Turkish Journal of Diabetes and Obesity / *Türkiye Diyabet ve Obezite Dergisi*
Original Article / Özgün Araştırma

Effects of Glargine u300 on Low-Density Lipoprotein (LDL), Triglyceride(TG) and Blood Glucose Levels: Real-Life Outcomes

Ahmet Toygar KALKAN, Bilge BAŞDOĞAN, Özge ÖZER, Fatma Belgin EFE, Medine Nur KEBAPÇI, Aysen AKALIN, Göknur YORULMAZ ✉

Eskisehir Osmangazi University, School of Medicine, Department of Endocrinology and Metabolism, Eskisehir, Turkey

Cite this article as: Kalkan AT et al. Effects of glargine u300 on low-density lipoprotein (LDL), triglyceride(TG) and blood glucose levels: real-life outcomes. Turk J Diab Obes 2022;2: 137-142.

ABSTRACT

Aim: In real life, we aimed to evaluate the effect of new generation insulin glargine u-300 on fasting blood glucose, HbA1c, LDL and triglyceride levels.

Material and Methods: This is a retrocspective cohort study. We retrospectively reviewed patients who applied to the Endocrinology and metabolism outpatient clinic of Eskişehir Osmangazi University in 2019, whose old generation basal insulin was replaced with glargine u-300 and whose antilipidemic treatment was not changed. We compared fasting blood glucose(mg/dl), HbA1c(%), LDL(mg/dl) and triglyceride(mg/dl) values at baseline and after 3 months. We also evaluated these data by separating them into genders. Shapiro–Wilk normality test was performed for continuous variables. Wilcoxon Signed Ranks test was performed for non-normally distributed variables.

Results: Data concerning 109 patients were analysed. The fasting blood glucose average and median value decreased in control after starting glarjin u-300. However, it was not statistically different (p=0.06). The HbA1c control value (8.8%) decreased statistically significantly compared to the baseline value (9.61%) (p<0.001). The LDL control value(116.6mg/dl) also decreased statistically significantly compared to the baseline value (124mg/dl) (p<0.001). Although Hba1c and LDL were significant, there was no significant difference in terms of triglycerides. When we evaluate the sexes separately, we see that fasting blood glucose, HbA1c, LDL and triglyceride values decrease more in men. Fasting blood glucose, which does not show statistically significant difference in women, has been shown to decrease significantly in men.

Conclusion: We think that showing statistically significant HbA1c and LDL decline with the Glarjin u-300 in real-life data is promising for further studies. At the same time, despite the significant decrease in fasting blood glucose in men, the inability to show it in women should be considered as data that need further evaluation.

Keywords: *Glargine u-300, LDL, HbA1c, Triglyceride*

Glargine u300'ün Düşük Yoğunluklu Lipoprotein (LDL), Trigliserid (TG) ve Kan Şekeri Düzeyleri Üzerindeki Etkileri: Gerçek Yaşam Sonuçları

ÖZ

Amaç: Gerçek hayatta yeni nesil insülin glarjin u-300'ün açlık kan şekeri, HbA1c, LDL ve trigliserit düzeylerine etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Eskişehir Osmangazi Üniversitesi Endokrinoloji ve Metabolizma polikliniğine 2019 yılında başvuran, eski nesil bazal insülin yerine glargine u-300 kullanılan ve antilipidemik tedavisi değişmeyen hastaları geriye dönük olarak inceledik. Başlangıçta ve 3 ay sonra açlık kan şekeri(mg/dl), HbA1c(%), LDL(mg/dl) ve trigliserit(mg/dl) değerlerini karşılaştırdık. Biz de bu verileri cinsiyetlere

ORCID: Ahmet Toygar Kalkan / 0000-0002-9709-1871, Bilge Başdoğan / 0000-0002-2617-7790, Özge Özer / 0000-0003-1795-329X, Fatma Belgin Efe / 0000-0002-1976-6060, Medine Nur Kebapçı / 0000-0002-8286-5256, Aysen Akalın / 0000-0003-3550-2871, Göknur Yorulmaz / 0000-0001-8596-9344

Correspondence Address / Yazışma Adresi:
Özge ÖZER
Eskisehir Osmangazi University, School of Medicine, Department of Endocrinology and Metabolism, Eskisehir, Turkey
Phone: +90 538 063 39 11 • E-mail: ozer1.ozge@gmail.com

DOI: 10.25048/tudod.1092781

Received / *Geliş tarihi* : 24.03.2022
Revision / *Revizyon tarihi* : 17.06.2022
Accepted / *Kabul tarihi* : 05.07.2022

ayırarak değerlendirdik. Sürekli değişkenler için Shapiro-Wilk normallik testi yapıldı. Normal dağılım gösteren değişkenler için paired sample t testi, normal dağılım göstermeyen değişkenler için Wilcoxon Signed Ranks testi uygulandı.

Bulgular: 109 hasta ile ilgili veriler analiz edildi. Açlık kan şekeri ortalaması ve medyan değeri kontrolde glarjin u-300'e başladıktan sonra azaldı. Ancak istatistiksel olarak farklı değildi(p=0,06). HbA1c kontrol değeri (%8,8) başlangıç değerine (%9,61) göre istatistiksel olarak anlamlı derecede azaldı (p<0,001). LDL kontrol değeri (116,6mg/dl) ayrıca başlangıç değerine (124mg/dl) kıyasla istatistiksel olarak önemli ölçüde azaldı (p<0,001). Hba1c ve LDL anlamlı olmasına rağmen trigliseridler açısından anlamlı fark yoktu. Cinsiyetleri ayrı ayrı değerlendirdiğimizde erkeklerde açlık kan şekeri, HbA1c, LDL ve trigliserit değerlerinin daha fazla düştüğünü görüyoruz. Kadınlarda istatistiksel olarak anlamlı farklılık göstermeyen açlık kan şekerinin erkeklerde önemli ölçüde düştüğü gösterilmiştir.

Sonuç: Gerçek hayat verilerinde Glarjin u-300 ile istatistiksel olarak anlamlı HbA1c ve LDL düşüşü göstermenin daha sonraki çalışmalar için umut verici olduğunu düşünüyoruz. Aynı zamanda erkeklerde açlık kan şekerindeki önemli düşüşe rağmen kadınlarda gösterilememesi daha fazla değerlendirilmesi gereken veriler olarak değerlendirilmelidir.

Anahtar Sözcükler: *Glargine u-300, LDL, HbA1c, Trigliserid*

INTRODUCTION

Diabetes Mellitus is a chronic disease that causes many morbidities and limits the standard of living. It is believed that in 2019 there were about 463 million diabetes patients, corresponding to 9.3% of adult people. (1) In 2009 it was estimated that 285 million people had diabetes (2) , increasing to 366 million in 2011 (3) , 382 million in 2013 (4), 415 million in 2015 (5) and 425 million in 2017 (6). In the projections made with the current data, it is reported that the rate of diabetes will continue to be one of the most important public health problems.

It has been reported that macrovascular diseases are the most important cause of increased mortality and morbidity in diabetic patients. (7) (8). Lipid abnormalities contribute to the development of atherosclerosis in diabetic patients together with glucose dysregulation. (9) Significant reduction in plasma LDL cholesterol levels after insulin therapy has been shown in diabetic patients who started insulin (10). For this reason, insulin therapy provides glucose regulation and decreases the LDL level provides an important advantage in the treatment.

In addition to the long acting insulin analogs used, new second generation basal insulin analogs such as insulin glargine 300 U / mL (Gla-300) have been developed to improve glycemic control and minimize the risk of hypoglycaemia. Gla-300 provides a more stable and prolonged pharmacokinetic and pharmacodynamic profile than insulin glargine u-100 (11). Also, randomized controlled studies have shown that lower hypoglycaemia occurs with similar glycemic control (12,13). In real-life studies, which were evaluated retrospectively in accordance with randomized controlled trials, it was shown that HbA1c reduction comparable to older generation basal insulins was achieved with decreased hypoglycemia (14,15).

In In this study, we aimed to evaluate what the new generation glargine u-300, which has been shown to be more potent, yield similar HbA1c reduction, and its real-life response. We also aimed to evaluate the effect of the more potent new generation glargine u-300 on LDL, based on the demonstration that the LDL level decreased in patients with basal insulin.

MATERIALS and METHODS

This is a retrospective cohort study Diabetic patients who applied to Eskişehir Osmangazi University Endocrinology and Metabolism outpatient clinic in 2019 were evaluated retrospectively. There is no study showing the effects of Glargine u300 on LDL. For this reason, the first 30 patients who were started on glargine u300 in 2019 were analyzed while performing the preliminary power analysis. The power was taken as 0.8 according to the mean and standard deviations obtained. It was observed that 0.81 power was provided with 14 patients. When the post-Hoc power analysis was performed, the power of the study was found to be 0.98. Patients whose basal insulin was replaced with glargine u-300 and whose antilipidemic therapy was not changed were recorded. As a result, 109 patients who met the criteria were included in the study.

The fasting blood glucose of 108 patients, the Hba1c value of 107 patients and the lipid profile of 96 patients were achieved. We recorded the initial values of patients at the onset of glargin u-300 and the first blood samples between 3-6 months. Age, gender, HbA1c(%), LDL(mg/dl), triglyceride(mg/dl) and fasting blood glucose(mg/dl) values were recorded. Glucose,LDL, tryglyceride was studied from plasma by spectrophotometric methods. HbA1c was studied by turbidimetric inhibition method.

The Local Ethics Committee of Eskisehir Osmangazi University approved the study protocol in accordance with the principles of the Declaration of Helsinki. (07.1.2020/48).

Statistical Analysis

Statistical analysis was performed with SPSS IBM Statistic 20. Shapiro–Wilk normality test was performed for contin-

uous variables. All variables were compared and it was seen that they were not normally distributed. Wilcoxon Signed Ranks test was performed for non-normally distributed variables. Mean±standard deviation and median (Quartiles) values were used for descriptive statistics. A 'p value' of less than 0.05 was considered statistically significant.

RESULTS

57.8% of the patients were female and 42.2% were male. The average age was calculated as 59.86 (22-85). The average age of women was 61.79 and the average age of men was 57.22.

Variables at the beginning of the glargine u-300 and 3 months after starting are shown in Table 1.

The fasting blood glucose average and median value decreased in control after starting glargine u-300. However, it was not statistically different (p=0.06). The HbA1c control value (8.8%) decreased statistically significantly compared to the baseline value (9.61%) (p<0.001). The LDL control value (116.6mg/dl) also decreased statistically significantly compared to the baseline value (124mg/dl) (p<0.001). Although Hba1c and LDL were significant, there was no significant difference in terms of triglycerides.

When we consider the sexes separately, we see that fasting blood glucose, HbA1c, LDL and triglyceride values decrease more in men. (Table 2 and 3). Fasting blood glucose, which does not show statistically significant difference in women, has been shown to decrease significantly in men.

Table 1: Initial characteristics of the patients included in the study

	Women, n=63 (57.8%)	Men, n=46 (42.2%)	Total, n=109
Age (mean)	62.11	57.37	60.08
Glucose (mean) (mg/dl)	193.29	187.68	190.90
LDL (mean) (mg/dl)	131.98	130.10	131.17
Trygliceride (mean) (mg/dl)	206.87	176.19	193.77
Hba1C (mean) %	9.48	9.45	9.48

Table 2: FPG, Hba1c, LDL, triglyceride initial and posttreatment values

n=109	Initial	Post treatment	*p*
Fasting plasma glucose (mg/dl) (median- 25%-75%)	189.50 (133.25-245.5)	171 (129-222)	0.06
Hba1c (%) (median- 25%-75%)	9.61 (8.22-10.54)	8.8 (7.8-10)	***<0.001***
LDL (mg/dl) (median- 25%-75%)	124 (102.9-153.9)	116,6 (98.22-139.65)	***<0.001***
Trygliceride (mg/dl) (median- 25%-75%)	156 (111.5-237)	148.5 (105.25-200.75)	0.323

Table 3: Variables of men

n=46	Initial	Post treatment	*p*
Fasting plasma glucose (mg/dl) (median- 25%-75%)	198 (139.25-241)	156.5 (126.25-201.5)	***0.028***
Hba1c (%) (median- 25%-75%)	9.64 (8.34-10.50)	8.6 (8.02-9.5)	***=0.001***
LDL (mg/dl) (median- 25%-75%)	124.95 (102.6-150.85)	113.7 (90.02-132.2)	***<0.001***
Trygliceride (mg/dl) (median- 25%-75%)	160 (100.25-243)	136.5 (95.5-191)	0.245

Table 4: Variables of women

n=63	Initial	Post treatment	*p*
Fasting plasma glucose (mg/dl) (median- 25%-75%)	184 (127.25-256.75)	181 (137.25-244.25)	0.520
Hba1c (%) (median- 25%-75%)	9.57 (8.13-10.59)	9,31 (7.75-10.22)	***=0.012***
LDL (mg/dl) (median- 25%-75%)	124 (102.5-156.4)	118 (96.75-142.02)	***=0.003***
Trygliceride (mg/dl) (median- 25%-75%)	156 (115-219)	167 (109.25-209.5)	0.826

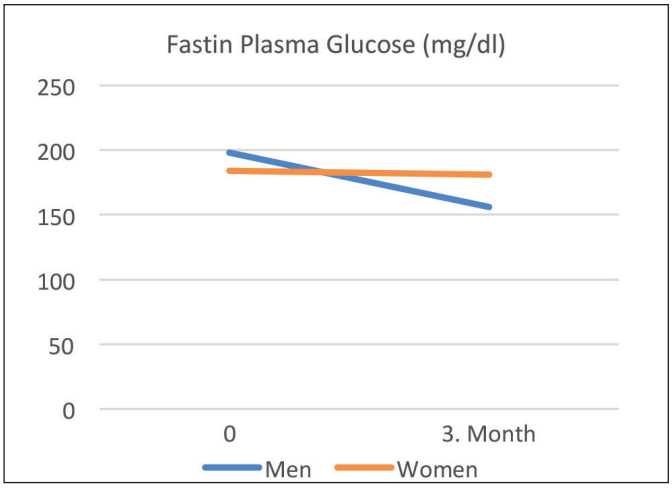

Figure 1: FPG of genders.

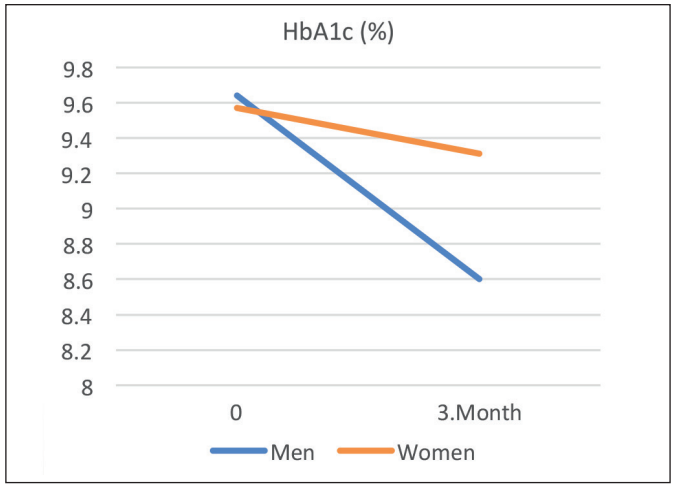

Figure 2: HbA1c of genders.

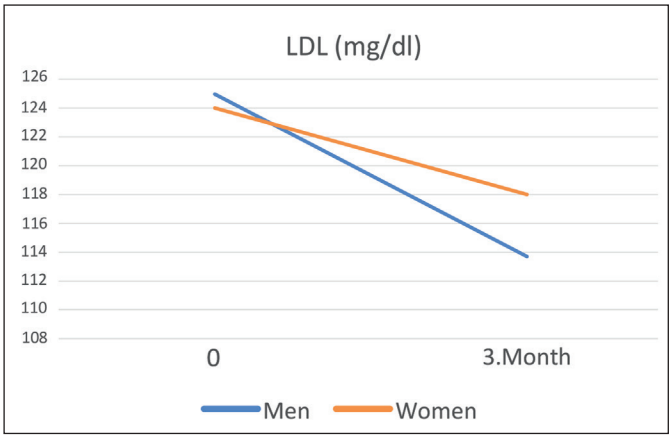

Figure 3: Low Density Lipoprotein of genders

DISCUSSION

Glargine u-300 is a new generation basal insulin. Although there are several randomized controlled trials about this insulin, we do not yet have clear information about real life data. It is one of the most prominent features reported to provide similar glycemic control with less hypoglycemia with older generation basal insulins. However, we do not have sufficient data in terms of its effect on plasma lipid profile and its effect on glycemia in real life. When we interpret the data obtained from our study, it was shown that there was a significant improvement in glycemic control. The absence of a control arm in our study is the limitation of our study. However, since our data are real-life values, our results provide clinically useful results.

Contrary to what has been shown in randomized controlled trials, a significant reduction in HbA1c levels is a condition we should consider. In fact, when we look at gender differences, a more significant decrease in fasting blood glucose and HbA1c in men can be considered as an important data for future research.

There are studies in the literature showing that there is a significant decrease in LDL value when older generation basal insulins are started in patients using oral antidiabetic medication (10). This gives us an idea that insulin may also have an antilipidemic effect. In our study, it was shown that there was a significant decrease in LDL values in patients whose old generation basal insulin was replaced with glargine

u-300. It is also an interesting detail that the current LDL decline is not accompanied by triglyceride decline. Because, triglyceride decrease has also been shown in patients who started on the old generation basal insulin (10). In women, the decrease in LDL levels without a significant decrease in fasting blood glucose should also be considered as a remarkable data. These data show us that the antilipidemic effect of glargine u-300 can be achieved by a different mechanism than basal insulin. However, in order to say this, further research is needed.

In conclusion, we found a significant decrease in HbA1c, fasting blood glucose and LDL values in patients who were replaced with old generation basal insulin, glargine u-300. Unlike randomized clinical studies, this improvement in blood glucose profile needs to be evaluated with further research.

Although triglyceride levels are stable, statistically significant decline in LDL levels also emerges as another detail that attracts attention. Considering that the most important cause of morbidity and mortality in diabetic patients is heart diseases, evaluation of the shown LDL decline with further researches will clarify this issue.

Another point to note is that blood glucose drops differ between genders. Not only the difference in blood glucose, but also in the lipid profile, there is a remarkable difference between the sexes in favor of men. This situation should be supported by further research.

One of our important limitations is that our study was retrospective and there was no control arm. However, the data we obtained can be considered remarkable for further research.

Acknowledgment

None.

Author Contributions

All authors contributed to the literature review and data collection.

Conflicts of Interest

There is no conflict of interest in our study. Our study is not funded by any institution.

Financial Disclosure

Our study is not funded by any institution.

Ethical Approval

The Local Ethics Committee of Eskisehir Osmangazi University approved the study protocol in accordance with the principles of the Declaration of Helsinki. (07.1.2020/48) .

Peer Review Process

Extremely peer-reviewed and accepted.

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