Medical Science

Trends of HBA1c and related side effects of dapagliflozin 10mg and semaglutide 1mg in adults with type 2 diabetes mellitus in King Abdulaziz Medical City, Riyadh, Saudi Arabia

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DISCOVERY
SCIENTIFIC SOCIETY

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ABSTRACT

Diabetes is a common disease characterized by impaired glycemic control in the body. High blood glucose readings are any fasting blood glucose more than or equal to 126 mg/dl, random blood glucose more than or equal to 200 mg/dl, or A1c level greater than or equal to 6.5%. We used a retrospective, chart review study design to collect the A1c readings in patients using Dapagliflozin 10mg. The total sample size was 107 participants. 57 participants were on Dapagliflozin, 33 on Semaglutide, and 17 were on a combination of Semaglutide and Dapagliflozin. Weight significantly decreased in participants using Dapagliflozin and Semaglutide combination (p<0.001) compared to those using Semaglutide alone (p<0.001). Additionally, HbA1c significantly decreased among participants using Dapagliflozin and Semaglutide (p<0.001) and those using Dapagliflozin alone (p<0.001). Even though SGLT-2 inhibitors weakly reduce HbA1c, we have found in our study that Dapagliflozin has significantly decreased A1c in addition to a reduction in weight especially among females.

Keywords: Type 2 diabetes mellitus, hba1c, semaglutide, dapagliflozin, sglt-2 inhibitors

1. INTRODUCTION

Diabetes is a worldwide disease characterized by impaired glycemic control in the blood and related organs (American Diabetes Association, 2023). In terms of its laboratory definitions, high glycemic levels are any fasting levels greater than or equal to 126 mg/dl, random blood glucose greater than or equal to 200 mg/dl, or A1c level greater than or equal to 6.5%, while a normal blood glucose level is anything lower than these cutoffs with the exception of pre-diabetes state (ElSayed et al., 2023). In terms of pharmacological management, there are mainly 2 ways of treatment, either oral or injectable medications. Oral medication options are wide and include old commonly used Sulfonylureas and newer agents such as the class of Sodium-Glucose Transporter Protein 2 inhibitors (SGLT-2). Injectable agents include insulin and Glucagon Like Peptide-1 Receptor agonists (GLP-1).

These oral and injectable agents vary in terms of their efficacy and side effect/safety profiles. Efficacy vary between oral agents. Furthermore, efficacy is mainly measured by degree of a1c reduction. For example, Sulfonylureas, whether started as monotherapy or add-on therapy, lowered a1c by a range of 1-2% from the baseline compared to placebo (Hirst et al., 2013). SGLT-2 agent Empagliflozin, on the other hand, decreases a1c by 0.7-0.9% from the baseline (Zimmermann, 2016). Locally in Saudi Arabia, physicians vary in their choice of first and second-line oral or injectable hypoglycemic agents for the treatment of their patients with type 2 diabetes mellitus. The DISCOVER study was a prospective study over a 3 year-period that reported physician's choice of hypoglycemic agents in many countries including Saudi Arabia (Al-Rubeaan et al., 2020).

Most commonly prescribed agents were Metformin, Gliclazide, and Glibenclamide, respectively (Al-Rubeaan et al., 2020). Although not commonly used as per this study, SGLT-2 inhibitors and GLP-1 agonists showed good efficacy and safety profiles as reported by many studies including a large study done in Saudi Arabia by (Butt et al., 2023). Given that not so many studies highlighted the efficacy of SGLT-2 agent Dapagliflozin and GLP-1 Agonist Semaglutide in Saudi Arabia and no studies done in NGHA, Riyadh, we aim to investigate the efficacy and safety profile of Semaglutide 1mg subcutaneous injection and Dapagliflozin 10mg within 1 year duration in patients treated in National Guard Hospital, Riyadh, Saudi Arabia.

2. MATERIALS & METHODS

This study implemented a retrospective, chart review study design and a non-probability convenient sampling technique to collect the A1c levels in patients using Dapagliflozin 10mg and Semaglutide 1mg subcutaneous injection in combination or alone before and after starting these medications. Included patients were those who started these medications from period of 1/1/2023 and reviewed their charts until 1/1/2024 to check for A1c reduction degree and occurrence of urinary side effects. Data was collected and cleaned in an Excel sheet and then imported to R software (version 4.2.2).

The normality of data was assessed using a histogram and the Shapiro-Walik test. Continuous variables were presented in median and interquartile ranges, while categorical were presented in numbers and percentages. Wilcoxon rank-sum test was used to assess the association between changes in Hemoglobin A1C, demographic and medical characteristics of participants. A paired Wilcoxon rank sum test was used to assess the significance of the change in weight and Hemoglobin A1C before and after using the medication. A p-value of less than 0.05 was considered significant.

3. RESULTS

The study included 107 participants with a median age of 57 years (interquartile range 48-64). Of these, 63% were females and 37% were males. Only 6.5% reported having side effects from diabetes medication. In terms of medication, 53.7% were on Dapagliflozin 10mg, 31% on Semaglutide 1mg injection, and 16% were on a combination of Semaglutide and Dapagliflozin. Regarding complications of diabetes mellitus, 26% were documented clinically to have complications directly related to type 2 diabetes mellitus. Table 1 shows a summary of our participants' demographic data. The median Hemoglobin A1C level before intervention was 9.10 (interquartile range 7.70-10.15), which decreased to 7.80 (interquartile range 6.80-8.65) after intervention. The median weight before intervention was 90 kg (interquartile range 82-109), which did not change after intervention (90 kg with interquartile range 79-100).

Table 1 Demographic data of the participants

Characteristic	N = 107 1
Age	57 (48, 64)
Gender	
Female	67 (63%)
Male	40 (37%)
Side effects	
No	100 (93%)
Yes	7 (6.5%)
Complications of diabetes mellitus	
No	81 (75.7%)
Yes	26 (24.3%)
Hemoglobin A1C before starting medication	9.10 (7.70, 10.15)
Hemoglobin A1C 1-year after starting medication	7.80 (6.80, 8.65)
Medication	
Dapagliflozin 10mg	57 (53.4%)
Semaglutide 1mg subcutaneous injection	33 (30.8%)
Semaglutide and dapagliflozin	17 (15.8%)
Weight before (kg)	90 (82, 109)
Weight after (kg)	90 (79, 100)

N= Number; 1= Median (IQR); n (%)

Table 2 shows that 75.7% of participants were found to have no complications of diabetes mellitus. However, out the 24.3% who had complication, 12%, 5.6% and 3.7% reported having retinopathy, nephropathy and ischemic heart disease, respectively. In terms of side effects, 3 participants reported gastrointestinal side effects mainly nausea and bloating after starting Semaglutide injections. Out of the 4 participants who had side effects after using Dapagliflozin 10mg, 2 of them had positive nitrates on urinalysis and urine dipstick but no reported symptoms and, hence, not treated and improved with increased water intake on follow-ups, 1 of them had candida urinary tract infection and 1 participant had recurrent vaginal candidiasis.

Table 2 Reported Complications of diabetes mellitus

Complications of diabetes mellitus	N = 1071
Ischemic heart disease	4 (3.7%)
Nephropathy	6 (5.6%)
Neuropathy	2 (1.8%)
Retinopathy	13 (12%)
Recurrent vaginal candidiasis	1 (0.9%)
None	81 (75.7%)

N= Number; 1= Median (IQR); n (%)

We have found that there is a statistically significant decrease in weight among participants using Dapagliflozin and Semaglutide combination (p-value= 0.04) compared to those using Semaglutide alone (p-value 0.005), with a higher decrease seen in Dapagliflozin and Semaglutide group as illustrated in (Table 3). Similarly, there is a statistically significant decrease in Hemoglobin A1C among participants using Dapagliflozin and Semaglutide (p-value<0.05) and those using Dapagliflozin alone (p-value= 0.03), with higher decrease seen in Dapagliflozin and Semaglutide group as seen in (Table 4).

Table 3 Weight change among participants using Dapagliflozin and Semaglutide combination versus those using Semaglutide alone

Weight change in Dapagliflozin and Semaglutide group	Mean	P-value
Before adding Dapagliflozin on Semaglutide	90 kg	0.04 with CI 95% (-0.86, -0.23)
After adding Dapagliflozin on Semaglutide	87 kg	
Weight change in Semaglutide alone group		
Before starting Semaglutide	91.5 kg	0.005 with CI 95% (-0.81, -0.30)
After starting Semaglutide	90 kg	

CI= Confidence interval

Table 4 Hemoglobin A1C change among participants using Dapagliflozin and Semaglutide combination versus those using Dapagliflozin alone

HbA1c change in Dapagliflozin and Semaglutide group	Mean	P-value
Before adding Dapagliflozin on Semaglutide	9.2	0.03 with CI 95% (-0.93, -0.54)
After adding Dapagliflozin on Semaglutide	7.6	
Hemoglobin A1c change in Semaglutide alone group		
Before starting Semaglutide	9.2	<0.05 with CI 95% (-0.80, -0.46)
After starting Semaglutide	8.2	

CI= Confidence interval

For age groups, participants aged 30-52 years (n=38) had a median change in Hemoglobin A1C of -5.20 (interquartile range -5.93, -4.03), which was statistically significant (p-value of 0.036). In contrast, participants aged 53 and above (n= 69) showed a smaller median difference of -1.40 (interquartile range -1.80, -0.30). Gender (p-value = 0.5) and presence of complications related to diabetes mellitus (p-value = 0.8) did not significantly influence the difference in Hemoglobin A1C levels. However, females exhibited a median difference of -1.55 (interquartile range -2.10, -0.68) compared to males who had a median difference of -2.30 (interquartile range -4.90, -0.50). Similarly, those without complications having a median difference of -1.40 (interquartile range -3.05, -0.40) versus those with complications showing a median difference of -1.75 (interquartile range -1.78, -1.73) (Table 5).

Table 5 Association between change in Hemoglobin A1C among Semaglutide and Dapagliflozin combination users and demographic and clinical characteristics

Characteristic	Median difference (IQR)	p-value1
Age		
30-52	-5.20 (-5.93, -4.03)	0.036
53 and above	-1.40 (-1.80, -0.30)	0.32
Gender	-	0.5
Female	-1.55 (-2.10, -0.68)	-
Male	-2.30 (-4.90, -0.50)	-
Complications of DM	-	0.8
No	-1.40 (-3.05, -0.40)	-
Yes	-1.75 (-1.78, -1.73)	-

N= Number; 1= p-value computed using Wilcoxon rank sum test
IQR= interquartile range

4. DISCUSSION

Dapagliflozin and Empagliflozin have little efficacy as it is mainly used by physicians for their cardiac and renal protective effects instead of relying on them for their hypoglycemic effects in Hemoglobin A1c reduction. The average HbA1c reduction by Dapagliflozin

and Empagliflozin is around 0.5% to 0.7% within of 1 year of continuous use (Feng et al., 2019). One of the main objectives of this paper was to address the effect of Dapagliflozin as monotherapy in lowering Hemoglobin A1C. In our study, there was a statistically significant reduction of HbA1c with Dapagliflozin 10mg as a single medication, which was reproduced in a meta-analysis of six randomized control trials (Feng et al., 2019). Regarding urinary side effect profile of Dapagliflozin, the percentage of patients who developed urinary side effects while being on Dapagliflozin alone was limited.

Out of 57 participants, only 4 patients had urinary complaints. Two individuals had positive nitrates on urinalysis and were completely asymptomatic, hence no treatment was needed. Furthermore, two other participants had candida urinary tract infection and recurrent vaginal candidiasis and subsequently underwent appropriate treatment and improved. According to a study by Johnsson et al., (2013) it was concluded that Dapagliflozin may slightly increase the risk of developing urinary tract infection. This is explained by the mechanism of action of SGLT-2 inhibitors. This group of drugs work by blocking glucose transport across Sodium-Glucose Transporter 2 which is located in the kidney. Therefore, more glucose is present in renal tubules, making it a favorable evnironment for microbial growth and hence development of urinary tract infections.

This paper also aimed to evaluate Dapagliflozin effect on weight and magnitude of reduction. In the group of patients who were on Dapagliflozin as monotherapy, there was no statistically significant reduction in weight (p-value >0.05), an observation that was reproduced by a recent study in 2024 (Han et al., 2024). In comparison, when Dapagliflozin 10mg was added to patients taking Semaglutide 1mg subcutaneous injection there was a statistically significant reduction in weight when compared to patient who used Semaglutide alone. This additive effect of weight reduction when adding Dapagliflozin to Semaglutide was also reported by a study done by (DeFronzo, 2017).

Similarly, Dapagliflozin monotherapy had a statistically significant effect in terms of lowering A1c. Furthermore, combination of Dapagliflozin and Semaglutide also showed significant reduction in A1c with a higher reduction among combination compared to either Dapagliflozin or Semaglutide alone. A1c reduction could be due to a possible synergistic effect of GLP-1 agonists and SGLT-2 inhibitors as both of these classes have a common effect on the kidney. However, we were unable to explain or find any study which explains mechanism of weight reduction with SGLT-2 inhibitors. Gender was not found to have any significant effect on A1c or weight change. However, the median A1c change among females using Dapagliflozin 10mg alone was 1.00-point reduction in A1c compared to the males who had a smaller median reduction of 0.70 points.

When compared to combination Dapagliflozin and Semaglutide, males had a higher median reduction of 2.30 points while females had 1.55-point reduction in A1c. Although both of these changes were not statistically significant, it may be significant if done on a higher sample size. To the best of our knowledge, there is currently no study that specifically measures and compares the gender difference between male and female regarding A1c reduction. One interesting study that was published by McGill et al., (2013) showed that females had smaller reductions in A1c compared to males when using insulin injections but no gender difference was found when using non-insulin agents including SGLT-2 inhibitors and GLP-1 agonists. Authors, therefore, advised that gender differences should be considered when individualizing treatment regimens (McGill et al., 2013).

The present study has multiple limitations. Firstly, Empagliflozin was not added as it was available in National Guard Hospital in Riyadh only prior to 2018 and was discontinued and replaced by Dapagliflozin afterwards. Secondly, the number of our participants, 107, is considered relatively low and further research with bigger sample size is recommended. Thirdly, the study was only limited to National Guard Hospital in Riyadh and did not other healthcare facilities and sectors in Saudi Arabia. Finally, the study utilized non-probability convenient sampling technique in data collection which may not produce the most robust evidence in this type of studies.

5. CONCLUSIONS

SGLT-2 inhibitors and GLP-1 agonists are relatively new and commonly used diabetic medication of various benefits. It is commonly known that SGLT-2 inhibitors have low efficacy in terms of Hba1c reduction. However, we have found in our study that Dapagliflozin 10mg has significantly decreased A1c in our patients along with significant reduction in weight especially among females either with or without Semaglutide subcutaneous injection combination.

Author Contributions
Khalid Ghalib Alharbi: Main author and main manuscript writing
Eman Ghalib Alharbi: Main author and main manuscript writing
Bader Abdulaziz Altulaihi: Data collection and manuscript editing/review
Meshal Abdulaziz Alhadlaq: Data collection and manuscript writing
Ali Ibrahim Alqobaisi: Data collection and manuscript writing
Khaled Ali Alkhudhairi: Data collection

Ethical Approval
The study was approved by Medical Ethics Committee of King Abdullah International Medical Research Center (KAIMRC) in Riyadh, National guard hospital with approval number IRB/0167/24.

Informed consent
Not applicable

Conflict of interest
The authors declare that there is no conflict of interests.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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