Comparison of the Impact of SGLT2-Inhibitors and Exenatide on Body Fat Composition

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ABSTRACT

Objective: To investigate the effect of SGLT2-i and GLP-1RA as an add-on therapy to metformin on weight loss and body composition, and to compare their effects on glucose and lipid parameters.

Study Design: A descriptive study.

Place and Duration of the Study: Goztepe Prof Dr Suleyman Yalcin City Hospital, from January 2016 to May 2021.

Methodology: The study included 50 patients with diabetes on metformin+SGLT2-i (dapagliflozin or empagliflozin, group 1) and 50 patients with diabetes on metformin+GLP-1 receptor agonist (RA, exenatide, group 2).

Results: The reduction in weight, BMI, total body, abdominal, leg, and arm fat percentage, and the improvement in body fat-free and muscle mass percentage were significantly higher in Group 2 ($p<0.001$, $p<0.001$, $p=0.014$; $p=0.031$, $p<0.001$; $p=0.002$ and $p=0.014$, $p=0.014$, respectively). The decline in abdominal fat mass in the GLP-1 RA group was also significant ($p=0.031$). There was a significant decrease in HbA1c, fasting glucose, and triglyceride levels ($p<0.001$, $p<0.001$, and $p=0.036$) with a significant increase in HDL-C ($p=0.015$). There was no significant difference between groups for glucose, HbA1c, and lipid parameters ($p>0.05$).

Conclusion: Both SGLT2 inhibitors and exenatide, when added to metformin therapy, were effective in reducing weight and body fat, more by the GLP-agonist. SGLT2-i had no significant impact on decreasing abdominal fat depicting that these agents do not have any benefit in treating visceral adiposity.

Key Words: *Type 2 diabetes mellitus, Obesity, GLP-1 receptor, SGLT2 inhibitor, Body fat distribution, Visceral adiposity.*

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INTRODUCTION

Approximately 82.5% of individuals with type 2 diabetes mellitus (DM) are obese, leading to the name "diabesity".[1] A 5-10% weight loss results in improved glycaemic control and significant reductions in cardiovascular risk in patients with diabetes.[2] The emerging epidemic of 'diabesity' raises the question of whether weight management and diabetes should be targeted as combined treatment strategies.[3] Currently, most guidelines recommend preferring the use of antidiabetic drugs with weight loss effects in the treatment of type 2 diabetes.[1] GLP-1 receptor agonists (GLP-1RA) and SGLT2 inhibitors (SGLT2-i) are glucose-lowering medications particularly recommended when there is a compelling need to reduce weight and also cardiovascular risk in diabetic people.[4,5]

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The antidiabetic drugs leading to weight loss are SGLT2-i and GLP-1RA. Sodium-glucose cotransporter 2 (SGLT2) inhibitors promote urinary glucose excretion by inhibiting renal glucose reabsorption by SGLT2, providing both glycaemic control and weight loss by developing a negative energy balance[6] and leading to a 1-5 Kg weight loss and reduction in fat mass.[5] Glucagon-like peptide-1 (GLP-1) is a peptide secreted from L cells in the small and large intestines. Glucagon-like receptor agonists (GLP-1 RAs), which have a potent incretin effect, lower glucose by enhancing insulin secretion and inhibiting glucagon secretion.[7] Besides, GLP-1RA induces weight loss by stimulating the satiety centre in the brain and slowing gastrointestinal motility.[8] Exenatide, a synthetic version of exendin-4, is a GLP-1RA.[9] Even though, the United States Food and Drug Administration (US FDA) has not approved exenatide for the treatment of obesity, a mean of 2-5 Kg weight loss, mainly as a result of decreased body fat mass, has been laid out in various studies.[9,10]

Research on the SGLT2-i and GLP-1RA effect on weight loss with the change in body composition is limited and concluded with conflicting results.[9,11-15] Furthermore, no research has been found that compared the effect of SGLT2-i and GLP1-RAs once a day as an add-on treatment to metformin on weight loss and change in body composition. The main objective of the study was to explore the effect of SGLT2-i (dapagliflozin 10 mg or

empagliflozin 10 mg once daily) and GLP-1RA (exenatide 10 mcg once daily) as an add-on therapy to metformin on weight loss and body composition. The second objective is to compare these two agents' effects on glucose and lipid parameters.

METHODOLOGY

Data of this retrospective cohort study was obtained from registries of the patients who consecutively attended the Diabetes and Obesity Outpatient Clinic of Goztepe Prof. Dr. Suleyman Yalcin City Hospital, between January 2016 to May 2021. The primary endpoint of this study was the change in weight, BMI, and body fat composition from baseline to the sixth month of follow-up. The secondary endpoint of the study was the change in HbA1c, fasting glucose, and lipid parameters. The study was approved by Research and Training Hospital Ethical Committee (2021/0277) on 26.05.2021.

Patients aged over 18 years, diagnosed with type 2 diabetes and using an SGLT2-i (dapagliflozin 10 mg, empagliflozin 10 mg), or GLP-1RA (exenatide 10 µg) as an add-on therapy to metformin were included. The patients who were using antidiabetic drugs other than metformin+SGLT2-i and metformin +exenatide and those with missing data were excluded.

Age, gender, occupation, educational status, marital status, having childhood obesity, comorbidities, smoking habits, physical activity level, eating habits, the drugs used, weight, height, body mass index (BMI), fat mass, fat-free mass, muscle mass, truncal, leg and arm fat mass and fasting glucose, haemoglobin A1c (HbA1c), triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) values were recorded from the files of the patients followed up in the diabetes obesity outpatient clinic, between January 2016 and May 2021, who met the inclusion criteria. The participants were followed up every 15 days for the first three months and then monthly with dietary counselling sessions and were prescribed a reduced calorie and balanced diet (50%-55% of energy as carbohydrate, 30% of energy as fat, and 15%-20% of energy as protein) of self-prepared foods to achieve weight loss.

The participants were divided into two groups. Patients using metformin+SGLT2-i were named as group 1, and the patients on metformin+GLP-1RA were identified as group 2. The weight, body fat composition, and biochemical parameter alterations at the end of the sixth month were evaluated, and the two groups were compared.

Each patient's height was measured with a stadiometer (SECA) standing without shoes. The weight, fat mass, fat-free mass, and muscle mass of each patient was measured with a bio-impedance analysis device (TANITA MC 780-MA, Tokyo, Japan). BMI was calculated with the Quetelet index (Kg/m^2). Blood samples were collected following a fasting period of 8 to 12 hours. Fasting blood glucose, TG, TC, LDL, and HDL levels were studied with Roche Cobas 8000 analyzer, while HbA1c was analysed using Primus MRDV with HPLC technique.

Data analyses were performed with the statistical software SPSS for IBM, version 25.0 (SPSS, Inc., Chicago, IL). Kolmogorov-Smirnov test was performed as a normality test. Data were normally distributed and were shown as mean ± SD. Significant differences were assessed using the student t-test. Categorical data were expressed as counts and percentages. A comparison of categorical data was performed using Fisher Exact test, when more than 20% of cells have expected frequencies <5, otherwise chi-square test was used. The p-value <0.05 was considered statistically significant. Primary and secondary endpoints were analysed using an ANCOVA model to eliminate the confounder effect of the baseline BMI, and the baseline BMI value was taken as a covariant.

RESULTS

The sociodemographic characteristics and the comorbidities of the participants are shown in Table I. The mean age of the participants of the total sample was 56.99±9.66 years. There was no significant difference in terms of age between groups 1 and 2 (p=0.841). The female-to- male ratio was significantly higher in the group 2 (p=0.003). No significant difference was detected between groups 1 and 2 in terms of comorbidities.

There was no difference between group 1 and group 2 regarding the HbA1c, fasting glucose, total cholesterol, LDL, HDL, and triglyceride baseline levels (p>0.05). While the baseline weight, BMI, total fat mass percentage, and arm and leg fat mass percentage of group 2 were significantly higher than group 1 (p<0.001), the fat-free mass percentage and muscle mass of group 2 were significantly lower than group 1 (p<0.001, Table I).

The changes in weight, BMI, and body fat composition from baseline and sixth month in the total sample are shown in Table II. There was a significant decrease in weight, BMI, total body fat, and leg and arm fat from baseline to the 6^{th} month in both groups (p<0.001). No significant difference was detected between the baseline and 6^{th}-month abdominal fat (p=0.27). A significant increase was observed in fat-free and muscle mass percentage from baseline to the 6^{th} month (p<0.001). The comparison of the differences between groups 1 and 2 in terms of change in weight, BMI, and body fat composition from baseline to the sixth month are also presented in Table II. The weight change was -3.32 Kg in group 1 and -7.04 Kg in group 2. BMI change in the six months for groups 1 and 2 was -1.29 and -2.77, respectively. It was observed that the decline in weight, BMI, total body, abdominal, leg and arm fat percentage was significantly higher in group 2 (p<0.001, p<0.001, p<0.001, p=0.031, a p<0.001 and p=0.002, respectively). The increment in body fat-free and muscle mass percentage was significantly higher in group 2 (p=0.014 and p=0.014, respectively). The decrease in abdominal fat in group 1 was not significant.

The decrease in HbA1c, fasting glucose and TG (p<0.001, p<0.001, and p=0.036, respectively) and increase in HDL-C (p=0.015) in total sample of 6 months was statistically significant. The change in other biochemical parameters from baseline to the sixth month was not statistically significant. The difference between groups in terms of yielding change in biochemical parameters was not statistically significant, as well (Table II).

Table I: The comparison of baseline characteristics of the participants.

	Group 1 (metformin + SGLT2-i) N=50		Group 2 (metformin + exenatide) N=50		Total sample N=100			
	n mean±SD	%	n mean±SD	%	n mean±SD	%	X^2 t	p
Age (years) (mean±SD)	57.70±9.64		56.28±9.72		56.99±9.66		-	0.841
Gender							8,680	0.003**
Male	17	34.00	4.0	8.00	21	21.00		
Female	33	66.00	46	92.00	79	79.00		
Childhood obesity	11	22.00	14	28.00	25	25.00	0.213	0.644
Smoking	11	22.00	13	26.00	24	24.00	0.055	0.815
Marital status							0.286	>0.99
Single	4	8.00	3	6.00	7	7.00		
Married	43	86.00	43	86.00	86	86.00		
Divorced	3	6.00	4	8.00	7	7.00		
Exercise habit							5.696	0.058
<30 min/week	36	72.00	45	9.00	81	81.00		
At least 30 min, 3 times/a week	8	16.00	4	8.00	12	12.00		
At least 30 min, 5 times/a week	6	12.00	1	2.00	7	7.00		
Eating habits							0.154	0.695
≥3 meals/a day	46	92.00	47	94.00	93	93.00		
<3 meals/day	4	8.00	3	6.00	7	7.00		
Snacking habit							0.000	>0.99
Present	41	82.00	41	82.00	82	82.00		
Absent	9	18.00	9	18.00	18	18.00		
Night eating habits							0.168	0.682
Present	32	64.00	29	58.00	61	61.00		
Absent	18	36.00	21	42.00	39	39.00		
Co-morbidities								
Hypertension	30	60.00	33	66.00	63	63.00	0.172	0.679
Cardiovascular diseases	4	8.00	8	16.00	12	12.00	0.852	0.356
Thyroid diseases	13	26.00	6	12.00	19	19.00	2.339	0.126
OSAS	3	6.00	2	4.00	5	5.00	-	0.500
Depression	6	12.00	3	6.00	9	9.00	-	0.243
COPD	1	2.00	2	4.00	3	3.00	-	0.500
Asthma	6	12.00	3	6.00	9	9.00	-	0.243
Weight (Kg)	99.4±17.05		92.6±16.91		106.27±14.36		-4.358	<0.001***
BMI (Kg/m2)	38.51±7.14		.35.25±7.6		41.78±4.87		-5.93	<0.001***
Total body fat mass percentage (%)	38.54±7.14		35.25±7.6		41.78±4.87		-5.11	<0.001***
Total body fat-free mass percentage (%)	61.49±7.15		64.75±7.6		58.23±4.87		5.11	<0.001***
Total body muscle mass percentage (%)	58.4±6,80		61.5±7,24		55.3±4.63		5.1	<0.001***
Abdominal fat-mass percentage (%)	15,87±3,49		15,34±3,72		16,42±3,19		-1.567	0.120
Arm fat mass percentage (%)	5.93±2.04		4.95±1.87		6.90±1.72		-5.432	<0.001***
Leg fat mass percentage (%)	16.70±4.50		14.97±4.77		18.44±3.46		-4.177	<0.001***
HbA1c (%)	7.04±0.86		7.13±0.85		6.95±0.88		1.01	0.32
Fasting glucose (mg/dl)	134.25±32.89		135.94±32.96		132.76±33.08		0.48	0.63
Total cholesterol (mg/dl)	202.48±37.69		203.86±33.25		201.10±41.95		0.37	0.72
LDL (mg/dl)	123.10±30.65		125.80±26.8		120.40±34.60		0.88	0.38
HDL (mg/dl)	47.84±11.44		47.86±10.36		47.82±11.97		0.02	0.99
Triglyceride (mg/dl)	153.11±62.67		151.02±54.61		155.2±70.31		-0.32	0.74

*Continuity Correction, Fisher's Exact Test, p-values of continuous variables were calculated using student t-test, p-values of categorical variables were calculated using Fisher's Exact test when more than 20% of cells have expected frequencies <5, otherwise chi-square test were used. SGLT2-i: Sodium-glucose Cotransporter 2 inhibitor; OSAS: Obstructive Sleep Apnea Syndrome; COPD: Chronic obstructive pulmonary disease, Independent sample t-test; * p<0.05, ** p<0.01, ***p<0.001; BMI: Body Mass Index; LDL: Low density lipoprotein; HDL: High density lipoprotein, Group 1: metformin+Sodium-glucose cotransporter inhibitor; Group 2: metformin+exenatide*

DISCUSSION

The results showed that both SGLT2 inhibitors (dapagliflozin 5 mg and empagliflozin 10 mg) and GLP-1 agonist, exenatide, when added to metformin therapy, were effective in reducing weight and body fat. The comparison of these two groups was in favour of the GLP-agonist. Weight loss has consistently been linked to lower cardiovascular risk and increased life expectancy in patients with type 2 diabetes in studies.[16] Furthermore, the DIRECT study demonstrated that weight loss of 15 Kg resulted in diabetes reversal.[17] Therefore, the effects of these two medications on weight further promote their use in type 2 diabetes.

The 3.32 Kg weight loss was observed in this study in the groups using metformin+SGLT2-i is similar to the other studies' findings which used dapagliflozin as the study medication.[18,19] Similarly, in a systematic review, it was indicated that the treatment with SGLT2-i resulted in a significant reduction in body weight ranging from –0.5 to -3.9 Kg (8-104 weeks study duration).[20] Twice a day exenatide use has been shown to lead to a mean of 3 Kg after 30 weeks when added to metformin[21], whereas a -7.2 Kg weight reduction was seen in this study.

Table II: The comparison of intergroup differences and repeated measures for body fat composition and biochemical parameters.

		Baseline	6th month	F	p	Effect size
Weight (Kg)	Total sample	99.44±17.0	94.26±15.9	118.523	<0.001***	0.547
*Group	Group 1	92.61±16.9	89.29±16.5	15.349	<0.001***	0.135
	Group 2	106.27±14.3	99.23±13.7			
BMI (Kg/m^2)	Total sample	38.59±6.5	36.56±5.9	118.76	<0.001***	0.55
*Group	Group 1	35.26±6.0	33.97±5.7	15.90	<0.001***	0.14
	Group 2	41.92±5.2	39.15±5.0			
Total body fat percentage (%)	Total sample	38.51±7.1	37.23±7.3	19.27	<0.001***	0.16
*Group	Group 1	35.25±7.5	34.98±8.1	6.305	0.014*	0.061
	Group 2	41.78±4.8	39.48±5.6			
Total body fat-free mass percentage (%)	Total sample	61.49±7.1	62.76±7.3	19.00	<0.001***	0.16
*Group	Group 1	64.75±7.6	65.00±8.1	6.289	0.014*	0.061
	Group 2	58.23±4.8	60.52±5.6			
Total body muscle percentage (%)	Total sample	58.40±6.7	59.60±7.8	18.54	<0.001***	0,16
*Group	Group 1	61.50±6.7	61.73±6.7	6.229	0.014*	0.060
	Group 2	55.47±7.8	57.47±8.0			
Abdominal fat percentage (%)	Total sample	15.88±5.5	15.64±5.4	1.20	0.277	0.012
*Group	Group 1	15.34±6.04	15.57±5.8	4.81	0.031*	0.047
	Group 2	16.42±4.5	15.71±4.2			
Leg fat percentage (%)	Total sample	5.93±2.8	5.53±2.5	41.558	<0.001***	0.298
*Group	Group 1	4.95±2.4	4.79±2.3	15.874	<0.001***	0.139
	Group 2	6.90±3.3	6.26±3.2			
Arm fat percentage (%)	Total sample	16.70±5.8	16.17±5.3	17.294	<0.001***	0.15
*Group	Group 1	14.96±2.3	14.84±2.2	10.123	0.002**	0.09
	Group 2	18.44±2.6	17.49±2.4			
HbA1c (%)	Total sample	7.04±0,86	6.59±0,76	34.85	<0.001***	0.262
*Group	Group 1	7.13±0.85	6.72±0.60	0.36	0.548	0.004
	Group 2	6.95±0.88	6.46±0.89			
Fasting Glucose (mg⁄dl)	Total sample	134.35±32.89	121.59±29.8	17.19	<0.001***	0.149
*Group	Group 1	135.94±32.96	122.28±20.0	0.09	0.771	0.001
	Group 2	132.76±33.08	120.90±37.3			
Total-C (mg⁄dl)	Total sample	202.48±37.6	196.49±40.1	3.17	0.078	0.031
*Group	Group 1	203.86±33.2	198.84±35.1	0.08	0.774	0.001
	Group 2	201.10±41.9	194.14±44.7			
LDL-C (mg⁄dl)	Total sample	123.10±30.6	118.32±33.7	2.53	0.115	0.025
*Group	Group 1	125.80±26.1	120.54±29.1	0.03	0.873	0.000
	Group 2	120.40±34.6	116,10±38,0			
HDL-C (mg⁄dl)	Total sample	47.84±11.1	49.14±10.94	6.11	0.015*	0.059
*Group	Group 1	47.86±10.3	49.80±10.92	1.48	0.227	0.015
	Group 2	47,82±11.9	48,48±11,04			
Triglyceride (mg⁄dl)	Total sample	153.11±62.6	141.92±60.3	4.50	0.036*	0.044
*Group	Group 1	151.02±54.6	142.12±57.9	0,19	0.665	0.002
	Group 2	155.20±70.3	141.72±63.2			

*Repeated measures ANCOVA Test; Related sample t test; * p<0.05, ** p<0.01, ***p<0.001; BMI: Body mass index, Group 1: met formin+Sodium-glucose cotransporter inhibitor; Group 2: metformin+exenatide. Repeated Measures ANOVA Testi, Dependent Sample t-test, * p<0.05, ** p<0.01, ***p<0.001.*

In the only study, to the authors' knowledge that evaluated the effects of an SGLT2 inhibitor (dapagliflozin) and a GLP-1 agonist (exenatide weekly) added to metformin therapy, (the duration-8 study), 28 weeks of using exenatide once a week and daily dapagliflozin resulted in -1.56 and -2.22 Kg, respectively, whereas combined use ended up with a – 3.55 Kg reduction.[22] The only significant weight loss was with the co-administration of both drugs, and there was no notable difference between the study medications use alone, whereas in the current study, with a significant -3.72 Kg difference, in favour of GLP-1 agonist, exenatide.

There are many different mechanisms yielding to weight loss with SGLT2-i and GLP-1RA use in type 2 diabetes, and further studies are still going on. Therefore, most studies also evaluated other parameters, such as fat and lean tissue mass, to gain further data. In a study conducted with dapagliflozin as an add-on therapy to metformin, the weight change was -2.42 Kg in 24 weeks, with a -1.1% decrease in the total fat mass.[13] Though, the weight change in the present trial was 3.32 Kg in the group on metformin+SGLT2-i, which is higher than in the prementioned study, the decrease in the total fat mass was -0.27%, suggesting mechanisms other than fat loss might be involved.

In the large-scale studies using exenatide twice daily or once weekly in one arm, mainly in the DURATION studies, although there was a weight reduction like 2 to 3 Kg, weight change was nonsignificant with the study medication. In the other studies comparing exenatide with other GLP-1 agonists, dulaglutide and semaglutide had significantly better weight reduction, which led to exenatide's use mainly for diabetes. However, real-world evidence and clinical experience showed a significant heterogeneity for both SGLT2-i and GLP-1RA. Moreover, there is limited data regarding the effects of exenatide on body composition. A study investigating the effect of short-term exenatide treatment on weight and regional fat distribution showed a mean of 0.5 Kg/m^2

decrease in BMI, 1 Kg weight reduction, and 1.2% decrease in fat percentage in three months.[12] However, in the current study, the reduction in BMI, weight, and fat mass percentage was higher (-1.77 Kg/m^2, -7.04 Kg, -2.30 %), most probably due to the extended study period. In another study in which the participants were followed up for 6 months, similar to the present study, 5.5 Kg weight loss was observed.[15] In Chen *et al*.'s study, while the fat percentage was not significantly reduced after exenatide treatment, the total body fat mass was significantly lowered by a mean of 0.8 Kg.[23]

The change in HbA1c, one of the second endpoints of the study, was a 0.45 % reduction in the patients using metformin+ dapagliflozin, which was similar to Hong *et al*.'s study indicated 0.42 % HbA1c reduction in 6 months.[19] In the metformin+ exenatide arm, when compared with the metformin+ SGLT2-i arm, there was a nonsignificant 0.49% decrease in HbA1c, which is lower than the percentage stated in the literature.[12,15] In a 6 month retrospective cohort study designed similarly to study, there was no difference in HbA1c between those using SGLT2-i and GLP-1RA, again unlike this study.[24] Due to the other study's retrospective nature, the participants used different SGLT2-i (canagliflozin, dapagliflozin, empagliflozin) and GLP-1 analogs (liraglutide, dulaglutide, exenatide, and exenatide ER). Furthermore, the prescription of additional antidiabetic agents, including medications with weight-gaining capacity, complicated the evaluation of the results. Though, the present study also had a retrospective design, the study's strength was the selection of patients only using metformin+exetanide and metformin+SGLT2-i. Prior studies have noted the importance of lean body mass, which is predominantly comprised of skeletal muscle since it acts as a primary site of glucose disposal and a significant predictor of basal metabolic rate; therefore, persons with a loss of skeletal muscle are prone to weight regain.[25] For that reason, the impact of exenatide and SGLT2 inhibitors (dapagliflozin and empagliflozin) on muscle mass was evaluated in the current study. Both of the agents were found to increase muscle mass percentage; however, the increment caused by exenatide was significantly higher.[12,14]

Very little was found in the literature comparing the effect of exenatide and SGLT2-i on weight and body composition. This study presented that the weight and body fat mass reduction caused by exenatide was significantly higher than SGLT2-i (dapagliflozin and empagliflozin). In a meta-analysis comparing the effects of GLP-1RA and SGLT2-İ on weight and fat mass, it was concluded that the difference between these effects was not statistically significant, unlike the findings reported in this study.[25] However, some limitations were mentioned in this meta-analysis. This meta-analysis compared the effects of several different SGLT and GLP 1 analogs, and the inclusion criteria of the studies included in the meta-analysis were various, which may be the reason for the contradiction with the present results.

Possible limitations of this work are the single-centre nature of the study, which also led to another limitation, the relatively small study population. Though this prevents further subgroup analysis, the results of the present study, which is a real-world efficacy study, still may add significantly to the current literature. Another limitation was that the patients' physical activities and exercise programs were not evaluated, which might have given additional information about the changes in body composition.

CONCLUSION

Both SGLT2-i and exenatide, when added separately to metformin, inadequately controlled type 2 diabetes, decreased weight and body fat composition, and increased body fat mass and muscle percentages. Exenatide seems to have an advantage on SGLT2-i on these parameters, though they seem to have a similar reduction effect on fasting glucose and HbA1c levels. Furthermore, SGLT2-i has no significant impact on decreasing abdominal fat depicting that these agents do not have any benefit in treating visceral adiposity.

ETHICAL APPROVAL:
The study was approved by Goztepe Prof Dr Suleyman Yalcin Research and Training Hospital Ethical Committee (2021/0277) on 26.05.2021.

PATIENTS' CONSENT:
Informed consents were obtained from all the patients included in the study.

COMPETING INTEREST:
The authors declare that there are no conflicts of interest concerning the materials or methods used in this study or the findings reported in this paper.

AUTHORS' CONTRIBUTION:
EA, HHM: Designed the study.
HHM: Analysed the data.
EA, HHM, AE, MS: Wrote the paper.
All the authors have approved the final version of the manuscript to be published.

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