RESEARCH ARTICLE / *Araştırma Makalesi*

Evaluation of Insulin and Glucagon-Like Peptide-1 Analog Sales in Turkey Before the Pandemic Period; Projection for Upcoming Years: A Market Analysis Study

Pandemi Dönemi Öncesinde Türkiye'de İnsülin ve Glukagon Benzeri Peptid-1 Analog Satışlarının Değerlendirilmesi; Önümüzdeki Yıllar İçin Projeksiyon: Bir Pazar Analiz Çalışması

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Geliş Tarihi / Received : **18.11.2021** Kabul Tarihi / Accepted: **07.10.2022** Çevrimiçi / Online: **16.03.2023**

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Cite this article/Atıf
Vural İM., Sis CO., Ulusoy KG., Yıldız O., Evaluation of insulin and glucagon-like peptide-1 analog sales in turkey before the pandemic period; projection for upcoming years: a market analysis study, Sakarya Med J 2023 ;13(1):48-54 DOI: 10.31832/smj.1021311

Abstract

Introduction	This study was designed to evaluate the box sale trends of insulin preparations and glucagon-like peptide-1 (Glp-1) analogs by their therapeutic categories in Turkey. Also, we aimed to project sale trends of these pharmaceuticals in next years.
Materials and Methods	We analyzed the data before the covid-19 pandemic and made predictions based on these data. This study analyzed retail and hospital box sales of insulin preparations from 4 therapeutic categories (fast/short-acting, intermediate-acting, premix, long-acting) and Glp-1 analogs.
Results	Total box sales of the insulin preparations were increased by %13,30 in the period examined. While fast/short-acting and long-acting insulin box sales increased with a decreasing upward trend, intermediate-acting and premix insulin box sales decreased.
Conclusion	Glp-1 analog sales increased rapidly in this period. Currently, newer pharmaceuticals have been entering Turkish market for diabetes treatment. Less insulin might be required if newer pharmaceuticals are more widely available in diabetes treatment. Also it will be useful to evaluate the effect of the pandemic on access to pharmaceuticals used in the treatment of chronic diseases in future studies.
Keywords	Diabetes mellitus; Insulin sales; Glucagon-like peptide-1 analog sales

Öz

Amaç	*Bu çalışmada, Türkiye'deki insülin preparatları ve glukagon benzeri peptid-1 (Glp-1) analoglarının terapötik kategorilerine göre kutu satış trendlerini değerlendirmek amaçlanmıştır. Ayrıca bu ilaçların önümüzdeki yıllardaki satış trendlerini de yansıtılması hedeflenmiştir.*
Yöntem ve Gereçler	*Covid-19 pandemisi öncesi verileri analiz edilmiş ve bu verilere dayanarak tahminlerde bulunulmuştur. Bu çalışmada, 4 terapötik gruptaki insülin preparatlarının (hızlı/kısa etkili, orta etkili, premiks, uzun etkili) ve Glp-1 analoglarının perakende ve hastane kutu satışlarını analiz edilmiştir.*
Bulgular	*İncelenen dönemde insülin preparatlarının toplam kutu satışlarının %13,30 oranında arttığı saptanmıştır. Hızlı/kısa etkili ve uzun etkili insülin kutusu satışları azalan artış trendi ile artarken, orta etkili ve premiks insülin kutu satışları azalmıştır. Glp-1 analog satışları bu dönemde hızla artmıştır. Diyabet tedavisi için Türkiye pazarına yeni ilaç grupları ve etken maddeler girmektedir.*
Sonuç	*Bu yeni ilaçların diyabet tedavisinde daha yaygın olarak kullanılması daha az insülin kullanımına neden olabilir. Ayrıca gelecekte yapılacak çalışmalarda pandeminin kronik hastalıkların tedavisinde kullanılan ilaçlara erişim üzerindeki etkisinin değerlendirilmesi faydalı olacaktır.*
Anahtar Kelimeler	*Diyabetes Mellitüs; İnsülin satışları; Glukagon benzeri peptid-1 analog satışları*

INTRODUCTION

Despite all the precautions taken, diabetes mellitus (DM) is a severe epidemic that continues to grow and threatens public health in the world and in Turkey[1-2]. The International Diabetes Federation (IDF) estimates that 463 million adults worldwide have diabetes, and 1.1 million children and adolescents have type 1 diabetes mellitus (T1DM). The prevalence of diabetes has reached epidemic rates and is expected to reach 760 million by 2030. With the aging population, urbanization and changing lifestyles, the incidence of diabetes, along with other chronic diseases, rapidly increase. It is known that approximately three-quarters (79%) of diabetic patients live in low- and middle-income countries[2]. According to the field research conducted in 2010, 'Turkey Diabetes, Hypertension, Obesity and Endocrinology Diseases Prevalence Study-II (TURDEP-II Study)', diabetes rate in Turkey was 13.7%. Also, in that study, it was determined that in 12 years, diabetes prevalence in Turkey increased by 90%1. IDF also reported that Turkey has the highest age-adjusted comparative prevalence (11.1%) in all over Europe, with over 6,6 million diabetes patients[2]. According to the TURDEP-II data, diabetes has already reached the prevalence of the World Health Organization and the IDF rates, which are expected to be reached in the 2030s.

DM is a progressive disease, and reducing the risk of microvascular and macrovascular complications is the primary goal in the treatment of the disease. Therefore, strict glycemic control is required along with oral anti-diabetic drugs (OAD). Insulin therapy is also essential to achieve this glycemic control which is applied in the treatment of Type 2 diabetes mellitus (T2DM) when the dietary and OAD combinations cannot achieve targeted glycemic control[3]. Various stresses, such as acute and chronic complications, pregnancy, surgery and severe hyperglycemia and all patients with T1DM are also indications for insulin use[4].

Insulin preparations are categorized into three groups according to their effect profiles: short/fast/very fast-acting, intermediate-acting, and long/very long-acting. Various combinations of short/fast acting and intermediate-acting insulin have been developed to facilitate insulin treatment, particularly in T2DM. These are called ready-to-use insulin preparations (premix insulin)[5]. Usually, it is recommended to add basal insulin (long-acting insulin analogs) to OAD once a day at the beginning of insulin therapy in T2DM[6-9]. Various combinations of premix insulin are used to facilitate insulin therapy when basal insulin and OAD combination therapy cannot achieve glycemic control, likewise in the case of basal-bolus, insulin therapy is difficult to administer. Intermediate-acting insulins, which are often used in combination therapies, are closely related to hypoglycemia. Therefore, among the insulin treatment regimens, intermediate-acting insulin treatment is not much preferred[9]. Treatment of T2DM includes daily single dose long-acting insulin or premix insulin with or without the combination of OADs10. T1DM treatment usually includes basal-bolus insulin therapy11, which is made up of a combination of basal (long-acting) and bolus (short-acting) insulins[12].

All over the world and in Turkey; Glucagon-like peptide-1 (Glp-1) analogs were added to T2DM treatment in the last decade. Glp-1 analogs should be added to treatment in patients with T2DM who do not have adequate glycemic control with insulin and OADs and combinations thereof. They are preferred in the second-and third-line treatment, especially in obese patients with T2DM (BMI≥30 kg/m2)[2]. The addition of a Glp-1 analog to the therapy in patients not achieving glycemic targets despite optimized basal insulin therapy is one of the recommended options[13]. The results of studies in obese T2DM patients showed that this combination therapy lowered required insulin doses, provided adequate glycemic control and minimalized insulin-dependent weight gain in those patients[14].

Increased T2DM rates support the growth of the insulin market. It was estimated that global insulin use will increase by 20% between 2018 and 2030 in T2DM15. On

the other hand, since the beginning of the 2000s shift between insulin categories was shown in T2DM treatment. Long-acting insulin analogs market share was increased in different countries' insulin markets[16-17]. In this retrospective study of the sales trends, we aimed to evaluate the box sale trends of the insulin preparations and Glp-1 analogs, a new therapy, by their therapeutic categories in Turkey. Also, we aimed to project the sales trends of these drugs in the coming years in the absence of pandemic conditions.

MATERIALS and METHODS

This study analyses retail and hospital box sales of insulin preparations from 4 therapeutic categories as fast/short-acting, intermediate-acting, premix (fast+intermediate) and long-acting insulins and Glp-1 analogs as well.

1. Data collection

Data used in this study were obtained from IQVIA Health, an international pharmaceutical consulting company that collects sales and price data from various countries. The company collects the data at the level within the pharmaceutical market supply and distribution chain that provides reliable information. The IQVIA data used here were on all pharmaceutical sales for the selected sample through retail pharmacies for 5 years between 2014 and 2019. The central unit of analysis here was the product, aggregated overpacks for each product. The data were used in quarterly periods starting from the last quarter of 2014 and ending in the third quarter of 2019. By using these 20-time points, market trends were estimated up to the last quarter of 2022.

2. The proposed model

The most used linear econometric methods in the estimation of time series are the Box-Jenkins methodology known as Autoregressive Integrated Moving Average (ARIMA) models. The method was developed by Box and Jenkins in 1976, and the foundations of this method were laid by Yule in 1927. Varieties of autoregressive moving average techniques (MA, AR, ARIMA, etc.) have become essential procedures in the analysis of time series. The method is widely used because it considers the stability and seasonality of the evaluated series at the same time and can be easily applied by using package programs.

According to the Box-Jenkins method, any variable is modeled using its own and stochastic error terms' historical values. The ARIMA model is preferred for estimating non-stationary time series whose mean and variance are not constant over time. The general representation of these models is an ARIMA (p, d, q). Here, "p" is the degree of autoregressive (AR) model, "q" is the degree of moving average (MA) model and "d" is the degree of differentiation18. The basic steps in the Box-Jenkins approach in the process of setting up the time series model can be considered in four stages such as determination of the time series model, model fitting, test, and estimation[18]. These steps were provided to estimate future trends by performing the best model for our case.

Mean Absolute Percentage Error (MAPE), Alternate Square Error (MSE), Mean Absolute Error (MAE), Root Mean Square Error (RMSE), Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC) criteria have been used to select the best model for the time series. Applying such generally accepted objective model selection criteria in the model determination stage allows avoiding a certain degree of subjectivity. The model with more minor selection criterion statistics could be preferable[19].

3. The results of the proposed model

In this study, all methods were performed using SPSS (version 22) software. In order to model the time series of insulin data, first, since the series was not stationary, the difference series were formed, and then many models were performed by giving various values to p and q parameters. The stability of the first difference sequence was analyzed, and then from this, it was deduced that the model was suitable. After testing the candidate models in which the primary criteria was to reach the best estimation, results were given by using selection criteria such as (MSE, RMSE, MAE, MAPE, AIC, BIC) (Table 1).

Table 1: Autoregressive Integrated Moving Average (ARIMA) models	
Glp-1 analogs	ARIMA(0,1,0)(1,0,0)
Fast-acting	ARIMA(1,1,0)(1,0,0)
Premix (fast+intermediate)	ARIMA(0,0,0)(0,1,0)
Intermediate-acting	ARIMA(0,1,0)(1,1,1)
Long-acting	ARIMA(0,1,0)(0,0,1)
Total	ARIMA(0,1,1)(1,0,0)

RESULTS

Total box sales of insulin preparations were 2.964.760 boxes (total of fast-acting, intermediate-acting, premix and long-acting insulin) in the first quarter which was investigated in this study. Box sales increased to 3.359.114 boxes in the last quarter, which was analyzed in this study, with 13,30% increase. While fast/short-acting and long-acting insulin box sales increased in that period (17,57% and 67,52%, respectively), intermediate-acting and premix insulin box sales decreased (35,86% and 27,08%, respectively). Glp-1 analogs sales increased rapidly in this period. Quarter box sales average by years are shared in the Table-2.

If an extraordinary situation does not occur, the upward trend in long-acting insulin and Glp-1 analogs box sales will continue with the applied models. While the total box sales of insulin preparations will be about 13,5 million boxes with a 10,4% increase in 2022 (Figure-1a), Glp-1 analogs box sales will be about 0,3 million with a 200% increase (Figure-2). Fast/short-acting and long-acting insulin box sales will be about 5,3 million and 5,1 million boxes, respectively, between 2020-2022. The box sales decrease of intermediate-acting and premix insulin will continue in the following years (Figure-1b)

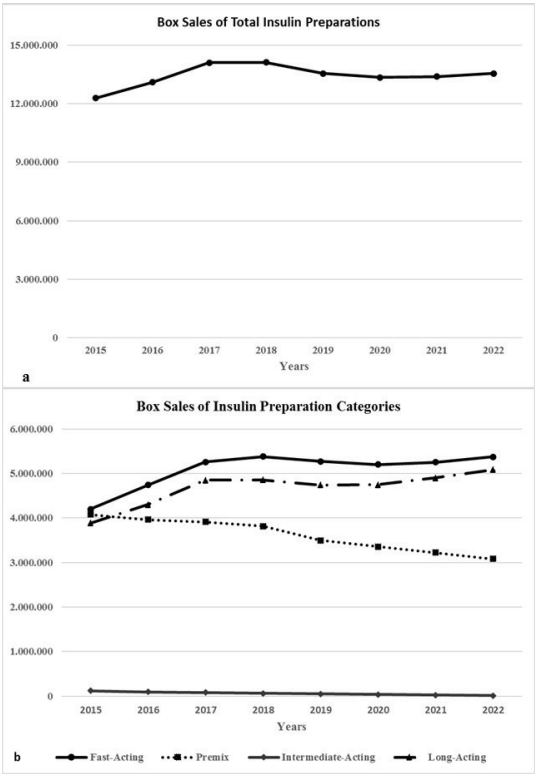

Figure 1: Annual, between 2015-2019, and projected, between 2020-2022, box sales of total (a) and categories of (b) insulin preparations in the Turkish market. Insulin preparations are categorized according to their duration of action as fast / short-acting, medium-acting, premix (fast-medium) and long-acting insulins.

Table 2: Annual, between 2015-2019, and projected, between 2020-2022, average sales of quarter box sales of total and categories of insulin and Glucagon-like peptide-1 (Glp-1) analog preparations in the Turkish market. Insulin preparations are categorized according to their duration of action as fast/short-acting, medium-acting, premix (fast-medium) and long-acting insulins.

Year	Quarter	Glp-1 Analogs	Fast-acting	Premix	Intermediate-acting	Long-acting	Total
2014	4th quarter	16.201	964.766	1.035.458	32.541	931.995	2.964.760
2015	Average of all quarters	23.416	1.049.749	1.019.446	29.030	971.510	3.069.736
2016	Average of all quarters	34.748	1.185.226	990.190	23.794	1.074.851	3.274.061
2017	Average of all quarters	46.033	1.315.020	977.718	20.746	1.212.309	3.525.793
2018	Average of all quarters	56.069	1.344.473	954.134	15.719	1.213.669	3.527.994
2019	Average of 3 quarters	60.779	1.331.551	885.787	11.419	1.196.838	3.425.595

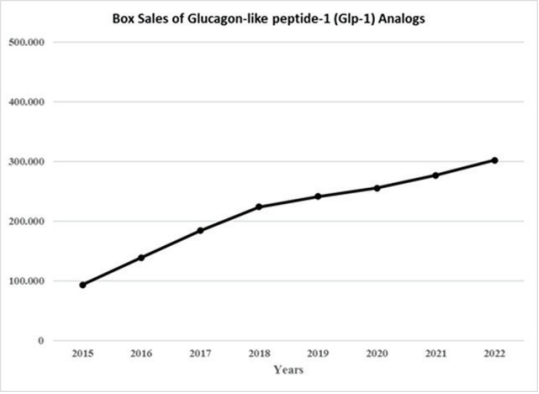

Figure 2: Annual, between 2015-2019, and projected, between 2020-2022, box sales of total Glucagon-like peptide-1 (Glp-1) analog preparations in the Turkish market.

DISCUSSION

Anti-diabetic pharmaceuticals are one of the leading therapeutic groups in pharmaceutical market share. According to the analysis, this situation will continue in the forthcoming years[28]. In this study, we demonstrated that total box sales of the insulin preparations were increased by %13,30 between the last quarter of 2014 and the third quarter of 2019. While fast/short-acting and long-acting insulin box sales increased with a decreasing upward trend, intermediate-acting and premix insulin box sales decreased. Also, Glp-1 analog sales increased rapidly in this period. Previously, it was demonstrated that a total of 4,2 million OAD preparation boxes were sold in 1998, while this number reached 38,1 million boxes in 2014 in Turkey[29]. Likewise, in Canada it was demonstrated that total insulin utilization increased 21% between 2010 and 2015[17]. Most of the insulins and insulin analogues currently authorized in the European Union (EU) were already available before 200530. Similarly, insulin have been on the Turkish market for a long time. Also, four biosimilar insulin analogues have been on the EU market since 2014[30]; furthermore, they have been available in Mexico, India, China and other parts of Asia for more than a decade[31]. First biosimilar insulin entered Turkish market in 2016. These biosimilars are improving insulin access worldwide. It was estimated that global insulin use will increase by 20% between 2018 and 2030 in T2DM[15]. According to the data of Turkish Social Security Institution, between 2008 and 2012, while spending on OAD decreased over the years, spending on insulin and analogues increased by an average of 15% each year compared to the previous year[32]. In our study, we showed that the rate of increase in total insulin box sales has been decreasing since 2017. We estimate that the increase trend in the insulin sales will continue slightly. Currently newer pharmaceuticals have been entering Turkish market for T2DM treatment. Less insulin might be required if newer drugs such as Glp-1 analogs and sodium-glucose co-transporter-2 (SGLT2) inhibitors will be more widely available in T2DM treatment. Future studies would analyze whether the plateau condition or slight increase in insulin box sales will continue.

In the treatment of T2DM, basal insulin or premix insulin or a combination of oral anti-diabetic agents and insulin analogs is recommended[10,26]. On the other hand, T1DM patients need daily insulin injections to maintain a glucose level in the appropriate range[2]. Basal-bolus insulin therapy should be preferred in those patients[11]. As 2000s, a shift in insulin utilization from the human insulin to human insulin analogs was observed. Long-acting insulin analogs' market share reached 50% in the beginning of the 2010s in US market[16]. The first biosimilar long-acting insulin analog, which might affect insulin preparations' market share, was approved for marketing in 2015 and then other biosimilars entered in US market, respectively[31]. It was demonstrated that the rate of utilization of long-acting insulin had increased between the years 2010-2015 also in Canada. In that period dispensing rate of intermediate-acting and premix insulin declined[17]. In our study, while the rate of increase in fast-acting insulin and long-acting insulin box sales have been decreasing since 2017, the increasing trend in these insulins will continue slightly. Also, intermediate-acting insulin and premix insulin box sales decreased year by year. These data are similar to both US and Canada data, which are mentioned above.

Glp-1 analogs entered Turkish pharmaceutical market in the beginning of the 2010s. According to the Turkish Social Security Institution rules, these pharmaceuticals are reimbursed in the second-and third-line treatment, especially in obese patients with T2DM. Despite these restricted rules, in our study, we demonstrated that Glp-1 analogs box sales increased rapidly in the second half of 2010s, although total insulin box sales reached the plateau in last years. The first Glp-1 analog product was approved in the EU in 2006. Thereafter, five more products of that class have been authorized, most recently in 2018[30]. The safety and effectiveness of Glp-1 analogs are confirmed by systematic reviews[33]. In a study, clinical characteristics of patients in which Glp-1 analogs were initiated from 2010 to 2018 in Northeast Italy were investigated. It was shown that 50% of patients who have initiated treatment between the years 2016 to 2018 were prescribed Glp-1 analog[34]. In different forecasts, it was estimated that the world Glp-1 analog market would grow in the following years. North America is the largest consumer of these pharmaceuticals[35-36]. In our study, we also predicted that if an extraordinary situation does not occur, the upward trend in Glp-1 analogs box sales will continue in upcoming years with a similar ratio. At the beginning of 2020, the first oral Glp-1 analog was licensed by European Medicines Agency (EMA). Therefore, it can easily be predicted that the market share of insulin and other antidiabetic pharmaceuticals would change. Also, in the last reports, it was stated that Glp-1 analogs might be considered a second-line treatment for T2DM after metformin, especially in obese patients who need to be avoided from hypoglycemia[37]. Considering these advancements, the impact of Glp-1 analogs on the sales and clinical use of insulin should be investigated in the coming years.

In conclusion, we showed that fast-acting insulin and long-acting insulin box sales upward trend is decreasing since 2017. This trend is expected to continue likewise over the next few years. On the other hand, premix and intermediate-acting insulin box sales are decreasing in last years and this decrease tends to continue in upcoming years. With this trend, we may say that intermediate-acting insulin will have a limited market share or will exit from Turkish market. It is considered that the increase in the sales of Glp-1 analogs will continue further due to the widespread use of these pharmaceuticals in recent years. Moreover, with the introduction of new pharmaceuticals such as dipeptidyl peptidase-4 (DPP-4) inhibitors and SGLT2 inhibitors, the market share balance of insulin and other antidiabetic pharmaceuticals would change, as well as treatment strategies. In this study, we analyzed the data before the covid-19 pandemic and made predictions based on these data. It will be helpful to evaluate the effect of the pandemic on access pharmaceuticals used in the treatment of chronic diseases in future studies.

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