Annals of Internal Medicine

Sodium–Glucose Cotransporter-2 Inhibitors: Lack of a Complete History Delays Diagnosis

Bruce R. Leslie, MD, MSPH; Leslie E. Gerwin, JD, MPH, MPA; and Simeon I. Taylor, MD, PhD

On 15 May 2015, the U.S. Food and Drug Administration (FDA) warned that administration of sodium–glucose cotransporter-2 (SGLT2) inhibitors could lead to ketoacidosis in patients with diabetes mellitus. This announcement came more than 2 years after the FDA's first approval of an SGLT2 inhibitor, although the phenomenon had been known for more than 125 years. Luminaries of diabetes research (including Josef von Mering, Frederick Allen, I. Arthur Mirsky, and George Cahill) had described ketosis and ketoacidosis induced by administration of the phytochemical phlorizin, the prototypical SGLT inhibitor, as well as in patients with familial renal glucosuria, a condition that is considered a natural model of SGLT2 inhibition. Neither government regulators nor manufacturers of SGLT2 inhibitors evinced an awareness of this extensive historical record. The absence of historical inquiry delayed notice of ketoacidosis as an adverse reaction, which could have reduced the burden of illness from these drugs.

Ann Intern Med. 2019;171:421-426. doi:10.7326/M19-1463 **Annals.org**

For author affiliations, see end of text.

On 15 May 2015, the U.S. Food and Drug Administration (FDA) warned in a Drug Safety Communication that sodium–glucose cotransporter-2 (SGLT2) inhibitors may lead to ketoacidosis in patients with type 2 diabetes mellitus (1). This discovery should not have been a surprise. For more than 125 years, investigators had described ketosis and ketoacidosis induced by the phytochemical phlorizin, the prototypical SGLT inhibitor, as well as in patients with familial renal glucosuria (FRG), a condition that is considered a natural model of SGLT2 inhibition. The story of SGLT2 inhibitor ketoacidosis offers a cautionary tale about how historical inquiry can provide valuable insights and accelerate recognition of risks associated with new drugs.

In Pursuit of History

Our exploration of the history of SGLT2 inhibitor ketoacidosis began in early 2014 when one of us (B.R.L.) learned, during employment in the pharmaceutical industry, about the accrual of spontaneous postmarketing reports of ketoacidosis submitted by health care professionals to the manufacturer of canagliflozin. Subsequently, a Freedom of Information Act request for FDA Adverse Event Reporting System (FAERS) data revealed that the FDA's receipt of these same reports began on 8 May 2013 (2). Seeking a precedent for this phenomenon, we did Boolean searches in PubMed and Google Scholar using the key words *phlorizin* (and its variant spellings), *renal glucosuria* or *glycosuria*, *ketoacidosis*, *ketones*, *ketosis*, and *acidosis*. We iteratively mined the bibliographies of articles and books retrieved by these searches for additional primary sources. Google Translate and native speakers provided translations of non–English-language publications. Two of us (B.R.L. and S.I.T.) had also worked in industry on the development of dapagliflozin, although we had not been aware of the extent of this literature until conducting the searches prompted by these postmarketing reports.

Phlorizin: The Basis of a Precedent

We focused our search on phlorizin because it is the progenitor of contemporary SGLT2 inhibitors. Initially isolated from the bark of apple trees as a treatment of malarial fever (3), phlorizin increases urinary elimination of glucose through competitive inhibition of SGLT2, the principal transporter for renal glucose reabsorption, and of SGLT1, a lesser glucose transporter in the kidney (4). Reductions in blood glucose after single doses of phlorizin in patients with diabetes (5), as well as favorable effects of phlorizin on glucose metabolism in partially pancreatectomized rats (6), foretold the promise of SGLT2 inhibitors in treatment of type 2 diabetes mellitus.

In 1999, pharmaceutical chemists described one of the first orally bioavailable derivatives of phlorizin (7), a prodrug known as T-1095. The authors cited a 1945 review that described acidosis and increased "acetone bodies" with phlorizin administration (8), although they did not discuss its implications. The manufacturer of T-1095 did not commercially develop this product.

Other chemists took a different biochemical approach in developing the SGLT2 inhibitors that are currently marketed. Phlorizin consists of a glucose molecule linked to an "aglycone" called phloretin. The O-glycosidic bond that joins them is subject to hydrolysis by endogenous enzymes. This results in reduced oral bioavailability and a relatively short half-life. To avert this problem, chemists eliminated the linking oxygen atom to yield a C-glycoside structure (9). They also modified both the glucose moiety and the aglycone to accomplish several objectives: increased selectivity for SGLT2 relative to SGLT1, increased potency for SGLT2, optimization of pharmacologic and pharmaceutical properties, and creation of intellectual property to protect marketing exclusivity. Notwithstanding these modifications, the structures of all marketed SGLT2 in-

See also:

Editorial comment 434

hibitors closely resemble that of phlorizin. Although phlorizin is sometimes called a "nonselective SGLT inhibitor," it has 9-fold selectivity for inhibition of SGLT2 relative to SGLT1 (10). This is similar to the 20-fold selectivity of sotagliflozin, albeit less than that of other available SGLT2 inhibitors (11). Moderate doses of phlorizin and dapagliflozin have similar effects on glucose excretion (12, 13). Taken together, these considerations provide a strong scientific basis for concluding that experience with phlorizin could offer insights into the pharmacologic responses to modern SGLT2 inhibitors.

From Phlorizin Diabetes to Ketoacidosis

By the time pharmaceutical chemists modified phlorizin's basic structure to create contemporary SGLT2 inhibitors, its ketogenic properties had long been known. At the end of the 19th century, the German physician Josef von Mering (1849–1908) recognized that phlorizin produced glucosuria. This discovery may have occurred while he was testing phlorizin during his studies of antipyretics, which would later lead to the discovery of acetaminophen (14). In a presentation to the German Congresses for Internal Medicine in 1886, von Mering called this phenomenon "phloridzin diabetes" (15). He ended a second presentation on this topic in 1887 with the observation, "In the case of phloridzin diabetes I have repeatedly been able to detect abundant amounts of acetone and oxybutyric [β-hydroxybutyric] acid in urine" (16).

Two years later, von Mering reported that normal dogs given phlorizin during prolonged fasting or with a carbohydrate-poor diet became listless and comatose or died. At necropsy, their livers were depleted of glycogen. In addition to glucose, their urine contained large amounts of ammonia, acetone, and β-hydroxybutyric acid, findings that resemble those in patients in diabetic coma (17). These observations were remarkable because dogs are comparatively resistant to starvation ketosis (18). Von Mering also induced ketosis in a man by giving him 10 g of phlorizin by mouth in the early morning, after which his urine contained glucose and "abundant amounts of acetone" (17). Other investigators confirmed von Mering's findings (19, 20). Von Mering is renowned in the field of diabetes research for his later collaboration with Oskar Minkowski in which they produced diabetes mellitus in a dog by removal of the pancreas (21).

Reports of ketosis induced by phlorizin appeared in the English-language literature in 1914. In a short communication, Stanley Benedict (1884–1936), inventor of Benedict reagent for detection of glucose, noted the ability of protein ingestion to diminish ketosis induced by phlorizin (22). In 1923 at the Rockefeller Institute for Medical Research in New York, Frederick Allen (1879–1964) published the results of extensive studies of acidosis in phlorizin-treated dogs (23). At the time of these experiments, before the commercial availability of insulin, Allen was the leading proponent of starvation diets in management of type 1 diabetes (24). He described ketonemia, ketonuria, and reductions in plasma bicarbonate concentration (carbon dioxide combining capacity) in phlorizinized dogs that had undergone fasting, diets poor in carbohydrates and high in fat, or partial pancreatectomy. Most dogs became weak and lethargic, and many died. Some exhibited the deep breathing characteristic of ketoacidosis. Acidosis resolved with glucose administration and was difficult to induce when the glycosuric response to phlorizin was diminished, as in a dog with chronic kidney disease. Other investigators confirmed the reduction in blood bicarbonate levels, and they further documented a reduction in blood pH (25, 26).

In 1942, I. Arthur Mirsky (1907–1974), a psychoanalyst with an abiding interest in metabolic research, applied phlorizin to a canine model of type 1 diabetes mellitus. Mirsky noted that although the depancreatized dog developed diabetes, it did not develop levels of ketonemia seen in ketoacidotic diabetic humans, even after starvation and withdrawal of exogenous insulin. He observed, however, that "severe diabetic acidosis and coma can be produced in the depancreatized dog by withdrawal of insulin and food plus the administration of a single dose of phlorizin" (27). In the absence of insulin in pancreatectomized dogs, ketogenesis was inhibited by administration of glucose in an amount sufficient to restore hepatic glycogen (28). Mirsky concluded that ketogenesis was enhanced by phlorizin when administered to patients with diminished reserves of hepatic glycogen. He presented his observations on the ketogenic effect of phlorizin at a meeting of the Association for the Study of Internal Secretions, the forerunner of the Endocrine Society, in New York in 1940 (29). He did so again at the first annual meeting of the American Diabetes Association in Cleveland on 1 June 1941. In his address to the American Diabetes Association, Mirsky described "administering phlorizin to a diabetic patient suffering from a non-specific infection. The glycosuria that ensues causes a decrease in liver glycogen and ketosis follows" (30). Thus, the capacity of infection to precipitate ketoacidosis in diabetic patients may be potentiated by concomitant SGLT inhibition. For his lifetime of work in diabetes research, Mirsky received the Banting Medal for Scientific Achievement from the American Diabetes Association in 1965.

Numerous publications throughout the past century reported phlorizin-induced hyperketonemia in various animals. Phlorizin caused marked increases in blood ketone levels in starved rabbits and cats (31). Rats given phlorizin while fasting had acetonemia up to 10 times greater than that in fasting controls; however, phlorizin did not produce additional ketonemia in nephrectomized animals, showing the importance of glucosuria (rather than extrarenal actions) in stimulating ketogenesis (32). Arterial concentrations of acetoacetate and 3-hydroxybutyrate (β-hydroxybutyrate) in fasting rats treated with phlorizin were similar to those seen in diabetic ketoacidosis induced by streptozotocin (33). In the insulinopenic model of alloxan diabetes in the dog, phlorizin administration caused blood pH to decrease to 7.17 (34). Veterinary scientists used phlorizin to induce ketosis in sheep and cattle (35, 36);

these investigators sought insight into gestational and lactational ketosis (debilitating conditions of ruminants), which threatened the dairy industry (37). Phlorizin administration stimulated gluconeogenesis and decreased the circulating insulin–glucagon ratio, thus enhancing the hepatic capacity for ketogenesis while increasing the availability of nonesterified fatty acids, the precursors of ketone bodies (38, 39). These effects were similar to those later described with SGLT2 inhibitors (40, 41).

Renal Glucosuria: The Risk for Ketosis

Familial renal glucosuria is an "experiment of nature" in which mutations in the gene for SGLT2 give rise to varying degrees of impaired reabsorption of renal glucose. The generally benign phenotype of patients with FRG reflects the safety of long-term pharmacologic inhibition of SGLT2. However, George Cahill (1927–2012), former research director of the Joslin Diabetes Center in Boston, appreciated the risk for accelerated ketosis during fasting in persons with genetic renal glucosuria (42). In 1930, Allan and Vanzant wrote of their experience with surgical patients: "In cases of renal glycosuria with excretion of a large amount of sugar (50 gm or more each day) severe acidosis may develop if the diet is restricted" (43).

In another report, a low-carbohydrate diet produced ketonuria and a reduced plasma bicarbonate level in a patient with renal glucosuria. With carbohydrate refeeding, the bicarbonate level increased to within the normal range (44). As early as 1918, physicians recognized that dietary carbohydrate restriction—which caused malaise, listlessness, and weakness, along with strongly positive test results for urinary ketones—proved harmful for patients with FRG (45, 46). A popular review of phlorizin includes a reference to "ketosis during pregnancy or starvation" in FRG (47). Thus, knowledge of the historical literature on renal glucosuria could also have alerted physicians and scientists to the role of SGLT2 inhibition in producing clinically significant ketosis.

The Historical Lessons Not Learned

In reviewing the meeting materials of the FDA's Endocrinologic and Metabolic Drugs Advisory Committee (48, 49) and the FDA drug approval packages for canagliflozin, dapagliflozin, and empagliflozin (50–52), we found no indication that manufacturers or regulators knew of the literature describing ketosis and ketoacidosis associated with phlorizin or FRG. In a slide presentation, the manufacturer of dapagliflozin cited von Mering's discovery of phlorizin glucosuria, but not his subsequent observations of ketosis (53). Preapproval reviewers noted increases in urinary ketone excretion in rodent toxicology studies of empagliflozin (54) and a doubling of serious adverse events of diabetic ketoacidosis among recipients of canagliflozin in clinical trials (55). Neither the manufacturers nor the FDA, however, acknowledged the possibility of a causal role for SGLT2 inhibition. Even as the FDA later prepared to issue a warning about ketoacidosis and mandate changes in the labeling of SGLT2 inhibitors, internal summary documents did not mention either phlorizin or FRG (56, 57).

Apparent unawareness of historical antecedents meant that manufacturers and regulators did not appreciate the implications of the hyperketonemia observed in preclinical studies and phase 2 clinical trials (58–61). In 1 study of 380 patients randomly assigned to receive canagliflozin in dosages of 100 to 200 mg/d, the concentration of circulating total ketone bodies increased to more than 3000 μmol/L in 22 patients and to more than 5000 μmol/L in 6 (62). These values fulfill one of the diagnostic criteria for diabetic ketoacidosis (63). Investigators claimed that these increases had "no apparent explanations" (62) and did not recognize that they represented a notable risk associated with canagliflozin.

To be sure, manufacturers followed classic clinical trial protocols for testing SGLT2 inhibitors. Participants adhered to standard diabetic diets; investigators supervised the use of concomitant medications, including insulin; and, on the basis of our own experiences monitoring clinical trials, we assume that physicians typically withdrew investigational drugs when participants had significant infections or surgery. This meant, however, that these trials avoided study drug administration during fasting, use of diets low in carbohydrates and high in fat, surgical stress, infection, and insulin insufficiency—situations in which phlorizin or FRG had been shown to promote ketosis or ketoacidosis. The result was a low incidence of ketoacidosis reported in registrational studies. A review of randomized clinical trials in the canagliflozin development program showed that dose-related incidence rates of serious adverse events of diabetic ketoacidosis and related events were 0.522 to 0.763 cases per 1000 patient-years among participants receiving canagliflozin versus 0.238 cases per 1000 patient-years in those treated with comparators (64). These small numbers did not highlight the risk to patients receiving the drug in settings other than controlled clinical trials.

In an approach that differed from those used in the published research of Western pharmaceutical companies, investigators in Japan measured increases in blood ketone bodies in response to SGLT2 inhibitors in human participants (60–62). In 2013, Japanese regulatory authorities reviewing ipragliflozin, the first SGLT2 inhibitor to gain their approval, expressed "concern that ipragliflozin may . . . induce acute diabetic complications associated with an increase in ketone bodies in patients with type 2 diabetes mellitus with decreased insulin secretion" (65). They considered an "increase in ketone bodies" to be an important potential risk of SGLT2 inhibitors, including dapagliflozin (66). They ordered that "precautionary statements will be included in the package insert in order to prevent . . . diabetic ketoacidosis" and prescribed additional, postmarketing surveillance of this risk (65, 66). Whether knowledge of the history of phlorizin or FRG also informed their decisions is not known.

Once the reporting of ketoacidosis as an adverse reaction to SGLT2 inhibitors surfaced, investigators did population-based studies to estimate its incidence. In a study of an insurance claims database, the crude incidence rate of diabetic ketoacidosis among new users of SGLT2 inhibitors with type 2 diabetes mellitus was 1.69 cases per 1000 patient-years (67). In a study based on audits of medical records, the incidence of diabetic ketoacidosis developing in the community or during a hospital admission was 1.02 cases per 1000 patient-years among users of SGLT2 inhibitors (68). Clinicians who adhere to conventional diagnostic criteria for diabetic ketoacidosis, which include severe hyperglycemia (69), might not diagnose ketoacidosis or apply this label to cases of euglycemic acidosis in patients treated with SGLT2 inhibitors (70). Thus, these publications may underestimate the overall incidence of ketoacidosis in patients receiving these medications. It is difficult to compare incidence rates across studies, but these population-based rates are nevertheless higher than rates reported for participants in clinical trials (64, 71, 72). This difference likely results from the effects of SGLT2 inhibition in patients whose diets, use of insulin, and concomitant clinical conditions differ markedly from those of clinical trial participants.

It took less than 6 weeks from the approval of the first SGLT2 inhibitor in the United States—canagliflozin on 29 March 2013—for FAERS to receive its first spontaneous postmarketing report of ketoacidosis. In the more than 2 years between the approval of canagliflozin and the FDA's initial Drug Safety Communication, FAERS received more than 150 reports of unique patients who were diagnosed with ketoacidosis or acidosis of unspecified cause after receipt of an SGLT2 inhibitor, including canagliflozin and the subsequently approved drugs dapagliflozin and empagliflozin. Most of the patients were hospitalized, and some episodes were deemed life-threatening (73). Spontaneous reports of adverse drug reactions made voluntarily by health care providers or patients to manufacturers and regulatory authorities are generally regarded as the "tip of the iceberg" of many more patients with these conditions. When the FDA issued its warning in May 2015, the announcement stated that its decision rested on an analysis of 20 cases. By not citing the historical literature, it failed to document the precedent for the association between pharmacologic inhibition or genetic deficiency of SGLT2 and ketoacidosis, which would have substantiated its inference of a causal role for SGLT2 inhibitors.

The story of SGLT2 inhibitor ketoacidosis illustrates how the drug approval process should incorporate historical inquiry. The history of ketoacidosis due to phlorizin or FRG could have been discovered at many points during the evolution of these drugs. The first opportunity arose during early development. Had scientists uncovered the literature pertaining to the ketosis of SGLT2 inhibition, they could have noted it as part of the investigational new drug applications and pursued additional laboratory or clinical investigation. The next opportunity came during submission of the new drug application. A literature review is generally a standard part of scientific and academic research. We could find no evidence that the manufacturers or the FDA did a comprehensive review that revealed the association between phlorizin or FRG and ketosis (48–52, 56, 57).

Additional opportunities for historical inquiry came in the postmarketing phase. Manufacturers who must submit a Periodic Benefit-Risk Evaluation Report or similar documents to regulatory authorities could have looked to history in investigating whether their drug had a causal relationship with reported adverse events. Researchers seeking to understand an adverse drug reaction without an obvious mechanism should focus attention on historical precedent. Advances in artificial intelligence have enabled use of computerized algorithms for such inquiries (74). In addition, regulatory authorities who monitor databases of postmarketing adverse event reports, including FAERS and the World Health Organization's VigiBase, should conduct or sponsor further investigation into the causes of adverse reactions to newly marketed drugs, including evaluating the historical literature.

Had scientists, manufacturers, investigators, or regulators been aware of the historical literature pertaining to ketosis and ketoacidosis with phlorizin and FRG, they might have initiated a more timely warning that could have spared many patients serious illness and obviated the lawsuits that followed. Instead, it took more than 2 years to announce the association between SGLT2 inhibitors and ketoacidosis, illustrating a general principle of medicine: Lack of a complete history can delay diagnosis.

From Seventh Doctor Consulting, Princeton, New Jersey (B.R.L.); Princeton University, Princeton, New Jersey (L.E.G.); and University of Maryland School of Medicine, Baltimore, Maryland (S.I.T.).

Acknowledgment: The authors thank Dr. Viktor Jörgens for drawing their attention to and translating a portion of the writings of Josef Freiherr von Mering.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-1463.

Corresponding Author: Bruce R. Leslie, MD, MSPH, Seventh Doctor Consulting, 213 Carnegie Center #3023, Princeton, NJ 08543; e-mail, seventhdoctor@gmail.com.

Current author addresses and author contributions are available at Annals.org.

References

1. **U.S. Food and Drug Administration.** FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. 15 May 2015. Accessed at www.fda.gov/media/92185/download on 15 July 2019.
2. **U.S. Food and Drug Administration.** FOIA (Freedom of Information Act) request received 16 June 2014.

3. **De Koninck L.** Ueber das phloridzin (phlorrhizin). Annalen der Pharmacie. 1835;15:75-7. Accessed at https://babel.hathitrust.org/cgi/pt?id=hvd.hx3bga&view=1up&seq=87 on 15 July 2019.
4. **Ghezzi C, Loo DDF, Wright EM.** Physiology of renal glucose handling via SGLT1, SGLT2 and GLUT2. Diabetologia. 2018;61:2087-97. [PMID: 30132032] doi:10.1007/s00125-018-4656-5
5. **Achard C, Delamare V.** L'exploration clinique des fonctions rénales par la glycosurie phloridzique. Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris. 1899;16:379-95. Accessed at https://babel.hathitrust.org/cgi/pt?id=iau.31858012030544&view=1up&seq=403 on 15 July 2019.
6. **Rossetti L, Smith D, Shulman GI, et al.** Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J Clin Invest. 1987;79:1510-5. [PMID: 3571496]
7. **Tsujihara K, Hongu M, Saito K, et al.** Na(+)-glucose cotransporter (SGLT) inhibitors as antidiabetic agents. 4. Synthesis and pharmacological properties of 4'-dehydroxyphlorizin derivatives substituted on the B ring. J Med Chem. 1999;42:5311-24. [PMID: 10639275]
8. **McKee FW, Hawkins WB.** Phlorhizin glucosuria. Physiol Rev. 1945;25:255-80. doi:10.1152/physrev.1945.25.2.255
9. **Meng W, Ellsworth BA, Nirschl AA, et al.** Discovery of dapagliflozin: a potent, selective renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. J Med Chem. 2008;51:1145-9. [PMID: 18260618] doi:10.1021/jm701272q
10. **Han S, Hagan DL, Taylor JR, et al.** Dapagliflozin, a selective SGLT2 inhibitor, improves glucose homeostasis in normal and diabetic rats. Diabetes. 2008;57:1723-9. [PMID: 18356408] doi:10.2337/db07-1472
11. **Gallo LA, Wright EM, Vallon V.** Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. Diab Vasc Dis Res. 2015;12:78-89. [PMID: 25616707] doi:10.1177/1479164114561992
12. **Chasis H, Jolliffe N, Smith HW.** The action of phlorizin on the excretion of glucose, xylose, sucrose, creatinine and urea by man. J Clin Invest. 1933;12:1083-90. [PMID: 16694183]
13. **Komoroski B, Vachharajani N, Boulton D, et al.** Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. Clin Pharmacol Ther. 2009;85:520-6. [PMID: 19129748] doi:10.1038/clpt.2008.251
14. **von Mering J.** Beiträge zur kenntniss der antipyretica. Therapeutische Monatshefte. 1893;7:577-87. Accessed at https://babel.hathitrust.org/cgi/pt?id=mdp.39015014692464&view=1up&seq=595 on 15 July 2019.
15. **von Mering J.** Ueber experimentellen diabetes. Verhandlungen des Congresses für Innere Medicin. 1886;5:185-9. Accessed at https://babel.hathitrust.org/cgi/pt?id=uc1.b3737333&view=1up&seq=209 on 15 July 2019.
16. **von Mering J.** Ueber diabetes mellitus. Verhandlungen des Congresses für Innere Medicin. 1887;6:349-58. Accessed at https://babel.hathitrust.org/cgi/pt?id=uc1.b3737334&view=1up&seq=375 on 15 July 2019.
17. **von Mering J.** Ueber diabetes mellitus. Zeitschrift für Klinische Medizin 1889;16:431-46. Accessed at https://babel.hathitrust.org/cgi/pt?id=mdp.39015074013585&view=1up&seq=455 on 15 July 2019.
18. **Lemieux G, Plante GE.** The effect of starvation in the normal dog including the Dalmatian coach hound. Metabolism. 1968;17:620-30. [PMID: 5656978]
19. **Geelmuyden HC.** Ueber die acetonurie bei phloridzinvergiftung. Hoppe-Seyler's Zeitschrift für Physiologische Chemie. 1898;26:381-8. Accessed at https://babel.hathitrust.org/cgi/pt?id=hvd.32044103062006&view=1up&seq=397 on 15 July 2019.
20. **Baer J.** Untersuchungen über acidose. 1. Die acidose beim phlorhizindiabetes des hundes. Archiv für Experimentelle Pathologie und Pharmakologie. 1904;51:271-88. Accessed at https://babel.hathitrust.org/cgi/pt?id=coo.31924057726188&view=1up&seq=289 on 15 July 2019.
21. **von Mering J, Minkowski O.** Diabetes mellitus nach pankreasexstirpation. Archiv für Experimentelle Pathologie und Pharmakologie. 1890;26:371-87. Accessed at https://babel.hathitrust.org/cgi/pt?id=hvd.32044103034237&view=1up&seq=389 on 15 July 2019.
22. **Benedict SR, Osterberg E.** The influence of feeding upon acidosis in the phlorhizinized dog. Proc Soc Exp Biol Med. 1914;12:45. doi:10.3181/00379727-12-27
23. **Allen FM, Wishart MB.** Experimental studies in diabetes series V–acidosis. 5. Acidosis in phlorizinized dogs. Journal of Metabolic Research. 1923;4:223-54. Accessed at https://babel.hathitrust.org/cgi/pt?id=inu.30000113161123&view=1up&seq=241 on 15 July 2019.
24. **Allen FM, Stillman E, Fitz R.** Total dietary regulation in the treatment of diabetes. In: Monographs of the Rockefeller Institute for Medical Research. Monograph 11. New York: The Rockefeller Institute for Medical Research; 1919. Accessed at https://archive.org/details/cu31924104225283 on 15 July 2019.
25. **Wierzuchowski M.** Intermediary carbohydrate metabolism. III. Vital action of glucose in phlorhizin diabetes. J Biol Chem. 1927;73:445-58. Accessed at www.jbc.org/content/73/2/445.short on 15 July 2019.
26. **Ets HN.** Some chemical changes of the blood produced by drugs. III. Phlorhizin. Am J Physiol. 1924;70:240-6. doi:10.1152/ajplegacy.1924.70.2.240
27. **Mirsky IA.** The etiology of diabetic acidosis. JAMA. 1942;118:690-4. doi:10.1001/jama.1942.02830090008002
28. **Mirsky IA, Heiman JD, Broh-Kahn RH.** The antiketogenic action of glucose in the absence of insulin. Am J Physiol. 1937;118:290-6. doi:10.1152/ajplegacy.1937.118.2.290
29. **Mirsky IA, Korenberg M, Nelson N, et al.** The hepatic glycogen reserves in diabetes mellitus. Endocrinology. 1941;28:358-67. doi:10.1210/endo-28-3-358
30. **Mirsky IA.** The etiology of diabetic acidosis. Proceedings of the American Diabetes Association. 1941;1:49-68.
31. **Gammeltoft A.** The significance of ketone bodies in fat metabolism. II. Blood ketone concentration in various animals during starvation and after phlorhizin poisoning. Acta Physiol Scand. 1950;19:280-7. doi:10.1111/j.1748-1716.1949.tb00158.x
32. **Amatruda TT Jr, Engel FL.** The role of the endocrine glands in ketosis. I. The ketosis of fasting. Yale J Biol Med. 1959;31:303-23. [PMID: 13660081]
33. **Ruderman NB, Ross PS, Berger M, et al.** Regulation of glucose and ketone-body metabolism in brain of anaesthetized rats. Biochem J. 1974;138:1-10. [PMID: 4275704]
34. **François R, Guest G.** Diabète alloxanique et phlorizinique acidotique. Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences. 1953;236:238-40. Accessed at https://gallica.bnf.fr/ark:/12148/bpt6k3188h/f238.item on 15 July 2019.
35. **Jackson HD, Burtis CA, Goetsch GD.** Effects of phlorizin and heparin on ketonemia in fasted, nonpregnant ewes. Am J Vet Res. 1966;27:885-90. [PMID: 6007739]
36. **Amaral-Phillips DM, McGilliard AD, Lindberg GL, et al.** Effects of decreased availability of glucose for dairy cows. J Dairy Sci. 1993;76:752-61. [PMID: 8463487]
37. **Shaw JC.** Ketosis in dairy cattle: a review. J Dairy Sci. 1956;39:402-34. doi:10.3168/jds.S0022-0302(56)94765-8
38. **Lyle RR, deBoer G, Mills SE, et al.** Glucose kinetics, plasma metabolites, and endocrine responses during experimental ketosis in steers. J Dairy Sci. 1984;67:2255-64. [PMID: 6389628]
39. **Overton TR, Drackley JK, Ottemann-Abbamonte CJ, et al.** Metabolic adaptation to experimentally increased glucose demand in ruminants. J Anim Sci. 1998;76:2938-46. [PMID: 9856405]
40. **Ferrannini E, Muscelli E, Frascerra S, et al.** Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest. 2014;124:499-508. [PMID: 24463454] doi:10.1172/JCI72227
41. **Merovci A, Solis-Herrera C, Daniele G, et al.** Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest. 2014;124:509-14. [PMID: 24463448] doi:10.1172/JCI70704
42. **Cahill GF Jr.** Fuel metabolism in starvation. Annu Rev Nutr. 2006;26:1-22. [PMID: 16848698]

43. **Allan FN, Vanzant FR.** Renal glycosuria, with ketosis during surgical complications. Am J Med Sci. 1930;180:670-6.
44. **Gorham Babson MDS.** Renal glycosuria: a hereditary and clinical study of one family. J Pediatr. 1940;17:781-90. doi:10.1016/S0022-3476(40)80023-1
45. Current medical literature. 93. Familial renal glycosuria. JAMA. 1918;71:694-5.
46. **Graham G.** My most interesting case. XXII. An early case of renal glycosuria. Practitioner. 1956;177:639-42. [PMID: 13370455]
47. **Ehrenkranz JR, Lewis NG, Kahn CR, et al.** Phlorizin: a review. Diabetes Metab Res Rev. 2005;21:31-8. [PMID: 15624123]
48. **U.S. Food and Drug Administration.** 2011 meeting materials, Endocrinologic and Metabolic Drugs Advisory Committee: July 19, 2011 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. Updated 30 September 2016. Accessed at https://wayback.archive-it.org/7993/20170403223919/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm252891.htm on 15 July 2019.
49. **U.S. Food and Drug Administration.** 2013 meeting materials, Endocrinologic and Metabolic Drugs Advisory Committee: January 10, 2013 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. Updated 2 March 2016. Accessed at https://wayback.archive-it.org/7993/20170403223914/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm331504.htm on 15 July 2019.
50. **U.S. Food and Drug Administration.** Drug approval package: Invokana (canagliflozin) tablets. 27 February 2013. Accessed at www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204042Orig1s000TOC.cfm on 15 July 2019.
51. **U.S. Food and Drug Administration.** Drug approval package: Farxiga (dapagliflozin) tablets. 11 February 2014. Accessed at www.accessdata.fda.gov/drugsatfda_docs/nda/2014/202293Orig1s000TOC.cfm on 15 July 2019.
52. **U.S. Food and Drug Administration.** Drug approval package: Jardiance (empagliflozin) tablets. 8 September 2014. Accessed at www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204629Orig1s000TOC.cfm on 15 July 2019.
53. **U.S. Food and Drug Administration; Bristol-Myers Squibb; AstraZeneca AB.** Slide 17: SGLT2 inhibition: botanical and genetic precursors. In: Slides for the July 19, 2011 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. 22 July 2011. Accessed at https://wayback.archive-it.org/7993/20170404152056/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Endocrinolo.gicandMetabolicDrugsAdvisoryCommittee/ucm264311.htm on 15 July 2019.
54. **Center for Drug Evaluation and Research.** Application no. 204629Orig1s000: pharmacology review(s): Jardiance (empagliflozin). 2013. Accessed at www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204629Orig1s000PharmR.pdf on 15 July 2019.
55. **Center for Drug Evaluation and Research.** Application no. 204042Orig1s000: cross discipline team leader review: canagliflozin. 2013. Accessed at www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204042Orig1s000CrossR.pdf on 15 July 2019.
56. **Chamberlain CE, Niak A.** Pharmacovigilance review: diabetic ketoacidosis as drug related adverse event. Food and Drug Administration; Center for Drug Evaluation and Research; Office of Surveillance and Epidemiology: 24 September 2014. OSE RCM no. 2014-530. FDA FOIA request obtained 21 May 2019.
57. **Chamberlain CE, Bright PL, Mathew J.** Diabetic ketoacidosis and ketoacidosis. Food and Drug Administration; Center for Drug Evaluation and Research; Office of Surveillance and Epidemiology: 15 July 2015. OSE RCM no. 2014-530. TSI no. 1383. FDA FOIA request obtained 16 April 2019.
58. **Devenny JJ, Godonis HE, Harvey SJ, et al.** Weight loss induced by chronic dapagliflozin treatment is attenuated by compensatory hyperphagia in diet-induced obese (DIO) rats. Obesity (Silver Spring). 2012;20:1645-52. [PMID: 22402735] doi:10.1038/oby.2012.59
59. **Yokono M, Takasu T, Hayashizaki Y, et al.** SGLT2 selective inhibitor ipragliflozin reduces body fat mass by increasing fatty acid oxidation in high-fat diet-induced obese rats. Eur J Pharmacol. 2014;727:66-74. [PMID: 24486393] doi:10.1016/j.ejphar.2014.01.040
60. **Inagaki N, Kondo K, Yoshinari T, et al.** Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. Diabetes Obes Metab. 2013;15:1136-45. [PMID: 23782594] doi:10.1111/dom.12149
61. **Kaku K, Watada H, Iwamoto Y, et al; Tofogliflozin 003 Study Group.** Efficacy and safety of monotherapy with the novel sodium/glucose cotransporter-2 inhibitor tofogliflozin in Japanese patients with type 2 diabetes mellitus: a combined phase 2 and 3 randomized, placebo-controlled, double-blind, parallel-group comparative study. Cardiovasc Diabetol. 2014;13:65. [PMID: 24678906] doi:10.1186/1475-2840-13-65
62. **Inagaki N, Kondo K, Yoshinari T, et al.** Efficacy and safety of canagliflozin alone or as add-on to other oral antihyperglycemic drugs in Japanese patients with type 2 diabetes: a 52-week open-label study. J Diabetes Investig. 2015;6:210-8. [PMID: 25802729] doi:10.1111/jdi.12266
63. **Savage MW, Dhatariya KK, Kilvert A, et al; Joint British Diabetes Societies.** Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. Diabet Med. 2011;28:508-15. [PMID: 21255074] doi:10.1111/j.1464-5491.2011.03246.x
64. **Erondu N, Desai M, Ways K, et al.** Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. Diabetes Care. 2015;38:1680-6. [PMID: 26203064] doi:10.2337/dc15-1251
65. **Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau.** Report on the deliberation results: Suglat tablets (ipragliflozin). 10 December 2013. Accessed at www.pmda.go.jp/files/000206796.pdf on 15 July 2019.
66. **Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau.** Report on the deliberation results: Forxiga tablets (dapagliflozin). 7 February 2014. Accessed at www.pmda.go.jp/files/000210230.pdf on 15 July 2019.
67. **Wang Y, Desai M, Ryan PB, et al.** Incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors and other antihyperglycemic agents. Diabetes Res Clin Pract. 2017;128:83-90. [PMID: 28448895] doi:10.1016/j.diabres.2017.04.004
68. **Hamblin PS, Wong R, Ekinci EI, et al.** SGLT2 inhibitors increase the risk of diabetic ketoacidosis developing in the community and during hospital admission. J Clin Endocrinol Metab. 2019;104:3077-87. [PMID: 30835263] doi:10.1210/jc.2019-00139
69. **Kitabchi AE, Umpierrez GE, Miles JM, et al.** Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32:1335-43. [PMID: 19564476] doi:10.2337/dc09-9032
70. **Peters AL, Buschur EO, Buse JB, et al.** Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. Diabetes Care. 2015;38:1687-93. [PMID: 26078479] doi:10.2337/dc15-0843
71. **Jabbour S, Seufert J, Scheen A, et al.** Dapagliflozin in patients with type 2 diabetes mellitus: a pooled analysis of safety data from phase IIb/III clinical trials. Diabetes Obes Metab. 2018;20:620-8. [PMID: 28950419] doi:10.1111/dom.13124
72. **Kohler S, Zeller C, Iliev H, et al.** Safety and tolerability of empagliflozin in patients with type 2 diabetes: pooled analysis of phase I-III clinical trials. Adv Ther. 2017;34:1707-26. [PMID: 28631216] doi:10.1007/s12325-017-0573-0
73. **U.S. Food and Drug Administration.** FOIA (Freedom of Information Act) requests received 16 June 2014–23 June 2015.
74. **Shetty KD, Dalal SR.** Using information mining of the medical literature to improve drug safety. J Am Med Inform Assoc. 2011;18:668-74. [PMID: 21546507] doi:10.1136/amiajnl-2011-000096

Current Author Addresses: Dr. Leslie: Seventh Doctor Consulting, 213 Carnegie Center #3023, Princeton, NJ 08543.
Prof. Gerwin: Program in Law and Public Affairs, Princeton University, 343 Wallace Hall, Princeton, NJ 08544.
Dr. Taylor: University of Maryland School of Medicine, MSTF 357-B, 655 West Baltimore Street, Baltimore, MD 21201.

Author Contributions: Conception and design: B.R. Leslie, L.E. Gerwin.
Analysis and interpretation of the data: B.R. Leslie, L.E. Gerwin.
Drafting of the article: B.R. Leslie, L.E. Gerwin.
Critical revision of the article for important intellectual content: B.R. Leslie, L.E. Gerwin.
Final approval of the article: B.R. Leslie, L.E. Gerwin, S.I. Taylor.
Collection and assembly of data: B.R. Leslie.