Potential Clinical Applications for Continuous Ketone Monitoring in the Hospitalized Patient with Diabetes

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Abstract

Purpose of Review In this review, the authors discuss potential clinical applications for continuous ketone monitoring (CKM) in a broad continuum of clinical settings from pre-hospital care and the emergency department to acute inpatient management and post-discharge follow-up.

Recent Findings Though in its early stages, the concept of a novel continuous ketone sensing technology exerts great potential for use in the detection and hospital management of DKA, namely to overcome diagnostic barriers associated with ketoacidosis in patients with diabetes and obtain real-time BOHB levels, which may be useful in understanding both patients’ response to treatment and DKA trajectory. Peri- and intra-operative use of CKM technology can potentially be applied in a number of urgent and elective surgical procedures frequently undergone by patients with diabetes and in the observation of patients during peri-operative fasting. In transitional care management, CKM technology could potentially facilitate patients’ safe transition through levels of care, following hospital discharge from a DKA episode.

Summary This evaluation of the literature presents the potential advantages of adopting CKM and integrating this technology into the care algorithm of patients at risk for ketoacidosis.

Keywords Diabetic ketoacidosis · DKA · Ketone · B-hydroxybutyrate · Monitor · Diabetes

Introduction

Continuous ketone monitoring (CKM) is a novel form of ketone testing technology which has only recently emerged in the diabetes technology research and development space [1, 2]. CKM sensor technology is based upon the continuous detection of ketone body concentrations, namely B-hydroxybutyrate (BOHB) — the most abundant ketone body present in diabetic ketoacidosis (DKA) [3]. The technological basis for continuously detecting analyte can be compared to existing real-time continuous glucose monitors (rtCGM), which themselves have immensely transformed the therapeutic management and quality of life for patients with diabetes (PWD) [2]. In their novel study, Alva and colleagues test for the first-time the feasibility of a CKM sensor based on wired enzyme technology, in vitro and in humans [1]. The CKM sensor, which detects interstitial fluid (ISF) BOHB levels over the course of a 14-day wear, required only a single retrospective calibration [1]. This novel and early CKM technology introduces a “new paradigm” for the detection of ketone bodies and exhibits potential applications for the detection of diabetic ketoacidosis (DKA) in PWD [2]. DKA is a severe metabolic complication characterized by its D: presence of diabetes, K: ketone body elevation, and A: metabolic acidosis [4]. Though typically seen in patients with type 1 diabetes (T1D), the condition is not exclusive to the former and can occur also in patients with type 2 diabetes (T2D), and in those with ketosis-prone diabetes [5, 6]. In this review, we evaluate current potential clinical applications for
CKM technology, as it applies to the inpatient setting and transitional care.

**Current State of Ketone Monitoring**

Despite their common use in both routine and acute management of the unwell patient with diabetes, urine ketone assays which detect acetocetate (AcAc) via the semi-quantitative nitroprusside reaction are subject to false results. Inappropriate storage conditions (e.g., bathrooms), strips exceeding expiry, or misinterpretation of colorimetric results contribute to their inaccuracy. False negatives can also occur with acidic urine (e.g., ingestion of large quantities of ascorbic acid), whereas sulfhydryl drugs (e.g., captopril) and highly colored urine have been implicated in false positives [3, 7, 8]. Reliance on urine dipsticks for identifying DKA onset and resolution is not ideal, as such tests do not assess for the major ketone implicated in DKA (B-OHB) and can over/underestimate DKA severity due to a “paradoxical” plateau or increase in concentration that occurs even as serum B-OHB clears [3, 7, 8]. Additionally, urine ketone tests depend on the hydration and voiding status of unwell patients who frequently present dehydrated and may have compromised renal function secondary to DKA [9–11]. These challenges along with time-lag in urine output make urine ketone measurement a less accurate reflection of the patient’s current state.

Though urine dipsticks are relatively cost-effective and painless, quantitative tests specific for B-OHB are comparatively more advantageous. Serum B-OHB greater than or equal to 3.8 mmol/L and 3.0 mmol/L in adults and children, respectively, may be used as a diagnostic for DKA in patients with uncontrolled diabetes [5, 12]. Currently, the American Diabetes Association (ADA) defines ketoadicosis as a pH < 7.3, bicarbonate < 18 mEq/L, positive presence of urine/serum ketones (by nitroprusside reaction method), glucose > 13.8 mmol/L, and depending upon severity, altered mental status [5, 10]. When comparing the diagnostic power of these measures, some in the literature have questioned whether serial measurement of blood gas pH (arterial or venous) has a significant impact on DKA management [13]. One novel study demonstrated that blood gas measures infrequently alter the diagnosis and management of patients with suspected DKA, despite the existing guidelines and widespread implementation of these tests [13, 14]. These findings warrant further investigation. Like pH, bicarbonate is also a non-specific parameter frequently used in DKA diagnosis; however, baseline bicarbonate levels in patients with pre-existing acid–base disorders may vary, and values are subject to acute changes secondary to nausea/vomiting and lactate accumulation [12, 15]. In their retrospective study, Sheikh-Ali and colleagues recommend a more precise definition for DKA namely, the criteria stated earlier. The literature largely supports the clinical utility of B-OHB as a quantitative measure, and despite their existing diagnostic criterion, the ADA too has acknowledged this utility, as B-OHB is the main ketone in DKA [5, 16].

Additionally, when compared with a routinely used urinalysis instrument which obtains a semi-quantitative measure of urine ketone bodies via the nitroprusside reaction, one kinetic enzymatic assay (Ranbut B-OHB assay on a Roche Cobas c502 Analyzer) employed in the laboratory setting for quantifying serum B-OHB demonstrated analytical superiority [17]. However, it is worthwhile mentioning that laboratory measurement of B-OHB may take too long and is not always readily available across facilities; hence, lab ketones are neither ideal for emergency workup for DKA nor for patients attempting home-care in sick management [10, 18, 19].

The advent of point-of-care (POC) blood ketone monitors addresses this need for reliable and expedient testing at home and in emergency settings. Sampling capillary blood through fingerstick provides the advantage of quantitative, speedy measure of the main ketone B-OHB, in a device format familiar to PWD (i.e., self-monitoring of blood glucose) [7]. In a retrospective study, Taboulet et al., compared capillary B-OHB measurements and urinary AcAc in the emergency department setting [19]. They determined that capillary B-OHB was the more effective and expeditious option. The study reported a median delay of 21 min between patients’ arrival to the ED and urine stick testing, but in 10% of cases, delays were more than 2 h — a critical lag [19]. The investigators also determined that with fingerstick ketones measuring 3 mmol/L or greater, it is not necessary to await bicarbonate values prior to initiating specific intervention for DKA, a timely heuristic; however, the same does not apply to urine dipsticks even at the maximum reading of three crosses [19].

POC devices measuring B-OHB have the ability to greatly improve home care and prevent progression of hyperketonemia to DKA. In a randomized clinical trial, Laffel and colleagues found assessment of blood B-OHB (via an integrated glucose-ketone monitor) was preferred by young people (3–22 years) with T1D over urine ketones during sick day management [20]. Increased compliance was observed in participants assigned to the blood ketone testing group compared to the urine ketone group during sick days. The former was associated with a significantly lower incidence of acute events (hospitalization and need for emergency assessment) (49% less than the urine ketone group) [20]. This data on efficacy of quantitative testing could reasonably be extrapolated to the adult diabetes population and other at-risk groups. Nevertheless, the study also alludes to the critical nature of patient education as an empowering tool for preventing or interrupting progression to a state
of acute metabolic decompensation from ketosis. Sick-day protocols help patients manage periods of intercurrent illness with actionable steps to prevent or detect impending hyperglycemic crises, thus preventing unnecessary hospitalization [5]. Patients are advised to contact clinicians early, to never discontinue insulin, and test frequently blood glucose and ketones — which can be conveniently and effectively achieved with the use of a bedside meter [5, 7, 21].

B-OHB compared to urine ketone body testing in the acute setting also appears to reduce professional burden and provide cost-reduction advantages [22]. Vanelli et al. evaluated the effectiveness of ketone testing methods (urine vs. BOHB) in pediatric patients diagnosed with T1D at first onset of DKA in the intensive care unit [22]. Quantitative monitoring of B-OHB demonstrated that ketosis in these patients resolved 4 to 9.5 h earlier than patients monitored for urinary ketone bodies (likely as the quantitative measure enabled earlier recording of ketosis resolution) [22, 23]. As a result, time for further clinical assessment and associated costs were saved.

Recent advancements have also explored the use of acetone, the third of the three physiologic ketone bodies, as a biomarker for DKA. Generated from the spontaneous decarboxylation of AcAc, acetone is excreted renally or through exhalation — the latter explains the characteristic “fruity” breath of patients in ketoacidosis and provides the basis for breath ketone testing [3, 24]. Qiao et al. assessed the feasibility of using acetone as a clinical biomarker by comparing acetone concentration (ppmv) from exhaled breath (determined via gas chromatography-mass spectrometry) against reference concentrations of blood B-OHB [25]. Sensitivity and specificity were determined to be 90.9% and 77.1%, respectively, and concentrations were significantly correlated with other markers of DKA [25]. For the hand-held sensors; however, the efficacy and technical performance of these newer technologies has yet to be validated and requires more in-depth clinical testing. However, successful performance could provide a more convenient, painless, and streamlined method of quantifying ketones.

**CKM in the Detection and Inpatient Management of DKA**

Continuous ketone monitoring has the potential to guide early pre-hospital intervention by emergency response teams and outpatient clinicians, at the level of ambulatory care. Here, a CKM device could provide emergency medical technicians (EMTs), suspecting DKA, with clear trends and basic threshold alarms that verify or rule-out the possibility of DKA. Evidence of rising ketones could prompt EMTs to begin necessary IV administration of isotonic fluids, modelling established emergency medicine protocols for fluid administration [26]. It would be valuable for these ambulatory CKMs to have secondary-end users based in the hospital (e.g., on-call diabetes specialists) who could potentially assist in optimizing treatment and improve inpatient outcomes.

For patients presenting to the emergency department with acute hyperglycemia and suspected DKA, the initial screening for ketones commonly occurs via urine dipstick, followed by further laboratory assessment on positive screens [27]. Despite being painless and relatively inexpensive, urine ketone tests present a number of key diagnostic limitations and accuracy concerns which diminish their value as a diagnostic tool for DKA [7]. Urine ketone tests based on the nitroprusside reaction provide semi-quantitative color-based results and detect only acetoacetate (AcAc), as opposed to B-hydroxybutyrate — the predominant ketone in DKA [3, 7]. This is clinically significant, as the ratio of BOHB:AcAc can rise as high as 10:1 (normal being 1:1) in severe DKA [3]. Furthermore, the semi-quantitative color results can be subject to false visual interpretation, which in the case of an interpreted false negative, may delay diagnosis and timely treatment. As patients with DKA often present with dehydration and diminished urine output, the time to next void could also delay urine collection/assessment of ketones and thus necessary treatment [7].

Point-of-care (POC) devices measuring distinctly BOHB levels have been compared to urine ketone tests in the ED [28]. In one cross-sectional retrospective study of pediatric diabetes patients presenting to the ED, BOHB measurements were observed to discriminate strongly for DKA and served as an accurate predictor for this serious condition [28]. Similarly, while point-of-care BOHB and urine dipstick testing were observed to be equally sensitive in DKA detection (98.1%) among adult ED patients, the former exhibited much greater specificity (78.6% for BOHB vs. 35.1% for urine dipstick) [27]. The same study described that full laboratory workups evaluating for DKA in their study sample could have been reduced by 56.9%, had BOHB been measured over urine ketones [27]. It is reasonable to assume such cost and resource expenditure associated with full laboratory workup could have been equally eliminated with the use of a reliable CKM technology. Additionally, whereas laboratory-based ketone analysis may take longer to process, CKM devices could avoid diagnostic delay and reduce the initial DKA determination time. While POC devices are certainly the superior alternative to urine tests, CKM would present to clinicians and designated end-users the added benefit of observing continuous real-time trends, as opposed to episodic values — which may be tested for sporadically — and meet the time-dependent needs necessary to reverse the potentially life-threatening condition that is DKA [1]. Interstitial fluid (ISF) BOHB measured by the CKM sensor, employed in Alva and colleagues’ feasibility
study, against the reference POC-capillary BOHB strip measurements (performed at least 8 times per day across the 14-day wear period) were well-correlated [1].

CKM devices could also be used to inform key decisions in the therapeutic inpatient management of DKA and gauge severity. Continuous real-time BOHB data could reveal the trajectory of DKA and the patient’s response to treatment, which according to current ADA guidelines, consists of insulin drip, fluid therapy, and electrolyte correction, namely potassium [5]. A key clinical endpoint for the first two interventions is reduced ketone synthesis which could be detected via CKM [29]. In one study, Orsini-Federici et al. demonstrated that following the restoration of an interrupted insulin infusion, capillary BOHB recovers significantly faster than blood glucose [30]. As insulin response aligns with reduction in BOHB levels, devices which prioritize and continuously measure BOHB, would enable clinicians to gauge treatment efficacy in real-time. The CKM sensor tested by Alva and colleagues demonstrated a quick response time to ketone concentration changes (< 4 min), where sequentially added ketone aliquots of 1 mM produced step responses at 1, 2, 3, 4, 6, and 8 mM [1]. Furthermore, the sensors demonstrated a linear response ($R^2=0.9994$) against ketone concentration, and good sensor stability with a total signal loss of 2.1% across a 14-day period of wear. Preliminary data from this study demonstrated the feasibility of measuring ISF ketones continuously via a CKM sensor [1].

As DKA resolves with treatment, BOHB is converted via oxidation back to AcAc, thereby increasing the presence of AcAc in urine [7]. This “paradoxical increase” in urine ketones is not an indication of worsening ketoacidosis, but of lowering plasma BOHB levels. In such instances, results from urine ketone assays based on the nitroprusside reaction could be misconstrued for treatment inefficacy and potentially lead to overtreatment with insulin and subsequent hypoglycemia [7]. A reliable CKM device could avoid such challenges associated with recognition of DKA resolution by providing clear trends in BOHB (e.g., steady fall in concentration) signaling treatment efficacy at ketone concentrations consistent with DKA resolution.

Furthermore, the hospital management of pediatric patients admitted with DKA as first presentation for diabetes diagnosis in children can result in functional and morphologic alterations to the brain [33, 34]. Prompt integration of a CKM-device into the hospital care and management of pediatric patients presenting with DKA at diagnosis would enable clinicians to carefully and effectively address the characteristic differences inherent to pediatric DKA patients compared to adults; namely, challenges associated with history-taking, delayed diagnosis of diabetes (which prolongs symptom duration), and active prevention of cerebral edema (the most common cause of death in pediatric patients with DKA) [35, 36]. A reliable CKM device would enable clinicians to closely and continuously track BOHB, which along with other clinical signs and biochemical analytes, could guide precise and adequate treatment with insulin and IV-fluids [36].

**CKM in Intraoperative and Perioperative Care**

**Emergency Surgery**

Another potential use case for CKM is in the perioperative and intraoperative care environment. It has been well established that PWD often develop multiple comorbidities including but not limited to cardiovascular disease (CVD), chronic kidney disease (CKD), hypertension, and hyperlipidemia [37, 38]. Thus, the requirements for surgery are increased within the diabetes population [39]. Comorbid CVD, in particular, places PWD at an elevated risk of myocardial infarction (MI) and cerebrovascular accident (CVA) [40, 41]. Such adverse cardiovascular events necessitate emergency intervention and timely surgery. It has been noted that patients’ metabolic stress response to surgery and general anesthesia can be a major precipitating factor for DKA, which itself contributes to elevated rates of morbidity and mortality in PWD following emergency surgery [39, 42]. Intraoperatively, stress-induced release of counter-regulatory hormones (epinephrine, glucagon, cortisol, growth hormone) effectively attenuates insulin activity [43]. Impaired pancreatic B-cell function conferred by surgical stress can also occur, further promoting a state of insulin-resistance. The resultant metabolic state lifts the insulin-induced inhibition of glycogenolysis, B-oxidation, and ketone body synthesis, and if left unaddressed can facilitate hyperglycemia and ketonemia characteristic of DKA [39]. Careful monitoring of key metabolites in PWD (namely BOHB) during and following emergency surgery is thus vital for the prompt recognition and treatment of impending DKA. CKM devices could potentially alert anesthesiologists and perioperative care teams to upward trends in BOHB and guide early intervention.
Furthermore, the likelihood of developing surgical site infections (SSIs) is increased in patients with diabetes [44]. As infection is known to precipitate DKA, simultaneous monitoring for sign of infection and abnormal ketone levels via CKM could mitigate acute metabolic decompensation [4]. Hyperglycemia is also associated with impaired wound healing and increased risk of infection, especially in post-operative cardiac surgery patients [43, 45]. In non-cardiac surgery patients, hyperglycemia also yields poorer patient outcomes and increased risk of developing infection [46]. Simultaneous monitoring for ketones and serum glucose in such instances would be greatly beneficial.

Other conditions which warrant emergency surgery in patients with diabetes where CKM could prove valuable include the acute abdomen, necrotizing fasciitis (NF), and the diabetic foot [47, 48]. As the abdominal manifestation of DKA resembles that of acute abdomen, improper workup may lead to unnecessary emergency surgery [4, 44, 49]. This presents an instance where pre-operative continuous monitoring of ketones with a CKM device could serve a valuable preemptive role to differentiate among pathology with similar presentation. Data output from the device could be followed up and further verified with radiological assessment [50].

**Elective Surgery**

**Bariatric Surgery**

Obesity is an established risk-factor for the development of T2DM. Both the extent of obesity as well as the site of fat accumulation can predispose individuals to metabolic syndrome, a cluster of metabolic abnormalities characterized by insulin resistance, hyperlipidemia, and hypertension [51]. Increased visceral adiposity or abdominal fat (large waist circumference, elevated BMI, endomorphic body type) in particular, enhances diabetogenic risk and is observed in many patients with T2D [52, 53]. Targeting and surgically modifying the gastrointestinal tract, a site of metabolic regulation, via bariatric surgery (weight-loss surgery, metabolic surgery), has been deemed a powerful tool to treat both obesity and associated T2D [54]. Mechanisms of achieving weight-loss and metabolic control vary and appear procedure-dependent [55]. In most cases, surgery produces significant weight-loss, improved glycemic control, and extended periods of T2D remission [56, 57].

Despite its high efficacy and utility, bariatric surgery has been observed to precipitate post-operative DKA in PWD and poses a significant potential use-case for CKM in both perioperative monitoring and transitional care. One study by Aminian et al. evaluated the clinical features of post-bariatric surgery DKA [58]. A total of twelve patients were assessed, all of whom developed DKA within 90 days post-surgery and at a median interval of 12 days between surgery and DKA onset. Six of the patients underwent laparoscopic Roux-en-Y, four of the patients underwent laparoscopic sleeve gastrectomy, and two underwent laparoscopic adjustable gastric banding. Eight patients had T1D, while four had T2D, and it was noted that all patients had poor preoperative glycemic control. One patient experienced two post-operative episodes of DKA, presenting with abdominal symptoms (pain, nausea, vomiting), and three patients had a prior history of DKA. It is worth noting that eight patients were adjudicated to have received inadequate insulin therapy/were non-adherent, and three of those patients developed DKA prior to hospital discharge. The study concluded that precipitating factors of post-bariatric surgery DKA include inadequate treatment with insulin or abruptly discontinued insulin therapy around the time of surgery, infection following surgery, severe dehydration, prolonged poor oral intake, and the effects of anesthesia and surgical stress [58]. In such circumstances, the continuous intra-perioperative surveillance of ketone levels via CKM could aid in the early recognition of progressing ketosis and guide expedient interventions (e.g., insulin therapy optimization) which may reduce the likelihood of developing post-operative complications like acute DKA.

Bariatric surgery is also associated with incidences of euglycemic DKA (EDKA), namely in patients taking sodium-glucose cotransporter 2 inhibitors (SGLT-2i). Though the mechanism has not been fully elucidated, it is widely recognized that PWD on oral SGLT-2i’s (e.g., canagliflozin) can develop EDKA [59]. Andalib and colleagues first reported post-bariatric surgery EDKA in patients taking SGLT-2i’s [60]. A number of other literature sources confirm this finding [61–63]. In such cases where patients develop DKA in the absence of elevated glucose (EDKA), DKA may initially be overlooked due to its “atypical presentation” and pose certain diagnostic challenges [59, 60]. It is reasonable to conclude that patients, whose particular diabetes phenotype responds favorably to ongoing treatment with SGLT-2i’s, would benefit from continuous monitoring of ketones intra-/perioperatively via CKM. Alerting care teams to rising ketones, incident at near-normoglycemic levels, could help overcome any diagnostic barriers associated with EDKA in an expedient, real-time manner. Integration of CKM into daily wear as a prophylaxis could prove beneficial to these high-risk patients, and potentially serve as a method of indirectly monitoring therapeutic safety of SGLT-2i’s in patients with T2D. Similarly, this prophylactic use for CKM could apply to instances where patients are on other diabetogenic medications, namely corticosteroids, various antipsychotic agents, and thiazide diuretics [5].

Rizo and Apovian describe a case in which post-bariatric surgery DKA occurred in a patient whose phenotype was neither categorically T1 nor T2, but was rather...
ketosis-prone diabetes mellitus (KPDM) [64]. Continuous monitoring for BOHB perioperatively in these such patients could also prove valuable.

**Other Elective Surgery**

Other routinely performed elective surgeries in PWD, include elective orthopedic surgery (e.g., total joint replacement). Oftentimes, preoperative management involves omission of diabetes medications and insulin which may perturb glucose homeostasis and result in transient hyperglycemia, augmenting the risk for DKA [65]. Poor glycemic control is known to contribute to elevated risk of surgical site infection (SSI) following orthopedic surgery, where infection itself enhances DKA risk [66, 67]. One study by Hikata et al. reported that poor preoperative glucose control (HbA1c ≥ 7.0%) was associated with a greater rate of developing SSI following thoracic and lumbar spinal arthrodesis compared to those with controlled diabetes (HbA1c < 7.0%) [68]. In the aforementioned study, 0.0% of patients with controlled diabetes developed SSI, whereas compared to 35.3% of patients with uncontrolled diabetes [68]. As infection may precipitate DKA, simultaneous monitoring of serum glucose and BOHB via CKM may prove particularly beneficial for PWD undergoing orthopedic surgery. Evaluating and classifying patients preoperatively according to their risk profile for DKA could be a useful determinant for CKM use intra/peroperatively and for a variety of elective surgical procedures.

**Perioperative Fasting**

CKM would also be valuable in PWD during periods of perioperative fasting, where in some cases oral intake is restricted at least one day following surgery [69]. Starvation ketoacidosis (SKA) caused by prolonged preoperative starvation and insufficient carbohydrate intake has been documented in non-diabetic surgical patients, and ketoacidosis following periods of prolonged fasting has been observed in patients with diabetes [70–72].

Due to a variety of reasons (e.g., surgical delay), prolonged starvation prior to surgery is not uncommon and could have consequences for the diabetes patient, as it may amplify the metabolic perturbance and insulin resistance associated with surgical stress [44, 73]. In such cases, progressing and unaddressed ketonemia could potentially exacerbate intra-/post-operatively and precipitate DKA. Hence, CKM could be a valuable tool to monitor ketone body levels, alongside fasting blood glucose levels, perioperatively.

**CKM in Transitional Care**

Patients may benefit from CKM at the level of transitional care, following hospital discharge. Transitional care management (TCM) comprises a variety of services which aim to promote the safe movement of patients across levels of healthcare, namely from the hospital to the patient’s community setting [74, 75]. The Transitional Care Components and Measures Workgroup (TCCMW) define a core aspect of transitional care as, “a critical element of traditional medical care, community-based services, and non-traditional services provided by the healthcare team that patients and caregivers should receive to promote positive health outcomes throughout periods of acute illnesses extending from hospital to home.” [76]. Among the goals of transitional care include reducing avoidable hospital readmission and the cost expenditure associated with preventable readmissions [76]. In most cases, DKA is largely considered an avoidable adverse incident, where proper diabetes management could prevent acute syndrome and recurrent DKA. It has been documented that incidence of recurrent DKA is associated with fragmentation of care [77]. Thus, ensuring safe transitions across levels of care could be greatly beneficial to patients with history of DKA. Reliable CKM devices could potentially play a significant role in this aspect of preventive medicine.

An evidence-based criterion for the use-case of CKM in transitional care would need to be developed and rigorously tested; however, a preliminary use-case could be aimed towards high-risk, recently-discharged patients with diabetes; namely, post-bariatric surgery patients, elderly patients admitted for a DKA episode and returning to the nursing home, patients with recurrent DKA, and adolescents or adults with psychiatric illness [58, 78–80]. In each instance, CKM settings could potentially be modified to designate caretakers, guardians, and primary care physicians as end-users, providing access to data that would enable early recognition/treatment of ketoacidosis.

At a time when the US healthcare system continues to transition from fee-for-service reimbursement to value- and quality-based care, high-risk care management resources are in growing demand to help address the complex needs of patients at time of discharge from the acute care setting. The COVID-19 pandemic has introduced an even greater demand for remote patient monitoring (RPM) of recently-hospitalized high risk patients [81, 82]. In RPM, CKM devices could potentially be used to streamline provider access to pertinent health data (BOHB levels) without any increased burden to patients (e.g., frequent doctor visits). CKM could play a vital role in augmenting multidisciplinary care provided to these patients with greatest need, and potentially be incorporated into various
high-risk care management programs which aim to track patients’ health outcomes, mitigate cost, and facilitate the attainment of health goals [83].

Conclusion

In summary, continuous ketone monitoring via CKM technology has many potential clinical applications, namely in the inpatient setting and transitional care management. The development of a reliable CKM technology could play a significant role in early DKA detection upon first presentation in the ED, by providing clinically-relevant BOHB data which itself is superior to the semi-qualitative nitroprusside-based urine data that are widely used. Real-time data output could aid in the inpatient management of DKA, approximation of DKA severity/trajectory, and also demonstrate valuable trend data which may inform clinicians to the patient’s treatment response. Furthermore, CKM presents a valuable potential use-case in the inpatient management of pediatric patients presenting with DKA at time of diabetes diagnosis. There are applications for CKM in the intraoperative and perioperative settings, as a method of detecting progressing ketosis or DKA conferred by surgical stress, anesthesia, infection, and peri-operative fasting. Distinctions for intra/perioperative CKM-use can be determined for patients undergoing emergency surgery and elective surgery. As bariatric surgery in particular is associated with DKA incidence, it would be valuable to tightly monitor ketones in patients following weight-loss surgery. Furthermore, the use of CKM following orthopedic surgery could enable perioperative care teams to detect any DKA associated with risk of SSI. CKM in transitional care would enable recently discharged diabetics, at high risk for DKA, to engage in preventive medicine, potentially participate in high-risk care management programs and remote patient monitoring, and safely receive continuous care across various levels of healthcare. Despite its great potential use, presently, there is a major dearth in the documented work on continuous ketone monitoring. Rigorous testing and further clinical study in the diabetes population, especially, is necessary to evaluate safety and efficacy in patients. The logistics of device design, the size of the sensor, threshold for alarms, feasibility of integrating multi-analyte sensors into a single CKM device, are among the many facets of this fascinating technology that need to be determined prior to any patient use. Nevertheless, this is an exciting and novel subset of ketone testing technologies which can reframe existing guidelines and treatment algorithms for DKA to potentially optimize patients’ quality of life and outcome.

Data Availability

No new datasets were generated or analyzed in this study.

Conflict of Interest

MJ has nothing to declare. JM is a consultant and a speaker of Medtronic on diabetes; he is also consultant of MannKind, Inc.; and a grant recipient of Dexcom, Inc.

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