News and Views

Another Feather in the Cap: Semaglutide may Soon be the First GLP-1 Treatment for Type 2 Diabetes Patients with CKD

Semaglutide reduced the progression of kidney disease, major adverse cardiovascular events (MACE) and kidney-related mortality in patients with type 2 diabetes patients with chronic kidney disease (CKD), according to topline results from the FLOW trial[1].

The trial met the primary composite end point by showing a significant and superior reduction in kidney disease progression, cardiovascular and kidney-related mortality by 24% in patients treated with once-weekly injectable semaglutide 1.0 mg compared to placebo. However, only the top line results have been released for now. The complete data is expected to be shared later this year.

The trial was halted early in October 2023 on the recommendation of the trials independent data monitoring committee last October after the results of an interim analysis showed superior efficacy[2].

The double-blind international superiority trial was launched in 2019 with the objective to compare injectable semaglutide 1.0 mg with placebo along with standard treatment for prevention of progression of kidney dysfunction and risk of death due to kidney and cardiovascular disease (CVD) in 3,533 patients with type 2 diabetes and CKD.

The primary end point consisted of five components assessing CKD progression and the risk of kidney and cardiovascular mortality, with both CKD and cardiovascular factors contributing to the risk reduction. These included: onset of persistent ≥50% reduction in estimated glomerular filtration rate (eGFR) according to the CKD-EPI3 equation compared with baseline, onset of persistent eGFR (CKD-EPI) <15 mL/min/1.73 m^2, initiation of chronic kidney replacement therapy (dialysis or kidney transplantation), death from kidney disease or death from CVD.

The secondary end points were yearly rate of change in eGFR1 (CKD-EPI), MACE (nonfatal myocardial infarction, nonfatal stroke, cardiovascular death) and all-cause mortality. CKD is a common complication of type 2 diabetes and according to the Centers for Disease Control and Prevention (CDC) 1 in 3 adults with diabetes have CKD. These encouraging results therefore come as a glimmer of hope for these patients. Martin Holst Lange, Executive Vice President Novo Nordisk said, in a press release, "*… the positive results from FLOW demonstrate the potential for semaglutide to become the first GLP-1 treatment option for people living with type 2 diabetes and chronic kidney disease*."

Semaglutide is currently FDA approved for the treatment of type 2 diabetes and obesity.

References

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No One Solution Works for All: Patient Selection for Renal Denervation to Treat Hypertension

Hypertension is usually managed through a combination of lifestyle changes and antihypertensive medications. But these are often wrought with challenges such as nonadherence to the prescribed treatment plan, side effects of medications, complex treatment regimens, comorbidities and cost of treatment, which hamper effective management of hypertension. Interventional approaches for treating hypertension are indeed emerging as potential options for patients who are struggling to control their blood pressure (BP) with lifestyle modifications and/or pharmacotherapy. These include renal denervation, baroreflex activation and cardiac neuromodulation.

Renal denervation has been shown to be a safe and effective method for treating hypertension, with BP-lowering effects comparable to antihypertensive medications. But does it work for all patients? The answer is no because no one solution works for all patients. Since it is an emerging therapeutic option, the specific populations that are most likely to benefit from renal sympathetic denervation (RDN) are still being defined.

In an article published in the journal *Blood Pressure*, Melvin Lobo and coauthors discuss the selection criteria of patients for renal denervation[1]. They note that the decision between using radiofrequency energy RDN or ultrasound RDN, depends on the preference of the operator conducting the procedure.

RDN has shown efficacy in a wide range of patients, including those who are unmedicated and those with more severe or resistant hypertension, who are at highest risk of cardiovascular events. Its role in isolated systolic hypertension is indeterminate with sham-controlled trials like the SPYRAL HTN-OFF MED Pivotal, RADIANCE-HTN SOLO, and RADIANCE-HTN TRIO excluding this patient group and Global SYMPLICITY Registry and the RADIOSOUND trial showing similar efficacy in patients with and without isolated systolic hypertension[2].

RDN is contraindicated in certain groups of patients. Notably secondary hypertension. Currently, there is no evidence supporting the use of RDN in patients with secondary forms of hypertension. Therefore, it is crucial to evaluate and rule out secondary causes before considering RDN as a treatment option. Other contraindications include impaired kidney function (eGFR <40 mL/min), renovascular disease, structural renal abnormalities, small renal arteries (diameter <3 mm), primary aldosteronism, valvular heart disease and pregnancy. Presently, there is insufficient data to recommend use of RDN in obstructive sleep apnea (OSA) patients.

It is essential to first confirm the diagnosis of hypertension before considering more invasive procedures like RDN as a treatment option, not just through office BP measurement, but also by ambulatory BP monitoring (ABPM) and standardized home BP monitoring. While RDN has demonstrated efficacy in lowering BP in individuals with established hypertension, its safety and efficacy in masked hypertension or white coat hypertension have not been conclusively established. ABPM can diagnose both masked hypertension and white coat hypertension.

It is also essential to first fully optimize lifestyle modification and drug therapy to boost BP control before they are selected for RDN. Here, single pill combinations, wherever possible, can play a role in improving patient adherence to treatment.

Sounding a note of caution, the authors say that uncontrolled hypertension during the workup for interventional therapy such as RDN, puts the patients at significant risks of cardiovascular events and death. Initiating antihypertensive medications or intensifying therapy during the assessment period must not be delayed to mitigate these risks.

To conclude, RDN is a multidisciplinary care pathway with hypertension specialists, interventionists and imaging specialists who have been trained in the procedure. Since shared decision-making, with the patient as an equal partner, is now central to patient care, they should be adequately informed about the potential benefits, risks and alternatives to RDN. This patient-centered approach ensures that individual preferences and values are taken into consideration, leading to more personalized and effective care. RDN should be offered to those who opt for the procedure provided it is the "most pragmatic route" to achieve control of their hypertension.

References

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Impact of Microplastics on Cardiovascular Health

Carotid artery disease patients found to have microplastics or nanoplastics (MNPs) in the atheromatous plaques were more than fourfold likely to experience a heart attack, stroke or death due to any cause over the next 3 years compared to those without MNPs, suggests a new study published March 7, 2024 in the *New England Journal of Medicine*[1].

For this prospective, observational study, researchers enrolled patients who were undergoing carotid endarterectomy for asymptomatic carotid artery disease and who were enrolled in the North American Symptomatic Carotid Endarterectomy Trial (NASCET). Their average age was 72 years and one-quarter of them were female. Over 50% of the participants were hypertensive, 33% had CVD and almost all were taking statins and antiplatelet drugs.

By analyzing the excised carotid plaque specimens for the presence of MNPs using sophisticated techniques such as pyrolysis-gas chromatography-mass spectrometry, stable isotope analysis, and electron microscopy as well as assessing inflammatory biomarkers with enzyme-linked immunosorbent assay and immunohistochemical assay, they aimed to understand the potential impact of MNPs on cardiovascular health. The primary end point, a composite of myocardial infarction, stroke or mortality, was compared between patients with and without evidence of MNPs in plaque.

A total of 304 patients with carotid artery disease were enrolled in the study; of these, 257 completed a mean

follow-up period of 33.7 months. Polyethylene, a plastic used in packaging such as plastic bags, plastic wraps, etc., was detected in the excised carotid artery plaque of 150 patients (58.4%). The average level of polyethylene detected was 21.7 μg/mg of plaque. In addition to polyethylene, measurable amounts of polyvinyl chloride (PVC) were detected in 31 patients (12.1%), with an average level of 5.2 μg/mg of plaque.

Electron microscopy revealed the presence of "visible, jagged-edged foreign particles among plaque macrophages and scattered in the external debris" in the carotid artery plaque, along with radiographic evidence of chlorine-containing particles, suggesting the presence of microplastics in the carotid artery plaque. Radiographic examination revealed that some of these particles included chlorine, which is commonly used to disinfect swimming pool water and is also present in household cleaning products.

At 33.7 months, 7.5% of patients without MNPs met the composite primary end point of nonfatal myocardial infarction, nonfatal stroke, or death from any cause compared to 20% of those with MNPs.

After adjusting for age, sex, body mass index, cholesterol, comorbidities, and prior cardiovascular events, in multivariable analysis, patients with detectable MNPs within the atheroma were found to be at a significantly higher risk for experiencing a primary end-point event compared to those without these substances, with a hazard ratio (HR) of 4.53.

Microplastics and nanoplastics are minute plastic particles that are ubiquitous in the environment. They can enter the body either through the skin, inhalation or ingestion. It is speculated that MNPs trigger inflammation, oxidative stress, cytotoxicity in the body affecting various systems including the heart[2].

This study highlights the association between MNPs within the carotid artery plaque and the elevated risk of adverse cardiovascular events. Since this association was noted over a period of 34 months, it is suggestive of the long-term effects of microplastics on cardiovascular health. This was an observational study and so does not prove cause and effect; yet, these are critical and decisive observations, which add to the fast emerging evidence of the environmental impact on human health. Further research is required to corroborate these findings and conclusively establish their causative role.

Encourage patients to reduce their use of single-use plastics to reduce exposure to microplastics. This is also how doctors can contribute to a healthier environment.

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Hepatic Steatosis and CKD risk

Individuals with metabolic dysfunction-associated fatty liver disease (MAFLD) and metabolic dysfunction-associated steatotic liver disease (MASLD) with more severe hepatic steatosis, are at a higher risk of developing CKD compared to those with mild or moderate hepatic steatosis. And even after remission of MAFLD/MASLD, those who had prior moderate to severe hepatic steatosis still were at a higher risk of CKD than those with mild steatosis. These findings were published March 5, 2024 in the *Journal of the American Heart Association*[1].

This study aimed to explore the relationship between hepatic steatosis, specifically in the context of MAFLD/MASLD and occurrence of CKD in the Chinese population. A total of 79,540 participants from the Kailuan cohort were included in the study. Hepatic steatosis was identified using ultrasound and the combination of hepatic steatosis with metabolic dysfunction was defined as MAFLD/MASLD. In addition, MASLD specifically excluded alcohol or other causes of liver disease. CKD was defined based on criteria such as an eGFR <60 mL/min/1.73 m^2 or positive proteinuria (≥1+).

After a median follow-up of 12.9 years, CKD occurred in 20,465 participants. After adjusting for potential confounders, there was an association between MAFLD and MASLD with CKD. The risk of CKD was higher in individuals with MAFLD and MASLD compared to those without these conditions. The HR for CKD among those with MAFLD was 1.12. The risk of CKD increased with increasing severity of hepatic steatosis. Similarly, consistent findings were observed when MASLD was used as the exposure.

Compared with persistent non-MAFLD, there was no statistical difference found in the risk of CKD in MAFLD remission (HR 1.04). However, MASLD remission still had a higher risk of CKD compared with persistent non-MASLD (HR 1.15). On subgroup analysis, based on the prior severity of hepatic steatosis, participants with mild MAFLD or MASLD who achieved remission did not show a statistically significant difference in the risk of CKD compared to those without MAFLD/MASLD. However, those with moderate/severe MAFLD/MASLD

who achieved remission still had a higher risk of CKD. These results suggest a potential link between liver diseases and the development of CKD in due course of time. The severity of hepatic steatosis may play a role in the association between liver diseases and CKD risk even after achieving remission.

The findings emphasize the importance of monitoring the risk of CKD in patients with MAFLD/MASLD. It suggests that more frequent CKD screening and early interventions may be necessary in individuals with hepatic steatosis, particularly those with moderate to severe hepatic steatosis.

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Impact of Induction Timing on Maternal and Neonatal Outcomes

About half of the women with prelabor rupture of membrane (PROM) experience spontaneous labor following induction of labor at 24 hours compared to 12 hours. But they were at higher risk of chorioamnionitis, suggests a retrospective study published in the *American Journal of Obstetrics & Gynecology*[1].

This study was conducted at a single tertiary center between 2020 and 2023 to investigate the maternal and neonatal morbidity outcomes between induction of labor at 12 hours in 802 women versus 24 hours in 962 women following PROM. Women presenting with complications necessitating immediate delivery and multiple pregnancies were excluded from the study group. The study protocol was updated on July 1, 2021 to extend the conservative management duration by administering oxytocin after 24 hours instead of 12 hours post-PROM. The rate of chorioamnionitis was compared between two induction protocols for women at term with PROM and who did not show signs of active labor upon admission.

Several differences were observed between the two groups. Half of the women (50.4%) in the 24-hour protocol group experienced spontaneous labor compared to the 12-hour protocol group (41.5%). They also had a higher rate of chorioamnionitis (7.5% vs. 4.7%). Cesarean deliveries occurred at similar rates between the two groups (16.3% vs. 17%).

A higher percentage of neonates born after the 24-hour protocol required intensive care with neonatal intensive care unit admission rate of 6.2% versus 3.6% in the 12-hour protocol group. They also required more antibiotics 5.7% vs. 2.9%) and also experienced respiratory distress (4.2% vs. 1.0%).

In the study, it was observed that among women with a previous vaginal delivery, the rate of inductions was lower following the 24-hour protocol compared to the 12-hour protocol (46.5% vs. 57.3%). However, maternal and neonatal outcomes were found to be similar between the two groups. On the other hand, among women with a previous cesarean delivery, the rates were lower following the 24-hour protocol compared to the 12-hour protocol, for oxytocin use (20.3% vs. 43.2%) and cesarean delivery (28.9% vs. 48.6%).

These findings suggest potential differences in induction practices and maternal and neonatal outcomes based on previous delivery history. These have potential implications for the management of term PROM. Hence, "shared decision-making" is crucial in the management of term PROM, state the authors. Women should be informed about the lower chance for induction and the higher risk of chorioamnionitis associated with the 24-hour induction protocol. They further suggest that parous women and those with a history of previous cesarean delivery may benefit from longer expectant management. Hence, past delivery history must be taken into consideration when making management decisions for term PROM.

Reference

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Not Just Sugar, Also Avoid High Salt Intake to Ward Off Risk of Type 2 Diabetes

Individuals who consume a proinflammatory diet containing processed foods, sugary drinks, refined carbohydrates, and unhealthy fats are at an 18% higher risk of developing type 2 diabetes compared to those who ate an anti-inflammatory diet. Those who habitually add salt to their food are also at a higher risk of type 2 diabetes, according to a study reported in the journal *Diabetes, Obesity and Metabolism*[1].

This study was conducted to investigate the relationship between a proinflammatory diet, routine salt intake, and incidence of new-onset type 2 diabetes among 1,71,094 participants from the UK Biobank. None of the study subjects had diabetes at the start of the study. They completed at least one 24-hour dietary questionnaire for the study. The Energy-adjusted Diet Inflammatory Index (E-DII) was calculated on the basis of 28 food parameters, while habitual salt intake was established

by self-reported frequency of adding salt to foods. The incidence of type 2 diabetes was tracked through linked medical records.

During the 13.5-year median follow-up period, 6216 participants were diagnosed with type 2 diabetes. Those with a high E-DII, indicating a proinflammatory diet, were at an 18% higher risk of developing type 2 diabetes compared to those with a low E-DII representing an anti-inflammatory diet. The relationship between E-DII and type 2 diabetes appeared to be linear after adjusting for major confounders. Interestingly, participants with a proinflammatory diet who also consistently added salt to their foods had the highest risk of type 2 diabetes incidence, with a HR of 1.60.

Anti-inflammatory diet includes plenty of fats and vegetables, whole grains, and healthy fats (omega-3 fatty acids). The association of high habitual salt intake with hypertension and kidney disease is well-established. To reduce these risks, it is important to monitor the daily salt intake and aim to consume no more than the World Health Organization (WHO) recommended daily limit <2,000 mg/day of sodium equivalent to <5 g/day salt, which is just under a teaspoon for most adults. Choosing fresh, whole foods over processed and packaged foods will help reduce intake of salt.

This study has emphasized the importance of promoting an anti-inflammatory diet and reducing salt intake as part of public health efforts to prevent onset of type 2 diabetes. By making healthier dietary choices, limiting intake of processed foods and reducing salt consumption, individuals may lower their risk of developing this chronic condition.

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Greater Pre-eclampsia Risk Linked to Higher Preterm Spontaneous Birth Risk

Women at high risk of pre-eclampsia in the first trimester are at 41% higher risk of spontaneous delivery all through the pregnancy, suggests a recent study published in the *American Journal of Obstetrics and Gynecology*[1].

Paolo I Cavoretto and coauthors carried out a secondary analysis of data from the Screening Programme for Pre-eclampsia trial, which assessed the effectiveness of two different methods for screening for preterm pre-eclampsia, the Fetal Medicine Foundation model versus a traditional history-based risk scoring system. A subgroup of women with spontaneous onset of delivery was categorized into three groups based on their risk for preterm pre-eclampsia as assessed by the Fetal Medicine Foundation model at 11 to 13 weeks of gestation: Group 1 (low risk) included women with risk of preterm pre-eclampsia <1/100, Group 2 (intermediate risk) with risk between 1/50 and 1/100 and Group 3 (high risk) with risk >1/50. Through this study, the investigators aimed to examine whether the estimated risk of pre-eclampsia correlates with the gestational age at spontaneous delivery in cases without pre-eclampsia.

Out of the 16,451 participants in the Screening Programme for Pre-eclampsia trial, the present study included 10,820 cases with delivery after spontaneous onset of labor. Group 1 had 9,795 cases, Group 2 had 583 cases and Group 3 had 442 cases. The distribution of gestational age at delivery varied among the groups, with different percentages of cases delivering at <28, <32, <35, <37, and <40 weeks. In Group 1, the percentage of cases delivering at gestational ages <28, <32, <35, <37, and <40 weeks were 0.29%, 0.64%, 1.68%, 4.52%, and 44.97%, respectively. In Group 2, the corresponding figures were 0.69%, 1.71%, 3.26%, 7.72%, and 55.23% and in Group 3, they were 0.45%, 1.81%, 5.66%, 13.80%, and 63.12% of cases. The study found that the curve profile of gestational age at spontaneous birth was significantly different between the three groups in both overall and also in pairwise comparisons.

The risk of spontaneous delivery increased by 18% among women at intermediate risk (vs. women at low risk). The risk rose by 41% among women at high risk for pre-eclampsia compared with women at low risk.

Overall, these findings point out the significance of early assessment of the risk of premature pre-eclampsia and its potential impact on the timing of spontaneous onset of labor. They suggest that the timing of spontaneous birth varies significantly based on the first-trimester risk assessment for preterm pre-eclampsia. Women with a higher risk for pre-eclampsia in the first trimester may give birth earlier than those at lower risk. The risk for spontaneous birth is four times higher at gestational ages of 24 to 26 weeks, three times higher at 28 to 32 weeks and two times higher at 34 to 39 weeks. Hence, close monitoring and potentially earlier interventions may be warranted in these cases to mitigate the risks associated with spontaneous birth and complications related to pre-eclampsia.

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