

Retrospective Observational Study to Observe Clinical Effectiveness of Add-on Canagliflozin 100 mg in Indian Type 2 Diabetes Patients with BMI>25 kg/m², in Real World Clinical Setting- A Specialized Population of Group A/B Officers Employees of Financial and Public Sectors

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Abstract With the changing life style in the recent decade risk of chronic non-communicable diseases (NCDs) like diabetes has increased globally. World Health Organization (WHO) projections show that NCDs will be responsible for a significantly increased number of deaths in the next decade, especially in urban sedentary population. We planned to assess GROUP A/B OFFICERS EMPLOYEES OF FINANCIAL AND PUBLIC SECTORS (nationalized banks, insurance sector, government and semi-government PCUS), as they belong to special workgroup who predominantly have sedentary life style [1]. The prevalence of sedentary lifestyle among bankers is high and as it kills some 5.3 million people every year, according to the WHO, and with the increase and aging of the population, these lifestyles will become increasingly more common in low- and middle-income countries like India. Lifestyles with little or no physical activity are the leading cause of obesity, and one of the main risk factors for diabetes and cardiovascular disease. According to the International labor organization (ILO), people who engage in little physical activity run a 20% or 30% greater risk of dying from above causes. [2] Sodium-glucose linked transporter (SGLT) type2 inhibitors, constituting the most recently available oral glucose-lowering drug category, exert their effect by increasing urinary glucose excretion. Optimal prescribing of agents within this category requires a full understanding of their risks in addition to their benefits. Besides improving glycaemia control, weight and blood

pressure some members of this class provide beneficial cardiovascular and Reno protective Effects. [7, 13] So the present retrospective observational study was aimed to observe clinical effectiveness of add-on Canagliflozin 100 mg in high risk sedentary population i.e. uncontrolled Indian Type 2 Diabetes mellitus (Type2DM) Patients with body mass index (BMI) >25 kg/m², includes group A/B officer employees of financial and public sectors who were already on other hypoglycemic, anti-hypertensive and lipid lowering agents. These data were analyzed over a period of 12 months (1 stJune2017-30may 2018) among above-said employees of various sectors in Jaipur. After Ethical clearances from institutional ethical committee, a total of 113 Type2DM participants were included at baseline, 13 were excluded from study and their annual health data's subsequently analyzed after add-on Canagliflozin 100 mg pre breakfast, with earlier pharmacological management with no dose adjustment during the entire period of study. Significant reduction glycated hemoglobin (HbA1c) was noted in, as we observed the target HbA1c near normal (p<0.0001). Significant weight reduction was found in two sub-groups in our study (p< 0.0001). Significant reduction of Triglyceride was noted in all study groups (p<0.0001), but same trend was not observed in LDL, HDL and TC, although reduction was definitely noted.

Keywords Add-on Canagliflozin, Group A/B Officers, Obesity, Financial and Public Sectors, Type 2 DM

1. Introduction

With the changing life style in the recent decade risk of chronic NCDs like diabetes has increased globally. WHO projections show that NCDs will be responsible for a significantly increased number of deaths in the next decade especially in urban sedentary population. [1] NCD deaths are projected to increase by 15% globally between 2010 and 2020 (to 44 million deaths).

We planned to assess special sedentary population of Group A/B OFFICERS EMPLOYEES OF FINANCIAL AND PUBLIC SECTORS (nationalized banks, insurance sector, government and semi-government PCUS), as they belong to special workgroup. The prevalence of sedentary lifestyle among bankers is high and as this life style is responsible for morbidities like diabetes, hypertension and CV deaths in some 5.3 million people every year, according to the WHO, and with the increase and aging of the population, these lifestyles will become increasingly more common in low- and middle-income countries like India.

Lifestyles with little or no physical activity are the leading cause of obesity, and one of the main risk factors for diabetes and cardiovascular disease. [5] According to the International labor organization (ILO), people who engage in little physical activity run a 20% or 30% greater risk of dying from above causes. Since this specialized population is of paramount importance for country development, has become a high risk group for NCD. When health behavior modification fails to achieve glycemic and metabolic goal targets, priority should be given to antihyperglycemic agents that are associated with weight loss or weight neutrality. Therefore, in the new era of SGLT2 inhibitors, as they constitute the most recently available oral glucose-lowering drug category, exert their effect by increasing urinary glucose excretion. Besides improving glycaemia control, weight and BP, some members of this class provide beneficial cardiovascular and Reno protective effects [7, 13].

Therefore, present study was planned to observe to role of add-on SGLT-2 inhibitors in a specialized diabetic population who is almost sedentary, having high body mass index (BMI) and involved in various financial and public sectors whose profession is predominantly chair-bound and a very little time or no time is spared for physical activates and who were already on other Anti-diabetic, Anti-Hypertensive and Lipid Lowering Agents over a span of one year (consecutive annual health check-ups).

1.1. Aims and Objective

Therefore, present study was aimed to observe retrospectively in real world settings about the clinical

effectiveness of ADD-ON Canagliflozin 100 mg in Type 2 Diabetes Patients (T2DM) with BMI more than 25 kg/m². The special attention was paid to assess the trends of HbA1C in overweight and obese type 2 diabetics in Group A/B OFFICERS EMPLOYEES OF FINANCIAL AND PUBLIC SECTORS who were already on other Anti-diabetic, Anti-Hypertensive and Lipid Lowering Agents over a year.

2. Methods

2.1. Inclusion Criteria

- T2DM participants on a stable anti-hyperglycemic regimen containing one or more anti-diabetic drug for at least 30 days and had HbA1c of more than 7 percent (%) at the time of, or within 2 weeks before Canagliflozin 100 mg initiation.
- T2DM participants as confirmed from annual medical check-ups record. /OPD records.
- T2DM participant having BMI>25kg/m² at the time of Canagliflozin 100 mg initiation.
- Participants having clinical assessment data (at least HbA1c and body weight) for at least two visits, that is (i.e.) visit at which treatment with Canagliflozin 100 mg was initiated or 2 weeks before initiation and follow-up visit, in accordance with the usual clinical practice.

2.2. Exclusion Criteria

Following patients were excluded from the study. Patients with:

1. type 1 diabetes or secondary forms of diabetes,
2. pregnant or lactating women,
3. patients with clinically significant renal or hepatic disease,
4. patients with congestive heart failure requiring pharmacological treatment,
5. patients with history of unstable angina, acute coronary syndrome within the past 6 months,
6. patients on anti-tubercular treatment,
7. patients on any other treatment for chronic ailments such as HIV, hepatitis B, hepatitis C,
8. chronic kidney failure,
9. patients with history of allergy to any of the investigational product/s,
10. chronic alcoholism,
11. Planned surgical intervention during the expected study duration, history of any surgical interventions during 3 months before enrollment.

Ethical clearances were obtained from institutional ethical committee to analyze the data. This retrospective cohort study used data as obtained from a large health plan database from above described sectors of their type2

diabetic employees who were (≥ 18 years) and were prescribed Canagliflozin from 1st September, 2016 to May 31, 2017 and were continuously enrolled in the health plan 12 months following the first Canagliflozin prescription claim (follow-up). Changes in glycemic control were evaluated, along with characteristics of enrolled patients and changes in treatment patterns. The database was observed over a period of 12 months (1st September 2017 to 30th May 2018) in the above specified groups in Jaipur. A database of 4890 employees was analyzed, about 980 were type 2 diabetic and among them about 60 % (588) patients were group A/B officers. Total 113 officers fulfilled the inclusion criteria and considering prevalence of Type 2 DM about 15- 20%, minimum required sample size was found to be 100. Total 113 employees were available for the study and screened. A predesigned and pretested questionnaire was used to collect the relevant information from study subjects. Data regarding age, sex, income, family history of diabetes mellitus and details regarding exercise was obtained. Body measurements like height, weight and waist circumference of were recorded using standard anthropometric devices as per recommended by WHO references.

Certain definition used in the study.

1. Age:

Age was recorded in completed years as revealed by subjects and categorized into 3 groups; age <35 years, 35-49 years and ≥ 50 years.

2. Waist circumference:

Males: Individuals with waist circumference <90cm were given a score as 0, $\geq 90 - 99$ cm as 10, and those with ≥ 100 cm as 20.

Females: Individuals with waist circumference 80cm were given a score as 0, $\geq 80 - 89$ cm as 10, and those with ≥ 90 cm as 20.

Family history of diabetes: present/absent. (Single parent/both parents)

3. Physical activity (PA):

Individuals were considered GOOD PA if they did leisure time exercise and in addition had physically demanding work in their occupation; individuals who either did exercise or performed physically demanding work AVERAGE PA and the individuals who neither did any exercise or who are leading a sedentary lifestyle POOR PA.

ECONOMICAL STATUS-A Central Civil Post with pay in the Pay Matrix between Level 10 and 18 or equivalent -GROUP A and central Civil Post with pay in the Pay Matrix between Level 6 and 9 or equivalent -GROUP B.

Observational study group included the eligible patients for this study were-

- Type 2 diabetic who were Group A/B officers of either sex aged between 18 and 65 years.

- Who were uncontrolled on previous antidiabetic management (monotherapy or combination therapy) means (fasting plasma glucose [FPG] level of ≥ 126 mg/dL and ≤ 200 mg/dL and/or 2 h postprandial plasma glucose [PPG] ≥ 200 mg/dl and/or glycosylated hemoglobin [HbA1c] levels $\geq 7.5\%$ and $\leq 10\%$ at screening).
- Who were prescribed Canagliflozin between 1st September, 2016 to May 31, 2017

2.3. Study Design

A total of 113 T2DM participants were analyzed, 13 were excluded from study (two patients had urinary tract infection during study subsequently excluded from the study, other discontinued due to their reasons like transfer to different place), and these patients had add-on Canagliflozin 100 mg pre breakfast, with earlier pharmacological management with no dose adjustment during the entire period of study. Previous hypoglycemic agents and their doses were changed according to FPG/HbA1C during follow up. Antihypertensive and lipid-lowering medication changes were only made if medically required. Block randomization technique with block size of 6 was followed using the statistical software. Demographic details including the current and past medical history, date of diagnosis, concomitant medications, and physical assessment, including height, weight, BMI, and vitals, were recorded at baseline. Following bio-chemical tests were analyzed as per their annual health records, at the time of baseline Screening-Fasting Plasma Glucose, Post Prandial Glucose (PPG), liver function test, urea and creatinine, lipid profile, thyroid function test, electrocardiogram-ray chest as per National Accreditation Board for Testing and Calibration Laboratories (NABL) standardized protocol.

FPG and PPG as monitored at baseline and subsequently on every visit and at end of 12 months recorded in their Outpatient Department (OPD) records were analyzed. HbA1c and all other screening tests done at baseline and 12 months' post-study treatment were scrutinized. As per their health records it was found that all patients were given, thorough training on using the glucometer for self-monitoring of blood glucose by a glucometer instruction sheet, to perform a 5-point home-based glucose monitoring once a week, on every Sunday. Omron HGM-112 Glucometer is one of the most trusted glucometer units was used as recommended by many health experts. The patients were advised to measure blood glucose using glucometer whenever they had symptoms of fatigue/sweating/giddiness/blurred vision and were further advised to take 2 teaspoons of sugar if the glucose value was <70 mg/dl and were also advised to call the health experts immediately. After consultation with dietician, the patients were provided with a diet plan to follow till the next visit and were also instructed to follow physical

activity as advised by the treating physician. During the follow-up visit, the FPG and PPG were measured by collecting venous blood samples. The patient's vital parameters as well as weight were also recorded. In each follow-up visit, the patient diary was reviewed for occurrence of instances of symptoms suggestive of hypoglycemia, drug compliance, and results of the home blood glucose monitoring. At the end of 12 months of treatment, the patients detail as per their annual health records were reanalyzed FPG, PPG, HbA1c, hematology, clinical chemistry including renal function test, liver function test and lipid profile, urinalysis, pregnancy test for female patients, and vitals including height and weight were recorded.

2.4. Statistical Methods

Statistical analysis was performed by MedCalc statistical software, a statistical software for biomedical research, including ROC curve analysis, method comparison and quality control tools. Continuous data was reported using the following descriptive statistics: number of observations (n), mean, standard deviation, minimum, and maximum. Mean and standard deviation were presented with minimum and maximum values. For

analyzing continuous data, Student's t-test was carried out. Categorical data were presented using frequency (n) with percentage (%), and comparison was done using Chi-square test. All P values for efficacy analyses were calculated at 0.05 level of significance. After ethical committee clearance statistical analysis was performed by MedCalc statistical software, a statistical software for biomedical research, including ROC curve analysis, method comparison and quality control tools.

2.5. Safety

The database reveals that only 5 participants reported episodes of symptoms suggestive of hypoglycemia, i.e., dizziness, sweating, or chills. The incidences of hypoglycemic symptoms were comparable the other studies. Of these, 3 were confirmed by glucometer readings. The patients themselves managed most of these episodes by consuming sugar or carbohydrate rich food without the necessity for seeking medical help. No severe hypoglycemia or symptoms related to severe hypoglycemia was recorded as per the patient's diary. None of the patients had any serious adverse event during the study.

3. Results

Table 1. Comparative account of study group like demographic and anthropometric indices, clinical parameters, previous drugs history, biochemical variables, side effects at baseline and after 12 months of add-on Canagliflozin 100 mg

parameters	Base-line	After 12 months of add-on canagliflozin therapy	p-value.
Total number of patients	113	100	-
age	55 ±10	54±8	-
Sex-male/female	91/22	82/18	-
weight	84.9±17.6	83.3± (18.1)	<0.5
Body height (cm)	167 ± 8	166 ± 6	
Body mass index (BMI) (kg/m ²)	34.1 ± 5.9	32.1 ± 4.1	<0.5
Waist circumference(male)	95 ± 8	89 ± 4	<0.5
Waist circumference(female)	83 ±6	81 ±2	<0.5
.Family h/o diabetes	39	34	
One parent diabetic	29	26	
both parent diabetic	10	8	
Physical activity(PA)			
GOOD PA	22	28	<0.5
AVERAGE PA	37	48	<0.5
POOR PA	54	24	<0.5
Systolic blood pressure (mm Hg)	129 (14)	124 (15)	<0.01
Diastolic blood pressure (mm Hg)	80 (10)	73 (17)	<0.005
Plasma glucose (mg/dL)	180 (78)	128 (81)	<0.0001
HbA1c (%)	8.4 (2.0)	6.9 (1.7)	<0.0001
HDL-C (mg/dL)	38 (11)	41 (12)	<0.068
TG (mg/dL)	211 (53)	167 (91)	<0.0001
LDL-C (mg/dL)	120 (39)	118 (36)	<0.7
Non-HDL-C (mg/dL)	111 (30)	104 (36)	<0.13
AST (IU/L)	39 (27)	39 (31)	<0.5
ALT (IU/L)	50 (40)	53 (48)	<0.5
Previous drug history			
Biguanides	98	96	-
Thiazolidinediones	17	17	-
DPP-4 inhibitors	95	95	-
α-GI	6	7	-
Glinides	2	1	-
GLP-1 analogues	0	0	-
Insulin	10	6	-
ACEi/ARB	65	65	-
Statins	30	30	-

(PA- Physical activity, ACE i: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blockers; α-GI: alpha-glucosidase inhibitor; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide 1.)

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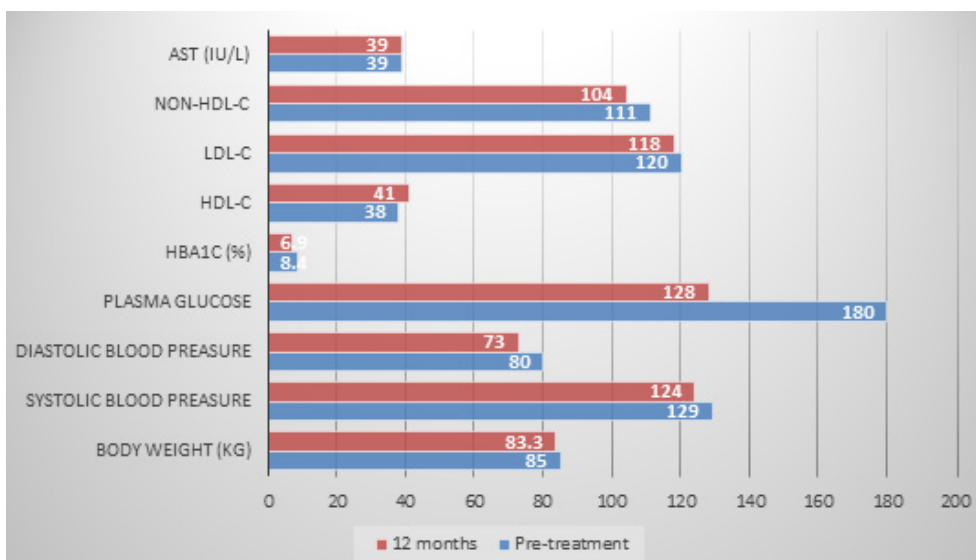


Figure 1. Significant changes noticed in the study group especially in SYSTOLIC BLOOD PRESUE, fasting plasma glucose, HbA1c after 12 months of add-on Canagliflozin 100 mg

Table 2. Age correlation/comparison with HbA1c, weight, at baseline (b) and after 12 months' add-on canagliflozin therapy

Patients AGE	Family h/o DM	Type 2 DM	HbA1c(base line)	HbA1c (base line)	p-value	WEIGHT	WEIGHT	p-value
< 35 yr	12	12	8.9±1.1	7.1±1.1	< 0.0001	86±2.1	81±2.1	< 0.0001
35-50 yr	20	49	8.8±1.4	6.8±1.4	< 0.0001	85±3.2	84±3.2	<0.0283
50-60 yr	12	39	8.7±1.6	6.9±1.6	< 0.0001	84±2.1	82±2.1	< 0.0001

(DM-diabetes mellitus, HbA1c-glycosylated haemoglobin)

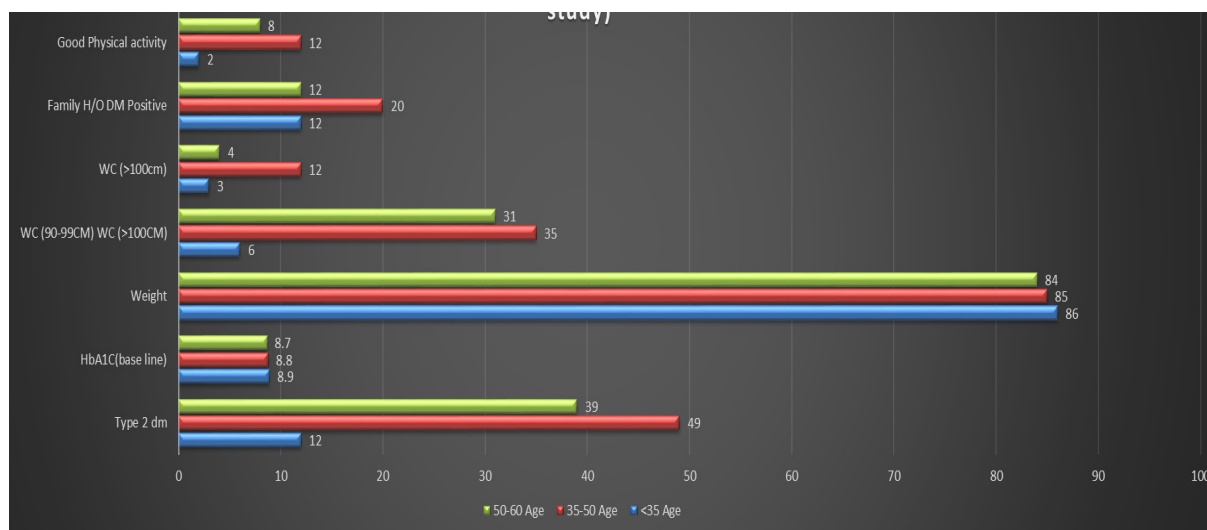


Figure 2. Age correlation with various parameters, HbA1c, weight, waist circumference, and family history of type 2 DM at the onset of study

Table 3. Age correlation /comparison with weight, waist circumference (WC) and physical activity at baseline(b) and after 12 months' add-on Canagliflozin therapy

Patients AGE	WC (90-99CM)-b	WC (90-99CM)-12 mth	WC (>100cm)	WC (>100cm)	GOOD PHYSICAL ACTIVITY	GOOD PHYSICAL ACTIVITY
< 35 yr	6	3	3	1	2	4
35-50 yr	35	30	12	10	12	14
50-60 yr	31	25	4	3	8	10

(WC-waist circumference)

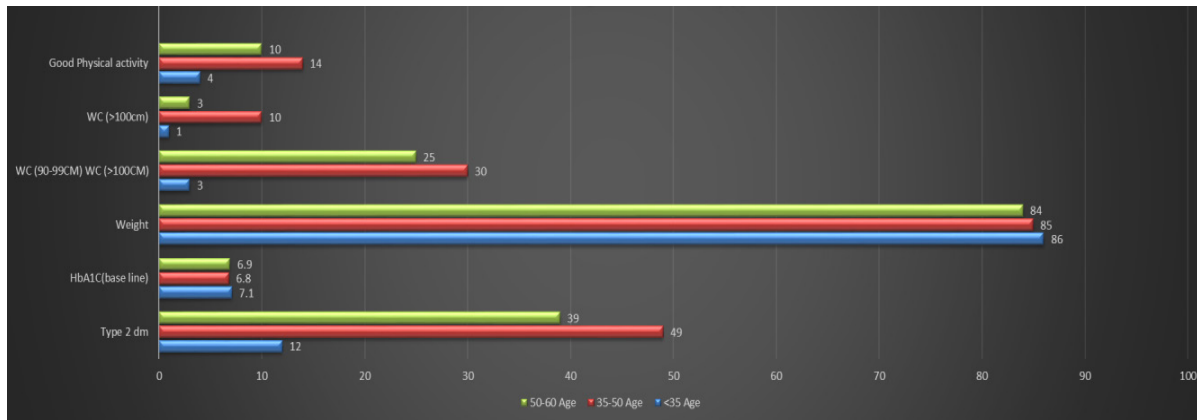


Figure 3. Impact on various age groups's parameters like HbA1C, weight, and waist circumference, after 12 months' add-on Canagliflozin therapy

4. Discussion

Over the past 4 decades, a huge number of the working population has shifted from manual labor associated with agriculture sector to physically less demanding office jobs. It was observed that the prevalence of diabetes was almost 3 times higher in individuals with light physical activity compared to those having heavy physical activity [1]. The prevalence of sedentary lifestyle among bankers is high and as this life style is responsible for morbidities like diabetes, hypertension and cardiovascular (CV) deaths in some 5.3 million people every year, according to the WHO, and with the increase and aging of the population, these lifestyles will become increasingly more common in low- and middle-income countries like India. [2, 3, 4]

In our study, according to Indian diabetes risk score (IDRS), physical activity of subjects was divided into 3 groups. Only 20 % were in regular habit of vigorous exercise and about 50%, were not doing any exercise. In our study, 26 subjects had positive family history of T2DM in one parent, 8 had positive history in both parents and 66 did not have any significant family history. Family history is a well-known risk factor for the development of T2DM. Having a 1st degree relative with the disease poses a 40% risk of developing diabetes. Family history reflects both inherited genetic susceptibilities and shared environmental exposures that include cultural factors. Thus family history of DM, may be useful tool to identify individuals at increased risk of the disease and target behaviour modifications that could potentially delay disease onset and improve health outcomes. As compared to general population other factors were prevailing more other than family history in this specialized population (66%) [5].

Type 2 diabetes (T2DM) is a complex disease with multiple defects, which generally require a combination of several pharmacological approaches to control hyperglycemia. Combining a dipeptidyl peptidase-4 inhibitor (DPP-4i) and a sodium-glucose cotransporter type 2 inhibitor (SGT2i) appears to be an attractive approach [6]. In patients with T2DM, Canagliflozin provided clinically meaningful body-weight reductions, and the weight loss

contributed to reductions in HbA1c and SBP [6, 7, 8]. Significant weight reduction was found in two sub-groups in our study ($p < 0.0001$) same trend of reduction was not achieved in group of 35-50 years, probably they did not follow a diet plan as advised by dietician or did not follow the instructions of physical activity as advised by their treating physician. Prior to the introduction of SGLT2 inhibitors, glucagon-like peptide-1 receptor (GLP-1) agonists were the only class consistently associated with body-weight reduction in patients with T2DM [11]. Overweight/obesity confer additional comorbidities to individuals with T2DM, and most patients with T2DM are overweight or obese [9]. The American Medical Association recognized obesity as a complex disease associated with comorbidities, including type 2 diabetes and cardiovascular disease (CVD) [9]. Most T2DM individuals manifest insulin resistance (metabolic syndrome), which is associated with multiple metabolic abnormalities, i.e., obesity, dyslipidemia, and hypertension, all of which are CV risk factors [10, 13]. While SGLT2-inhibitors can exert a beneficial effect on CV risk by having favorable effects on weight and blood pressure, and also other favorable hemodynamic effect [7,13,14]. Significant reduction of triglycerides was noted in all study groups ($p < 0.0001$), but same trend was not observed in LDL, HDL and total cholesterol, although reduction was definitely noted, it is in commensurate with the study conducted by Ferrannini et al. SGLT2 inhibitors cause a small increase in plasma LDL and HDL cholesterol and a decrease in plasma triglycerides; LDL/HDL cholesterol ratio remains unchanged [12, 13, 14]. The mechanism by which SGLT2 inhibitors cause these changes in lipid profile remains unknown. Weight loss can explain, in part, the decrease in triglycerides and increase in HDL cholesterol [15].

Significant reduction of HbA1c was noted in all three groups, as we achieved the target HbA1c near normal ($p < 0.0001$). A recent study found that less than half of newly diagnosed T2 DM patients achieve an HbA1c $< 7\%$, the American Diabetes Association target [16]. If nutritional guidance, physical activity, and lifestyle

interventions are not successful, and pharmacologic therapies are indicated, then the choice of anti-diabetic medications should take into consideration, the effects of these drugs on adipose tissue function and dysfunction, which in turn, affects major cardiovascular risk factors and cardiovascular disease [17]. L.Ji et.al. observed in their study in Asian population who were already on metformin alone or in combinations with sulfonylurea, on week 18, Canagliflozin 100 and 300 mg provided significant reductions from baseline in HbA1c compared with placebo (-0.97, -1.06 and -0.47%, respectively; $p < 0.001$) [13]. The dose requirements of other anti-hypoglycemic agents were significantly reduced and sulfonylureas and insulin had been withdrawn in 23 and 4 patients respectively over a span of one year. Previous studies have also observed that hypoglycemia is quite frequent when Dapagliflozin or Canagliflozin is used in combination with insulin or insulin secretagogue therapy [15,18]. Chang Hee Jung, Jung Eun Jang and Joong-Yeo in their study considered SGLT2 Inhibitor a Novel Therapeutic Agent for T2DM and advised that, physicians should reduce the dose of insulin or insulin secretagogue at the time these SGLT2 inhibitors are initiated. However, in active comparator trials, hypoglycemia has been shown to be less frequent in patients receiving Dapagliflozin or Canagliflozin compared with those receiving insulin secretagogue therapies [18, 19].

Therefore, as SGLT2 inhibitors have a unique mechanism of action that is independent of insulin secretion or the degree of insulin resistance, the efficacy of this class of drugs is anticipated not to decline with progressive β -cell failure or in the presence of severe insulin resistance [20]. However, as the efficacy of these agents is dependent on glomerular filtration, these therapeutic benefits are limited to a subset of diabetic patients with normal renal function or mild renal dysfunction [17, 18]. Although SGLT2 inhibitors appear to be well tolerated, increased risks of genital infections, and in some studies, urinary tract infections have been reported [21, 22]. Although long-term safety data are required to determine the significance of these observations, time will tell whether this increase in frequency of genitourinary infections will be tolerated by diabetic patients. This study had several limitations. First the number of female patients is much less than their male counterpart, in the groups. Second, the duration of treatment period was short.

5. Conclusions

Leading a sedentary lifestyle is becoming a significant public health issue. Sedentary lifestyles appear to be increasingly widespread in many nations despite being linked to a range of chronic health conditions. From this study we can conclude that, 55% of high risk population of banking, insurance and public sector in Jaipur city were

sedentary which constitute a potential threat to the banking, other financial industries and public sectors and adequate intervention is required on how they (sedentary bankers), can adopt healthier lifestyles, once they develop diabetes. If DM pharmacologic therapies are indicated, then the choice of anti-DM medications should take into consideration the effects of such agents on adipose tissue function and dysfunction, which in turn, affects major CVD risk factors and CVD. The magnitude of the global diabetes problem and the unmet needs of current anti-diabetic agents are the primary drivers behind the effort to identify new treatment modalities. Although currently available data indicate that SGLT2 inhibitors fulfill these unmet needs to some extent, larger studies with longer follow-up periods are warranted to establish the long-term safety and efficacy of SGLT2 inhibitors in specialized group of populations.

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