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Evaluation of Hematological and Metabolic Changes in Diabetic Patients the Impact of Novel Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT-2) Pharmacotherapy

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ABSTRACT

Background: A class of drugs called SGLT-2 is used to control diabetes by preventing the kidneys from reabsorb glucose and increasing its excretion in urine. **Objective:** To assess the impact of novel Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitors pharmacotherapy on hematological and metabolic changes in diabetic patients. **Study Design:** Descriptive Cross-Sectional Study. **Settings:** The study was conducted at Department of Pathology, Mohi-ud-Din Islamic Medical College, Mirpur AJK Pakistan. **Duration:** September 2021 to February 2022. **Methods:** The study included 130 individuals who had poorly managed type 2 diabetic mellitus (T2DM). We collected data before starting SGLT-2 inhibitor therapy and again three months later after starting medication. Before and throughout the research, participants had their weight, body mass index (BMI), blood pressure (BP), haemoglobin A1c (HbA1c), serum glutathione peroxidase (SGPT), and a battery of tests to evaluate their metabolic and haematological profiles assessed. **Results:** The average age was 49.51 years (standard deviation ± 9.1), and out of the total, 78 were female and 52 were male, accounting for 60%. At 82.5 kg (SD ± 15.2), the average body weight was recorded, while the average BMI was 30.2 kg/m² (SD ± 4.5). The average of the two measurements, diastolic and systolic, was 85 and 135 mm Hg, respectively, with a standard deviation of 12 and 10, respectively. Significant increases were noted in haemoglobin, hematocrit, and red blood cell count, with haemoglobin increasing from 12.5 ± 1.2 g/dL to 12.8 ± 1.3 g/dL ($p < 0.001$), 39.2 ± 2.6% ($p < 0.001$), and 4.5 ± 0.4 million/µL to 4.6 ± 0.4 million/µL ($p = 0.002$), respectively. **Conclusion:** In conclusion, our study underscores the safety and efficacy of SGLT-2 inhibitors as an oral anti-diabetic therapy, highlighting their capacity to improve both hematological and metabolic profiles.

Keywords: *Diabetes, Hematological parameters, Type 2 diabetes mellitus, Hemoglobin.*

INTRODUCTION

Diabetes mellitus is a chronic metabolic illness that is globally concerning. It is characterised by high blood sugar levels due to problems with insulin secretion, insulin action, or both. It encompasses a spectrum of diseases with various etiologies, which encompasses the death of pancreatic beta cells by the immune system, reduced responsiveness to insulin, and impaired production of insulin.[1,2] Left untreated or poorly managed, diabetes can lead to serious complications, including cardiovascular disease, nephropathy, retinopathy, and neuropathy, posing significant health burdens worldwide.[3,4] Effective management of diabetes through lifestyle adjustments, medication, and regular monitoring is essential for preventing or postponing the development of these problems and enhancing overall quality of life.[5]

Global prevalence of diabetes exceeded 415 million individuals in 2015. Projections indicate a significant

increase, with an estimated rise to 640 million by the year 2040.[6,7] Managing type-2 diabetes mellitus generally involves choosing an antidiabetic medication from a diverse range of pharmacologic categories. These medications work through many processes, including increasing the release of insulin, enhancing insulin sensitivity, and slowing down the absorption of glucose.[8] Patients diagnosed with Type-2 diabetes typically initiate therapy by taking oral medications such as metformin or sulfonylureas, alongside implementing lifestyle modifications. As the disease advances, a significant number of persons shift towards combination therapy. A considerable proportion of patients require three or more drugs, which may include insulin. In addition to insulin, there are other alternative treatment options available, including as glucagon-like peptide-1 receptor agonists, thiazolidinediones, long and intermediate-acting insulins and dipeptidyl peptidase-4 inhibitors.[9,10]

By investigating the effects of SGLT2 inhibitors on hematological parameters, particularly in diabetic patients receiving treatment at a tertiary care hospital, this study aims to contribute novel insights into the comprehensive physiological effects of these medications. Understanding how SGLT2 inhibitors influence hematological parameters can provide valuable information for clinicians, potentially uncovering additional benefits or adverse effects associated with their use, thereby enhancing patient care and treatment strategies in diabetic populations. This study seeks to bridge existing knowledge gaps in the literature regarding the hematological effects of SGLT2 inhibitors, offering potential advancements in diabetes management and patient outcomes.

METHODS

This study was conducted at the Mohi-ud-Din Islamic Medical College, Mirpur AJK Pakistan, from September 2021 to February 2022. It was a cross-sectional study. The study involved a cohort of 130 diabetic patients who were treated SGLT2 inhibitors. The study involved male and female patients diagnosed with Type 2 diabetes mellitus that were 18 years old or older and were prescribed SGLT2 inhibitors as part of their diabetes treatment. In order to be included, it was necessary to provide comprehensive medical records, which included initial hematological measurements and subsequent follow-up information. Patients were additionally obligated to give informed consent for their participation. Patients with Type 1 diabetes mellitus, a history of hematological illnesses not related to diabetes, pregnancy or breastfeeding during the research period, and incomplete medical records were excluded.

Baseline hematological parameters were recorded for each patient before initiating treatment with SGLT2 inhibitors. Hematological parameters were reassessed at regular intervals after the initiation of treatment with SGLT2 inhibitors. Follow-up visits were scheduled at 3 months after the start of treatment.

Statistical analysis was conducted to assess alterations in hematological parameters pre- and post-treatment with SGLT2 inhibitors. The significance of variations between baseline and follow-up values was evaluated using chi square, with a significance level established at $p < 0.05$.

RESULTS

With 52 people (40%) being male and 78 people (60%) being female, the mean age was 49.51 years (SD ± 9.1). 82.5 kg (SD ± 15.2) was the mean body weight, and 30.2 kg/m² (SD ± 4.5) was the mean BMI. Mean systolic blood pressure was 135 mm Hg (SD ± 12) and mean diastolic blood pressure was 85 mm Hg (SD ± 10). Plasma glucose averaged 190 mg/dL (SD ± 80), and HbA1c averaged 9.1 (SD ± 1.8). Empagliflozin 10 mg was the most prescribed (55 prescriptions, 42%), followed by Dapagliflozin 5 mg (30 prescriptions, 23%). Canagliflozin 100 mg, Ipragliflozin 25 mg, Tofogliflozin 20 mg, and Luseogliflozin 2.5 mg had prescription rates of 20 (15%), 15 (12%), 10 (8%), and 5 (4%) respectively given in table 2.

Table 1: A preliminary look at the participants who agreed to take SGLT2 inhibitors as part of the study

Variables	Characteristic	Value
Age (years)	Mean±SD	49.51 ± 9.1
Gender	Male	52 (40%)
	Female	78(60%)
Body weight (kg)	Mean±SD	82.5 ± 15.2
BMI (kg/m²)	Mean±SD	30.2 ± 4.5
Systolic BP (mm Hg)	Mean±SD	135 ± 12
Diastolic BP (mm Hg)	Mean±SD	85 ± 10
Plasma glucose (mg/dL)	Mean±SD	190 ± 80
HbA1c	Mean±SD	9.1 ± 1.8

Table 2: Patients initiated on SGLT2 inhibitors at baseline

SGLT2 Inhibitor	Prescription (%)
Dapagliflozin 5 mg	30 (23%)
Luseogliflozin 2.5 mg	5 (4%)
Tofogliflozin 20 mg	10 (8%)
Empagliflozin 10 mg	55 (42%)
Ipragliflozin 25 mg	15 (12%)
Canagliflozin 100 mg	20 (15%)

The Significant increases were noted in haemoglobin, hematocrit, and red blood cell count, with haemoglobin increasing from 12.5 ± 1.2 g/dL to 12.8 ± 1.3 g/dL ($p < 0.001$), 39.2 ± 2.6% ($p < 0.001$), and 4.5 ± 0.4 million/µL to 4.6 ± 0.4 million/µL ($p = 0.002$), respectively. From 90 ± 5 fL to 91 ± 5 fL, the mean corpuscular volume increased ($p = 0.015$), and from 32 ± 2 pg to 33 ± 2 pg, the mean corpuscular haemoglobin rose ($p = 0.008$). Furthermore, table 3 shows that the mean corpuscular haemoglobin concentration increased from 34 ± 1 g/dL to 35 ± 1 g/dL ($p < 0.001$).

Both the fasting plasma glucose level and the haemoglobin A1c level decreased significantly, with the former dropping from 190 ± 80 mg/dL to 155 ± 60 mg/dL ($p < 0.001$) and the latter from 9.1 ± 1.8% to 7.8 ˆ 1.5% ($p < 0.001$). Additionally, as shown in table 4, HDL cholesterol levels increased from 45 ± 10 mg/dL to 48 ± 11 mg/dL ($p < 0.001$), and triglyceride levels fell from 180 ± 60 mg/dL to 160 ± 50 mg/dL ($p = 0.002$).

Table 3: Variations in Haematological Parameters Following Three Months of Administration of SGLT2 Inhibitor

Hematological Parameter	Pre-treatment	3 months	P-value
Hemoglobin	12.5 ± 1.2	12.8 ± 1.3	<0.001
Hematocrit	38.5 ± 2.5	39.2 ± 2.6	<0.001
Red Blood Cells	4.5 ± 0.4	4.6 ± 0.4	0.002
Mean Corpuscular Volume	90 ± 5	91 ± 5	0.015
Mean Corpuscular Hemoglobin	32 ± 2	33 ± 2	0.008
Mean Corpuscular Hemoglobin Concentration	34 ± 1	35 ± 1	<0.001

Table 4: Metabolic Parameter Changes After 3 Months of SGLT2 Inhibitor Administration

Metabolic Parameter	Pre-treatment	3 months	P-value
Fasting Plasma Glucose	190 ± 80	155 ± 60	<0.001
HbA1c	9.1 ± 1.8	7.8 ± 1.5	<0.001
Body Weight	82.5 ± 15.2	80.2 ± 14.5	<0.001
BMI	30.2 ± 4.5	29.5 ± 4.0	<0.001
Systolic BP	135 ± 12	128 ± 10	<0.001
Diastolic BP	85 ± 10	82 ± 8	0.003
HDL Cholesterol	45 ± 10	48 ± 11	<0.001
Triglycerides	180 ± 60	160 ± 50	0.002

DISCUSSION

SGLT2 inhibitors have garnered attention in recent years due to their established role in glycemic control. However, emerging evidence suggests that these medications may exert broader physiological effects beyond glucose metabolism, including alterations in hematological parameters. By examining parameters such as hemoglobin levels, hematocrit, red blood cell count, and others, this discussion aims to elucidate any discernible trends or alterations induced by SGLT2 inhibitor therapy. Understanding the hematological effects of SGLT2 inhibitors is crucial for clinicians in optimizing patient care and treatment strategies, particularly in diabetic populations prone to hematological abnormalities.[11,12]

Comparing the results of our study with those reported by Saleem *et al*. (2022), our study reported a mean age of 49.51 years, while Saleem *et al*. (2022) reported a higher mean age of 53.80 years. Saleem *et al*. (2022) reported a lower baseline HbA1c level (8.23%) compared to our study (9.1%), indicating potentially better glycemic control in their study population prior to intervention. Our study reported a higher mean body weight (82.5 kg) and mean BMI (30.2 kg/m²) compared to Saleem *et al*. (2022) (81.78 kg and 31.35 kg/m², respectively).[13]

In comparing our results with other studies, notable similarities and differences emerge in the reported statistics following SGLT2 inhibitor administration. There were consistent findings of decreased liver enzyme levels, indicating potential hepatoprotective effects of SGLT2 inhibitors. However, while our study focused primarily on hematologic parameters, demonstrating significant increases in hemoglobin from 12.5 ± 1.2 g/dL to 12.8 ± 1.3 g/dL ($p < 0.001$), hematocrit from 38.5 ± 2.5% to 39.2 ± 2.6% ($p < 0.001$), and red blood cell count from 4.5 ± 0.4 million/µL to 4.6 ± 0.4 million/µL ($p = 0.002$), Katsuyama *et al*. (2016) explored a broader range of metabolic and cardiovascular markers.[14] In comparing our study results with those reported by Wang *et al*. (2021), both studies provide insights into the hematologic effects of SGLT2 inhibitors, albeit through different methodologies and perspectives. Our study demonstrated significant increases in hemoglobin, hematocrit, and red blood cell count following SGLT2 inhibitor administration, corroborating the findings of Wang *et al*. regarding the significant increase in hematocrit levels associated with SGLT2 inhibitor treatment. Specifically, our study showed a significant increase in hematocrit from 38.5 ± 2.5% to 39.2 ± 2.6% ($p < 0.001$), whereas Wang *et al*. reported a significant increase in hematocrit levels across various SGLT2 inhibitors, including dapagliflozin, canagliflozin, and empagliflozin, with weighted mean differences ranging from 1.96% to 3.44% ($p < 0.001$).[15] These findings align with previous research, including

Aamir *et al*. (2022), which similarly reported significant reductions in HbA1c levels.[16]

Furthermore, our study's findings regarding HDL cholesterol align with those reported by Monami *et al*. (2014), who also found significant increases in HDL-C levels following SGLT2 inhibitor treatment.[17] Additionally, our study's results regarding blood pressure reduction are consistent with previous research by Ku *et al*. (2019), Sohail *et al*. (2021), and expert analyses, which collectively demonstrate the beneficial effects of SGLT2 inhibitors on blood pressure parameters.[18,19] Our study's findings align with the observations of Raza *et al*. (2019), as well as other expert analyses, which have demonstrated the beneficial effects of SGLT2 inhibitors. [20]

CONCLUSION

In conclusion, our study underscores the safety and efficacy of SGLT-2 inhibitors as an oral anti-diabetic therapy, highlighting their capacity to improve both hematological and metabolic profiles. The results indicate that SGLT-2 inhibitors could be beneficial supplementary treatment options for individuals with diabetes who are already on oral anti-diabetic medications for glucose control.

LIMITATIONS

Limitations encompass the single-center nature of the study.

SUGGESTIONS / RECOMMENDATIONS

Future multicenter trials with expanded cohorts and extended follow-up periods.

CONFLICT OF INTEREST / DISCLOSURE

No conflict of interest.

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