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Ketone Body in Heart Failure Patients with Diabetes: Pathophysiology and the Potential Therapeutic Benefit: a Literature Review

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SOUHRN

Kontext: Je obecně známo, že léčba srdečního selhání je založena na inhibici systému renin-angiotensin-aldosteron a snižování aktivity sympatického autonomního nervového systému. Při léčbě srdečního selhání se však zřídkakdy zvažuje možnost ovlivnění metabolismu. Je třeba poznamenat, že srdeční selhání se často vyskytuje současně s diabetem. Proto musí léčba příznivě ovlivňovat obě tato onemocnění. V průběhu patofyziologického přechodu k srdečnímu selhání může dojít k rozvoji metabolických abnormalit a jako alternativních zdrojů energie lze použít kyselinu mléčnou, ketolátky a aminokyseliny. Spojitost ketolátek s oběma onemocněními byla prokázána. Pro pacienty se srdečním selháním a diabetem by léčba s použitím ketolátek mohla být přínosná.
Cíl: Vypracovat komplexní přehled preklinických a klinických studií zkoumajících léčebné účinky ketolátek u srdečního selhání.
Metoda: Tato studie je přehledem literatury dostupné v online databázích a vyhledané pomocí klíčových slov uvedených v biomedicínském slovníku (tezauru) Medical Subject Headings (MeSH). Hledanou intervencí byla terapie ketolátkami (3-hydroxybutyrát sodný, sodium-3-OHB) nebo inhibitorem sodíko-glukózového transportéru typu 2 (SGLT2) jako aktivátorem tvorby ketolátek. Zaměřili jsme se na výsledky léčby a jakékoli zaznamenané nežádoucí účinky ketózy.
Výsledky: Bylo vybráno celkem 14 studií (šest u lidí a osm se zvířaty) zabývajících se léčebnými účinky ketolátek. Terapii ketolátkami (3-OHB sodný) nebo intervenci inhibitorem SGLT2 podstoupilo celkem 8 742 (8 zdravých jedinců) účastníků studií.
Závěr: Ketoterapie a systémová regulace ketózy se zdají být slibnými způsoby léčby díky změnám metabolismu srdcí pacientů s diabetem a srdečním selháním. Tato studie by se mohla stát literárním základem pro další výzkum s cílem určit bezpečnost a hranice účinnosti dlouhodobé léčby ketolátkami.

Keywords:
Diabetes mellitus
Heart failure
Ketone body
Ketone therapy

ABSTRACT

Background: Common knowledge of heart failure treatment target is to intervene in the renin-angiotensin-aldosterone system and the sympathetic autonomic nervous system. However, metabolic aspect in the therapy of heart failure is rarely discussed. It is worth noting that heart failure often co-exist with diabetes. Thus, there is a need for a treatment that can be beneficial for these two diseases. During the pathophysiological transition to heart failure, metabolic abnormalities may occur, and lactic acid, ketone bodies, and amino acids may be used as alternative energy sources. Ketone body has been shown to be associated with these two diseases. Treatment using ketone body may be beneficial to treat patients with heart failure and diabetes.
Objective: To provide a comprehensive review of preclinical and clinical studies on the therapeutic effects of ketone bodies for heart failure.
Method: This study is literature reviews on online databases using keywords according to the Medical Subject Headings (MeSH). The focused intervention is ketone bodies therapy (sodium-3-OHB) or SGLT2i as ketone inducer. We focused on the result of therapy and any ketosis side effect recorded.

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Results: A total of 14 studies (6 human studies and 8 animal studies) related on the therapeutic effects of ketone bodies was selected. A total of 8,742 (8 healthy participants) participants was involved in ketone bodies therapy (sodium-3-OHB) or SGLT2i intervention.
Conclusion: Ketogenic therapy and systemic ketosis regulation show promise based on metabolic changes in the hearts of patients with diabetes and heart failure. This study may provide a literature basis for further research to determine the safety and efficacious limitations of long-term ketone body therapy.

Introduction

Heart failure is a global phenomenon due to its high incidence in developing countries.[1] According to Lam (2015), heart failure is more common in Southeast Asia than it is worldwide. It is thought to affect 1% to 2% of adults in developing countries. The lack of statistics on the prevalence of heart failure may cause this estimate to rise.[2] Additionally, patients with heart failure in Southeast Asia are more likely to have more severe symptoms, require mechanical ventilation more frequently, have longer hospital stays, and have higher hospital mortality.[3]

As an essential organ that works continuously, the heart consumes adenosine triphosphate (ATP) more than seven times its weight per day. The majority of the metabolic resources (50–75%) needed by adult cardiac muscle cells to produce ATP are fatty acids, with 25–50% of the energy used by mitochondria for metabolism comes from glucose.[4] The heart may also use lactic acid, ketone bodies, and amino acids in small amounts as energy sources in addition to fatty acids and glucose. The percentage of these metabolic sources that are used may differ depending on the state of nutrition and the heart's function. For instance, the heart uses glucose primarily during the fetal stage and switches to using fatty acids as a source of ATP generation during the postnatal stage.[5,6] Failure to meet energy requirements will result in cardiac failure. Increasing ATP production in the heart in a bioenergy--efficient way might be the solution.

The heart's use of its metabolic fuel sources could change. These metabolic changes, which include an initial disruption in the oxidation of fatty acid followed by a change in the oxidation of glucose, may occur during the pathophysiological transition to heart failure. This process occurs at the early-stage pathogenesis of heart failure, such as the cardiac muscle hypertrophy creation phase in chronic hypertension patients or the ischemia phase in coronary heart disease patients. Cardiomyocyte mitochondria may be reprogrammed, resulting in decreased fatty acid oxidizing capacity and increased glucose oxidation and glycolysis. Due to the fatty acids as the primary fuel for a healthy heart, the mentioned metabolic reprogramming event causes a decrease in ATP production.[5,7]

There may be additional processes involved in concomitant heart failure and diabetic mellitus (DM). Because of their insulin resistance, diabetic patients' hearts are unable to use glucose as their primary energy source. Due to this circumstance, there is a forced metabolic shift whereby fatty acid sources become the only source of ATP generation. This alteration results in the formation of oxidative stress, which raises the oxygen demand of the heart tissue and ultimately lowers the heart's activity efficiency. This may occur because the oxidation of fatty acids requires more oxygen per mole than the oxidation of glucose. These factors suggest that specific management and greater attention are needed for heart failure with DM comorbidity.[8] The use of alternative energy sources to meet the metabolic requirement for the heart's activity could be one of the targets for heart failure management, especially with DM comorbid.

Evidence suggests that increasing the metabolism of additional energy sources, such as ketone bodies, in adequate quantities can improve energy metabolism efficiency and minimize oxidative stress. Composed of 4-carbon molecules synthesized by the ketogenesis process, ketone bodies can be broken down and utilized in tissues via the ketolysis pathway, forming acetone, acetoacetate, and beta-hydroxybutyrate as ketone molecules. Beta-hydroxybutyrate (-OHB) is the most prevalent ketone body in blood circulation. An adequate level of -OHB in blood circulation has been shown to improve hemodynamics in heart failure patients.[9]

Various preclinical and clinical researches have shown that ketone bodies have a therapeutic effect on heart failure. Exogenous ketone body administration may improve circulatory function and avoid pathological remodeling in the process leading to heart failure. These investigations could point to novel intervention targets for the pharmaceutical therapy of heart failure. The discovery of changes in metabolism and the utility of the ketone body in heart failure patients with diabetes led to a more in-depth and wide debate about the ketone body's therapeutic potential.[10] In order to lower the risk of HF hospitalization and death, SGLT2i have been suggested for patients with HFrEF based on the 2021 ESC guideline.[11] Both individuals with and without diabetes may benefit from SGLT2i's potential mode of action in HF.[12] This raise question on why ketone body treatment is not advised in guidelines similar to SGLT2i.

This review aims to give a thorough overview of the correlation between DM and heart failure, as well as an analysis of the metabolism and utilization of ketone bodies in physiological conditions and how these relate to changes in heart failure and DM conditions. Additionally, it reviews a number of recent studies on the therapeutic effects of ketone bodies in both preclinical and clinical settings.

Methods

This study is a literature review related to the use of ketone body therapy on heart failure. The literature search was carried out on the PUBMED and SCIENCEDIRECT databases using keywords according to the Medical Heading

Subject (MeHS), namely "(Keton) AND (Bodies) AND (Ketosis) AND (Heart failure) AND (Diabetes mellitus) AND (Left ventricular dysfunction)". The population of related study could be human or animal without specific limitation. The intervention is ketone bodies therapy (sodium--3-OHB) or SGLT2i as ketone inducer. The comparison of the ketone therapy could be placebo, other HF agents, or no comparison. We focused on the result of therapy and any ketosis side effect recorded.

Results

A total of 14 studies (six human studies and eight animal studies) related on the therapeutic effects of ketone bodies was selected. A total of 8,742 (eight healthy participants) participants was involved in ketone bodies therapy (sodium-3-OHB) or SGLT2i intervention. From the total six of human studies, empagliflozin was used in two studies, dapagliflozin in two studies, and ketone infusion of sodium-3-OHB also in two studies. While in animal studies, empagliflozin was used in four studies, dapagliflozin in two studies, and ketone infusion of sodium-3-OHB also in two studies. **Table 1** shows the result of the search.

Discussion

1. Correlation of heart failure and diabetes mellitus

Epidemiology of DM and heart failure

Heart failure and diabetes mellitus (DM) are two diseases that could co-exist in a patient. Heart failure is one of DM comorbidities and vice versa. Diabetes affects the elderly (60 years) at a rate ranging from 10 to 47% in patients with heart failure who require hospitalization. The percentage of diabetic patients with heart failure ranges from 9 to 22%, which is four times greater than the healthy population. A study showed that heart failure patients with DM have worse clinical symptoms and prognosis, and significantly increased mortality risk.

As a result, DM is regarded as a significant independent risk for determining the mortality risk in patients with heart failure. The American Heart Association (AHA) and the European Society of Cardiology (ESC) developed management guidelines for heart failure and diabetes mellitus (DM) based on these findings.[24]

Pathophysiology of DM and heart failure

Diabetes mellitus contributes to the pathogenesis of heart failure through systemic, myocardial, and cellular pathways. According to another study, vasculo-myocardial damage – which includes tissue fibrosis, higher risk of thrombosis, vasculopathy, and myocardial hypertrophy – is what causes heart failure brought on by diabetes. These processes are thought to be all brought on by lipotoxicity and glucotoxicity.[24,25]

Diabetes mellitus can cause structural heart damage through the ischemia/infarction mechanism. Hyperglycemia and hyperinsulinemia are known to accelerate the establishment of atherosclerosis by increasing the proliferation of vascular smooth muscle, then followed by inflammation and oxidative stress. This causes endothelial dysfunction leading to vasculopathy. Endothelial dysfunction, combined with high levels of low-density lipoprotein (LDL), will trigger leukocyte and platelet adhesion, resulting in thrombosis, inflammation, and atherosclerotic plaque formation in coronary arteries.[24,25]

In the absence of ischemia/infarction related to coronary heart disease (CHD), diabetes mellitus may produce myocardial abnormalities. Diabetic cardiomyopathy is the medical term for this illness. Rubler et al. coined this phrase in 1972 after discovering cardiomegaly in DM patients without severe CHD. "Diabetic cardiomyopathy" term has been used to describe systolic and/or diastolic dysfunction in diabetic patients, who have no other known cardiomyopathy causes, such as CHD, hypertension, or valvular heart disease, for a long. In diabetic cardiomyopathy, left ventricular hypertrophy in imaging studies accompanied by hyperinsulinemia or insulin resistance is a significant diagnostic criterion.[24] Hyperglycemia can cause myocardial hypertrophy by causing the production of advanced glycation end products (AGEs). AGEs have been shown to limit collagen turnover, increasing the production of fibrotic tissue and interfering with myocardial relaxation function.

In addition to these mechanisms, hyperglycemia stimulates the renin-angiotensin-aldosterone (RAS) system, resulting in angiotensin II and aldosterone overproduction, which has been linked to myocardial hypertrophy via the transforming growth factor beta (TGF-) pathway. Insulin causes mitosis and increases the lifespan of cardiac cells, therefore hyperinsulinemia contributes to myocardial hypertrophy.[26]

The mechanism of heart failure in DM patients is also linked to the "energy-starvation" hypothesis, which states that the heart muscle cannot use glucose as an energy source due to poor glucose metabolism. As a result, the heart undergoes a forced metabolic shift in which all of its energy production is assigned to a fatty acid source. Excessive fatty acid oxidation causes fat accumulation in cardiomyocytes, which triggers lipo-toxicity that damages contractile proteins and causes apoptosis in cardiomyocytes. These mechanisms are associated with DM conditions with lipid accumulation in heart tissue based on studies using cardiac magnetic resonance imaging. Analysis of myocardial tissue in DM patients showed an increase in the number of cardiomyocytes undergoing apoptosis.[24,25]

2. Ketone body and its metabolism

Ketone body metabolism in normal heart

Ketone substances consist of four carbon molecules, including acetone, acetoacetate, and beta-hydroxybutyrate (β-OHB). The liver produces β-OHB, the most common type in the circulation (78%), through a process called ketogenesis. This process, which results in the transformation of fatty acids and some ketogenic amino acids into ketone bodies, is triggered during fasting when the insulin-to-glucagon ratio drops. They provide 5–20% of daily energy requirements from the 300 grams produced, and are used as an energy source during fasting, low-carb diets, and after vigorous exercise.[9,23] Keto-

Table 1 – Studies related on the therapeutic effects of ketone bodies

Author	Population	Intervention	Main findings
Human study			
Verma, 2016[13]	10 people with cardiovascular disease and diabetes mellitus	Pre- and post-empagliflozin study	Empagliflozin enhances echocardiographic parameters and decreases left ventricular mass.
Gormsen, 2017[14]	Eight healthy participants	Randomized crossover experiment comparing saline infusion to sodium-3-OHB	The infusion of ketone reduces the absorption of glucose while increasing myocardial blood flow by 75%
Nielsen, 2019[15]	Sixteen patients with lower ejection fraction because of heart failure	Randomized crossover study comparing isotonic saline to 3-OHB infusion	A ketone application increases cardiac blood flow by 75% while decreasing glucose absorption
McMurray, 2019[16]	4744 people with a lower ejection fraction who suffer from cardiac failure	Randomised crossover study comparing placebo with dapagliflozin	Dapagliflozin is not linked to underlying diabetes mellitus and lowers the risk of cardiovascular death or worsening heart failure
Packer, 2020[17]	3730 people with with class II, III, or IV heart failure and an ejection fraction of 40% or less	Double-blind trial study by comparing placebo with empagliflozin (10 mg once daily) in addition to recommended therapy	Empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes
Selvaraj, 2022[18]	234 people with HFrEF	Targeted metabolomics in a placebo-controlled trial of sodium-glucose cotransporter-2 inhibitors in HFrEF	Dapagliflozin increased ketone-related components compared with placebo. However, only physiologic levels of ketosis were observed.
Animal study			
Joubert, 2017[19]	Mice with lipodystrophies	Dapagliflozin only	In patients with heart hypertrophy, dapagliflozin treatment markedly improves diastolic function
Lee, 2017[20]	Wistar male rats undergoing coronary ligation had normoglycemia	Dapagliflozin and control	In cardiac fibrosis, dapagliflozin decreases
Verma, 2018[21]	Diabetes mellitus in mice	Empagliflozin and control	Cardiac ATP generation is increased by empagliflozin, but not by ketone oxidation
Abdurrachim, 2019[6]	Mice suffering from heart failure, hypertension, diabetes, and obesity	Empagliflozin and control	Empagliflozin lowers the quantity of ketone the heart uses, however, it has little effect on fibrosis or hypertrophy of the left ventricle
Horton, 2019[5]	Rats with transaortic constriction/myocardial infarction and dogs with cardiomyopathy induced by tachycardia	Mice given a ketogenic and regular diet; dogs with heart failure receiving 3-OHB infusion against not being given it	In a dog model, 3-OHB infusion dramatically reduced systolic dysfunction and left ventricular remodeling, while a ketogenic diet reduced left ventricular remodeling in mice
Santos-Gallego, 2019[22]	Heart failure following LAD artery ligation in pigs without diabetes	Empagliflozin and control	Pigs given empagliflozin alternate between using branched-chain amino acids, ketones, and fatty acids as substrates
Yurista, 2019[23]	Mice model following myocardial infarction without developing diabetic mellitus	Empagliflozin and control	After myocardial infarction, empagliflozin dramatically increases ejection fraction, reduces hypertrophy, gets rid of fibrosis, and lessens oxidative stress. In the heart, empagliflozin stimulates the expression of ketogenic enzymes and ketone body transporters.
Thai, 2021[9]	Diabetes mellitus model mice	Administration of ketone esters and control	Ketone esters enhance heart systolic and diastolic function, mitochondrial biogenesis, oxygen consumption efficiency, and cell tolerance to oxidative stress

ne molecules are transported into tissues by monocarboxylate transporters (MCTs), where they undergo ketolysis in mitochondria. β-OHB and acetoacetate are converted by essential enzymes such as Bdh1 and SCOT into Acetyl-CoA, which then proceeds to the tricarboxylic acid cycle (TCA) to create ATP. Genetic deficiencies affecting the SCOT, ACAT, and MCT1 enzymes can cause recurrent ketoacidosis.[4,23,27]

Ketone consumption is increased in heart failure and diabetes to maintain metabolic balance. Mice lacking the SCOT or Bdh1 genes exhibit cardiac abnormalities due to loss of ketone metabolism.

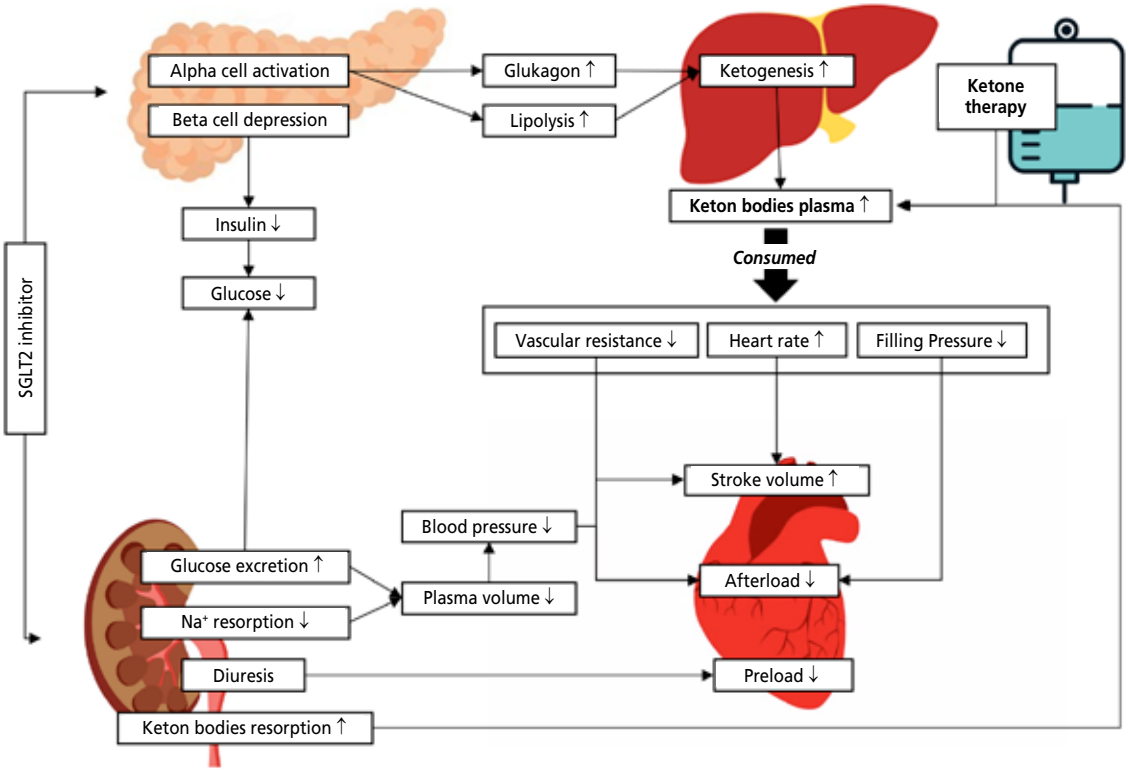

Fig. 1 – Schematic diagram mechanisms of action of SGLT2i related to ketogenesis and the potential ketone therapy

3. Heart failure-related changes in ketone body metabolism

Cardiac changes are characteristic of early heart failure, starting with myocardial hypertrophy, which reduces fatty acid oxidation capacity. Reliance switches to less effective glycolysis in cardiac failure. Hypertrophied hearts compensate for reduced fatty acid oxidation with increased glycolysis at lower workloads. Insulin resistance and other variables may cause changes in glucose utilization over time, which can result in energy deficiency and decreased heart failure glucose and fatty acid utilization.[5]

Ketone body metabolism in diabetic patient with heart failure

Type 1 diabetes and type 2 diabetes can both have major effects on the ketogenic body. In those with type 1 diabetes, routine glucose, and ketone testing is essential to preventing ketonemia, which can quickly worsen in the absence of insulin therapy. Elevated blood ketone levels in type 2 diabetes are associated with impaired glucose management because of low insulin and high glucagon levels, which promote the breakdown of fat in the liver to produce hepatic ketogenesis.[10,27] Diabetic hearts rely less on oxidizing glucose and more on oxidizing fatty acids.[9,27,28]

The potential benefits of ketone body therapy for diabetes and heart failure

Ketone supplementation has the potential to treat heart failure, particularly in patients with a low ejection fraction (HFrEF). According to one study, giving 3-hydroxybutyrate ketone bodies increased cardiac output by 40%. This rise was associated with decreased vascular resistance, elevated heart rate, enhanced stroke volume, and reduced filling pressure. While the fundamental cause of this effect is still unknown, the study suggests that people with preserved ejection fraction (HFpEF) may reap similar benefits.

This presents intriguing opportunities for improving vasodilator effects and systolic function in HFpEF patients by using ketone therapy.[7] Patients with diabetes and heart failure show changes in their heart's metabolism and ketone body utilization, suggesting that ketone treatment or modifications to systemic ketosis may be beneficial. To optimize this approach, research should focus on establishing the optimum methods for inducing ketosis in heart failure patients, such as dosage, preparation, and delivery (oral or intravenous). To adequately analyze outcomes, a larger study incorporating varied patient groups, including those with diabetes, is required.[4,16]

4. The role of SGLT2i therapy as keton inducer for diabetes and heart failure

In individuals with and without diabetes, SGLT2i has proven treatment causes a slight ketosis, which may be the mechanism of action for its beneficial effects in heart failure.[12] Based on Selvaraj et al, (2022) study, the level of **ßOHB** and associated C4-OH were raised in a placebo-controlled experiment assessing circulating metabolites in HFrEF patients after 12 weeks of SGLT2i therapy. Furthermore, the mentioned study show that Dapagliflozin increased ketone-related components compared with placebo. However, only physiologic levels of ketosis were observed.[18] Moreover, SGLT2i also decreased insulin

attenuated inflammation in diabetes type II. In separated literature study about potential side effect of SGLT2i in inducing euglycemic diabetic ketoacidosis (EDKA), suggesting that in mild hyperketonemia caused by SGLT2i, beta-hydroxybutyrate is freely taken up by the cells as a source of energy, especially by the cardiac muscles. This usage of energy source helps the tissues work efficiently, and reducing cardiovascular (CV) mortality by 38%, hospitalization for heart failure by 35%, and death from any cause by 32%.[29]

Based on some literature,[4,12,30] we try to formulate a simple schematic diagram showing mechanisms of action of SGLT2i related to ketogenesis and the usage of the keton bodies in by the cardiac muscles, as well as the potential ketone therapy which discussed above (**Fig. 1**). However, some literatures suggest that SGLT2i has inconsistent ketosis effect, and mechanisms other than ketosis (enhanced glucose and fatty acid oxidation) may also mediate the cardiometabolic effects of SGLT2i.[12,21]

Conclusion

Ketogenic therapy and systemic ketosis regulation show promise based on metabolic changes in the hearts of patients with diabetes and heart failure. Further research is required to determine the safety and efficacious limitations of long-term ketone body delivery, taking into account the effects on the liver and the acid-base balance. It is critical to determine the most effective method of inducing ketosis in patients with heart failure (dosage, preparation, oral vs. intravenous), as well as the outcomes must be assessed in a range of patient populations, including those with diabetes.

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