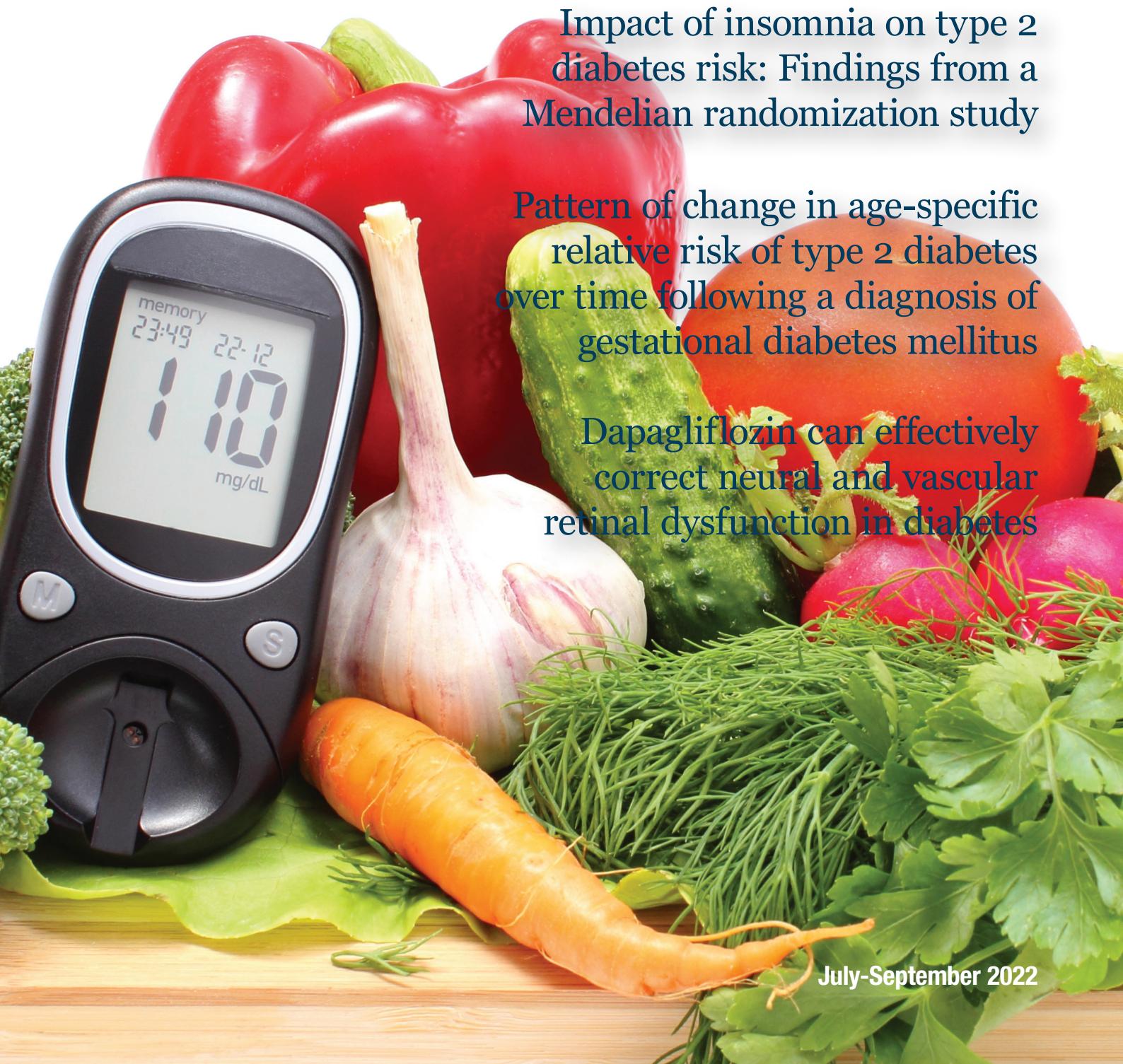


Diabetes GATE

OFFICIAL JOURNAL OF INTERNATIONAL FEDERATION OF DIABETES & CARDIOMETABOLIC DISORDERS (AMSTERDAM)

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Impact of insomnia on type 2 diabetes risk: Findings from a Mendelian randomization study

Pattern of change in age-specific relative risk of type 2 diabetes over time following a diagnosis of gestational diabetes mellitus

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Ref: * Clin Pharmacol Ther. 2009 May;85(5):513-9

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Diabetes GATE

is the official journal of
**International Federation of
Diabetes & Cardiometabolic
Disorders (Amsterdam).**

Published 4 times in a year.

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IFDCD Address:
WTC Tower B – 9th Floor
Strawinskyalaan, Amsterdam.

CONTENTS

EXPERT OPINION

Impact of insomnia on type 2 diabetes risk:
Findings from a Mendelian randomization
study

4



Pattern of change in age-specific relative risk
of type 2 diabetes over time following a
diagnosis of gestational diabetes mellitus

9



Dapagliflozin can effectively correct neural
and vascular retinal dysfunction in diabetes

16

Ascertaining the safety and efficacy of
vildagliptin-metformin treatment in newly
diagnosed type 2 diabetic patients

19

Evaluating the association between diabetic
nephropathy and proton pump inhibitors

21

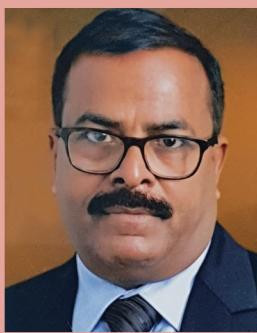


JOURNAL SCAN

DIABETES: NATURE & SCOPE

KEY JOURNALS CITED

- BMJ
- BMJ Open
- Circulation
- Diabetes
- Diabetes Care
- JAMA
- Journal of Diabetes Complications
- Lancet
- Lancet Diabetes Endocrinol
- N Engl J Med (NEJM)
- Obes Rev
- Obesity (Silver Spring)



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Impact of insomnia on type 2 diabetes risk: Findings from a Mendelian randomization study

Sleep deprivation due to interrupted sleep or a reduction in sleep duration has been associated with increased insulin resistance and higher plasma glucose levels. Studies have also shown that both short and long sleep durations are linked with a considerably increased risk of type II diabetes. Insomnia, daytime napping, and evening preference (chronotype) have been linked in previous observational studies to a greater risk of type 2 diabetes. Nonetheless, the causal effects of sleep traits on blood sugar levels remain ambiguous owing to potential biases from residual confounding and reverse causality.

In this context, a group of researchers conducted a study that aimed to explore the effects of sleep traits on glycated hemoglobin (HbA1c). Of note, the researchers used a statistical technique called Mendelian Randomization (MR) to examine how five sleep traits - insomnia, sleep duration, daytime sleepiness, napping, and chronotype - were related to average glycemic levels assessed by HbA1c (primary outcome) and glucose (secondary outcome) in the general population. Using MR, which groups people according to genetic variants, allowed the researchers to remove any potential bias, which are otherwise more common with conventional observational multivariable regression (MVR).

The researchers used data from the UK Biobank [for MVR and one-sample MR (1SMR) analyses] ($n = 336999$; mean age, 57 years; 54% female) and the genome-wide association studies from the Meta-Analyses of Glucose and Insulin-Related Traits Consortium (MAGIC) (for 2SMR analysis) ($n = 46368$; 53 years; 52% female).

Across all analyses including MVR, 1SMR, 2SMR, and their sensitivity analyses, it was observed that a higher frequency of insomnia symptoms (usually vs. sometimes or rarely/never) resulted in higher HbA1c levels (MVR 0.05 SD units [95% CI 0.04–0.06]; 1SMR 0.52 [0.42–0.63]; 2SMR 0.24 [0.11–0.36]). When participants with diabetes and those with HbA1c ≥ 48 mmol/mol were excluded, results of MVR and 1SMR were somewhat attenuated but remained consistent with those of the main analyses.

The researchers found no clear evidence for an effect of other sleep traits on blood sugar levels. For context, in the MVR and 1SMR analysis, longer 24-h sleep duration was associated with lower HbA1c levels; 2SMR analyses did not support a strong causal effect. Likewise, in the 1SMR analysis, there was evidence that short sleep duration increased HbA1c and that long sleep duration reduced HbA1c.

Findings of this study are consistent with those from previous observational and MR studies that demonstrated an association between insomnia and higher T2D risks. In the present study, the findings were extended in the wider population and after excluding people with diabetes.

In a nutshell, this study demonstrated that frequent insomnia symptoms cause higher blood sugar levels, thus suggesting a causal role of insomnia in type 2 diabetes. These findings could aid in developing and evaluating lifestyle and/or pharmacological interventions that improve insomnia to help prevent or treat diabetes.

Reference

1. Liu J, Richmond RC, Bowden J, et al. Assessing the Causal Role of Sleep Traits on Glycated Hemoglobin: A Mendelian Randomization Study. *Diabetes Care*. 2022;45(4):772-781.

Comparative efficacy of statins based on their effects on non-high density lipoprotein cholesterol in patients with diabetes and cardiovascular risk

- Strong emerging data has confirmed that since non-high density lipoprotein cholesterol (non-HDL-C) includes many potentially atherogenic lipid particles, it may not be any less atherogenic than low-density lipoprotein cholesterol (LDL-C). Reduction of non-HDL-C by statin is therefore deemed a rational treatment approach to reduce high cardiovascular (CV) risk, including in patients with diabetes.
- This literature search involved a systematic review and network meta-analysis that compared efficacy of different statins in CV risk prevention based on their effects on levels of non-HDL-C in patients with diabetes. An online search of database on Cochrane Central Register of Controlled Trials, Medline, and Embase was undertaken; those randomized controlled trials that compared treatment with different statins in adult patients with type 1 and type 2 diabetes were selected for this analysis. Additionally, placebo-controlled trials were also included in this search.
- While the primary study outcome was effect of statins on non-HDL-C levels, secondary study outcomes included changes in levels of LDL-C and total cholesterol, three point major CV events (non-fatal stroke, non-fatal myocardial infarction, and death related to cardiovascular disease), and discontinuations secondary to adverse events.
- Among the statins evaluated in this analysis, rosuvastatin at high- (-2.31 , 95% credible interval -3.39 to -1.21 mmol/L) and moderate- (-2.27 , -3.00 to -1.49) intensity doses, and simvastatin (-2.26 , -2.99 to -1.51) and atorvastatin (-2.20 , -2.69 to -1.70) at high-intensity doses were shown to be the most effective in reducing non-HDL-C compared with placebo.
- Atorvastatin and simvastatin were seen to be effective at all dose intensities and pravastatin at low dose intensity in significantly reducing levels of non-HDL-C. Even though other statins reduced non-HDL-C, reduction was not significant compared to placebo.
- In subgroup analysis, all statins at their dose intensities could significantly reduce non-HDL-C in patients with low-to-medium risk except fluvastatin, pravastatin, and rosuvastatin at low intensity doses; in high-risk patients, atorvastatin at high dose intensity was deemed the best statin while fluvastatin at low dose intensity was shown to be the worst. No significant differences were found in drug discontinuations, non-fatal strokes, and CV deaths.
- Hence this systematic review suggested that rosuvastatin at moderate- and high-intensity doses, and both simvastatin and atorvastatin at high-intensity doses were potentially the most effective statins at moderately reducing non-HDL-C levels in patients with diabetes.

Rosuvastatin at moderate- and high-intensity doses, and both simvastatin and atorvastatin at high-intensity doses were potentially the most effective statins at moderately reducing non-HDL-C levels in patients with diabetes

Hodkinson A, Tsimpida D, Kontopantelis E, Rutter MK, Mamas MA, et al. Comparative effectiveness of statins on non-high density lipoprotein cholesterol in people with diabetes and at risk of cardiovascular disease: systematic review and network meta-analysis. *BMJ*. 2022 Mar 24;376:e067731.

Low- and very-low carbohydrate diets for remission in type 2 diabetes

- Type 2 diabetes is associated with hyperglycemia, and therefore carbohydrate restriction is a standard management approach practiced in these patients for several decades. However, the efficacy and safety of this approach has generated considerable interest in the past few years. This online search, a systematic review and meta-analysis of CENTRAL, Medline, Embase, CINAHL, CAB, and grey literature sources was performed to evaluate efficacy and safety of low carbohydrate diets (LCDs) and very low carbohydrate diets (VLCDs) in type 2 diabetes.
- All randomized controlled trials that evaluated efficacy of at least 12 weeks duration of LCD and VLCD in adults with type 2 diabetes were included. The primary outcomes of the study were remission of diabetes

(HbA1c <6.5% or fasting glucose <7.0 mmol/L, with or without the use of diabetes medication), weight loss, HbA1c, fasting glucose, and adverse events; secondary outcomes of the study included health-related quality of life and biochemical laboratory data.

- The study results showed higher rates of remission in diabetic patients, defined as HbA1c < 6.5% independent of medications, with LCD compared with control diets; however for remission defined as HbA1c < 6.5% in the absence of diabetes medication, smaller, non-significant effect size remissions were reported.
- In subgroup analysis, patients using insulin showed fewer remissions (both definitions of remission) after 6 months of LCD compared to patients not using insulin. In addition, LCD was seen to increase weight loss, reduce medication use, and improve triglyceride concentrations at six months; although most benefits were seen to wane at 12 months; however given that only sparse data on remissions with LCD and VLCD at 12 months was available, findings of benefits of restricted carbohydrate diet at 6 months diminishing by 12 months could not be confirmed with certainty.
- Subgroup assessments also showed that VLCD was less effective than LCD for weight loss at six months, although this effect was explained by diet adherence. Finally, while LCD had no significant difference in quality of life and VLDL-C at 6 months, there was clinically important worsening of quality of life and LDL-C at 12 months.
- Hence, based on moderate-to-low certainty evidence, it appeared plausible that 6 months of LCD could improve rates of remission in diabetes without adverse consequences, though the benefits can diminish by 12 months.

Goldenberg JZ, Day A, Brinkworth GD, Sato J, Yamada S, et al. Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: systematic review and meta-analysis of published and unpublished randomized trial data. *BMJ*. 2021;372:m4743.

Six months of low carbohydrate diet could improve rates of remission in diabetes without adverse consequences

BMJ OPEN

Effect of obesity on diabetic retinopathy in patients with type 2 diabetes

- Several risk factors are known to predispose to diabetes. Obesity is a well-established risk factor of type 2 diabetes, and the association between these two has been known for past many decades. However, the link between obesity and diabetic retinopathy (DR), a microvascular complication of diabetes, still remains unclear. While some previous studies have reported protective effect of obesity on DR, others have shown that obesity may in fact increase incidence of DR. This study was conducted to clarify the link between DR and four obesity-related indices namely body mass index (BMI), waist to hip ratio (WHR), waist to height ratio (WHtR) and body adiposity index (BAI) in patients with diabetes. The study enrolled 2305 patients with diabetes; primary study outcome was the effect of obesity-related indices on DR, diabetic macular edema (DME), and vision-threatening DR (VTDR). Based on BMI, patients were divided into three categories [normal (18.5-22.9 kg/m²), overweight (23.0-25.0 kg/m²) and obese (>25.0 kg/m²)] while WHR, WHtR and BAI were divided into quarters.
- Among the study participants, 336 (14.58%) developed DR, 93 (4.03%) developed DME, and 98 (4.25%) patients developed VTDR. Ophthalmological findings of any DR, DME and VTDR were more frequent in patients who were overweight than in normal weight or obese patients. Also, prevalence of these eye findings was noted to be higher in patients with higher BMI/WHR or lower WHtR/BAI. In univariate regression model, WHR correlated positively with DR, while WHtR and BAI correlated negatively with DR, DME and VTDR. Another prominent finding of this study was that while obesity (BMI >25.0 kg/m²) appeared to be protective for VTDR, second-quarter WHtR was a significant risk factor. The study results therefore appeared to confirm that general obesity and centripetal obesity was a protective factor in the development of DR and VTDR.

Li W, Gong X, Wang W, Xiong K, Meng J, et al. Association of different kinds of obesity with diabetic retinopathy in patients with type 2 diabetes. *BMJ Open*. 2022;12(5):e056332.

Metformin and its effects on risk of age-related macular degeneration in patients with type 2 diabetes

- Age-related macular degeneration (AMD) is a retinal degenerative disease, similar to diabetic retinopathy, which is also a potential cause of blindness, particularly in the elderly. Metformin, a biguanide, is one of the earliest-introduced and first-line antidiabetic therapies.
- This retrospective study attempted to evaluate the effect of metformin on development of AMD in patients ≥50 years of age and with type 2 diabetes ≥10 years of duration. The evaluation process included review of medical records of 1891 patients with type 2 diabetes who were subsequently followed-up in a single ophthalmology center.
- The final analysis included records of 324 patients. Among them 209 used metformin while 115 did not. Ophthalmological findings of AMD were noted in lesser percentage of patients who used metformin compared to those who did not (15.8% vs 45.2%, respectively, $p<0.0001$). Moreover, metformin also appeared to protect against AMD progression; patients who had used metformin prior to their ophthalmology visit were less likely to progress to any AMD ($p<0.0001$).
- In subgroup analysis, metformin was shown to protect against the development of early AMD but there was no significant protection against the development of late AMD in type 2 diabetes. While age, expectedly, was a significant risk factor associated with AMD risk; level of serum HDL cholesterol was also significantly associated with late AMD. In a subsequent analysis, high cumulative dose of metformin (daily average dose of at least 1500mg) and cumulative duration > 5 years were seen to impart greater protective effects.
- The results therefore appeared to confirm protective effects of metformin against development of any AMD and early AMD, but no significant association between late AMD and metformin was noted.

Jiang J, Chen Y, Zhang H, Yuan W, Zhao T, et al. Association between metformin use and the risk of age-related macular degeneration in patients with type 2 diabetes: a retrospective study. *BMJ Open*. 2022;12(4):e054420.

Metformin appears to exert protective effects against development of age-related macular degeneration

Add-on treatment with tirzepatide to titrated insulin glargine in type 2 diabetes with suboptimal glucose control: The SURPASS-5 randomized clinical trial

- Tirzepatide is a recently-introduced dual glucose-dependent insulinotropic polypeptide (GIP)/ glucagon-like peptide-1 (GLP-1) receptor agonist, deemed an attractive therapeutic option for type 2 diabetes in the future owing to its ability to address multiple pathophysiological alterations underlying development of the disorder.
- This study included patients with type 2 diabetes with suboptimal glycemic control and evaluated the potential efficacy of tirzepatide as an add-on therapy to titrated insulin glargine. The study was a multicenter randomized phase 3 trial and conducted in medical research centers of 8 countries. The study design involved randomizing patients to 1:1:1:1 treatment with once-weekly add-on subcutaneous injections at doses of 5 mg, 10 mg, 15 mg tirzepatide, or volume-matched placebo to patients of type 2 diabetes on once-daily insulin glargine with or without metformin.
- Results after study completion at 40 weeks showed that mean change in HbA1c from baseline was -2.40% with 10 mg tirzepatide and -2.34% with 15 mg tirzepatide compared to -0.86% with placebo. Tirzepatide 5 mg showed -2.11% changes in mean HbA1c from baseline. On the other hand mean changes in body weight from baseline was -5.4 kg with 5 mg tirzepatide, -7.5 kg with 10 mg tirzepatide, and -8.8 kg with 15 mg tirzepatide, compared to + 1.6 kg with placebo.

Tirzepatide shows glucose-lowering efficacy as add-on treatment to insulin glargine in patients with type 2 diabetes

- Among the study participants who completed follow-up, treatment was prematurely discontinued by 10%, 12%, 18%, and 3% participants in the tirzepatide 5 mg, 10 mg, 15 mg, and placebo groups, respectively. When a comparison was made between patients treated with all doses of tirzepatide and placebo, higher percentage of patients on tirzepatide achieved HbA1c < 7% compared to those on placebo (85-90% vs 34%, respectively).
- Results from this study therefore confirmed glucose-lowering efficacy of tirzepatide as add-on treatment to insulin glargine compared to placebo in patients with suboptimally-controlled type 2 diabetes.

Dahl D, Onishi Y, Norwood P, Huh R, Bray R, et al. Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial. *JAMA*. 2022;327(6):534-545.

JOURNAL OF DIABETES AND ITS COMPLICATIONS

Moderate-intensity resistance exercise may be effective in improving blood glucose and pregnancy outcomes in patients with gestational diabetes mellitus

- Gestational diabetes mellitus (GDM) is a significant high incidence metabolic disorder globally, which can have detrimental effects on normal pregnancy with increased risk of adverse pregnancy outcomes.
- In a randomized controlled trial, a total of 99 patients with GDM were randomly categorized into an experimental group and a control group, with an aim to explore the effects of a structured moderate-intensity resistance exercise program on blood glucose levels and other health-related indicators in patients with GDM.
- Patients in both groups were provided the same personalized diabetes diet guidance, routine prenatal care, and online education intervention; however, those in the experimental group were subjected to an additional moderate-intensity resistance exercise program.
- Post-intervention blood glucose levels were lower in both groups as compared to before intervention. However, a greater change post-intervention in the average fasting blood glucose and the 2 h postprandial blood glucose was reported in the experimental group versus the control group (Figure 1). Also, the insulin utilization rate, the amount of insulin (Figure 2), gestational weight gain, and blood pressure were lower in the experimental group versus the control group. No statistically significant difference was reported in the incidence of post-intervention adverse pregnancy outcomes between the two groups.
- In a nutshell, findings of this study suggested that moderate-intensity structured resistance exercise was effective in ameliorating blood glucose control, insulin use, gestational weight gain and blood pressure in patients with GDM.

Figure 1: Change in blood glucose levels post-intervention between the two groups of patients with gestational diabetes mellitus

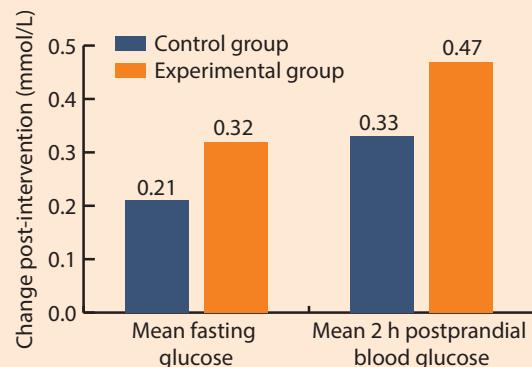
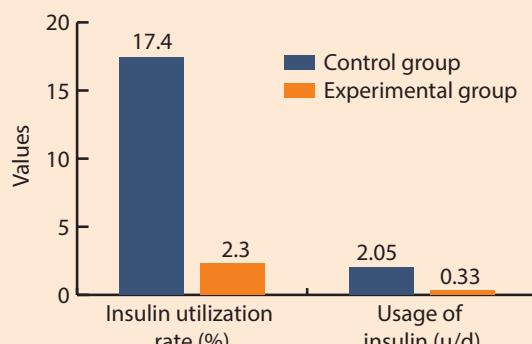
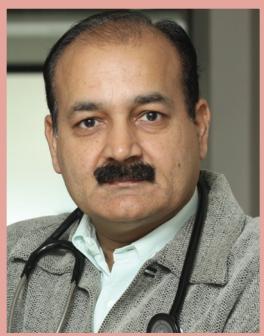


Figure 2: Insulin use between the two groups of patients with gestational diabetes mellitus during the intervention period



Huifen Z, Yaping X, Meijing Z, Huibin H, Chunhong L, et al. Effects of moderate-intensity resistance exercise on blood glucose and pregnancy outcome in patients with gestational diabetes mellitus: A randomized controlled trial. *J Diabetes Complications*. 2022;36(5):108186

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Pattern of change in age-specific relative risk of type 2 diabetes over time following a diagnosis of gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is defined as glucose intolerance of varying severity first detected during the present pregnancy. It is thought to be caused by pancreatic β -cell dysfunction in women who already have insulin resistance. Women with a history of GDM are at increased risk of future diabetes, predominantly type 2 diabetes, as are their children i.e. trans-generation transmission occurs. This suggests that a diagnosis of GDM during pregnancy may reveal an underlying susceptibility for type 2 diabetes and serve as a predictor of future disease risk. Because the probability of GDM recurrence increases when a woman has more than one GDM-affected pregnancy, it is likely that the risk of type 2 diabetes will rise as well after several affected pregnancies.

Type 2 diabetes can be prevented or delayed through suitable interventions among high-risk populations. Women who develop GDM during pregnancy are a readily identifiable group who could potentially benefit from early preventive lifestyle measures. Consequently, identifying women at highest risk of acquiring type 2 diabetes after a pregnancy with GDM and studying the persistence of this risk over time appears critical for public health. Knowing the duration of risk, on the other hand, could help women and physicians choose how long they should focus on diabetes screening after giving birth.

In this context, a study was conducted that aimed to assess the manner in which risk of type 2 diabetes changed with BMI and the total number of GDM-affected pregnancies; it also aimed to explore the pattern of change in age-specific relative risk of type 2 diabetes over time following a diagnosis of GDM.

The investigators used data of 50884 women from the Sister Study – a prospective observational cohort study – to evaluate the reproductive histories in relation to risk of type 2 diabetes. Among the study participants who initially did not have diabetes, 3,370 were diagnosed with diabetes during the 10-year follow-up. There was an overall estimated hazard risk (HR) of 2.50 (95% CI 2.15–2.91) for the association between history of any GDM and a later diagnosis of type 2 diabetes. Moreover, history of ≥ 1 pregnancies with GDM predicted elevated age-specific risk of type 2 diabetes, with a hazard ratio of 3.87, 6–15 years after an affected pregnancy. The estimated risk of developing type 2 diabetes increased sharply with multiple affected pregnancies. Women with >3 affected pregnancies who were within 6–15 years of their last GDM diagnosis had an approximately seven times increased risk of developing type 2 diabetes versus those without a GDM diagnosis. The age-adjusted relative risk of type 2 diabetes declined with time since the most recent GDM diagnosis, with an estimated 24% reduction of the hazard ratio per decade; however, the risk remained elevated for >35 years.

In a nutshell, a history of GDM predicted considerably increased rates of type 2 diabetes. Each additional GDM-affected pregnancy substantially increased the relative risk of type 2 diabetes. Although the estimated hazard ratio declined with time after a pregnancy with GDM, it remained elevated for >35 years. These findings suggest that women who were ever diagnosed with GDM should be provided adequate screening for type 2 diabetes, even later in life.

Reference

- Diaz-Santana MV, O'Brien KM, Park YM, et al. Persistence of Risk for Type 2 Diabetes After Gestational Diabetes Mellitus. *Diabetes Care*. 2022;45(4):864-870.

JOURNAL OF DIABETES AND ITS COMPLICATIONS

Exploring the association between glycated hemoglobin and mortality or end-stage kidney disease in patients with diabetic kidney disease

- Chronic kidney disease is a common and morbid complication of diabetes. Owing to the rising underlying prevalence of obesity and diabetes, the prevalence of diabetic kidney disease (DKD) has grown substantially over the past two decades. DKD is a leading cause of end-stage kidney disease (ESKD), and is associated with markedly reduced lifespan.
- Although intensive glucose-lowering therapy is effective in reducing the risk of developing DKD, its effects on progression and complications of existing DKD remain ambiguous.
- With an aim to help define the risk-benefit balance of tight glycemic control among persons with diabetes and established CKD, a team of researchers examined the associations of HbA1c with risks of progression to ESKD and death in a clinic-based cohort. The premise of the study was that higher HbA1c concentrations would be associated with increased risks of ESKD and death.
- A total of 618 participants from the Seattle Kidney Study were included (308 of them had diabetes), and were evaluated for associations of HbA1c with a composite of ESKD or death.
- The results revealed 343 instances of composite outcome over a median follow-up of 4.2 years (11.5 per 100 person-years). Death was the first event in 158 individuals.
- Among participants with diabetes (in both crude and adjusted analyses), there was no association between higher HbA1c levels and the risk of the composite outcome (HR (95% CI): 0.99 (0.88, 1.10) per 1% additional HbA1c, $p = 0.79$).
- Among participants with diabetes, HbA1c was not associated with risk of ESKD or mortality; the associations did not change when the participants were stratified between insulin users and non-users.
- Thus, it could be concluded that in the referred population of established DKD, higher HbA1c concentration was not associated with increased risk of ESKD or death.

In patients with established diabetic kidney disease, higher HbA1c concentrations may not be associated with increased risks of end-stage kidney disease or death

Limkunakul C, de Boer IH, Kestenbaum BR, Himmelfarb J, Ikizler TA, et al. The association of glycated hemoglobin with mortality and ESKD among persons with diabetes and chronic kidney disease. *J Diabetes Complications*. 2019;33(4):296-301.

THE LANCET

Effect of intravitreal faricimab with extended dosing in patients with diabetic macular edema

- Faricimab is a novel angiopoietin-2 and vascular endothelial growth factor-A bispecific antibody.
- YOSEMITE and RHINE are two randomized, double-masked, non-inferiority trials conducted across 353 sites worldwide, which are designed to assess the efficacy, safety, and durability of faricimab in patients with diabetic macular edema (DME).
- Investigators report 1-year findings from the YOSEMITE and RHINE trials with an aim to reduce treatment burden and optimise patient outcomes in DME.
- In the YOSEMITE and RHINE trials, adults with vision loss due to centre-involving DME were randomized (1:1:1) to receive intravitreal faricimab 6·0 mg every 8 weeks, faricimab 6·0 mg per personalised treatment interval (PTI), or aflibercept 2·0 mg every 8 weeks up to week 100.
- PTI dosing intervals were modified every 4 weeks up to every 16 weeks based on disease activity at active dosing visits.
- Primary outcomes included mean change in best-corrected visual acuity at 1 year, averaged over weeks 48, 52, and 56.

- Out of a total of 3247 patients that were screened for eligibility in YOSEMITE (n=1532) and RHINE (n=1715), 940 patients were enrolled into YOSEMITE and 951 patients were enrolled into RHINE.
- Thus, a total of 1891 patients were randomized to receive faricimab every 8 weeks (YOSEMITE n=315, RHINE n=317), faricimab PTI (n=313, n=319), or aflibercept every 8 weeks (n=312, n=315).

The results were as follows:

- Non-inferiority for the primary endpoint was achieved with faricimab every 8 weeks
 - » Adjusted mean vs aflibercept every 8 weeks in
 - YOSEMITE 10.7 ETDRS letters [97.52% CI 9.4 to 12.0] vs 10.9 ETDRS letters [9.6 to 12.2]
 - RHINE 11.8 ETDRS letters [10.6 to 13.0] vs 10.3 ETDRS letters [9.1 to 11.4]
 - » Adjusted mean vs faricimab PTI
 - YOSEMITE 11.6 ETDRS letters [10.3 to 12.9], RHINE 10.8 ETDRS letters [9.6 to 11.9].
- Incidence of ocular adverse events was comparable between treatment groups
 - » Faricimab every 8 weeks (YOSEMITE 31%, RHINE 43%)
 - » Faricimab PTI (YOSEMITE 34%, RHINE 37%)
 - » Aflibercept every 8 weeks (YOSEMITE 33%, RHINE 36%).
- In a nutshell, faricimab therapy with adjustable dosing up to every 16 weeks was associated with robust vision gains and anatomical improvements, thus suggesting that faricimab may have the potential to extend treatment durability for patients with diabetic macular edema.

*ETDRS = Early Treatment Diabetic Retinopathy Study

Wykoff CC, Abreu F, Adamis AP, Basu K, Eichenbaum DA, et al; YOSEMITE and RHINE Investigators. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. *Lancet*. 2022;399(10326):741-755.

THE LANCET

Effect of blood pressure lowering on the risk of new-onset type 2 diabetes

- Lowering of blood pressure (BP) is a well-acknowledged approach for preventing microvascular and macrovascular complications in patients with diabetes; however, its role in the prevention of diabetes per se is less clear.
- In this context, a study was conducted to evaluate the effect of BP lowering on the risk of new-onset type 2 diabetes and to establish the comparative effects of five major BP lowering drug classes on that risk.
- This was a one-stage individual participant data meta-analysis, wherein individual-level data from large-scale randomised trials of BP lowering drugs were used to investigate the differential effects of five major classes of antihypertensive drugs on the risk of new-onset type 2 diabetes.
- A total of 145939 participants (60.6% men) from 19 randomized controlled trials were included in the one-stage individual participant data meta-analysis. A total of 22 trials were included in the individual participant data network meta-analysis

Faricimab therapy with adjustable dosing up to every 16 weeks was associated with robust vision gains and anatomical improvements, thus suggesting that faricimab may have the potential to extend treatment durability for patients with diabetic macular edema

Blood pressure lowering is an effective strategy for the prevention of new-onset type 2 diabetes. The conventional antihypertensive drugs exert varying effects on diabetes, likely attributed to their differing off-target effects, with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers having the most favorable outcomes

- Over a median follow-up of 4·5 years, a total of 9883 participants were diagnosed with new-onset type 2 diabetes
- Across all trials, reduction in systolic BP by 5 mmHg reduced the risk of type 2 diabetes by 11% (hazard ratio 0·89 [95% CI 0·84–0·95]).
- Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) reduced the risk of type 2 diabetes compared with placebo, with a relative risk (RR) of 0·84 (95% CI 0·76–0·93, 59% direct evidence) for ACEIs and RR 0·84 (0·76–0·92, 60% direct evidence) for ARBs.
- However, β blockers (RR 1·48 [1·27–1·72]) and thiazide diuretics (RR 1·20 [1·07–1·35]) were found to increase the risk of type 2 diabetes compared with placebo.
- No effect was observed for calcium channel blockers (CCBs) compared with placebo (RR 1·02 [95% CI 0·92–1·13]).
- Thus, it could be concluded that BP lowering is an effective strategy for the prevention of new-onset type 2 diabetes. The conventional antihypertensive drugs exert varying effects on diabetes, likely attributed to their differing off-target effects, with ACEIs and ARBs having the most favorable outcomes.

Nazarzadeh M, Bidel Z, Canoy D, Copland E, Wamil M, et al; Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure lowering and risk of new-onset type 2 diabetes: an individual participant data meta-analysis. *Lancet.* 2021;398(10313):1803–1810.

DIABETES

Exploring the potential cardiovascular effects of incretin-based therapies

- With the increasing worldwide prevalence of diabetes and obesity, risk of debilitating CV complications also increases. Since there exists a significant association between diabetes and CV risk, glucose-lowering therapies that are safe for the CV system must be utilized.
- Incretin hormones, including GLP-1 and GIP, are gut hormones secreted in response to nutrient intake that maintain glycemic control by regulating insulin and glucagon release. GLP-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase 4 (DPP-4) inhibitors used for the treatment of type 2 diabetes, are drug classes that improve glucose regulation through stimulating the actions of gut-derived incretin hormones or inhibiting their degradation, respectively.
- Cardioprotection mediated by GLP-1RA likely results from various contributing factors, which include decrease in inflammatory processes and body weight, improvements in vascular function that decrease BP, attenuation of atherosclerosis, and cardiomyocyte-independent actions that improve myocardial function.
- Furthermore, with DPP-4 inhibitors, moderate improvements in classic cardiovascular risk factors, including HbA1c, BP, fasting, and postprandial blood lipids, were reported, though much lower in magnitude than those observed with GLP-1 RAs, consistent with the sustained elevation in physiological GLP-1.
- Evidences strongly support cardioprotective ability of GLP-1R activation, whereas DPP-4 inhibitors are not despite increasing physiological GLP-1 action. Therefore, two incretin-based therapies cannot be considered equivalent despite a shared glucose-lowering mechanism of action. It will be imperative for the field to continue defining the mechanisms responsible for GLP-1R-induced cardioprotection in people with type 2 diabetes and to better understand the cardiac biology of other DPP-4 substrates.

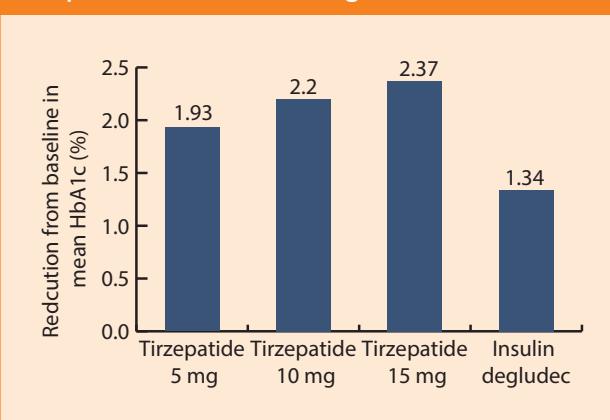
DPP-4 inhibitors bring about moderate improvements in classic cardiovascular risk factors, including HbA1c, BP, fasting, and postprandial blood lipids, albeit in relatively lower magnitude than those observed with GLP-1 receptor agonists

Ussher JR, Greenwell AA, Nguyen MA, Mulvihill EE. Cardiovascular Effects of Incretin-Based Therapies: Integrating Mechanisms With Cardiovascular Outcome Trials. *Diabetes.* 2022;71(2):173–183.

Efficacy of once-weekly tirzepatide versus once-daily insulin degludec in patients with type 2 diabetes: Findings from the SURPASS-3 trial

- Tirzepatide is a novel dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist that is being developed for the treatment of patients with type 2 diabetes.
- An open-label, parallel-group, multicentre, multinational, phase 3 study was conducted to assess the efficacy and safety of tirzepatide versus titrated insulin degludec in patients with type 2 diabetes inadequately controlled by metformin with or without sodium-glucose cotransporter-2 (SGLT2) inhibitors.
- Patients were randomized (1:1:1:1) to treatment with once-weekly subcutaneous injection of tirzepatide (5, 10, or 15 mg) or once-daily subcutaneous injection of titrated insulin degludec.
- The primary efficacy outcome was non-inferiority of tirzepatide 10 mg or 15 mg, or both, versus insulin degludec in mean change from baseline in HbA1c at week 52.
- The modified intention-to-treat population was 1437 patients from the tirzepatide 5 mg (n=358), tirzepatide 10 mg (n=360), tirzepatide 15 mg (n=359), and insulin degludec (n=360) groups.
- Mean baseline HbA1c was decreased after 52 weeks of treatment by 1.93%, 2.20%, and 2.37% in the tirzepatide 5, 10, and 15 mg groups, respectively, compared with a decrease of 1.34% in the insulin degludec group.
- The estimated treatment difference (ETD) versus insulin degludec ranged from -0.59% to -1.04% for tirzepatide ($p<0.0001$ for all tirzepatide doses) (Figure 3).
- The proportion of patients achieving HbA1c target of <7.0% at week 52 was greater in all three tirzepatide groups (82%-93%) versus the insulin degludec group (61%).
- All three tirzepatide doses reduced mean body weight from baseline at week 52 (-7.5 kg to -12.9 kg); whereas insulin degludec caused a weight gain of 2.3 kg.
- The ETD versus insulin degludec ranged from -9.8 kg to -15.2 kg for tirzepatide ($p<0.0001$ for all tirzepatide doses).
- Mild-to-moderate gastrointestinal events (nausea, diarrhoea, and vomiting) and decreased appetite were the most frequent adverse events in the tirzepatide groups.
- Severe hypoglycemia and blood glucose <54 mg/dL was reported in 1–2% patients in the tirzepatide groups versus 7% patients in the insulin degludec group.
- Thus, it could be concluded that tirzepatide, as compared to titrated insulin degludec, provided superior improvements in glycemic control and body weight at week 52, with lower risk of hypoglycemia, in patients with type 2 diabetes.

Figure 3: Reduction from baseline in mean HbA1c following treatment with different doses of tirzepatide versus insulin degludec



Tirzepatide, as compared to titrated insulin degludec, provided superior improvements in glycemic control and body weight at week 52, with lower risk of hypoglycemia, in patients with type 2 diabetes

Ludvik B, Giorgino F, Jódar E, Frias JP, Fernández Landó L, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. Lancet. 2021;398(10300):583-598.

CIRCULATION**Effect of combined treatment with sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists in type 2 diabetes**

- Sodium-glucose cotransporter-2 (SGLT2) inhibitors and GLP-1RAs have been used widely because of their efficacy in reducing cardiovascular and kidney outcomes among patients with type 2 diabetes. GLP-1RAs reduce the risk of atherosclerotic ischemic events and have a modest effect on kidney function and perhaps heart failure, whereas SGLT2 inhibitors reduce the risk of heart failure, kidney function decline, and kidney outcomes, with a modest effect on myocardial infarction and no effect on stroke. Both these drug classes exert a potent synergistic effect on heart failure hospitalization, which could be ascribed to reduction in ischemic heart failure by GLP-1 RAs coupled with beneficial diuretic, myocardial, and anti-inflammatory effects of SGLT2 inhibitors on heart failure regardless of ejection fraction. Therefore, it becomes considerable to use these 2 drug classes in combination to achieve greater benefits for patients than either drug class alone.
- The AMPLITUDE-O trial (Effect of Efpeglenatide on Cardiovascular Outcomes) demonstrated salutary effects of efpeglenatide, a GLP-1 RA, on major adverse cardiovascular events (MACEs), expanded MACEs, renal composite outcome, MACEs or noncardiovascular death, and heart failure hospitalizations, which appeared to be independent of concurrent SGLT2 inhibitor use. Thus, combined treatment with SGLT2 inhibitors and GLP-1 RAs has the potential to yield substantial benefits across a wide range of cardiovascular outcomes among patients with type 2 diabetes.

Lam CSP, Ramasundarahettige C, Branch KRH, Sattar N, Rosenstock J, et al. Efpeglenatide and Clinical Outcomes With and Without Concomitant Sodium-Glucose Cotransporter-2 Inhibition Use in Type 2 Diabetes: Exploratory Analysis of the AMPLITUDE-O Trial. *Circulation*. 2022;145(8):565-574.

Combined treatment with sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists yields substantial benefits across a wide range of cardiovascular outcomes among patients with type 2 diabetes

CIRCULATION**Impact of diabetes on the association between different measures of obesity and heart failure risk**

- There lies an association between obesity, diabetes and a higher risk of heart failure (HF). A study was conducted among 10,387 participants, out of which 25.1% were diabetic. During a 5-year follow-up, 447 participants developed HF (4.3%). Significant association was found between higher levels of each adiposity measure (overall obesity, central obesity, fat mass) and higher HF risk per 1 SD higher body mass index (BMI)=1.15, waist circumference=1.22 and fat mass=1.13.
- A significant interaction was noted between diabetes status and measures of BMI and waist circumference for the risk of HF. In stratified analysis, higher measures of each adiposity parameter were significantly associated with higher HF risk in individuals with diabetes per 1 SD higher BMI=1.29 and waist circumference=1.48; fat mass=1.25 but not those without diabetes, including participants with prediabetes and euglycemia. Risk percentage of overall obesity, abdominal obesity, and high fat mass for incident HF was higher among participants with diabetes (12.8%, 29.9%, and 13.7%, respectively) versus those without diabetes ($\leq 1\%$ for each). Therefore, there exists a strong association between higher BMI, waist circumference and fat mass with greater risk of HF among older adults, particularly among those with prevalent diabetes.

There exists a strong association between higher BMI, waist circumference and fat mass with greater risk of heart failure among older adults, particularly among those with prevalent diabetes

Patel KV, Segar MW, Lavie CJ, Kondamudi N, Neeland IJ, et al. Diabetes Status Modifies the Association Between Different Measures of Obesity and Heart Failure Risk Among Older Adults: A Pooled Analysis of Community-Based NHLBI Cohorts. *Circulation*. 2022;145(4):268-278.

Ascertaining the effect of liraglutide on pulmonary function in individuals with type 2 diabetes

- In patients with type 2 diabetes, there is decrease in indices of forced expiration and lung volume and diffusion capacity as compared to age-matched healthy populations. This could be due to changes in lung elasticity and decreased muscle strength; mediated by insulin resistance, advanced glycation end products accumulation, and a pro-inflammatory state. Furthermore, defects in the surfactant layer lining in the wall of the alveoli might also be linked as a contributing factor that impairs airway caliber regulation in type 2 diabetes.
- With the damaging of the alveolar-capillary barrier, surfactant proteins A and D (SP-A and SP-D) leak from the alveolar space into the bloodstream and are useful systemic biomarkers for assessing lung injury. Experimental studies have shown that GLP-1 ameliorates lung fibrosis, thus resulting in a decrease in serum SP-D levels. Researchers conducted a study to evaluate the effect of liraglutide, a GLP-1 RA, on pulmonary function and circulating levels of SP-D in patients with type 2 diabetes.
- It was a double-blind, randomized, crossover, placebo controlled clinical trial that included 76 patients with a baseline forced expiratory volume in 1 s (FEV₁) <90% of that predicted. Serum level of SP-D was used as a biomarker of alveolar-capillary barrier integrity. A significant improvement of glycemic control accompanied by significant reduction in BMI was reported in patients with liraglutide after the 7-week treatment period. No differences were observed in FEV₁ between the liraglutide and placebo groups. However, with liraglutide treatment, forced vital capacity (FVC) increased by 5.4% (from 78.9% ± 12.9% to 84.3% ± 14.6% of predicted), whereas there were no changes among those on placebo (from 79.1% ± 9.3% to 79.4% ± 13.3%; Figure 4). Prevalence of a non-obstructive ventilatory defect among participants receiving liraglutide decreased from 40.0% to 21.7%. With liraglutide treatment, decrease in serum SP-D concentration: 196.4 ng/mL at baseline vs 169.6 ng/mL at 7 weeks was noted. However, no significant changes were observed in serum SP-D under placebo (Figure 5).
- Conclusively, short-term treatment with liraglutide yields a significant increase of FVC in patients with diabetes, associated with a significant decrease of circulating SP-D; thus, signifying beneficial effect in the alveolar-capillary function.

Figure 4: Treatment effect on spirometric values from baseline to 7 weeks with liraglutide versus placebo

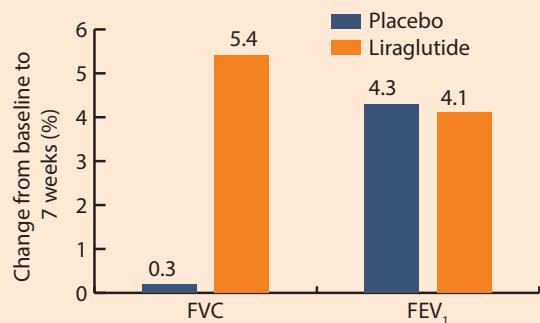
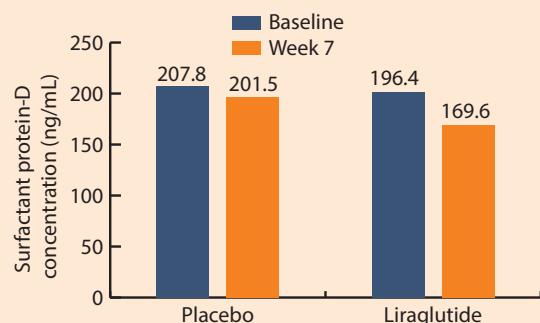


Figure 5: Effect of liraglutide versus placebo on surfactant protein-D concentration



López-Cano C, Ciudin A, Sánchez E, Tinahones FJ, Barbé F, et al. Liraglutide Improves Forced Vital Capacity in Individuals With Type 2 Diabetes: Data From the Randomized Crossover LIRALUNG Study. *Diabetes*. 2022;71(2):315-320.

EXPERT OPINION

**Dr Banshi Saboo**

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Dapagliflozin can effectively correct neural and vascular retinal dysfunction in diabetes

Dapagliflozin is a selective, potent, and reversible SGLT2i for the treatment of type 2 diabetes, including in patients with kidney and cardiovascular disorders. This study evaluated effects of this antidiabetic agent on the neural and vascular retina, exploring benefits, if any, with its use in patients with diabetic retinopathy. This experimental study involved treating 5-week-old db/db male mice, an animal model of type 2 diabetes, with a test diet containing dapagliflozin. Retinal response was assessed by electroretinogram (ERG) using an LKC NGIT-100 recording machine. Neural retina of the mice was removed and retinal vasculature stained with periodic acid and Schiff's base to assess acellular capillary numbers. Additionally, complete blood count analysis, mRNA levels of inflammatory cytokine, and effect of the drug on cultured human retinal endothelial cells, including wound healing and endothelial cell migration assays were also performed.

The results were promising. While diabetes significantly increased a-wave amplitude on ERG, it was significantly decreased after dapagliflozin treatment. Treatment also significantly decreased b-wave amplitude in the db/db mice. Additionally, treatment with dapagliflozin decreased acellular capillary numbers, deemed a positive response as an increase in acellular capillary number is classically seen in diabetic retinopathy. Reduction in wound closure and glucose uptake by cultured human retinal endothelial cells was also associated with dapagliflozin use. Overall, dapagliflozin treatment in this experimental study, appeared to preserve visual functions and reduce microvascular dysfunction. Benefits with treatment were also noted at the cellular level, with decrease in wound healing and glucose uptake in retinal endothelial cells. These results may suggest the potential of dapagliflozin to effectively correct neural and vascular dysfunction of the retina in diabetes.

Reference

1. Luo Q, Leley SP, Bello E, Dhami H, Mathew D, Bhatwadekar AD. Dapagliflozin protects neural and vascular dysfunction of the retina in diabetes. *BMJ Open Diabetes Res Care*. 2022;10(3):e002801.

DIABETES

Effect of SGLT inhibition on counterregulatory hormone response to hypoglycemia in type 1 diabetes

- Hypoglycemia accounts for significant morbidity and mortality in patients with type 1 diabetes and presents as a major obstacle to achieving optimal glycemic control for such people. It is because of impaired glucagon counter-regulatory response, that such patients are at an increased risk of hypoglycemia. In healthy individuals, glucagon secreted from the alpha-cells of the pancreatic islets stimulates hepatic glucose production to reverse hypoglycemia; the rescue response being lost in individuals with type 1 diabetes shortly after diagnosis. This diminished response could be due to abolished beta- to alpha-cell paracrine signaling, leading to an impaired ability to defend against, and recover from, hypoglycemia.
- To address this defect, use of SGLT inhibitors as adjunctive treatments to insulin has been approved for use in type 1 diabetes. SGLT inhibitors decrease insulin dosing requirements and improve glycemic control without increasing, and potentially even decreasing, the risk of hypoglycemia.
- A study was done to assess if SGLT inhibition restored the glucagon counter regulatory hormone response to hypoglycemia. It included 22 adults with type 1 diabetes who were treated with the SGLT2 inhibitor dapagliflozin (5 mg daily) or placebo for 4 weeks. It was observed that basal glucagon concentrations were 32% higher following dapagliflozin versus placebo, with a median within-participant difference of 2.75 pg/mL. However, this increase in basal glucagon levels did not correlate with decreased rates of hypoglycemia and hence, did not appear to be protective in avoiding hypoglycemia. During hypoglycemic clamp, SGLT inhibition did not change counterregulatory hormone concentrations, time to recovery from hypoglycemia, hypoglycemia symptoms, or cognitive function.
- Therefore, though dapagliflozin increased basal glucagon concentrations, SGLT inhibitor treatment did not restore the impaired glucagon response to hypoglycemia. Hence, it was proposed that clinical reduction in hypoglycemia associated with these agents is a result of changes in diabetes care (e.g., lower insulin doses or improved glycemic variability) as opposed to a direct, physiologic effect of these medications on alpha-cell function.

Hypoglycemia accounts for significant morbidity and mortality in patients with type 1 diabetes and presents as a major obstacle to achieving optimal glycemic control

Boeder SC, Gregory JM, Giovannetti ER, Pettus JH. SGLT2 Inhibition Increases Fasting Glucagon but Does Not Restore the Counterregulatory Hormone Response to Hypoglycemia in Participants With Type 1 Diabetes. *Diabetes*. 2022;71(3):511-519.

DIABETES CARE

Association between osteocalcin and risk of incident diabetes and diabetic kidney disease

- Osteocalcin is not only a marker of bone formation; this non-collagenous protein is a metabolically active hormone that is involved in the regulation of glucose and lipid metabolism.
- A study was done to examine the relationship between osteocalcin and the risk of incident diabetes and DKD in total of 5,396 participants without diabetes (nondiabetes subcohort) and 1,174 participants with diabetes and normal kidney function (diabetes subcohort).
- Higher osteocalcin levels were linearly associated with a decreased risk of diabetes in the nondiabetes subcohort. Osteocalcin levels were linearly inversely associated with incident DKD in the diabetes subcohort.
- Findings of the study inferred that there is an association between lower osteocalcin levels and increased risk of incident diabetes and DKD.

Xiaoqi Ye, Rong Yu, Fusong Jiang, et al. Osteocalcin and Risks of Incident Diabetes and Diabetic Kidney Disease: A 4.6-Year Prospective Cohort Study. *Diabetes Care*. 2022;45(4):830–836.

DIABETES CARE

Appraising the association of baseline HbA1c with cardiovascular and renal outcomes

- SGLT2 inhibitors have been recommended by current guidelines to patients with type 2 diabetes and established or at high risk for atherosclerotic cardiovascular disease (ASCVD), irrespective of HbA1c levels.
- Association of HbA1c with cardiovascular and renal outcomes was studied by a group of researchers.
- In the Dapagliflozin Effect on Cardiovascular Events trial (DECLARE-TIMI 58), 17,160 patients with type 2 diabetes were randomly assigned to dapagliflozin or placebo for a median follow-up of 4.2 years.
- Results revealed that higher baseline HbA1c was associated with a higher risk of cardiovascular death or hospitalization for heart failure (HHF); MACE, including cardiovascular death, myocardial infarction, and ischemic stroke; and cardiorenal outcomes.
- The risk of cardiovascular death/HHF, HHF, and cardiorenal outcomes, with no heterogeneity by baseline HbA1c was less with dapagliflozin in comparison to placebo.
- This study suggested that although higher HbA1c levels were associated with greater cardiovascular and renal risk, dapagliflozin was effective in all subgroups irrespective of baseline HbA1c, including patients with HbA1c <7%.

As compared to placebo, dapagliflozin was associated with lower risk of cardiovascular death/hospitalization for heart failure, hospitalization for heart failure, and cardiorenal outcomes, with no heterogeneity by baseline HbA1c

Cahn A, Wiviott SD, Mosenzon O, Goodrich EL, Murphy SA, et al. Association of Baseline HbA1c With Cardiovascular and Renal Outcomes: Analyses From DECLARE-TIMI 58. *Diabetes Care*. 2022; 45 (4): 938–946.

DIABETES CARE

Relationship between changes in physical activity and the risk of dementia in patients with new-onset type 2 diabetes

- A Nationwide Cohort Study investigated the association between interval changes in physical activity (PA) and dementia risk among patients with new-onset type 2 diabetes.
- In this study, a total of 133,751 participants newly diagnosed with type 2 diabetes in a health screening were included. PA level changes were categorized into continuous lack of PA, decreaser, increaser, and continuous PA groups. Dementia was determined using dementia diagnosis codes and antidementia drug prescriptions.
- Results revealed that regular PA was associated with lower risks of all-cause dementia (adjusted hazard ratio [aHR] 0.82), Alzheimer disease (AD) (aHR 0.85), and vascular dementia (VaD) (aHR 0.78). It was also observed that increasers who started to engage in regular PA had a lower risk of all-cause dementia (aHR 0.86).
- It was demonstrated that regular PA was independently associated with lower risks of all-cause dementia, AD, and VaD among individuals with new-onset type 2 diabetes. Thus, regular PA should be encouraged to prevent dementia in high-risk populations and those with new-onset type 2 diabetes.

Regular physical activity was independently associated with lower risks of all-cause dementia, Alzheimer disease, and vascular dementia among individuals with new-onset type 2 diabetes

Yoo JE, Han K, Kim B, et al. Changes in Physical Activity and the Risk of Dementia in Patients With New-Onset Type 2 Diabetes: A Nationwide Cohort Study. *Diabetes Care*. 2022; 45 (5): 1091–1098.

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Ascertaining the safety and efficacy of vildagliptin- metformin treatment in newly diagnosed type 2 diabetic patients

With the data available from International Diabetes Federation (IDF), India has the second-highest number of patients with diabetes aged between 20 and 79 years as of 2019. Due to progressive nature of diabetes and increase in complications, treating patients with T2DM with antidiabetic agents is most burdensome. Though metformin has been the most recommended monotherapy for the initial treatment of T2DM, a substantial proportion of patients require combination therapy in order to maintain glycemic control in the long run. Fixed dose combination therapies are effective, both in reducing the dosage of antihyperglycemic agents and in reducing their unwanted effects. Glimepiride plus metformin has been used widely in Indian population due to its low acquisition cost and efficacy in improving glycemic control. However, its use is associated with side effects such as weight gain and hypoglycemic events.

Vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor and an oral antidiabetic agent possess moderate efficacy with a good overall safety profile including low risk of hypoglycemia, low risk of oedema, lipid neutral effect, and weight neutrality. When used as an add-on treatment or initial combination therapy along with metformin, good glycemic control has been achieved due to complementary mechanism of action. Considering this, investigators aimed to compare the safety and efficacy of glimepiride and vildagliptin as add-on therapy to metformin in newly diagnosed patients with T2DM.

A total of 100 patients with T2DM were included and were divided into two groups: group A ($n = 50$) received vildagliptin plus metformin, and group B ($n = 50$) received glimepiride plus metformin. In both the groups, patients received metformin only (500 mg BID) for initial 6 weeks, followed by metformin (500 mg BID) and vildagliptin (50 mg BID) for up to 24 weeks in group A and metformin (500 mg BID) and glimepiride (2 mg BID) for up to 24 weeks in group B.

Both groups saw significant improvements in HbA1c, fasting and post-prandial plasma glucose from the baseline to week-24 (group A FBG : 188.40 mg/dL to 109.60 mg/dL, PPG: 395.64 mg/dL to 133.32 mg/dL; group B FBG : 206.68 mg/dL to 110.52 mg/dL, PPG 410.50 mg/dL to 136.66 mg/dL). Safety outcomes did not show any events of hypoglycemia with vildagliptin. Mild hypoglycemia was reported with glimepiride in five patients (10%).

In conclusion, the combination of metformin with vildagliptin or metformin with glimepiride gave similar improvements in HbA1c control and post prandial glucose, however, the Vildagliptin/metformin combination had a better safety profile with a lower risk of hypoglycemia.

Reference

1. Kumar S. Comparison of Safety and Efficacy of Glimepiride-Metformin and Vildagliptin- Metformin Treatment in Newly Diagnosed Type 2 Diabetic Patients. *Indian J Endocrinol Metab.* 2021;25(4):326-331.

DIABETES CARE

Association of SGLT2 inhibitors with diabetic ketoacidosis compared with DPP-4 inhibitors and sulfonylureas in type 2 diabetes

- The present study explored the association of SGLT2 inhibitors with diabetic ketoacidosis compared with DPP-4 inhibitors and sulfonylureas in patients with type 2 diabetes.
- In this comparative cohort study, two pairwise comparisons: 1) SGLT2 inhibitors versus DPP-4 inhibitors and 2) SGLT2 inhibitors versus sulfonylureas were done. The main outcome was diabetic ketoacidosis present on hospital admission.
- In cohort 1 ($n = 85,125$ for SGLT2 inhibitors and $n = 85,125$ for DPP-4 inhibitors), the incidence rates of diabetic ketoacidosis per 1,000 person-years were 6.0 and 4.3 for SGLT2 inhibitors and DPP4 inhibitors, respectively (Figure 6).
- In cohort 2 ($n = 72,436$ for SGLT2 inhibitors and $n = 72,436$ for sulfonylureas), the incidence rates of diabetic ketoacidosis per 1,000 person-years were 6.3 and 4.5 for SGLT2 inhibitors and sulfonylureas, respectively (Figure 7).
- In Cox proportional hazards regression models, the use of SGLT2 inhibitors was associated with a higher rate of diabetic ketoacidosis compared with DPP-4 inhibitors.
- Hence, newly prescribed SGLT2 inhibitors had a higher rate of diabetic ketoacidosis in comparison to DPP-4 inhibitors and sulfonylureas in patients with type 2 diabetes.

Dawwas GK, Flory JH, Hennessy S, et al. Comparative Safety of Sodium–Glucose Cotransporter 2 Inhibitors Versus Dipeptidyl Peptidase 4 Inhibitors and Sulfonylureas on the Risk of Diabetic Ketoacidosis. *Diabetes Care*. 2022; 45 (4): 919–927.

Figure 6: Incidence of diabetic ketoacidosis in cohort 1 (SGLT 2 inhibitors versus DPP-4 inhibitors)

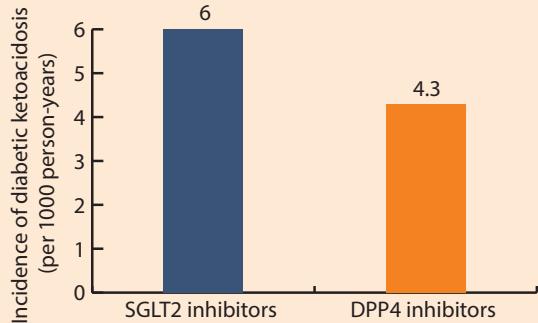
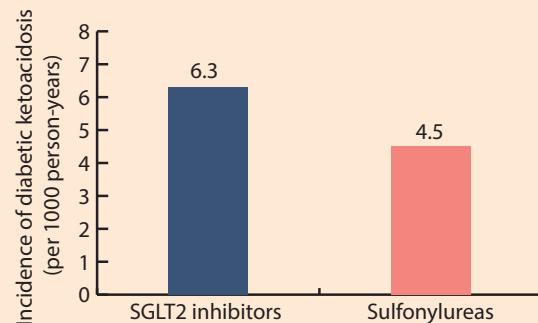


Figure 7: Incidence of diabetic ketoacidosis in cohort 2 (SGLT 2 inhibitors versus sulfonylureas)





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Evaluating the association between diabetic nephropathy and proton pump inhibitors

Diabetes mellitus (DM) is one of the most common noncommunicable diseases in the world, affecting an estimated 462 million people (6.28%). Only in 2017, DM was responsible for almost 1 million deaths, making it the ninth largest cause of mortality. It also causes various complications in patients with DM due to long term effects such as diabetic retinopathy, nephropathy, neuropathy, and autonomic dysfunction. Proton pump inhibitors (PPIs) are widely used and, due to their safety profile, they are also available over the counter. PPIs are commonly prescribed to diabetic patients because they are at increased risk of gastroesophageal reflux due to impaired gastrointestinal (GI) motility. Moreover, diabetic nephropathy (DN) can cause GI symptoms like nausea and vomiting, which necessitates the usage of a PPI.

PPIs are commonly used in individuals with diabetes, and they are especially good at lowering risk in people who have upper gastric reflux disease. Also, PPIs help with glycemic control by stimulating gastrin, which stimulates β -cells in the pancreas, resulting in greater insulin release and better diabetes management. Despite the therapeutic benefits of these medications, there is substantial evidence of nephropathy development as a result of PPI use.

PPIs are commonly provided to patients with DM, and diabetic nephropathy is one of the most well-known consequences of the disease. In accordance to this, a case-control study was conducted with an aim to explore the association between PPI use and DN. A total of 200 volunteers were recruited, including 100 each in the case and the control group. The cases were defined as those patients diagnosed with type II DM, glycemic levels controlled on treatment and were diagnosed by the treating physician with DN as per the American Diabetes Association Guidelines. The controls were defined as those patients with type II DM, glycemic levels controlled on treatment, but with no evidence of DN. A greater proportion of participants in the cases group used PPI (62%), as compared to the control group (42%; $p = 0.005$). Pantoprazole was the most often used PPI. PPI consumption for a longer period of time was associated with an increased risk of DN.

Findings of the study suggest a significant association between the use of PPIs and DN in patients with type 2 DM. Because PPIs provide various benefits in diabetic patients, such as glycemic control and relief from gastro-esophageal symptoms, a risk-benefit analysis for long-term PPI usage in DM is necessary.

Reference

- Raj JP, Pinto RW, Tomy SK, Kulkarni SM. Diabetic Nephropathy and Proton Pump Inhibitors - Pilot Case-Control Study. *Indian J Nephrol*. 2022;32(2):127-131.

BMJ OPEN DIABETES RES CARE**Higher risk of heart failure in women with type 2 diabetes and coronary artery disease than men: The gender interaction**

- Generally, women with diabetes are perceived to have a lower risk of cardiovascular events than men.
- A recent retrospective registry study from Japan however suggests that women with both type 2 diabetes and coronary artery disease (CAD) may have a higher risk of heart failure than men.
- The study enrolled 7785 consecutive patients (mean age, 67.6 years) with both type 2 diabetes and CAD at 70 teaching hospitals, with a mean follow-up period of 1328 days.
- Results showed that women with both type 2 diabetes and CAD had a significantly higher risk of hospitalization for heart failure than men (HR, 1.26).
- The relationship between heart failure risk and achieved LDL-cholesterol and systolic BP, but not HbA1c, differed between women and men, with statistically significant interactions ($p=0.009$ and $p=0.043$, respectively).
- Thus, women with type 2 diabetes and CAD have a higher risk of heart failure than men.
- Given the significant gender interaction in association between heart failure risk and risk factor management, particularly regarding LDL-c and systolic BP; effectiveness of risk factor management may differ between men and women regarding prevention of heart failure among patients with type 2 diabetes and CAD.

Women with type 2 diabetes and coronary artery disease are at higher risk of heart failure than men

Fujita Y, Morimoto T, Tokushige A, et al. Women with type 2 diabetes and coronary artery disease have a higher risk of heart failure than men, with a significant gender interaction between heart failure risk and risk factor management: a retrospective registry study. *BMJ Open Diabetes Res Care*. 2022 Apr;10(2):e002707.

DIABETES CARE**Improvement of cognitive impairment with empagliflozin in frail older adults with type 2 diabetes and heart failure with preserved ejection fraction**

- A study aimed to assess the effect of empagliflozin in cognitive impairment in frail older adults with diabetes and heart failure with preserved ejection fraction (HFpEF).
- This was a prospective study that included a total of 162 frail older adults with HFpEF and diabetes.
- Montreal Cognitive Assessment scores at baseline and after 1 month were 19.80 ± 3.77 vs. 22.25 ± 3.27 ($p < 0.001$) in the empagliflozin group, 19.95 ± 3.81 vs. 20.71 ± 3.56 ($p = 0.26$) in the metformin group, and 19.00 ± 3.71 vs. 19.1 ± 3.56 ($p = 0.81$) in the insulin group.
- Moreover, a marked amelioration of physical impairment was noted in the empagliflozin and metformin groups but not in the insulin group.
- The study findings highlight the significant beneficial effects of empagliflozin on cognitive and physical impairment in frail older adults with diabetes and HFpEF.

Empagliflozin, an SGLT2 inhibitor, exhibits significant beneficial effects on cognitive and physical impairment in frail older adults with diabetes and heart failure with preserved ejection fraction

Mone P, Lombardi A, Gambardella J, et al. Empagliflozin Improves Cognitive Impairment in Frail Older Adults With Type 2 Diabetes and Heart Failure With Preserved Ejection Fraction. *Diabetes Care*. 2022; 45 (5): 1247–1251.

Incidence of atrial fibrillation in elderly patients with type 2 diabetes

- Type 2 diabetes (T2D) and advanced age are known risk factors for atrial fibrillation (AF); which is a significant risk factor for cardiovascular disease (CVD) and is showing increasing incidence worldwide.
- A recent study from Japan – the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD2) study –evaluated the incidence of AF in elderly patients with T2D and compared the prognosis between patients with/without AF.
- JPAD2 study is a follow-up cohort study of the JPAD trial, which is a randomized controlled clinical trial initiated in 2002 in 2535 patients with T2D to examine whether low-dose aspirin prevents CVD.
- After completion of the JPAD trial, the current study followed up the patients until 2019 and evaluated the incidence of AF, together with comparing the incidence of cerebral cardiovascular events in elderly patients with T2D with/without AF.
- Results showed that during the median follow-up period of 10.9 years, 132 patients developed AF (incidence rate: 5.14/1000 person-years).
- The adjusted HRs for cerebral cardiovascular events, stroke, coronary artery disease (CAD), heart failure, and all-cause death in elderly patients with T2D with versus without AF were 1.65, 1.54, 1.96, 5.17, and 1.82, respectively.
- Annually, 1 in 200 elderly Japanese patients with T2D are estimated to develop AF.
- This patient subgroup of elderly with T2D with AF requires careful follow-up given the elevated risk for CVD in them.

Type 2 diabetes and advanced age are known risk factors for atrial fibrillation; which is a significant risk factor for cardiovascular disease and is showing increasing incidence worldwide

Matsumoto C, Ogawa H, Saito Y, et al. Incidence of atrial fibrillation in elderly patients with type 2 diabetes mellitus. *BMJ Open Diabetes Res Care*. 2022 Mar;10(2):e002745.

Association of metformin in pregnancy and risk of adverse long-term outcomes: A register-based cohort study

- The authors of this register-based cohort study aimed to investigate if maternal pregnancy exposure to metformin is associated with increased risk of long-term and short-term adverse outcomes in the child.
- It included singleton children born with maternal pregnancy exposure to metformin or insulin (excluding maternal type 1 diabetes): metformin only (n=3967), insulin only (n=5273) and combination treatment (metformin and insulin; n=889).
- It was found that exposure to metformin or combination treatment versus insulin was not associated with increased risk of long-term outcomes in the main or sensitivity analyses.
- Increased risk of small for gestational age (SGA) was observed for metformin (IPTW-weighted OR 1.65, 95% CI 1.16 to 2.34); increased risk of large for gestational age, preterm birth and hypoglycemia was observed for combination treatment.

No increased long-term risk was observed with pregnancy exposure to metformin, compared with insulin. Also, the increased risk of SGA associated with metformin versus insulin suggests caution in pregnancies with at-risk fetal undernutrition

- Moreover, no increased risk was observed for neonatal mortality, hyperglycemia, or major congenital anomalies.
- Outcomes of this study revealed no increased long-term risk associated with pregnancy exposure to metformin (alone or in combination with insulin), compared with insulin. Also, the increased risk of SGA associated with metformin versus insulin suggests caution in pregnancies with at-risk fetal undernutrition. The increased risks of adverse outcomes at birth associated with combination treatment may reflect confounding by indication or severity.

Brand KMG, Saarelainen L, Sonajalg J, et al. Metformin in pregnancy and risk of adverse long-term outcomes: a register-based cohort study. *BMJ Open Diabetes Res Care*. 2022 Jan;10(1):e002363.

CIRCULATION

Investigating the effectiveness and tolerability of dapagliflozin in type 2 diabetes according to baseline blood pressure: Observations from DECLARE-TIMI 58 Trial

- DECLARE-TIMI 58 trial (Dapagliflozin Effect on Cardiovascular Events - Thrombolysis in Myocardial Infarction 58) showed improved heart failure and kidney outcomes in patients with type 2 diabetes with or at high risk for atherosclerotic cardiovascular disease when treated with dapagliflozin.
- The present study was done to analyze the efficacy and safety of dapagliflozin stratified according to baseline systolic blood pressure (SBP).
- Patients with type 2 diabetes and either previous atherosclerotic cardiovascular disease or atherosclerotic cardiovascular disease risk factors were randomly assigned to dapagliflozin or placebo in the DECLARE-TIMI 58 trial.
- Overall, dapagliflozin reduced SBP by 2.4 mmHg (95% CI, 1.9-2.9; P<0.0001) compared with placebo at 48 months
- The beneficial effects of dapagliflozin on hospitalization for heart failure and renal outcomes were found to be consistent across all baseline SBP categories, with no evidence of modification of treatment effect (P interactions=0.28 and 0.52, respectively)
- Among normotensive patients, the hazard ratios were 0.66 (95% CI, 0.42-1.05) and 0.39 (95% CI, 0.19-0.78), respectively, for hospitalization for heart failure and the renal-specific outcome.
- Thus, findings of this study suggested that dapagliflozin provides cardiorenal benefits in patients with type 2 diabetes at high atherosclerotic cardiovascular disease risk independent of baseline blood pressure.

Dapagliflozin provides cardiorenal benefits in patients with type 2 diabetes at high atherosclerotic cardiovascular disease risk independent of baseline blood pressure

Furtado RHM, Raz I, Goodrich EL, et al. Efficacy and Safety of Dapagliflozin in Type 2 Diabetes According to Baseline Blood Pressure: Observations From DECLARE-TIMI 58 Trial. *Circulation*. 2022 May 24;145(21):1581-1591.

SGLT2 inhibitors: A paradigm shift in diabetes therapy

INTRODUCTION

Insulin resistance and progressive beta-cell failure are the key pathogenic mechanisms responsible for the progression of type 2 diabetes. Presence of chronic hyperglycemia in diabetic individuals, referred as 'glucotoxicity', facilitates pancreatic beta-cell failure, which underscores the importance of strict glycemic control in the management of type 2 diabetes.

Presence of 'clinical inertia' in diabetes management, progressive beta-cell decline, treatment-related weight gain, and hypoglycemia are some of the major obstacles in achieving optimal glycemic control in diabetic population. Therefore, advent of novel pharmacological options with mechanism of action independent of insulin secretion or action represent a paradigm shift in diabetes management. Inhibiting the sodium-glucose cotransporter 2 (SGLT2), which has a chief role in reabsorption of glucose in the kidney, has been developed as a promising therapeutic approach in the management of diabetes. This section reviews the role of kidneys in glucose homeostasis, focuses on unique mechanism of action of SGLT2 inhibitors and their clinical effectiveness in achieving normoglycemia in subjects with type 2 diabetes.¹

ROLE OF KIDNEYS IN GLUCOSE HOMEOSTASIS

Glucose transport in the kidney

Robust data support the vital role of the kidneys in plasma glucose homeostasis via renal gluconeogenesis and glucose reabsorption from the glomerular filtrate. Under normal circumstances, approximately 180 g of glucose is filtered each day and is almost completely reabsorbed by the proximal tubule (PT), thus maintaining normal glucose balance. The renal glucose transport across the epithelial cells of PT is coupled with the transport of sodium and is mediated by specific sodium-glucose cotransporters. SGLT1 and SGLT2 are transporter molecules with distinct characteristics that actively transport glucose across the renal glomerular membrane. SGLT2 is a low-affinity, high-capacity glucose transport protein which accounts for 90% of glucose reabsorption from the initial part of the PT, while the remaining 10% of glucose reabsorption is mediated by the high-affinity, low-capacity transporter SGLT1 from the distal part of the PT. Glucose transport is mainly facilitated by the transport of sodium across the concentration gradient (maintained by primary active transport of sodium through the basolateral epithelial membrane) into the interstitial fluid. Once glucose is absorbed across the luminal epithelium, it passively diffuses across the basolateral membrane into the plasma via the facilitative glucose transporter, GLUT2.

As the plasma glucose concentration is increased, there is a linear increase in the filtered amount of glucose and the reabsorptive capacity of SGLTs. The plasma glucose concentration above which the glucose cotransporter capacity becomes saturated and the maximum reabsorptive capacity of the renal tubules is exceeded (T_{max}) is called the renal glucose threshold (RTG) and is estimated to be ~ 200 mg/dl. Once this threshold is exceeded, the glucose excretion rate

Inhibiting the sodium-glucose cotransporter 2, which has a chief role in reabsorption of glucose in the kidney, has been developed as a promising therapeutic approach in the management of diabetes

SGLT2 inhibitors have the unique mechanism of action of lowering renal glucose reabsorption and increasing urinary glucose excretion, thus reducing hyperglycemia, in diabetes without affecting insulin sensitivity or secretion

increases (glycosuria) parallel to the filtered glucose load. However, as the Tmax is approached, the actual thresholds for both absorption and excretion differ from theoretical predictions, and this phenomenon is termed 'splay'. Splay represents the variability in the maximum reabsorptive capacity of individual nephrons.^{2,3}

RATIONALE FOR USE OF SGLT2 INHIBITORS

In non-diabetic subjects, renal glucose reabsorption conserves glucose to meet the energy needs of the body between meals. However, this response becomes maladaptive in patients with diabetes as glycosuria is not observed even with plasma glucose levels well above the threshold level.⁴ Previous preclinical data suggest that patients with type 2 diabetes exhibit almost 20-40% increase in Tmax (as hyperglycemia upregulates SGLT2 activity) thereby further increasing renal glucose reabsorption and exacerbating hyperglycemia.⁵ Of note, the increased glucose uptake is accompanied by increased sodium reabsorption, which in turn may cause hypervolemia and increase in blood pressure (BP).^{2,6} The pathophysiological mechanisms of hyperglycemia in diabetes now encompass the contribution of the kidneys.

In patients with diabetes, the goals of therapy are achieving adequate glycemic control and preventing the development of complications. With elucidation of the role of renal glucose reabsorption exacerbating hyperglycemia, SGLT2 has emerged as an attractive target in the treatment of diabetes. SGLT2 inhibitors block SGLT2, thus inhibiting renal glucose reabsorption and increasing urinary glucose excretion. They offer a novel therapeutic approach in treating hyperglycemia.

SGLT2 INHIBITORS: MECHANISM OF ACTION AND POTENTIAL ADVANTAGES

Inhibitors of SGLT2 have the unique mechanism of action of lowering renal glucose reabsorption and increasing urinary glucose excretion, thus reducing hyperglycemia, in diabetes without affecting insulin sensitivity or secretion. These agents appear promising and offer an additional tool in the therapeutic armamentarium.^{1,7}

Phlorizin, obtained from the root bark of the apple tree, was the first agent developed to inhibit SGLTs in the kidney. Although effective in achieving normoglycemia through renal glucose excretion, low bioavailability, non-specificity of action (inhibition of both SGLT1 and SGLT2) and related GI side-effects curtailed its use in patients with diabetes. These limitations of phlorizin have been overcome by the development of selective SGLT2 inhibitors.^{2,8}

Several SGLT2 inhibitors are now available or are in different stages of clinical development. Canagliflozin and dapagliflozin, available in Europe, have recently received approval from The US Food and Drug Administration (FDA) for use in the management of type 2 diabetes. Ipragliflozin has recently been approved for use in Japan. Several other SGLT2 inhibitors are currently in various stages of drug development. Common to these agents is a dose-dependent increase in renal glucose excretion.⁹⁻¹¹

SGLT2 inhibitors possess an attractive pharmacokinetic profile and exhibit several potential benefits over other therapeutic options in diabetes. They exhibit excellent oral bioavailability, long half-life which allows once-daily dosing, and lower propensity for drug-drug interactions. No alteration in pharmacokinetic parameters has been observed in patients with mild or moderate renal or hepatic impairment.¹² Use of these drugs ameliorate

hyperglycemia with a significantly lower risk of hypoglycemia due to their insulin independent action. In addition, the glycosuria associated with SGLT2 inhibition is associated with caloric loss, thus providing a potential benefit of weight loss. The mild diuretic effect of these drugs causes lowering of BP. Given their insulin independent action, these drugs are a treatment option both in recent-onset and long-standing diabetes when limited drug options exist owing to progressive beta-cell damage (Box 1).²

Box 1 Potential advantages of SGLT2 inhibitors

- Excellent oral bioavailability, long half-life and low propensity for drug-drug interactions
- Effective plasma glucose control
- Promotes weight loss
- Low propensity for causing hypoglycemia
- Effective in patients with long-standing diabetes
- Modest reductions in BP, plasma uric acid and lipid levels
- Synergistic effect with other antihyperglycemic agents

Based on information from:

1. Abdul-Ghani MA, DeFronzo RA, Norton L. Sodium–Glucose Co-transporter 2 Inhibition – A Novel Strategy for Glucose Control in Type 2 Diabetes. *European Endocrinology*. 2011;7(1):30-5.
2. Scheen AJ. Evaluating SGLT2 inhibitors for type 2 diabetes: pharmacokinetic and toxicological considerations. *Expert Opin Drug Metab Toxicol*. 2014 Jan 3.
3. Dziuba J, Alperin P, Racketa J, et al. Modeling Effects of SGLT-2 Inhibitor Dapagliflozin Treatment vs. Standard Diabetes Therapy on Cardiovascular and Microvascular Outcomes. *Diabetes Obes Metab*. 2014 Jan 20.

Additional beneficial effects of SGLT2 inhibition include modest reductions in BP, lipid levels and plasma uric acid which improve the cardiovascular risk profile.¹³ Furthermore, SGLT2 inhibitors when used in combination with other antiglycemic agents have shown a synergistic effect in improving glycemic control. As these agents specifically target the kidney, data to date support a favorable safety profile with lower potential for treatment-related adverse events.^{2,6} Additionally, recent trials have shown the effectiveness of SGLT2 inhibitors to reduce several cardiovascular risk factors.^{13,14} Recently, the potential role of these drugs in renoprotection in chronic kidney disease has also been suggested but warrants further investigation.¹⁵

Although SGLT2 is responsible for almost 90% of the renal glucose reabsorption from the PT, it is noteworthy that SGLT2 inhibitors block only 30-50% of glucose reabsorption. As the clinical efficacy of these agents is dependent on the amount of glycosuria produced, various hypotheses have been promulgated to explain this therapeutic paradox based upon the unique pharmacokinetic and pharmacodynamic profile of SGLT2 inhibitors. One hypothesis suggests that the renal capacity to secrete the drug becomes saturated and limits the amount of SGLT2 inhibitor available at the SGLT2 site. It has also been postulated that renal secretion of SGLT2 inhibitors may occur at a site distal to the location of SGLT2 and, thus, may not effectively block the upstream SGLT2. Current hypotheses do not satisfactorily explain this puzzling limitation and further elucidation is required.^{16,17}

CLINICAL EFFECTIVENESS

Dapagliflozin is the SGLT2 inhibitor which has most recently received FDA approval for use in patients with type 2 diabetes.¹⁸ The drug offers an attractive pharmacokinetic profile. It exhibits 1200 times more selectivity for inhibiting SGLT2 over SGLT1 and almost 30-fold greater potency than phlorizin for SGLT2 inhibition in humans.^{4,19,20} Clinical trials demonstrate the efficacy of dapagliflozin in patients with diabetes when used as monotherapy or as add-on therapy. Phase

SGLT2 inhibitors when used in combination with other antiglycemic agents have shown a synergistic effect in improving glycemic control

Because SGLT2-inhibitors exhibit an insulin independent action, there is no risk of hypoglycemia

III clinical trials of dapagliflozin at dose of 5 and 10 mg for 24 weeks in treatment naïve patients demonstrated clinically and statistically significant improvements in HbA1c levels and plasma glucose levels with significant reduction in weight.²¹ Moreover, robust data now indicate the clinical effectiveness of dapagliflozin as add-on therapy with metformin,²² glimepiride,²³ pioglitazone²⁴ and insulin-based therapy²⁵ with significant reduction in HbA1c and weight loss with lower rates of hypoglycemia. Dapagliflozin reduces total body weight by lessening body fat, both visceral and subcutaneous.²⁶ Results of one such study in patients with type 2 diabetes inadequately controlled on metformin are summarized in Table 1.²²

Table 1 Efficacy of dapagliflozin in patients with type 2 diabetes inadequately controlled on metformin

Parameters	Change after dapagliflozin treatment
HbA1c	-0.3%
Weight	-4.54 kg
Waist circumference	-5.0 cm
Fat mass	-2.80 kg

Based on information from: Bolinder J, Ljunggren O, Johansson L, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Diabetes Obes Metab.* 2013 Aug 1.

Interestingly, dapagliflozin has been shown to exhibit similar glycemic efficacy to glipizide at 52 weeks, when used as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin.²⁷ Contemporary evidence²⁸ also suggests improvement in insulin sensitivity with dapagliflozin. Recent trials have shown beneficial effects of dapagliflozin in lowering BP, improving the lipid profile and lowering the serum uric acid level.^{13,14} Similar results have been observed with the SGLT2 inhibitor canagliflozin²⁹ (FDA-approved) and those in different stages of clinical development like LX4211.³⁰

SAFETY PROFILE

Hypoglycemia is always a concern in the management of diabetes. Because SGLT2-inhibitors exhibit an insulin independent action, there is no risk of hypoglycemia.^{31,32} The drug-related glycosuria is associated with the adverse events of urinary tract infections and fungal genitourinary infections.³³

Long-term use of these agents is associated with risk of deterioration of renal function. However, familial renal glycosuria (similar impaired function of SGLT2) is characterized by an asymptomatic clinical course and normal kidney function despite excessive glycosuria which is a compelling evidence in support of long-term use of SGLT2 inhibitors.³⁴

In addition, these agents offer an attractive pharmacokinetic profile¹² and a limited susceptibility to drug-drug interactions.³⁵ Moreover, no pharmacokinetic alteration has been reported in patients with renal/hepatic impairment.¹² Dapagliflozin use versus placebo has been shown to improve the health-related quality of life in patients with type 2 diabetes mellitus^{36,37} and no effect has been seen on bone mineral density and bone turnover markers.²² Chronic safety concerns regarding the carcinogenic potential of these drugs has been suggested in certain trials but this observation has been refuted by a recent report which showed no increased cancer risk with long-term administration of SGLT2 inhibitors.^{38,11} Therefore, the studies to date are promising but further studies evaluating long-term safety and efficacy are needed.³²

CONCLUDING REMARKS

SGLT2 inhibitors represent a novel and promising approach in achieving adequate glycemic control in patients with type 2 diabetes. Given the insulin independent action of these drugs, they may be a potential option even during the late stage of the disease with progressive decline in beta-cell function.

REFERENCES

1. Paisley AN, Yadav R, Younis N, et al. Dapagliflozin: a review on efficacy, clinical effectiveness and safety. *Expert Opin Investig Drugs*. 2013 Jan;22(1):131-40.
2. Abdul-Ghani MA, DeFronzo RA, Norton L. Sodium-Glucose Co-transporter 2 Inhibition – A Novel Strategy for Glucose Control in Type 2 Diabetes. *European Endocrinology*. 2011;7(1):30-5.
3. Chao EC, Henry RR. SGLT2 inhibition — a novel strategy for diabetes treatment. *Nature Reviews Drug Discovery*. 2010;9(7):551-9.
4. Poudel RR. Renal glucose handling in diabetes and sodium glucose cotransporter 2 inhibition. *Indian J Endocrinol Metab*. 2013 Jul;17(4):588-93.
5. Rahmoune H, et al. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. *Diabetes*. 2005;54, 3427–3434.
6. Chao EC. SGLT-2 Inhibitors: A New Mechanism for Glycemic Control. *Clinical Diabetes*. 2014;32(1): 4-11.
7. Jabbour SA, Goldstein BJ. Sodium glucose co-transporter 2 inhibitors: blocking renal tubular reabsorption of glucose to improve glycaemic control in patients with diabetes. *Int J Clin Pract*. 2008 Aug;62(8):1279-84.
8. Dokken B. The Kidney as a Treatment Target for Type 2 Diabetes. *Diabetes Spectrum*. 2012; 25(1): 29-36.
9. FDA approves Farxiga to treat type 2 diabetes. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm380829.htm>.
10. Traynor K. Dapagliflozin approved for type 2 diabetes. *Am J Health Syst Pharm*. 2014 Feb 15;71(4):263.
11. Rosenwasser RE, Sultan S, Sutton D, et al. SGLT-2 inhibitors and their potential in the treatment of diabetes. *Diabetes Metab Syndr Obes*. 2013 Nov 27;6:453- 467.
12. Scheen AJ. Evaluating SGLT2 inhibitors for type 2 diabetes: pharmacokinetic and toxicological considerations. *Expert Opin Drug Metab Toxicol*. 2014 Jan 3.
13. Dziuba J, Alperin P, Racketa J, et al. Modeling Effects of SGLT-2 Inhibitor Dapagliflozin Treatment vs. Standard Diabetes Therapy on Cardiovascular and Microvascular Outcomes. *Diabetes Obes Metab*. 2014 Jan 20.
14. Ptaszynska A, Hardy E, Johnsson E, et al. Effects of dapagliflozin on cardiovascular risk factors. *Postgrad Med*. 2013 May;125(3):181- 9.
15. Gilbert RE. Sodium-glucose linked transporter-2 inhibitors: potential for renoprotection beyond blood glucose lowering? *Kidney Int*. 2013 Nov 20.
16. Liu JJ, Lee T, DeFronzo RA. Why Do SGLT2 inhibitors inhibit only 30-50% of renal glucose reabsorption in humans? *Diabetes*. 2012 Sep;61(9):2199-204.
17. Abdul-Ghani MA, DeFronzo RA, Norton L. Novel hypothesis to explain why SGLT2 inhibitors inhibit only 30-50% of filtered glucose load in humans. *Diabetes*. 2013 Oct;62(10):3324-8.
18. Brooks AM, Thacker SM. Dapagliflozin for the treatment of type 2 diabetes. *Ann Pharmacother*. 2009 Jul;43(7):1286-93.
19. Han S, Hagan DL, Taylor JR, et al. Dapagliflozin, a selective SGLT2 inhibitor, improves glucose homeostasis in normal and diabetic rats. *Diabetes*. 2008 Jun;57(6):1723-9.
20. Demaris KM1, White JR. Dapagliflozin, an SGLT2 inhibitor for the treatment of type 2 diabetes. *Drugs Today (Barc)*. 2013 May;49(5):289-301.
21. Ji L, Ma J, Li H, Mansfield TA, et al. Dapagliflozin as monotherapy in drugnaive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. *Clin Ther*. 2014 Jan 1;36(1):84-100.e9.
22. Bolinder J, Ljunggren O, Johansson L, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Diabetes Obes Metab*. 2013 Aug 1.
23. Strojek K, Yoon KH, Hruba V, Elze M, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2011;13:928-938.
24. Rosenstock J, Vico M, Wei L, et al. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. *Diabetes Care*. 2012;35:1473-1478.
25. Wilding JP, Woo V, Soler NG, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann Intern Med*. 2012;156:405-415.
26. Bolinder J, Ljunggren Ö, Kullberg J, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. *J Clin Endocrinol Metab*. 2012 Mar;97(3):1020-31.
27. Nauck M, del Prato S, Meier JJ, et al. [Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin]. *Dtsch Med Wochenschr*. 2013 Apr;138 Suppl 1:S6- 15.
28. Mudaliar S, Henry RR, Boden G, et al. Changes in insulin sensitivity and insulin secretion with the sodium glucose cotransporter 2 inhibitor dapagliflozin. *Diabetes Technol Ther*. 2014 Mar;16(3):137-44.
29. Forst T, Guthrie R, Goldenberg R, et al. Efficacy and Safety of Canagliflozin Over 52 Weeks in Patients With Type 2 Diabetes on Background Metformin and Pioglitazone. *Diabetes Obes Metab*. 2014 Feb 15.
30. Zambrowicz B, Freeman J, Brown PM, et al. LX4211, a dual SGLT1/SGLT2 inhibitor, improved glycemic control in patients with type 2 diabetes in a randomized, placebo-controlled trial. *Clin Pharmacol Ther*. 2012 Aug;92(2):158-69.
31. Cuypers J, Mathieu C, Benhalima K. SGLT2-inhibitors: a novel class for the treatment of type 2 diabetes introduction of SGLT2-inhibitors in clinical practice. *Acta Clin Belg*. 2013 Jul-Aug;68(4):287-93.
32. Neumiller JJ, White JR Jr, Campbell RK. Sodium-glucose co-transport inhibitors: progress and therapeutic potential in type 2 diabetes mellitus. *Drugs*. 2010 Mar 5;70(4):377-85.
33. Berhan A, Barker A. Sodium glucose co-transport 2 inhibitors in the treatment of type 2 diabetes mellitus: a meta-analysis of randomized double-blind controlled trials. *BMC Endocr Disord*. 2013 Dec 17;13(1):58.
34. Idris I, Donnelly R. Sodium-glucose co-transporter-2 inhibitors: an emerging new class of oral antidiabetic drug. *Diabetes Obes Metab*. 2009 Feb;11(2):79- 88.
35. Scheen AJ. Drug-Drug Interactions with Sodium-Glucose Cotransporters Type 2 (SGLT2) Inhibitors, New Oral Glucose-Lowering Agents for the Management of Type 2 Diabetes Mellitus. *Clin Pharmacokinet*. 2014 Jan 14.
36. Grandy S, Langkilde AM, Sugg JE, et al. Health-related quality of life (EQ-5D) among type 2 diabetes mellitus patients treated with dapagliflozin over 2 years. *Int J Clin Pract*. 2014 Feb 6.
37. Grandy S, Hashemi M, Langkilde AM, et al. Changes in weight loss-related quality of life among type 2 diabetes mellitus patients treated with dapagliflozin. *Diabetes Obes Metab*. 2014 Jan 20.
38. Reilly TP, Graziano MJ, Janovitz EB, et al. Carcinogenicity Risk Assessment Supports the Chronic Safety of Dapagliflozin, an Inhibitor of Sodium-Glucose Co-Transporter 2, in the Treatment of Type 2 Diabetes Mellitus. *Diabetes Ther*. 2014 Jan 29.

**SGLT2 inhibitors,
owing to
an insulin-
independent action,
may be considered
a potential option
even during the
late stage of
type 2 diabetes
with progressive
decline in beta-cell
function**

NOTES

DIABETES GATE



Pterocarpus marsupium - 150 mg, Withania somnifera - 100 mg, Salacia reticulata - 100 mg,
Gymnema sylvestre -50 mg, Curcuma longa - 25 mg & Vitis vinifera - 10 mg Tablets

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Teneligliptin 20 mg & Metformin Hydrochloride (SR) 500 mg Tablets

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Omega-3 Marine Triglycerides, Methylcobalamin, Zinc Gluconate,
Chromium Picolinate Selenium, Folic Acid & Vitamin B6 Capsules



