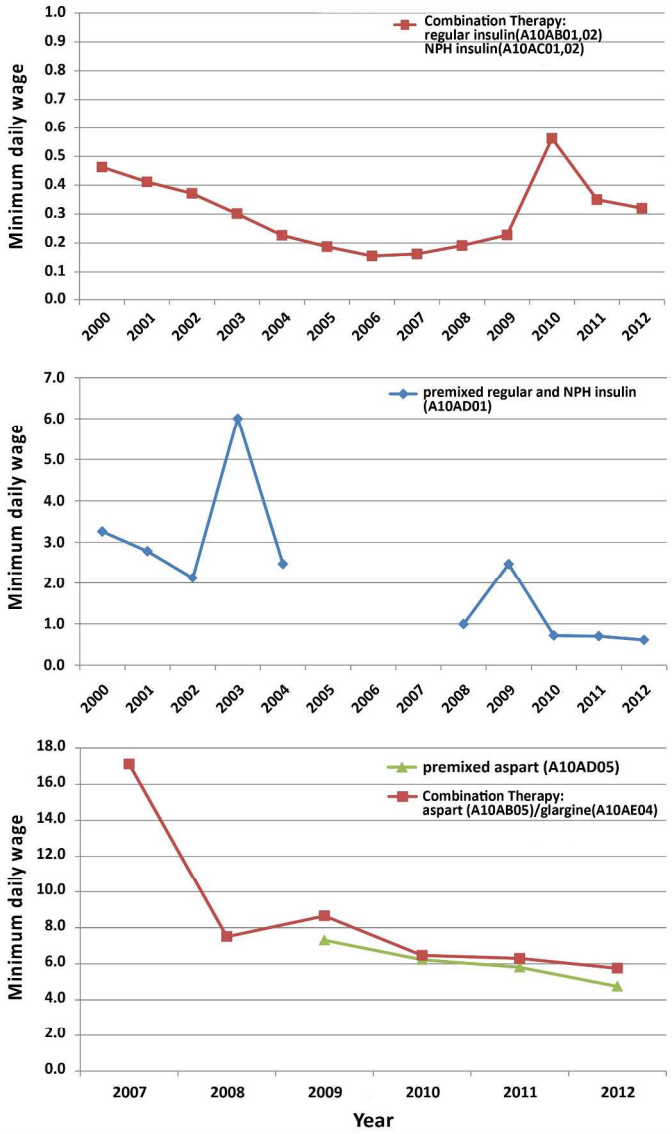

Figure 6- Affordability of Insulin preparations in Iran

178x304mm (300 x 300 DPI)