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*Original Article*

# The Influence of Gender and Age on Laparoscopic Sleeve Gastrectomy Short-Term Outcomes in Type-2 Diabetic Obese Patients

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## ABSTRACT

***Background*** Bariatric surgery has come out as an effective treatment for morbid obesity due to its effects as stabilized weight loss and remission of obesity related comorbidities like type 2 diabetes. Postoperative weight loss is affected by many factors and predictors of weight loss after bariatric surgery are controversial. This study has been performed to evaluate the impact of gender and age on the short-term outcomes of laparoscopic sleeve gastrectomy (LSG) in type 2 diabetic (T2D) obese patients.

***Material and Methods*** In this retrospective study, the records of morbidly obese patients with a body mass index (BMI )≥40 kg/m$^2$, aged between 18-65 years old who underwent LSG and were followed-up for at least 6 months postoperatively were reviewed. Patients were subdivided into two groups according to age (≥50 y,<50 y), gender (female, male) and compared.

***Results*** The study included 25 patients, 17 (68%) female and 8 (32%) male, 14 (56%) were in <50 years old group and 11 (44%) were in ≥50 years old group. At the postoperative 6$^{th}$ month, there was a significant decrease in weight, BMI, diastolic blood pressure, fasting blood glucose, postprandial glucose and HbA1c in both gender and age groups (p<0.05). A significant decrease was observed in triglyceride (TG) at 6$^{th}$ month in both gender. While a significant increase in high-density lipoprotein (HDL) was observed in patients aged ≥50 (p=0.028), no significant change was observed in the younger group. There was a positive correlation between change in total cholesterol(TCh), TG and age (respectively; r=0.436, p=0.030, r=0.528, p=0.007).

***Conclusions*** LSG is an effective treatment method for morbid obesity for younger (<50 y) and advanced aged (≥50 y) T2D patients in both genders. The percentage changes in the decreament of TG in male gender and TCh in younger age were more prominent in short-term follow-up.

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## Introduction

In the last decade, both type 2 diabetes and obesity have been increasing epidemically worldwide. In TURDEP II study performed in Turkey in 2010, the prevalence of diabetes was found to be 13.7% and obesity 32%.[1] Bariatric surgery has come out as an effective treatment for morbid obesity due to its effects as stabilized weight loss and remission of obesity related comorbidities like type 2 diabetes. Laparoscopic sleeve gastrectomy (LSG) has been increasingly applied in our country in parallel with the world due to its advantages such as relative technical simplicity, permanent weight loss, endoscopy feasibility, having the chance of revision, and the need for less vitamin support throughout life.[2] Although bariatric surgery is the most effective therapy for obesity, postoperative weight loss is affected by many factors. Bariatric surgery results can be implicated by many physiological, epidemiological and psychosocial parameters, but studies evaluating potential predictors of weight loss after bariatric surgery are controversial.[3,4] This study has been carried out to evaluate the impact of gender and age on the short-term outcomes of LSG in type 2 diabetic obese patients.

## Material and Methods

The study was conducted after the approval of the local Ethics Committee in accordance with the Helsinki Declaration. In this retrospective study,the records of morbidly obese patients with a body mass index (BMI) ≥40 kg/m$^2$, aged between 18-65 years old who admitted to our Endocrinology and Metabolism outpatient clinics and underwent sleeve gastrectomy were reviewed. Patients who were followed up for at least 6 months postoperatively were included in the study. Gender, age, height, weight, BMI (calculated according to the formula=weight (kg)/height(m)$^2$), insulin usage, diastolic blood pressure (DBP), systolic blood pressure (SBP), fasting blood glucose (FBG), postprandial blood glucose (PPG), hemoglobin A1c (HbA1c), alanine aminotransferase (ALT), total cholesterol (TCh), high-density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and triglyceride (TG) were recorded retrospectively from files of the subjects. The percent of excess Body Mass Index Lost (%EBMIL) was calculated with the formula ([Preoperative BMI-current BMI]/[preoperative BMI-25])x100. Patients were subdivided into two groups according to age (≥50 y, <50 y), gender (female, male) and compared regarding changes in the mentioned parameters.

*Statistical Analysis*

Descriptive statistics for the numerical variables following nonnormal distribution were expressed as median (min-max). Shapiro-Wilk test was used to determine whether the data followed a normal distribution. In the comparison of two independent groups showing normal distribution, Independent Sample T test was used. Nonparametric tests were used for data that did not show normal distribution. Mann-Whitney U test was used to determine whether there was a significant difference between the mean values of independent data following nonnormal distribution in the presence of two groups. Wilcoxon test was used to determine whether there was a significant difference between the mean values of dependent data following nonnormal distribution. Pearson chi-square, Fisher Exact tests were used to determine whether there was a correlation between the categorical variables or whether they were independent of each other. The correlation between the numerical variables was determined using Spearman's Correlation Analysis. All statistical analyses were performed using IBM SPSS Statistics version 20.0 and a p-value of 0.05 was considered statistically significant.

## Results

*Gender*

Twenty five patients fulfilling the criterias were included in our study. Among them, 17 (68%) were females and 8 (32%) were males. The median age was 50 (25-59) years for females and 42.5 (18-57) years for males. Initial BMI values were 50.8 kg/m$^2$ (42.1-78.1) and 45.2 kg/m$^2$ (40.4-52.5) for females and males respectively, significantly higher in the female gender (p=0.049). Baseline ALT values in males were significantly higher compared to females (p<0.001). In the preoperative evaluation, no significant difference was observed between

the two genders in terms of other demographic and laboratory parametersas well as insulin usage percentages and doses used *(Table 1)*.

At the postoperative 6th month, there was a significant decrease in weight, BMI, DBP, FBG, PPG and HbA1c values in both gender compared to baseline *(Table 2)*. Although there was a significant decrease in SBP (p=0.001) and ALT (p=0.003) values in female patients, no significant change was observed in males. Concerning lipid parameters, a significant decrease was observed in TG values at 6th month compared to baseline in both gender (p=0.014 for females, p=0.017 for males, respectively). There was no significant change in TCh, HDL and LDL values. Insulin treatment was discontinued at the postoperative 6th month in all males and in 3 of the 5 females. Insulin dose was significantly reduced in the other 2 female patients. %EBMIL was found to be 49.66±12.67 in females and 64±15.8 in males, and it was significantly higher in male gender (p=0.023). There was not any significant difference among genders in terms of the percentage changes of all parameters.

*Age*

When the patients were grouped according to age, 14 (56%) were in <50 years old group and 11 (44%) were in ≥50 years old group. Although at baseline the weights of the patients in <50 years old group were significantly higher than the other group (p=0.013), there was no significant difference between the groups in terms of BMI. There was also no difference among the groups in terms of parameters other than weight before the operation *(Table 1)*.

At the postoperative 6th month, there was a statistically significant decrease in weight, BMI, DBP, FBG, PPG, HbA1c, ALT and TG values compared to baseline in both groups (p<0.05). While a significant increase in HDL was observed in patients aged 50 and over (p=0.028), no significant change was observed in the <50 years old group. The percentage change of the TCh values in the patients aged <50 years was found to be significantly higher than the changes in patients aged 50-years and over (p=0.015). At the postoperative 6th month, insulin treatment was discontinued in 3 of 4 patients <50 years

**Table 1.** Baseline demographic and laboratory characteristics of patients in gender and age groups

| | Female (n=17) | Male (n=8) | $p^1$ | Age <50 years (n=14) | Age ≥50 years (n=11) | $p^2$ |
|---|---|---|---|---|---|---|
| Age (year) | 50 (25-59) | 42.50 (18-57) | 0.511 | 38±9.72 | 53.33±2.74 | **<0.001** |
| Weight (kg) | 130 (103-190) | 137 (121-159) | 0.884 | 140.5 (121-178) | 121 (103-190) | **0.013** |
| BMI (kg/m$^2$) | 50.8 (42.1-78.1) | 45.2 (40.4-52.5) | **0.049** | 51.4 (40.4-78.1) | 46.2 (40.9-69.9) | 0.183 |
| Insulin usage (%) | 5 (29.4%) | 5 (62.5%) | 0.194 | 4 (28.6%) | 6 (54.5%) | 0.241 |
| Insulin dosage (U/day) | 83 (42-150) | 44 (10-100) | 0.421 | 63.50 (10-150) | 77 (10-100) | 0.914 |
| SBP (mmHg) | 135 (120-170) | 132.5 (125-170) | 1 | 130 (120-170) | 135 (120-170) | 0.267 |
| DBP (mmHg) | 85 (70-100) | 80 (80-90) | 0.157 | 80 (70-100) | 80 (80-90) | 0.687 |
| FBG (mg/dL) | 133 (94-288) | 149 (92-238) | 0.932 | 125 (92-193) | 165 (94-288) | 0.075 |
| PPG (mg/dL) | 166 (124-307) | 186 (111-347) | 0.887 | 169 (111-347) | 180 (124-307) | 0.434 |
| HbA1c (%) | 7 (5.7-9.9) | 7.7 (5.7-10.4) | 0.977 | 6.55 (5.7-10.4) | 8.3 (5.7-9.9) | 0.222 |
| ALT (IU/L) | 22 (12-53) | 55 (33-90) | **p<0.001** | 37 (13-90) | 22 (12-60) | 0.183 |
| LDL cholesterol (mg/dL) | 126 (63-228) | 118 (45-189) | 0.475 | 118 (45-195) | 161 (81-228) | 0.149 |
| HDL cholesterol (mg/dL) | 40 (27-58) | 39.5 (28-60) | 0.887 | 39 (27-60) | 41 (28-58) | 0.609 |
| TG (mg/dL) | 215 (79-401) | 179 (86-355) | 0.977 | 222 (79-401) | 187 (98-258) | 0.373 |
| TCh (mg/dL) | 214 (114-306) | 199.5 (129-268) | 0.475 | 213 (114-269) | 214 (148-306) | 0.267 |

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting blood glucose, PPG: postprandial blood glucose, HbA1c: hemoglobin A1c, ALT: alanine aminotransferase, HDL: high-density lipoprotein, LDL: low density lipoprotein, TG: triglyceride, TCh: total cholesterol.
$p^1$ comparison of initial and parameters of in gender groups.
$p^2$ comparison of initial and parameters of in age groups.

**Table 2.** Comparison of baseline and six month values of clinical and laboratory parameters in gender groups

| Parameteres | Female (n=17) | | | | Male (n=8) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 6th month | Δ | P* | Baseline | 6th month | Δ | P** | P*** |
| Weight (kg) | 130 (103-190) | 97 (79-156) | -0.25 (-0.32/-0.17) | **<0.001** | 137 (121-159) | 92.5 (85-125) | -0.27 (-0.45/-0.02) | **0.012** | 0.374 |
| BMI (kg/m$^2$) | 50 (42.1-78.1) | 38.3 (29.7-63.2) | -0.25 (-0.32/-0.17) | **<0.001** | 45.2 (40.4-52.5) | 31.5 (28.7-41.8 | -0.21 (-0.45/-0.02) | **0.012** | 0.374 |
| SBP (mmHg) | 135 (120-170) | 120 (110-160) | -0.07 (-0.21/0.00) | **0.001** | 132.5 (125-170) | 130 (110-140) | -0.11 (-0.19/0.08) | 0.092 | 0.798 |
| DBP(mmHg) | 85 (70-100) | 80 (60-90) | -0.1 (-0.25/0.00) | **0.002** | 80 (80-90) | 75 (70-80) | -0.11 (-0.18/0.00) | **0.025** | 0.932 |
| FBG (mg/dL) | 133 (94-288) | 100 (73-184) | -0.27 (-0.61/0.16) | **0.001** | 149 (92-238) | 90.5 (74-127) | -0.18 (-0.54/1.00) | **0.025** | 0.669 |
| PPG (mg/dL) | 166 (124-307) | 124 (98-188) | -0.31 (-0.6/-0.01) | **<0.001** | 186 (111-347) | 118 (101-173) | -0.23 (-0.64/0.57) | **0.012** | 0.932 |
| HbA1c (%) | 7 (5.7-9.9) | 5.5 (4.7-6.8) | -0.26 (-0.53/-0.01) | **<0.001** | 7.7 (5.7-10.4) | 5.8 (5.3-6.7) | -0.21 (-0.43/-0.03) | **0.012** | 0.798 |
| ALT (IU/L) | 22 (12-53) | 14 (6-34) | -0.38 (-0.82/0.24) | **0.003** | 55 (33-90) | 33 (11-82) | -0.56 (-0.78/1.48) | 0.176 | 0.406 |
| LDL cholesterol (mg/dL) | 126 (63-228) | 139 (43-253) | 0.17 (-0.32/0.54) | 0.522 | 118 (45-189) | 126.5 (48-189) | 0.05 (-0.08/0.28) | 0.237 | 0.344 |
| HDL cholesterol (mg/dL) | 40 (27-58) | 44 (32-81) | 0.07 (-0.15/1.06) | 0.065 | 39.5 (28-60) | 44.5 (30-52) | 0.13 (-0.36/0.33) | 0.623 | 0.977 |
| TG (mg/dL) | 215 (79-401) | 135 (90-237) | -0.22 (-0.73/0.88) | **0.014** | 179 (86-355) | 91.5 (84-182) | -0.47 (-0.75/0.02) | **0.017** | 0.086 |
| TCh (mg/dL) | 214 (114-306) | 209 (95-354) | -0.02 (-0.22/0.31) | 0.723 | 199.5 (129-268) | 185 (96-249) | -0.03 (-0.26/0.11) | 0.327 | 0.549 |

p* comparison of initial and sixth month parameters of female group.
p** comparison of initial and sixth month parameters of male group.
p*** comparison of Δfemale and Δmale.

of age, and in 5 of 6 patients >50 years of age. A significant reduction in dose was observed in patients who continued insulin. %EBMIL was 56.68±17.02 in the younger group and 51.62±12.8 in the elderly group, and no significant difference was observed (p=0.412). There was also not any significant difference between groups in terms of percentage changes of other parameters *(Table 3).*

When the relationship between the changes in the clinical and laboratory parameters of the patients and age is examined, there was a statistically significant and positive correlation between change in TCh, TG and age (respectively; r=0.436 p=0.030, r=0.528 p=0.007). There was no significant correlation between the change of other parameters and age.

## Discussion

In this preliminary retrospective study, our results indicated that both females and males benefited from LSG concerning weight and metabolic parameters in both groups younger than and equal to or older than 50 years of age in a 6 months follow-up period. At the 6th month of the evaluation, the percentage changes in the decreament of TG in male gender and TCh in younger age were more prominent.

Although the beneficial effects of bariatric surgery are known, there is a significant difference in the demand for bariatric surgery in men and women, and it is known that bariatric surgery is performed more in women.[5] Studies have reported that 63-82% of cases undergoing bariatric surgery are women.[6] It is well recognised that men generally tend to underutilise healthcare services compared to women. The reasons for this are multifactorial, including social, economic and cultural motivations.[7,8] Besides these differences in demand, it is thought that there may be differences between the genders in the postoperative results of bariatric surgery.

Obesity and diabetic status differ between genders due to significant differences in fat storage and metabolism, insulin resistance, blood pressure, lipid profile, endothelial dysfunction and systemic inflammation.[9,10] But little is known about the influence of these findings on the outcome of obesity surgery. Bariatric Outcome Longitudinal Database (BOLD) study results show that bariatric surgery efficiency is higher for female patients.[11] A recently published study demonstrated that female gender is an independent predictor of greater weight loss and %EBMIL, 1 year after bariatric surgery.[12] In another study, LSG was

**Table 3.** Comparison of the baseline and sixth month values of clinical and laboratory parameters in age groups and comparison of their percent changes

| Parameteres | Age <50 (n=14) | | | | Age ≥50 (n=11) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 6th month | Δ | P* | Baseline | 6th month | Δ | P** | P*** |
| Weight (kg) | 140.5 (121-178) | 104 (85-144) | -0.28 (-0.45/-0.19) | **0.001** | 121 (103-190) | 92 (79-156) | -0.23 (-0.3/-0.17) | **0.003** | 0.095 |
| BMI (kg/m$^2$) | 51.4 (40.4-78.1) | 37.4 (28.7-63.2) | -0.28 (-0.45/-0.19) | **0.001** | 46.2 (40.9-69.9) | 36 (29.1-57.3) | -0.23 (-0.3/-0.17) | **0.003** | 0.095 |
| SBP (mmHg) | 130 (120-170) | 120 (110-160) | -0.07 (-0.21/0.08) | **0.008** | 135 (120-170) | 130 (115-140) | -0.07 (-0.18/0) | 0.007 | 0.809 |
| DBP (mmHg) | 80 (70-100) | 72.5 (60-90) | -0.11 (-0.25/0) | **0.004** | 80 (80-90) | 80 (70-85) | -0.11 (-0.13/0) | **0.011** | 0.317 |
| FBG (mg/dL) | 125 (92-193) | 87 (73-184) | -0.32 (-0.54/0.16) | **0.005** | 165 (94-288) | 111 (92-129) | -0.21 (-0.61/0.07) | **0.004** | 0.727 |
| PPG (mg/dL) | 169 (111-347) | 104 (98-188) | -0.31 (-0.64/-0.05) | **0.001** | 180 (124-307) | 130 (119-173) | -0.21 (-0.57/-0.01) | **0.003** | 0.501 |
| HbA1c (%) | 6.55 (5.7-10.4) | 5.4 (4.70-6.20) | -0.17 (-0.43/-0.03) | **0.001** | 8.30 (5.7-9.9) | 6 (4.7-6.8) | -0.26 (-0.53/-0.01) | **0.003** | 0.851 |
| ALT (IU/L) | 37 (13-90) | 15 (6-82) | -0.49 (-0.82/1.48) | **0.023** | 22 (12-60) | 14 (8-35) | -0.33 (-0.78/0.24) | **0.029** | 0.317 |
| LDL cholesterol (mg/dL) | 118 (45-195) | 122.5 (43-181) | 0.003 (-0.32/0.28) | 0.615 | 161 (81-228) | 136 (117-253) | 0.17 (-0.20/0.54) | 0.169 | 0.647 |
| HDL cholesterol (mg/dL) | 39 (27-60) | 41.5 (30-66) | 0.06 (-0.36/0.35) | 0.530 | 41 (28-58) | 46 (34-81) | 0.07 (-0.13/1.06) | **0.028** | 0.244 |
| TG (mg/dL) | 222 (79-401) | 113.5 (88-237) | -0.44 (-0.75/0.88) | **0.009** | 187 (98-258) | 135 (84-205) | -0.21 (-0.53/0.36) | **0.014** | 0.183 |
| TCh (mg/dL) | 213 (114-269) | 183.5 (95-264) | -0.13 (-0.26/0.14) | **0.026** | 214 (148-306) | 217 (184-354) | 0.06 (-0.18/0.31) | 0.286 | **0.015** |

p* comparison of initial and sixth month parameters of age <50 group.
p** comparison of initial and sixth month parameters of age ≥50group.
p*** comparison of Δ age<50 group and Δ age≥50group.

more effective in obese male than in obese female in terms of %EBMIL.[3] However, Kennedy-Dalby *et al.*[4] reported in a cohort study that there was no gender difference in terms of %EBMIL at 2-year follow-up. In our study, %EBMIL was found to be significantly higher in male in short-term, but the lower baseline BMI of males can be thought to contribute to this result.

The reason for the different response to bariatric surgery between males and females is still unclear.[13] Another study examining the weight loss and metabolic effects of bariatric surgery on women and men showed a significant decrease in BMI, weight loss percentage and HbA1c values for both genders in the first year after surgery, no significant difference was observed among both genders regarding the changes of parameters stated.[4] Although it is known that bariatric surgery provides significant weight control and resolution of type 2 diabetes even in the short term[14], many studies have shown that there is no difference between genders in respect of weight loss and type 2 diabetes improvement.[15,16] In our study, it was seen that there was a significant decrease in weight, BMI, FPG, PPG and HbA1c values in the 6th month of treatment compared to the baseline in females and males who had LSG. Besides, similar to the literature, there was no significant difference between genders with regard to the percentage changes of these parameters.

In different studies, it is emphasized that some differences between genders in bariatric surgery results may be associated with varying cardiovascular risk profiles.[17] In a study conducted in Europe, at the end of 1-year follow-up, there was a significant decrease in both SBP and DBP, but no difference was observed in respect to percentage changes between genders. In our study, there was no significant change in the value of SBP in men, while there was a significant decrease in DBP. There was also no difference between genders in terms of percentage changes in DBP. In another study, the cardiovascular effects of bariatric surgery in women and men were evaluated by calculating the total cholesterol/HDL ratio, and a significant decrease was detected in both sexes, but no significant difference was observed in percentage changes between genders.[4] In our study, there was a significant decrease in TG value at the 6th month compared to baseline in men and women underwent LSG, while no significant change was found in other lipid parameters. Nevertheless, the percentage of TG change was not significantly different between genders.

The number of patients suffering from obesity and its comorbidities increase with the age, especially in the population aged 50 years and over. Therefore, the treatment of morbid obesity has become increasingly important, especially in the elderly population. Studies show that the majority of the patients selected for bariatric surgery were younger than 50 years, despite the fact that the prevalence of obesity is higher in the older age groups.[18] Nevertheless, although sleeve gastrectomy is not more risky in the elderly population, its outcomes on weight loss and comorbidities in older patients are less known.[19] The effectiveness of bariatric surgery in the older ages has been previously investigated. For instance, in a study comparing the patients over 60 years with those under 50 years for up to 22 months after LSG showed better results in the younger age group for BMI% change.[20] In a study conducted in our country, it is stated that age may be the determining factor for weight loss after LSG and that weight loss is less in patients over the age of 40 years.[21] Many studies have shown that the mean excess of weight loss was lower for the older patients and those younger than 45 years tended to have greater %BMI loss and %EBMIL than the older patients.[22,23] Chang *et al*.[24] also indicated that age was identified as an independent risk factor for weight loss in long-term follow-up. However, Robert *et al*.[25] showed age not to be a predictive factor of weight loss failure at 1 year. A recent study in India revealed that %EBMIL at the 6$^{th}$ month postoperatively did not differ between those over and under 65 years of age.[26] In another research, which used an age of 55 years as the cut-off point, there was no significant difference in weight loss and BMI after 24 months of follow-up.[27] In a comparative study by Burchett *et al*.[28], there was not any significant difference in weight loss and comorbidities such as diabetes between older and younger age groups. In this study, cut-off value for age was determined as 50 years based on the previous studies in the literature. We also used 50 years as cut-off for age in our study. Our study indicated a significant decrease in weight, BMI, DBP, FBG, PPG and HbA1c in both age groups. However, in the short-term follow-up of 6 months, the change of these parameters and %EBMIL did not differ significantly between the groups in accordance with the literature.

It is known that therapeutic interventions in diabetic patients are more effective in elderly patients to improve hypercholesterolemia. In the Action for Health Diabetes (AHEAD) program, interventions were effective in inducing larger relative improvements in HDL and waist circumference among the older participants when compared with the youngers. Lifestyle changes have often been promoted to explain these better outcomes in older patient groups.[29] In our study, there was a significant decrease in TG in both age groups after LSG in diabetic obese patients, but no significant change was observed in LDL value. While in younger group HDL did not change significantly, there was a significant increase in HDL level in the elderly group (≥50 y). Although the percentage of TCh change is significantly higher in the young group compared to the older group, the percentage of TG and TCh decrease increases with age (positive corelation). These good results in the older group can be explained by the fact that these patients being more aware of the negative consequences induced by obesity on their health as reported in some studies.[30] This makes them more likely to have a better motivation to change lifestyle and adhere to postoperative follow-up instructions.

In conclusion, sleeve gastrectomy is an effective treatment method for morbid obesity for younger (<50 y) and advanced aged (≥50 y) type 2 diabetic patients in both genders. In our study, no difference was observed in terms of weight loss, SBP and DBP values and changes in glycemic and lipid parameters between genders in short-term 6 months follow-up. There is no significant difference between the younger and older age groups in terms of the parameters other than TCh that decreased in the <50 years old age group. On the other hand, there is a positive correlation between age and percentage decreases of TCh and TG. Studies involving longer follow-up periods and higher number of patients are needed to reveal the effect of gender and age on the results of bariatric surgery concerning weight, metabolic parameters and positive effects on type 2 diabetes.

***Conflict of interest***

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

***Authors' Contribution***

Study Conception: OE, PS, HP, AY, CE; Study Design: OE, PS, HP, AY, CE; Supervision: OE, PS, HP, AY, CE; Funding: OE, CE; Materials: OE, HP, CE; Data Collection and/or Processing: OE, HP, PS; Statistical Analysis and/or Data Interpretation: AY, PS, CE; Literature Review: OE, PS, HP; Manuscript Preparation: OE, PS, CE; and Critical Review: OE, PS, CE.

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