

# Current situation analysis of diabetic home care patient

 Meltem Sertbas,<sup>1</sup>  Ozlem Guduk,<sup>1</sup>  Ozden Guduk,<sup>2</sup>  Zeynep Yazici,<sup>3</sup>  Selma Dagci,<sup>4</sup>  
 Yasar Sertbas<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Health Sciences University Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Turkey

<sup>2</sup>Health Institutes of Turkey, Istanbul, Turkey

<sup>3</sup>Department of Cardiology, Siyami Ersek Training and Research Hospital, Istanbul, Turkey

<sup>4</sup>Department of Internal Medicine, Health Sciences University, Umraniye Training and Research Hospital, Istanbul, Turkey

## ABSTRACT

**OBJECTIVE:** Diabetes, is one of the primary diagnosis for admission to home health care units. Although there are many studies about elderly diabetic patients, there are not so much study of home care patients with diabetes. The aim of this study is to analyze the current status of diabetic home care patients with their biochemical data and medications.

**METHODS:** This was a retrospective study, including 256 diabetic patients who were following up by the Home Health Unit of Istanbul Provincial Health Directorate Public Hospitals Services-2. In this study, we analyzed the current biochemical data of the patients with their medications.

**RESULTS:** In this study, 185 female (72.3%), 71 males (27.7%) patients were recruited with the mean HbA1c of 8.25±1.77. Among these patients, 65% of the them were using oral antidiabetic (OAD) and 58% were using insulin. There were 21 (8.2%) patients who were not receiving any treatment. While patients who were using only oral antidiabetic have better A1c levels (A1c: 7.73±1.45), insulin using patients had HbA1c levels as high as the patients who were not using any medication. This may be due to progression of diabetes, fear of hypoglycemia or insufficient insulin use. While metformin was the most commonly used OAD with 38% usage rate. When compared for HbA1c levels, there was no difference between the types of insulin used (p=0.167).

**CONCLUSION:** As a result, it's important to plan regular visits and personalized treatment with keeping in mind the benefit to risk ratios in home-care diabetic patients.

*Keywords: Antidiabetics; diabetes mellitus; home care services.*

**Cite this article as:** Sertbas M, Guduk O, Guduk O, Yazici Z, Dagci S, Sertbas Y. Current situation analysis of diabetic home care patient. North Clin Istanbul

Gradually aging population leads to an increase in the incidence of chronic diseases [1]. Type 2 Diabetes Mellitus (DM), which is one of the most common chronic diseases in the world, is a health problem that is emphasized both in terms of the negative health situations created over individuals and the financial burden that countries put on the health systems [2, 3]. The global diabetes burden has increased significantly in recent years and is expected to affect more than 642 million

adults by 2040 [4]. According to the American Diabetes Association 2018, the high prevalence of Diabetes Mellitus by 25% and prediabetes by 50% in a population over 65 years old is further increasing the importance of DM [5, 6]. In addition to the increasing incidence of diabetes in developing countries, studies predict that the number of patients with diabetes will be twice as high in the near future, especially among people over 60 years of age [7].

*Received:* October 03, 2019 *Accepted:* October 22, 2019 *Online:* October 25, 2019

**Correspondence:** Dr. Yasar SERTBAS. Saglik Bilimleri Universitesi Fatih Sultan Mehmet Egitim ve Arastirma Hastanesi, Ic Hastaliklari Anabilim Dalı, Istanbul, Turkey.

Tel: +90 532 300 00 28 e-mail: yserzincan24@gmail.com

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In order to provide more efficient health care services to the elderly population, legislation related to the execution of home health services in Turkey published by the Ministry of Health has been launched with the document number 3895 on February 1<sup>st</sup>, 2010. In the scope of the directive, home health services include the provision of medical care and rehabilitation of bed-dependent patients with a specialized staff within the home and family environment of the person instead of the health institutions and organizations. In this sense, patients' treatment follow-ups, necessary examinations, the provision of medical care and rehabilitation services, and provision of oral and dental health services will be performed by the home health units [8].

The use of home health services is increasing in terms of providing services to patients with mobilization problems in a comfortable environment, protecting the patient from hospital infections and preventing unnecessary hospitalizations. Diabetes, as the primary diagnosis for admission to home health care, is located just behind cerebrovascular events or heart failure. It is the leading diagnosis with the combination of primary and secondary diagnoses [9–11]. Although there are many studies about elderly diabetic patients in the literature, there is not enough specific study of home care patients with diabetes. The aim of this study is to analyze the current status of diabetic home care patients with their biochemical data and medications.

## MATERIALS AND METHODS

In this study, we have recruited the patients, who were visited by the Home Health Unit, which operates within the scope of Istanbul Provincial Health Directorate Public Hospitals Services-2, between January 01 and December 31, 2018. The patients' information was retrospectively scanned from the database and totally 256 diabetic patients who were examined for blood sugar monitoring were included in this study.

The present study was carried out in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and approved by the Ethics Committee of the Fatih Sultan Mehmet Education and Research Hospital (FSMEAH- 28.3.2019- 42).

### Statistical Analysis

All analyses were performed using the statistical package for the social sciences (SPSS) program version 22.0 for Windows. The results of all parameters belonging to patients were given as mean±standard deviation. The

1-sample Kolmogorov–Smirnov test was used to assess the distribution of the data. Numerical variables more than 2 different groups were compared using either the one way Anova test or Kruskal Wallis due to their distributions. Categorical variables were analyzed by the  $\chi^2$  test. Probability values were 2-tailed, and a P value of less than 0.05 was considered significant.

## RESULTS

In this study, we have recruited 185 female (72.3%), 71 male (27.7%) patients with the mean age of  $79.8 \pm 10.2$ . Table 1 presents the demographic data and biochemical parameters of the patients.

When they were classified according to the drugs they used, it was seen that 65% of the patients were using oral antidiabetic (OAD) and 58% were using insulin.

**TABLE 1.** Demographic and biochemical parameters of the patients

	Mean	SD
Age (year)	79.78	10.2
Glycolized Hemoglobin (HbA1c)	8.25	1.77
Total Cholesterol (mg/dl)	185.34	46.627
HDL Cholesterol (mg/dl)	41.38	11.53
LDL – Cholesterol (mg/dl)	122.02	95.560
Triglyceride (mg/dl)	141.60	58.432

SD: standard deviation; HDL: high density lipoprotein; LDL: Low density lipoprotein.

**TABLE 2.** Effects of diabetic drug groups on blood sugar regulation

Classification according to drug usage	n	Glycolized Hemoglobin (HbA1c)		p
		Mean	SD	
Only insulin usage	69	8.46	1.60	0.01
Insulin + OAD usage	79	8.54	2.07	
Only OAD usage	87	7.73	1.45	
No antidiabetic drug usage	21	8.56	1.95	

SD: standard deviation; OAD: oral antidiabetic drug.

21 (8.2%) patients were not receiving any treatment. In Table 2, patients were divided into 4 different groups according to their diabetic drug usage. Patients who were using only OAD, had better blood sugar regulation than other groups. On the other hand, blood glucose levels were higher in patients using insulin (alone or in combination with OAD). They were even as high as the results of patients who were not using any medication ( $p>0.05$ ).

In the study, 65% (n=166) of the patients were using OAD and Table 3 shows the usage of Oral Anti-diabetics, according to their classes. Metformin was the most commonly used OAD with a 39 % utilization rate.

In total, 58% (n=148) of the patients were using insulin and there was no statistically significant difference between them in terms of long-acting, intensive (long and short-acting) and mixed insulin usage ( $p>0.05$ ) (Table 4).

**TABLE 3.** Usage of oral anti-diabetics, according to their classes

Oral Anti-diabetic	n	%
Metformin	101	39
Insulin Secretagogues	61	24
Thiazolidinediones	6	2
Oral dipeptidyl peptidase 4 inhibitors	64	25
Glucagon-like peptide 1 receptor agonists	2	0.7
Sodium–Glucose Cotransporter 2 Inhibitors	12	5
Alpha glucosidase inhibitors	12	5

% = (n/256).

**TABLE 4.** Types of insulin use and their relationship with HbA1c

Classification of insulin usage	n	%	Glycolized Hemoglobin (HbA1c)		p
			Mean	SD	
Long acting insulin	55	21	8.14	1.62	0.167
Long + short acting (intensive usage)	56	22	8.79	2.17	
Mixt insulin usage	36	14	8.61	1.63	

SD: standard deviation.

Although many studies have been conducted with elderly diabetic patients previously, there are only few studies related to bed-dependent diabetic home health patients in the literature. In this study, we investigated demographic data, drug usage and their effects on HbA1c levels in diabetic patients being followed up in the context of home health services.

## DISCUSSION

American Diabetes Association (ADA) recommends that the A1c test should be performed at least two times a year in patients who are meeting treatment goals and quarterly in patients without in glycemic control [12]. According to ADA recommendations, the HbA1c target is <6.5% in young adults without a risk of hypoglycemia, whereas it is <8% in patients with complications at risk of hypoglycemia or with limited life expectancy [12]. ADA also established new goals for HbA1c for older diabetic patients in 2019. Older adults with few coexisting chronic illnesses and intact cognitive function were recommended to have lower glycemic goals as HbA1c <7.5% (58 mmol/Mol), while those with multiple coexisting chronic illnesses and cognitive impairment recommended to have less stringent glycemic goals like HbA1c <8.0-8.5% (64-69 mmol/Mol) [13]. In different studies, it has also demonstrated that the best survival was presented in old diabetic patients with an HbA1c levels between 7.0 to 8.0 % [14, 15]. In some guidelines the target HbA1c levels were determined according to fragility index or functional dependence, like HbA1c targets were taken <8.5 for patients with higher fragility index (index: 6-8) or dementia [16, 17]. According to our observations, home care diabetic patients in Turkey have HbA1c levels  $8.25\pm 1.77\%$ , which seems to be in the target values of guidelines.

Although many studies have been conducted regarding the efficacy and indications of diabetes medications, there are not so many studies about the distribution of drugs used by home care diabetic patients. In some of these studies, in addition to mostly used oral antidiabetic agents, the insulin usage rates were ranging between 20% -30% [18, 19]. In our study, the rate of oral antidiabetic use was 65%, while the rate of insulin use was 58% (30% only insulin use and 28% for insulin + OAD). In our study, excessive insulin use can be explained with the higher age, more complications and higher diabetes duration of home care patients unlike other studies. In the

study the patients using only OAD had better blood glucose regulation than other groups ( $p < 0.05$ ). On the other hand, blood glucose levels were higher in patients using insulin (alone or in combination with OAD) and even it was as high as in the patients who did not use any medication ( $p > 0.05$ ). In our opinion, the reason of the high HbA1c levels may be due to the progression of diabetes, insufficient use of insulin, or fear of hypoglycemia of patients.

In accordance with the literature, in our study, 65% of the patients were using OAD. In the literature metformin was presented as a first line treatment option for elderly diabetics as in young adults [13, 20–22]. It can be safely used by diabetic patients with glomerular filtration rate  $> 30$  ml/min/1.73 m<sup>2</sup>. It improves peripheral insulin sensitivity and decrease hepatic glucose output [23, 24]. The most common side effects are nausea, vomiting, abdominal discomfort and diarrhea [25]. Although clinical studies have shown that only 5% of subjects discontinue metformin due to gastrointestinal symptoms, this may be particularly worrying in the frail elderly population with poor appetite and low daily low-calorie intake. Vitamin B12 deficiency should also be considered in long term use [26]. Although it is rare, Metformin associated lactic acidosis (MALA) is another fatal complication, which occurs more frequently in elderly patients with renal impairment [25]. In our study, even though the majority of patients used metformin (39%), this rate was lower than other studies. This was attributed to the fact that older patients were less tolerant of metformin (GIS intolerance) and had more renal and cardiovascular complications.

Thiazolidinediones (TZDs) are the second class of insulin sensitizers. They reduce insulin resistance in peripheral tissue and also decrease hepatic gluconeogenesis [21]. Since TZDs do not cause hypoglycemia and can be given to patients with renal failure, they might be thought to be an alternative medication for treatment of DM. Apart from these good aspects, their use has been drastically limited in the past years due to concerns about worsening heart failure due to fluid retention [27], decreased bone density [28], and increased risk of bladder cancer [29]. Thus use in older patients with underlying bone disease, family history of cancer and heart disease, could potentially be problematic. In our observation 2% of home care patients were using these drugs and we thought that they would be used as a second-line option for patients who have not achieved their glycemic targets on alternative therapies (metformin,

sulfonylureas, insulin).

Dipeptidyl peptidase-4 (DPP-4) inhibitors are responsible for preventing the degradation of incretins, mainly glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP1). They reduce the blood glucose concentration by increasing the insulin synthesis and decreasing the glucagon production [30]. However, it's important to be careful about reported side effects as pancreatitis [31], nasopharyngitis [32], and heart failure [33]. In case of severe renal impairment, dose adjustment should be taken into consideration [34]. Although there are some side effects with low percentages, since GLP-1 is a blood glucose dependent enzyme without risk of hypoglycemia, and negligible gastrointestinal side effects, they are favorable in the treatment of older patients [13, 21, 35]. According to our observations clinicians were preferring this OAD as a second line treatment (%25 usage of DPP4inh.) after metformin in home care patients.

GLP-1 is a gastrointestinal hormone which is involved in glucose homeostasis primarily by stimulating glucose-dependent insulin release from pancreatic islets, slowing gastric emptying [36], inhibiting post-meal glucagon release, and increasing satiety in the brain, thereby contributing to reduced food intake [37]. GLP-1 agonists are a class of antidiabetic agents that mimics the action of glucagon like peptide. In this class both exenatide and liraglutide demonstrate their effects by reducing blood glucose, lowering A1c and resulting progressive, dose dependent weight loss [21]. These agents well tolerated in the elderly patients as much as younger ones with low risk of hypoglycemia when used with metformin [38, 39]. Other than these beneficial effects they may be associated with nausea, vomiting, diarrhea and pancreatitis [38]. We should also pay attention to weight loss, that may not be desirable in some elderly patients with cachexia [40]. In our study, there were only 2 patients using these groups of drugs. These low usage may be due to the fear of the side effect that we mentioned before.

Alpha-glucosidase enzyme converts complex polysaccharide carbohydrates into monosaccharides, so its inhibition slows the absorption of glucose and decreases the post-prandial blood glucose concentrations. Although Alpha-glucosidase inhibitors have a safety profile with no hypoglycemia risk and any other severe adverse effects, gastrointestinal side effects of flatulence and diarrhea limits their use in older patients [20–22]. In our study the 5% usage rate seems to be low when compared

with other studies, which may be due to their gastrointestinal intolerance in older patients [18].

The sodium-glucose co-transporter 2 (SGLT2) in the proximal tubule is responsible for reabsorbing the filtered glucose load up to 90% [41]. Its inhibition can lead to lower the blood glucose levels. There are some studies available in the literature for older diabetic patients that shows the efficacy of SGLT-2 inhibitors with the improvement of glycemic control, body weight and blood pressure [42]. They also have no hypoglycemic effects on the older patients, but since they may cause volume depletion, increase urinary tract infection, decrease in bone mineral density with a significant increase of fracture and rarely causing diabetic ketoacidosis, these drugs should be used cautiously [42–44]. We have observed that 12 of 256 (5%) Homecare patients were using these types of drugs. We thought that these drugs can be used in suitable patients if A1c levels goes above target.

Diabetes Canada Clinical Practice Guidelines Expert Committee recommended that Insulin regimens in older adults should be individualized [35]. Once daily basal insulin, is a simple way of starting insulin in the elderly. Long acting, once Daily insulins are effective in patients with preserved pancreatic function, which have advantages of relative lack of hypoglycemia risk and flexibility in time of administration [22]. Basal bolus injection with a combination of one long acting insulin and three preprandial rapid acting insulins mimic physiological insulin secretion. Long term use in elderly patients is inconvenient due to its complexity and high risk of hypoglycemia [44]. Pre-mixed insulin analogues can be administered before or after meals [45] and result in better and more durable control than basal insulins alone [46], but at the expense of more hypoglycemia and greater weight gain [47]. Due to IDF recommendations for elderly people if oral glucose lowering agents are contraindicated or not tolerated, a long acting basal insulin is an alternate option. In addition, if the desired goals cannot be achieved, it is recommended to use mix insulin along with triple OAD [44]. In our study, we have found that 58% of the patients were using insulin and when they were evaluated for the types of insulin there was no difference among the insulin types in HbA1c levels ( $p > 0.05$ ).

## Conclusions

The increase in life expectancy together with the developing technology causes a rapid increase of the elderly

population in home care patients. Although diabetes is frequently seen in home care patients, the data regarding glycemic control are minimal. Due to the high levels of HbA1c, especially in patients taking insulin, it should be ensured that insulin injection educations should be reviewed intermittently and closer blood sugar monitoring should be provided. As a result, we think that planning regular visits and personalized treatment with keeping in mind the benefit to risk ratios in diabetic patients are an inevitable part of Home health care.

**Ethics Committee Approval:** This study, which was approved by the ethical board of the Ethics Committee of the Fatih Sultan Mehmet Education and Research Hospital (FSMEAH-28.3.2019- 42).

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Authorship Contributions:** Concept - YS, OG; Design- MS, ZY, OG; Supervision-YS, OG, MS; Materials-SD, OG, MS; Data collection and processing- YS, OG, SD, ZY; Analysis and interpretation- MS, OG, YS, SD; Writing- MS, OG, ZY; Critical review- YS, OG.

## REFERENCES

1. Ünal B, Ergör G, Horasan GD, Kalaça S, Sözmen K. Türkiye kronik hastalıklar ve risk faktörleri sıklığı çalışması. Sağlık Bakanlığı Yayın No: 909; 2013. ISBN: 978-975-590-461-0.
2. Raghupathi W, Raghupathi V. An empirical study of chronic diseases in the United States: A visual analytics approach. *Int J Environ Res Public Health*. 2018 Mar 1;15 (3). pii: E431. doi: 10.3390/ijerph15030431.
3. Jaul E, Barron J. Age-Related diseases and clinical and public health implications for the 85 years old and over Population. *Front Public Health* 2017 Dec 11;5:335. doi: 10.3389/fpubh. 2017.00335. eCollection 2017.
4. Umpierrez GE, Pasquel FJ. Management of inpatient hyperglycemia and diabetes in older adults. *Diabetes Care* 2017 Apr; 40 (4): 509-517. doi: 10.2337/dc16-0989. Review.
5. American Diabetes Association 11. Older Adults: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 2018 Jan; 41 (Suppl 1): S119-S125. doi: 10.2337/dc18-S011.
6. Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, et al. Diabetes in older adults. *Diabetes Care* 2012 Dec; 35 (12): 2650-2664.
7. Satman İ, İmamoğlu Ş, Yılmaz C, Ayvaz G, Çömlekçi A. Türkiye’de ve Dünya’da diyabet, Türkiye Endokrinoloji ve Metabolizma Derneği Diabetes Mellitus Çalışma ve Eğitim Grubu Raporu. *Turk JEM* 2012; (16) 1:2-47.
8. Directive on the Procedures and Principles of Home Health Care Services Provided by the Ministry of Health. (2010). <https://www.saglik.gov.tr/TR,11271/saglik-bakanliginca-sunulan-evde-saglik-hizmetlerinin-uygulama-usul-ve-esaslari-hakkinda-yonerge.html>
9. O’Reilly CA. Managing the care of patients with Diabetes in the Home Care Setting. *Diabetes Spectrum* 2005;18 (3): 162-166.
10. Subası N, Oztek Z. Türkiye’de karşılanamayan bir gereksinim: Evde bakım hizmeti. *TSK Koruyucu Hekimlik Bülteni* 2006;5(1):19-31.

11. İsik O, Kandemir A, Erisen MA, Fidan C. Evde sağlık hizmeti alan hastaların profili ve sunulan hizmetin değerlendirilmesi. *Hacettepe Sağlık İdaresi Dergisi* 2016;19(2):171-186.
12. American Diabetes Association 6. Glycemic Targets: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 2019 Jan; 42 (Suppl 1): S61-S70. doi: 10.2337/dc19-S006.
13. American Diabetes Association 12. Older Adults: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 2019 Jan; 42 (Suppl 1): S139-S147. doi: 10.2337/dc19-S012. Review
14. Huang ES, Liu JY, Moffet HH, et al. Glycemic control, complications, and death in older diabetic patients: The diabetes and aging study. *Diabetes Care* 2011;34:1329-36.
15. Hamada S, Gulliford MC. Mortality in individuals aged 80 and older with type 2 diabetes mellitus in relation to glycosylated hemoglobin, blood pressure, and total cholesterol. *J Am Geriatr Soc.* 2016;64:1425-31.
16. International Diabetes Federation. Managing older people with type 2 diabetes global guideline. Brussels, Belgium: International Diabetes Federation (IDF), 2013 <http://www.idf.org/sites/default/files/IDF-Guideline-for-older-people>
17. Diabetes Canada Clinical Practice Guidelines Expert Committee, Meneilly GS, Knip A, Miller DB, Sherifali D, Tessier D, Zahedi A. Diabetes in Older People. *Can J Diabetes* 2018 Apr;42 Suppl 1:S283-S295. doi: 10.1016/j.cjcd.2017.10.021.
18. Bela Patel, Bhavit Oza, Kamlesh P. Patel, Supriya D. Malhotra, Varsha J. Patel Pattern of antidiabetic drugs use in type-2 diabetic patients in a medicine outpatient clinic of a tertiary care teaching hospital. *International Journal of Basic & Clinical Pharmacology* 2013;2(4): 485-491.
19. Kannan, Arshad, Kumar S. A study on drug utilization of oral hypoglycemic agents in type-2 diabetic patients. *Asian Journal of Pharmaceutical and Clinical Research* 2011;4(4):60-64.
20. LeRoith D, Biessels GJ, Braithwaite SS. Treatment of Diabetes in Older Adults: An Endocrine Society\* Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2019 May 1;104 (5): 1520-1574. doi: 10.1210/je.2019-00198.
21. Kezerle L, Shalev L, Barski L. Treating the elderly diabetic patient: special considerations. *Diabetes Metab Syndr Obes.* 2014;7:391-400.
22. Bajwa SJ, Sehgal V, Kalra S, Baruah MP. Management of diabetes mellitus type-2 in the geriatric population: Current perspectives. *Pharm Bioallied Sci.* 2014 Jul; 6 (3): 151-7. doi: 10.4103/0975-7406.130956.
23. Bailey CJ, Turner RC. Metformin. *N Engl J Med.* 1996;334(9): 574-579
24. Stumvoll M, Nurjhan N, Perriello G, et al. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med.* 1995;333(9):550-554.
25. Sertbas M, Sertbas Y, Ordu O et al. Myocardial injury and acute renal failure associated with lactic acidosis due to suicide attempt with metformin. *J Pak Med Assoc.* 2016 Feb;66(2):223-5
26. De Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ.* 2010;340:c2181.
27. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med.* 2004;351(11): 1106-1118.
28. Grey A. Skeletal consequences of thiazolidinedione therapy. *Osteoporos Int.* 2008;19(2):129-137.
29. Colmers IN, Bowker SL, Majumdar SR, Johnson JA. Use of thiazolidinediones and the risk of bladder cancer among people with type 2 diabetes: a meta-analysis. *CMAJ.* 2012;184(12): E675-E683.
30. Campbell RK. Rationale for dipeptidyl peptidase 4 inhibitors: A new class of oral agents for the treatment of type 2 diabetes mellitus. *Ann Pharmacother.* 2007;41(1):51-60.
31. Buse JB, Bethel MA, Green JB, et al. Pancreatic Safety of Sitagliptin in the TECOS Study. *Diabetes Care* 2017 Feb;40(2):164-170.
32. Sarashina A, Sesoko S, Nakashima M, et al. Linagliptin, a dipeptidyl peptidase-4 inhibitor in development for the treatment of type 2 diabetes mellitus: a Phase I, randomized, double-blind, placebo-controlled trial of single and multiple escalating doses in healthy adult male Japanese subjects. *Clin Ther.* 2010 Jun;32(6):1188-204. doi: 10.1016/j.cleas.2010.06.004.
33. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med.* 2013 Oct; 369 (14): 1317-1326.
34. Bergman AJ, Cote J, Yi B, et al. Effect of renal insufficiency on the pharmacokinetics of sitagliptin, a dipeptidyl peptidase-4 inhibitor. *Diabetes Care* 2007;30(7):1862-1864
35. Meneilly GS, Knip A, Miller DB, et al. Diabetes in Older People. *Canadian Journal of Diabetes* 2018; 42(1): S283-S295
36. Nauck MA, Niedereichholz U, Ertler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol.* 1997;273 (5 Pt1): E981-E988.
37. Koliaki C, Doupis J. Incretin-based therapy: a powerful and promising weapon in the treatment of type 2 diabetes mellitus. *Diabetes Ther.* 2011;2(2):101-121.
38. Bode BW, Brett J, Falahati A, et al. Comparison of the efficacy and tolerability profile of liraglutide, a once-daily human GLP-1 analog, in patients with type 2 diabetes  $\geq 65$  and  $< 65$  years of age: A pooled analysis from phase III studies. *Am J Geriatr Pharmacother* 2011; 9: 423-433.
39. Meneilly GS, Roy-Duval C, Alawi H, et al. Lixisenatide therapy in older patients with type 2 diabetes inadequately controlled on their current antidiabetic treatment: the GetGoal-O randomized trial. *Diabetes Care* 2017;40:485-93.
40. Davies MJ, D'Alessio DA, Fradkin J. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018;41:2669-2701.
41. Ünlüsoy MC, Akuç S, İnceli Hİ. Diyabet Tedavisinde SGLT2 İnhibitörleri FABAD. *J. Pharm. Sci* 2018; 43(2): 157-170, 2018.
42. Elmore LK, Baggett S, Kyle JA, et al. A review of the efficacy and safety of canagliflozin in elderly patients with type 2 diabetes. *Consult Pharm* 2014;29:335-46.
43. Bode B, Stenlof K, Sullivan D, et al. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: A randomized trial. *Hosp Pract (Minneapolis)* 2013;41:72-84.
44. International Diabetes Federation Guideline Development Group. Diabetes Global guideline for type 2 diabetes. *Res Clin Pract.* 2014 Apr; 104 (1): 1-52. doi: 10.1016/j.debris.2012.10.001. Epub 2014 Feb 5.
45. Warren ML, Conway MJ, Klaff LJ, et al. Postprandial versus preprandial dosing of biphasic insulin aspart in elderly type 2 diabetes patients. *Diabetes Res Clin Pract.* 2004;66:23-9.
46. Galic E, Vrtovec M, Bozиков V, et al. The impact of the timing of Humalog Mix25 injections on blood glucose fluctuations in the postprandial period in elderly patients with type 2 diabetes. *Med Sci Monit.* 2005;11:187-92.
47. Khamseh ME, Haddad J, Yang W, et al. Safety and effectiveness of biphasic insulin aspart 30 in different age-groups: A1chieve sub-analysis. *Diabetes Ther.* 2013;4:347-61.283-S295. doi: 10.1016/j.cjcd.2017.10.021.