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EDITORIAL

Current and future impact of clinical gastrointestinal research on patient care in diabetes mellitus

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Abstract

The worldwide rise in the prevalence of obesity supports the need for an increased interaction between ongoing clinical research in the allied fields of gastrointestinal medicine/surgery and diabetes mellitus. There have been a number of clinically-relevant advances in diabetes, obesity, and metabolic syndrome emanating from gastroenterological research. Gastric emptying is a significant factor in the development of upper gastrointestinal symptoms. However, it is not the only mechanism whereby such symptoms occur in patients with diabetes. Disorders of intrinsic pacing are involved in the control of stomach motility in patients with gastroparesis; on the other hand, there is limited impact of glycemic control on gastric emptying in patients with established diabetic gastroparesis. Upper gastrointestinal functions related to emptying and satiations are significantly associated with weight gain in obesity. Medications used in the treatment of diabetes or metabolic syndrome, particularly those related to pancreatic hormones and incretins affect upper gastrointestinal tract function and reduce hyperglycemia and facilitate weight loss. The degree of gastric emptying delay is significantly correlated with the weight loss in response to liraglutide, a glucagon-like peptide-1 analog. Network meta-analysis shows that liraglutide is one of the two most efficacious medical treatments of obesity, the other being the combination treatment phentermine-topiramate. Interventional therapies for the joint management of obesity and diabetes mellitus include newer endoscopic procedures, which require long-term follow-up and bariatric surgical

procedure for which long-term follow up shows advantages for individuals with diabetes. Newer bariatric procedures are presently undergoing clinical evaluation. On the horizon, combination therapies, in part directed at gastrointestinal functions, appear promising for these indications. Ongoing and future gastroenterological research when translated to care of individuals with diabetes mellitus should provide additional options to improve their clinical outcomes.

Key words: Obesity; Gastric emptying; Diabetes mellitus; Gastric bypass; Bariatric surgery; Weight loss

Core tip: The worldwide prevalence of obesity continues to rise. Delayed gastric emptying and impaired gastric accommodation result in upper gastrointestinal symptoms, through intrinsic nerve and pacemaker dysfunction. Glycemic control has a limited effect on gastric emptying in diabetic gastroparesis. Treatment of diabetes with pancreatic hormones and incretins inhibits gastric emptying, reduces hyperglycemia, and facilitates weight loss. Meta-analysis shows that glucagon-like peptide-1 analog, liraglutide, is one of the two most efficacious treatments of obesity. Bariatric surgery and endoscopic interventions are efficacious in diabetes and obesity, but long term follow-up is required for endoscopic interventions as well as for newer bariatric procedures. On the horizon, combination therapies directed at gastrointestinal function appear promising for these indications.

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INTRODUCTION

In a recent international study of 195 countries, the prevalence of obesity doubled in more than 70 countries since 1980[1]. This worldwide rise in the prevalence of obesity supports the need for an increased interaction between ongoing clinical research in fields of gastrointestinal medicine/surgery and diabetes mellitus. There have been a number of clinically-relevant advances in diabetes, obesity and metabolic syndrome, emanating from gastrointestinal research. These advances include newer information in pharmacological or medical care, endoscopic procedures, and bariatric surgical procedures.

The most exciting gastrointestinal research areas relevant to diabetes are focused on the stomach and on weight loss, with the goals of resolution of hyperglycemia and/or prevention of secondary complications of diabetes mellitus. Ongoing studies have focused on the stomach because patients with diabetes develop upper gastrointestinal symptoms, including the syndrome of gastroparesis. In addition, pharmacological treatments and bariatric procedures directed to the stomach have been the most efficacious treatments of obesity. Some of these clinical gastrointestinal research observations are considered likely to impact patient care in diabetes mellitus and/or obesity and may thus lead to improved patient outcomes.

OBSERVATIONS RELATED TO UPPER GASTROINTESTINAL SYMPTOMS AND GLYCEMIC CONTROL IN DIABETES MELLITUS

Delayed stomach emptying is associated with upper gastrointestinal symptoms

Based on a systematic review of the literature, including 92 gastric emptying studies (26 breath test, 62 scintigraphy, 1 ultrasound, and 3 wireless motility capsule) there is an association between optimally measured delayed gastric emptying and upper gastrointestinal symptoms[2]. Twenty-five of these studies provided quantitative data for meta-analysis (15 scintigraphy studies enrolling 4056 participants and 10 breath test studies enrolling 2231 participants). Evaluating the studies that used optimal gastric emptying test methodology, there were significant associations between gastric emptying and nausea, vomiting, abdominal pain, and early satiety/fullness in patients with upper gastrointestinal symptoms; gastric emptying and early satiety/fullness in patients with diabetes; and gastric emptying and nausea in patients with gastroparesis.

Gastric motor functions and other features in referred patients with diabetes with upper gastrointestinal symptoms

Among 108 adult patients with diabetes mellitus (60.2% females; median age 49.0 years; 71.3% with type 2 diabetes mellitus; one-third insulin dependent with median hemoglobin A1C 6.7%) presenting with upper gastrointestinal symptoms, the manifestations of diabetic triopathy (peripheral neuropathy, nephropathy, and retinopathy) were uncommon at the time of presentation[3]. Nausea was the most common symptom (80.6%). Gastric emptying was rapid in 37% and slow in 19%. Gastric accommodation was abnormal in 39%. There was normal gastric accommodation and gastric emptying in 28% and 40.3% of the patients with type 2 diabetes mellitus had accelerated gastric emptying at one hour. These observations emphasize the importance of measuring these functions in patients with upper gastrointestinal symptoms in order to individualize treatment, such as with a dopamine D_2 antagonist or a 5-hydroxytryptamine receptor (5-HT_4) agonist for patients with delayed gastric emptying and a 5-HT_{1A} agonist in patients with impaired gastric accommodation.

Histopathological features and expression in the intrinsic mechanisms involved in gastric motor functions

In different morphological studies based on light microscopy examination of full-thickness gastric biopsies and immunofluorescence, there is evidence of reduction in the pacemaker cell repertoire (interstitial cells of Cajal[4,5] and fibroblast-like cells positive for platelet-derived growth factor alpha[6]), reduced numbers of neurons expressing nNOS[4], and reduced numbers of M2 macrophages, which normally express the mannose receptors (CD206) and heme oxygenase-1, mediate cell repair, and have anti-inflammatory roles[5]. Other studies show increase in CD68 immunocytes, suggesting immune-mediated damage to these pacing mechanisms[6], and this may be aggravated in the presence of vagal denervation, a common sequel of longstanding type 1 diabetes mellitus. Normally, the efferent vagus nerve signals release of norepinephrine from splenic nerves, activating the β2-adrenergic receptor expressed on T cells, and macrophages and other immune cells, suppressing the release of pro-inflammatory cytokines[7]. In summary, the interplay of vagal neuropathy, intrinsic neuropathy and immune modulation are considered combination factors leading to the gastric motility disorder.

Role of hyperglycemia in diabetic gastroparesis

The role of hyperglycemia in diabetic gastroparesis is unclear. On the one hand, there is epidemiological evidence of association of glycemia with upper gastrointestinal symptoms[8], documentation of poor glycemic control in 36% patients admitted to the hospital for exacerbations of diabetic gastroparesis[9], kidney and pancreas transplants improve gastric emptying and associated gastrointestinal symptoms[10]. Conversely, hemoglobin A1C was not a statistically significant predictor of abnormal (compared to normal) gastric emptying of solids in a study of 129 patients[11], and long-term blood glucose control had no significant effect on gastric emptying in type 2 diabetes mellitus[12].

Role of stomach emptying on glycemic control

The available literature suggests that the stomach emptying does have an impact on glycemic control, and not only in patients with gastroparesis. Some published reports confirm the notion that gastroparesis impacts glycemic control: (1) patients with gastroparesis as documented in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort, gastroparesis was associated with relatively worse glycemic control, as assessed by glycosylated hemoglobin[13]; (2) there is poor glycemic control in 36% patients admitted to the hospital for exacerbations of diabetic gastroparesis[9]; and (3) in insulin-treated patients with gastroparesis, delayed gastric emptying may increase the potential for a mismatch the timing of exogenous, preprandial, insulin and the actual delivery of nutrients such as glucose from the stomach to be absorbed from in the small intestine. In a study involving 11 type 1 patients, less insulin was required to achieve euglycemia during the first 120 min after a meal in the 5 with gastroparesis, and more between 180-240 min[14]. In addition, there is also evidence that the rate of gastric emptying has a major impact on the glycemic response to carbohydrate-containing meals in health and diabetes, particularly the initial postprandial increment[15]. Therefore, it is now appreciated that postprandial glycemic excursions make a major contribution to "overall" glycemic control as assessed by hemoglobin A1C. Delayed gastric emptying in type 1 diabetes has recently been reported to be associated with an overall increase in blood glucose during the day; this may reflect the mismatch between the preprandial insulin and the later absorption of food due to the delayed gastric emptying[16].

OBSERVATIONS RELATED TO GASTROINTESTINAL HORMONES IN OBESITY

Role of gastric emptying in the beneficial effects of GLP-1 analogs

Liraglutide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist, is approved for treatment of obesity; however, the mechanisms of action of liraglutide are incompletely understood and include increase in satiety, increase in resting energy expenditure, and direct effects on appetite centers in the brain[17]. In a randomized, double-blind, placebo-controlled trial of subcutaneous liraglutide (3.0 mg) in 40 patients at Mayo Clinic, liraglutide delayed gastric emptying of solids at 5 wk and 16 wk, and there was significantly greater weight loss and lower volume of a nutrient drink to reach the maximum tolerated volume in the liraglutide group than in the placebo group. The effects of liraglutide on weight loss are associated with delay in gastric emptying of solids, and the measurement of gastric emptying (*e.g.*, at 5 wk of treatment) may be a biomarker of responsiveness and may help to select individuals for prolonged treatment with this class of drug[18].

The effect of GLP-1 receptor agonist on weight loss does not appear to be impacted by the presence of metabolic derangements such as type 2 diabetes. However, there is evidence of a significant correlation in the weight loss induced by liraglutide and delay of gastric emptying[18].

Incretin combinations for obesity

Incretin and pancreatic hormones [*e.g.*, amylin, glucagon, glucose-stimulated insulinotropic peptide (GIP), GLP-1 and peptide tyrosine tyrosine (PYY)] generally inhibit upper gastrointestinal motor function[19] or secretion (*e.g.*, oxyntomodulin). Moreover, many of these hormones also exert central effects that reduce appetite[20], and some

Table 1 Bariatric endoscopic procedure

Intraluminal devices
Intragastric balloon
Orbera[a]
ReShape[a]
Obalon[a]
Duodeno-jejunal bypass sleeve (EndoBarrier)
Aspiration therapy (AspireAssist)
Intraluminal suturing
Endoscopic sleeve gastroplasty
Transoral gastroplasty

[a]In order of date approved by United States Food and Drug Administration.

(*e.g.*, GLP-1 analogs or GLP-1 receptor agonists) are efficacious in the treatment of obesity[21].

Several combined incretin hormones have been tested in the context of obesity. Co-administration of GLP-1 with glucagon in humans increased energy expenditure and reduced food intake[22,23]. A unimolecular dual incretin consisting of PEGylated GLP-1 and GIP co-agonist maximized metabolic benefits in rodents, monkeys, and humans[24].

The combination of GLP-1 and PYY_{3-36} also exerts synergistic effects with a reduction of 30.4% of food intake compared to placebo and more than the sum of each hormone independently, suggesting a synergistic effect[25]. Acute, continuous, subcutaneous infusion for 10.5 h/d of GLP-1, PYY, and oxyntomodulin (summarized as GOP) was administered at doses that replicate postprandial levels observed after Roux-en-Y gastric bypass in a placebo-controlled, crossover study. GOP reduced food intake with a mean reduction of 32% without significantly altering resting energy expenditure[26].

Combined bariatric endoscopy with pharmacotherapy

One study compared the effects of an intragastric balloon in 64 patients compared to a combination of balloon plus liraglutide, up to 1.8 mg/d, in 44 patients matched for body mass index (BMI) at baseline[27]. The mean weight loss after balloon removal was 8.3 kg greater in the balloon plus liraglutide group than in the balloon alone group, and the advantage persisted 6 mo post-balloon removal in the group receiving liraglutide[27].

BARIATRIC ENDOSCOPIC PROCEDURES

The development of endoscopic interventions for treatment of obesity and diabetes mellitus has focused on two areas (Table 1), the placement of intraluminal devices and intraluminal suturing[28,29].

Intraluminal devices

The first intragastric balloon, the Garren-Edwards bubble, was approved by the United States Food and Drug Administration in 1985. The United States Food and Drug Administration has now approved 3 separate intragastric balloon systems in the past 3 years: The Orbera balloon, the ReShape balloon, and the Obalon balloon. Delayed gastric emptying has been identified as a mechanism for weight loss in individuals who have undergone insertion of a fluid-filled intragastric balloon[29], which raises the question of their utility in individuals with diabetic gut autonomic neuropathy. After the intraluminal balloons are removed, individuals required a maintenance program (which has not yet been standardized) to prevent weight regain. Our previous concern[29] that specialized training is needed for the use of these devices appears to be supported by three warnings (in February 2017, August 2017, and June 2018) from the United States Food and Drug Administration with regards to issues related to intragastric balloons including multiple deaths related to intragastric balloons. Two major reviews in the past two years examined the 30+ year experience with intragastric balloons[30,31]. Brethauer *et al*[30] concluded that more study was required in patients with type 2 diabetes mellitus. Popov *et al*[31] concluded that intragastric balloons were more effective that diet alone for an initial improvement of metabolic risk factors, but that their conclusions are limited by the small number of participants and the lack of long-term follow-up data.

Some countries have the availability of a duodeno-jejunal bypass sleeve, termed the EndoBarrier. This impermeable fluoropolymer sleeve with a nitinol anchor is deployed from the duodenal bulb and into the jejunum under fluoroscopic and endoscopic guidance. A clinical trial of this device in the United States in individuals with diabetes mellitus was halted early due to the development of liver infections. Three studies involving the EndoBarrier in individuals with type 2 diabetes mellitus have been published in the past one year. Betzel *et al*[32] were able to implant the device in 185 out of 198 participants. Sixty-nine percent of the participants were able to complete a one year program prior to removal of the device. Hemoglobin A1C levels declined by a mean of 9%, but no long term data was available. Forner *et al*[33] reported their findings in 114 individuals who maintained an EndoBarrier for a mean of 51.1 wk after its placement; the authors reported that mean Hemoglobin A1C was not significantly improved but that 6 subjects developed device obstructions, 5 individuals had gastrointestinal hemorrhage, 2 individuals developed liver abscesses, and 1 individual developed acute pancreatitis. Patel *et al*[34] reported a multicenter trial involved EndoBarrier Placement in 45 individuals with type 2 diabetes. Thirty-one individuals (69%) completed the 12 mo study. The mean hemoglobin A1C reduction at 12 mo was 0.8% below baseline. After explant, these subjects were only followed for an additional 6 mo.

The AspireAssist (Aspire Bariatrics, King of Prussia, Pennsylvania, United States) was approved by the United States Food and Drug Administration in 2016. A specialized aspiration tube (with both an intragastric portion with holes to permit aspiration as well as a skin port) is placed percutaneously at upper endoscopy into an individual's stomach. Stomach contents are then

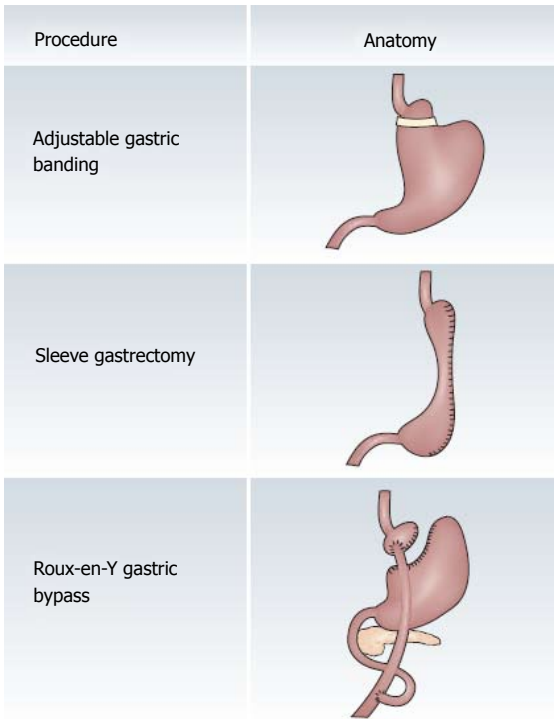

Figure 1 Comparison between bariatric surgical procedures. The top cartoon depicts the adjustable gastric band which limits the types of food consumed postoperatively by patients. The middle cartoon depicts the vertical sleeve gastrectomy which limits the volume of food consumed postoperatively by patients. The lower cartoon depicts the Roux-en-Y gastric bypass which limits volume of food consumed, may alter absorption of macronutrients, and alters release of intestinal incretins (Reproduced with the permission of Nature Publishing Group from Bal *et al*. *Nature Rev Endocrinol* 2012; **8**: 544-556).

aspirated 20 min after a meal containing more than 200 kcal. A recent European trial examining the aspiration tube described a decrease in Hemoglobin A1C from 7.8% at baseline to 6.8% at only 1 year post-placement and mean percent weight loss of 19.2% at 4 years post-placement[35].

As described above, long-term weight loss and metabolic results are not available for these endoscopic devices. Therefore their role in the treatment of obese individuals with diabetes mellitus remains to be defined.

Intraluminal suturing

Formation of an endoscopic sleeve gastroplasty or a transoral gastroplasty has been described by using intraluminal suturing devices during upper endoscopy. The Mayo Clinic, Rochester, Minnesota United States reported a method in 2013 for an endoscopic sleeve gastroplasty. This procedure involves the use of a commercially available suturing device (OverStitch, Apollo Endosurgery, Austin, Texas United States), and the endoscopic sleeve gastrectomy is the predominant intraluminal technique presently described in the literature. Development of an endoscopic procedure to mimic the surgical vertical sleeve gastrectomy could reduce the risks of a gastric leak or perforation and of general anesthesia. However, results from the surgical literature support the importance of obtaining long-term weight loss data. When the Mayo Clinic, Rochester, Minnesota, United States reported their results from the surgical non-banded vertical gastroplasty, only 31% of patients were judged to have persistent excess weight lost after 4 years[36]. A proposed mechanism for weight loss after the endoscopic sleeve gastrectomy is slowing of gastric emptying, which raises the question of its utility in individuals with diabetic gut autonomic neuropathy. Further research should better define the potential long-term role of intraluminal suturing in weight loss and the treatment of obese individuals with diabetes mellitus.

BARIATRIC SURGERY

Bariatric surgical procedures

The well described and worldwide utilized bariatric surgical procedures[37] include the adjustable gastric band, the vertical sleeve gastrectomy, and the Roux-en-Y gastric bypass (Figure 1). By 2014, there were 579000 yearly bariatric surgical procedures of which 45.9% were the vertical sleeve gastrectomy, 39.6% were the Roux-en-Y gastric bypass, and 7.4% were the adjustable gastric band[38]. The adjustable gastric band systems now use a soft, silicone ring which is placed around the upper part of the stomach approximately 4 cm below the gastroesophageal junction and is connected to an access port by tubing to adjust the band volume. Restriction of the proximal stomach is altered by addition or removal of sterile saline through the access port and there is no cutting or stapling of the stomach or bypass of small intestine. The vertical sleeve gastrectomy or gastric sleeve resection can be completed with a single step restrictive operation. By resection of 60% to 80% of the stomach along the greater curvature, multiple staplers can produce a tubular gastric pouch. Weight loss after vertical sleeve gastrectomy appears to involve several potential mechanisms in addition to restriction in the size of meal portions[39]. In the Roux-en-Y gastric bypass, there is complete division of native stomach with production of a gastric pouch of less than 30 mL. The surgeon divides the jejunum 30 to 70 cm distal to the junction of the duodenum with the jejunum. The location of the jejuno-enteric anastomosis determines the lengths of the Roux limb (*e.g.*, the gastric pouch to the jejuno-enteric anastomosis) and the common channel (*e.g.*, the jejuno-enteric anastomosis to the ileocecal valve). A common channel that is shorter than 120 cm can induce a severe malabsorptive disorder. The mechanisms of weight loss after gastric bypass are complex and can include upper gut bacterial overgrowth, a common intestinal disorder in individuals with diabetes mellitus, as well as glucose malabsorption[40]. Studies of glucose malabsorption after gastric bypass are of interest because jejunal administration of glucose appears to suppress plasma levels of the orexigenic hormone, acyl ghrelin[41]. Further studies of the mechanisms of weight loss after bariatric surgery are clearly important since a proportion of individuals have poor long-term weight loss[42].

Table 2 Long term weight loss after bariatric surgery

Ref.	Study[a]	Type of surgery[b]	Follow up	Result (%)[1]
[52]	MA	AGB	⩾ 10 yr	EWL: 47.4
[52]	MA	VSG	⩾ 5 yr	EWL: 53.2
[52]	MA	RYGB	⩾ 10 yr	EWL: 63.5
[44]	MCS	AGB	15 yr	MWL: 13.0
[44]	MCS	RYGB	15 yr	MWL: 27.0
[53]	SCS	VSG	8 yr	EWL: 67.0
[54]	SCS	VSG	8 yr	EWL: 51.1
[55]	MCS	VSG	10 yr	EWL: 70.5
[56]	SR	AGB	3-5 yr	EWL: 45.0
[56]	SR	VSG	3-5 yr	EWL: 64.5
[56]	SR	RYGB	3-5 yr	EWL: 65.7

[a]MA: Meta-analysis; MCS: Multi-center study; SCS: Single-center study; SR: Systematic review; [b]AGB: Adjustable gastric band; VSG: Vertical sleeve gastrectomy; RYGB: Roux-en-Y gastric bypass; [1]EWL: Mean percentage excess weight loss; MWL: Mean weight loss.

Long term mortality after bariatric surgery

The potential importance of bariatric surgery in individuals with diabetes mellitus was well publicized following a 2007 report that after a mean follow up of 7.1 years, individuals who underwent gastric bypass surgery had a 40% decrease in their adjusted long-term mortality (but by 92% for diabetes) compared to the control group[43]. This landmark study has been supported by a report of decreased mortality compared to usual care at 16 years in the Swedish Obese Subjects trial[44]. In a national study from Israel, bariatric surgery at a mean follow up of 4.5 years was shown to lower all-cause mortality compared to usual care obesity management[45]. Finally, in a recent examination of the American National Health and Nutrition Examination Survey, it was reported that bariatric surgery can result in a relevant reduction of mortality in the United States obese population[46].

Long term weight loss after bariatric surgery

Evaluation of the results reported for the different major bariatric surgical procedures may vary dependent upon whether single center data or multicenter data is examined. The largest discrepancy appears in reports concerning the adjustable gastric band, which may in part explain its decreased worldwide utilization. Several major reports in the past one year have supported major weaknesses of the adjustable band. In a single center report from Switzerland, after over 10 years of follow up, 71% of patients had lost their gastric band and only 15% of patients had good to excellent results[47]. In a French national study of 52868 patients up to 7 years after adjustable gastric banding, the band removal rate was about 6% per year[48]. In a study from the state of New York, among 16444 patients who underwent adjustable gastric banding, with at least four years of follow up the rate of revisions/conversions was 26.0%[49]. An early meta-analysis reported that bariatric surgery does result in a weight loss of 20 to 30 kg, which is maintained for up to 10 years[50]. A follow up meta-analyses in 2013 by Gloy and associates reported in a shorter follow up that individuals allocated to bariatric surgery lost a mean of 26 kg more body weight[51]. Representative reports of long-term weight loss after bariatric surgery are summarized in Table 2. The most effective bariatric surgical procedure for weight loss at up to 15 years of post-operative follow up is the Roux-en-Y gastric bypass surgery[44,52]. The least effective major bariatric surgical procedure in long term studies of weight loss is the adjustable gastric band[44,52,56].

Long term control of diabetes mellitus after bariatric surgery

A joint statement by international diabetes organizations supports consideration of bariatric surgery in individuals with diabetes mellitus and: BMI ⩾ 40 kg/m^2, BMI 35-39.9 kg/m^2 and inadequate control of hyperglycemia with optimal medical therapy, or BMI 30-34.9 kg/m^2 and inadequate control of hyperglycemia with oral or injectable medications[59]. In the United States, individuals with diabetes mellitus considering bariatric surgery are evaluated if they fulfill National Institutes of Health criteria, which is a BMI of ⩾ 35 kg/m^2, while in other countries individuals with diabetes and a BMI as low as 25 kg/m^2 may be considered for Roux-en-Y gastric bypass. Specific bariatric surgical procedures such as the vertical sleeve gastrectomy may not be effective for treatment of individuals with type 1 diabetes mellitus[60]. A meta-analysis comparing non-surgical treatment for obesity with bariatric surgery concluded that individuals allocated to bariatric surgery had a higher remission rate of type 2 diabetes[51]. A second meta-analysis with 5 years of follow-up confirmed a significant decline in the relative risk of diabetes after bariatric surgery[61]. Representative reports of long-term control of diabetes mellitus after bariatric surgery are summarized in Table 3. The most effective bariatric surgical procedure for remission of diabetes mellitus at up to 6 years of post-operative follow up is the Roux-en-Y gastric bypass surgery[56,62]. The least effective major bariatric surgical procedure in long term studies of remission of diabetes mellitus is the adjustable gastric band[56,62]. The importance of remission of diabetes is supported by a report of decreased incidence of microvascular and macrovascular complications in post-operative bariatric patients compared to controls[58]. These published results do support the importance of ongoing development of more effective bariatric surgical procedures for the treatment of individuals with obesity and type 2 diabetes mellitus.

BARIATRIC PROCEDURES UNDER DEVELOPMENT

Gastrointestinal surgeons who specialize in bariatrics have seen an improvement in weight related comorbidities for decades. Encouraged by mounting evidence of resolution

Table 3 Long term control of diabetes mellitus after bariatric surgery

Ref.	Type of study[a]	Surgery[b]	Follow up	Result[1]
[53]	SCS	VSG	8 yr	NoRMRxDM: 43.4%
[54]	SCS	VSG	8 yr	NoRMRxDM: 37%
[56]	SR	AGB	3-5 yr	NoRMRxDM: 28.6%
[56]	SR	RYGB	3-5 yr	NoRMRxDM: 66.7%
[57]	SCS	RYGB	9 yr	NoRMRxDM: 73%
[58]	MCS	AGB	15 yr	NoRMRxDM: 38%
[58]	MCS	RYGB	15 yr	NoRMRxDM: 35%
[62]	NPBCS	AGB	6 yr	NoRMRxDM: 32%
[62]	NPBCS	VSG	6 yr	NoRMRxDM: 41%
[62]	NPBCS	RYGB	6 yr	NoRMRxDM: 58%
[63]	SCS	AGB	10 yr	NoRMRxDM: 18%

[a]SCS: Single-center study; SR: Systematic review; MCS: Multi-center study; NPBCS: Nationwide population-based cohort study; [b]AGB: Adjustable gastric band; VSG: Vertical sleeve gastrectomy; RYGB: Roux-en-Y gastric bypass; [1]NoRMRxDM: No requirement for medical therapy for diabetes mellitus.

or substantial improvement in diseases such as diabetes mellitus, hyperlipidemia, and hypertension, leaders in the field created a paradigm shift by renaming the American Society of Bariatric Surgery as the American Society of Metabolic and Bariatric Surgery in 2007 (ASMBS.org; accessed on July 15, 2018). Gastrointestinal surgeons continue to manipulate the gastrointestinal tract in an effort to maximize the physiologic benefit to the individual patient. Restrictive procedures (*i.e.*, vertical sleeve gastrectomy, adjustable gastric banding, and the largely abandoned vertical banded gastroplasty) provide a benefit usually in proportion to the absolute weight loss achieved. Newer endoscopic and surgical procedures including the intragastric balloon, vBloc (described below), and aspirational therapy have more modest results.

Procedures that combine restriction with malabsorption by bypassing a portion of the foregut and midgut do provide measurable changes in comorbid conditions out of proportion to absolute weight loss. The traditional "gold standard" of surgical weight loss procedures, the Roux-en-Y gastric bypass, can provide rapid glucose control for patients. This procedure may take advantage of the "foregut hypothesis" that bypassing the foregut reduces or suppresses the secretion of anti-incretin hormones, which in turn leads to improvement of blood glucose control[64]. Proponents of the "hindgut hypothesis" feel this improvement is more likely secondary to rapid delivery of nutrients to the distal small intestine, which facilitates the release of hormones such as GLP-1[64,65]. Procedures which take advantage of this scenario include the biliopancreatic diversion/duodenal switch. Based upon these previous observations and notions, more recent modifications to this malabsorption procedure have shown favorable results in treatment of metabolic diseases, with up to 4 years of follow up[66,67]. Further refinements in these procedures will likely yield more promising results which may be able to be individualized for specific patient needs.

Another area of ongoing, active clinical research has been vagal nerve stimulation, based on the important role the vagus nerve plays in regulation pathways involving short-term regulation of dietary intake. The therapy termed vBloc for Vagal BLOCking therapy (ReShape Lifesciences, San Clemente, California United States) uses intermittent intra-abdominal high-frequency electrical currents for vagal blocking. At laparoscopy, electrodes are placed on the two vagal trunks near the gastroesophageal junction. There is no anatomical modification and an external controller is used to program the device. Vagal nerve stimulation with vBloc in a 2 year study has shown promise for weight loss (mean of 21% of excess weight loss), but with only an marginal impact on diabetes (only a 0.3% decline in hemoglobin A1C)[68]. Further evaluation is therefore required to determine which patients with obesity and diabetes mellitus may benefit from this bariatric procedure.

CONCLUSION

The worldwide prevalence of obesity continues to rise. This rise increases the incidence of type 2 diabetes mellitus with subsequent requirements for additional health care in countries across the world. This supports the need for an increased interaction between ongoing clinical research in the allied fields of gastrointestinal medicine/surgery and diabetes mellitus. Among the clinically-relevant advances in diabetes, obesity, and metabolic syndrome emanating from gastroenterological research, delayed gastric emptying and impaired gastric accommodation result in upper gastrointestinal symptoms, through intrinsic nerve and pacemaker dysfunction. Glycemic control has a limited effect on gastric emptying in diabetic gastroparesis. Treatment of diabetes with pancreatic hormones and incretins inhibits gastric emptying, reduces hyperglycemia, and facilitates weight loss. The GLP-1 analog, liraglutide, is one of the two most efficacious treatments of obesity. New bariatric endoscopic procedures have been developed for weight loss in individuals with obesity, but long term follow-up with regards to maintenance of weight loss and control of hyperglycemia in individuals with diabetes is required prior to mass introduction of these endoscopic interventions. Bariatric surgical procedures are efficacious

in diabetes and obesity, but a proportion of individuals have poor long-term weight loss after bariatric surgery. On the horizon, combination therapies directed at gastrointestinal function and newer bariatric surgical procedures appear promising for individuals with obesity and type 2 diabetes mellitus.

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EDITORIAL

Unhealthy eating habits around sleep and sleep duration: To eat or fast?

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Abstract

Traditionally, breakfast skipping (BS), and recently late-night dinner eating (LNDE), have attracted attention in public health because they can predispose to cardiometabolic conditions such as obesity and type 2 diabetes. Intriguingly, it has become evident that short duration of sleep elicits similar health risks. As LNDE, BS, and short sleep can be closely related and can aggravate each other, these three should not be considered separately. In this context, LNDE (or its equivalents, snacking or heavy alcohol consumption after dinner) and BS may be representative unhealthy eating habits around sleep (UEHAS). While it is important to take energy in the early morning for physical and intellectual activities, attaining a fasting state is essential for metabolic homeostasis. Our previous UEHAS studies have shown that BS without LNDE, *i.e.*, BS alone, is not associated with obesity and diabetes, suggesting the possibility that BS or taking a very low energy breakfast, which could yield fasting for a while, may prevent obesity and diabetes in people with inevitable LNDE. Further studies considering UEHAS and short sleep simultaneously are needed to elucidate the effects of these unhealthy lifestyles on cardiometabolic diseases.

Key words: Breakfast skipping; Late-night dinner eating; Sleep; Fasting; Hungry

Core tip: Breakfast skipping (BS), late-night dinner eating (LNDE), and short duration of sleep have attracted attention because they elicit similar health risks: Obesity and type 2 diabetes. However, to-date these factors have been considered separately in terms of their health risks. LNDE and BS may be representative unhealthy eating habits around sleep

(UEHAS). It is important to take energy in the early morning, whereas attaining a fasting state is essential for metabolic homeostasis. Therefore, BS or taking a very low energy breakfast may prevent obesity and diabetes in people with LNDE. Consideration of UEHAS and short sleep deserves further study.

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MAIN CONTENT

Traditionally, breakfast skipping (BS) has been considered to contribute to various cardiometabolic conditions including obesity and type 2 diabetes not only in children and adolescents, but also in adults including the elderly[1-5]. However, conflicting results have been reported[6-8], probably because definitions of breakfast and BS have not been established yet[9,10]. Multiple confounding factors, including age, sex, morbidities, and dietary culture, may also affect the outcomes, although these confounders are usually statistically adjusted for. Moreover, for the past decade, it has been argued that BS may result from conditions in the preceding night, such as late-night dinner eating (LNDE), eating snacks after dinner, or drinking alcohol until immediately before going to bed[11-15].

Simultaneously, the quality and quantity of sleep, which usually manifest as short or long duration of sleep, may affect conditions in the early morning such as appetite for the breakfast meal[16-19]. Of note, short duration of sleep has been robustly associated with similar cardiometabolic conditions to those associated with BS and LNDE, such as obesity, diabetes, and metabolic syndrome, as well as increased mortality[20-23]. Taken together, the effect of short sleep on the above health risks may include the effect of BS, and vice versa. However, short sleep (or possibly long sleep) and BS have rarely been considered together. Circadian misalignment may be prevalent in individuals with LNDE, BS, and short sleep. Because LNDE, BS, and short sleep can be closely related and can aggravate each other[9,11,13,15], these three factors should not be considered separately in terms of health and cardiometabolic conditions. In this context, LNDE and BS may be representative unhealthy eating habits around sleep (UEHAS) (Figure 1). Taken together, specific features can form when UEHAS and short sleep (UEHASs) are combined because of the relationships between them, whereas sleep and UEHAS are sufficiently independent in individuals with good sleep and healthy eating-habits around sleep (SHEHAS).

It is reasonable to assume that BS prolongs the fasting state and results in a lack of energy in the morning, which can result in hampered physical and intellectual activities and possibly in larger meal consumption later in the day[9,24], though conflicting outcomes have been reported[25-28]. However, this theory may be exclusively applicable to healthy people without LNDE, *i.e.*, those who do not take dinner late at night. Of note, LNDE may be associated with hyperglycemia[12,29-31], which remains until early morning. A time period of less than 6 h from LNDE to the end of a short sleep falls short of the 8-10 h criteria commonly used for overnight fasting[32,33], although the definition of overnight fasting has not been definitively established. Theoretically, therefore, LNDE within 2 h of going to bed combined with a short (< 6 h) sleep does not yield a fasting state in the early morning. If people with LNDE sleep for a normal length of time, the opportunity for breakfast consumption may be missed because they do not have enough time to take a breakfast meal (Figure 1).

As mentioned by numerous experts, it is important to take energy in the early morning for healthy physical activity, whereas attaining a fasting state for a certain period in the day, usually during sleep because sleep involves equal or lower energy expenditure than resting energy expenditure[34,35], is essential for metabolic homeostasis. Adequate fasting especially during sleep can enable plasma glucose to return to the preprandial level and plasma insulin to decline to baseline level, which prevents over-secretion of insulin and has a protective action for β-cell function in the pancreas. Having an appetite, *i.e.*, a feeling of hunger, for breakfast may be inappropriate if the body is not in a fasting state (etymologically, taking a breakfast without fasting beforehand does not constitute a break of fasting). Consumption of breakfast without adequate fasting may lead to an absence of the fasting state throughout the day, which results in sustained hyperglycemia and elevated insulin secretion.

Meanwhile, in view of the time course, LNDE can affect the quantity and the quality of the following sleep[36,37], which may in turn affect the conditions of the next morning, *i.e.*, eating breakfast. Studies concerning the effect of LNDE on sleep are limited and the underlying mechanisms remain poorly understood. LNDE can deteriorate circadian rhythms and the secretion of leptin, peptide-YY, melatonin, orexins, and ghrelin[38-41]. LNDE, which can result in sleep with a full stomach, may cause gastroesophageal reflux disease[42,43] and reduced diet-induced thermogenesis[38,44], both of which reduce the quality of sleep. Additionally, higher circulation volumes consisting of a large volume of water and high concentrations of sodium and glucose in the trunk circulation may burden the heart, vessels, and kidney, possibly resulting in arrhythmia and incidents of proteinuria, as observed in our previous studies[11,45].

Shorter time periods between dinner and sleep, and between sleep and breakfast, can intensify the plausible effect of the postprandial condition after LNDE on sleep and the effect of poor sleep on breakfast, respectively (Figure 1). In addition, LNDE may affect conditions in the early morning after wakeup, especially when the duration

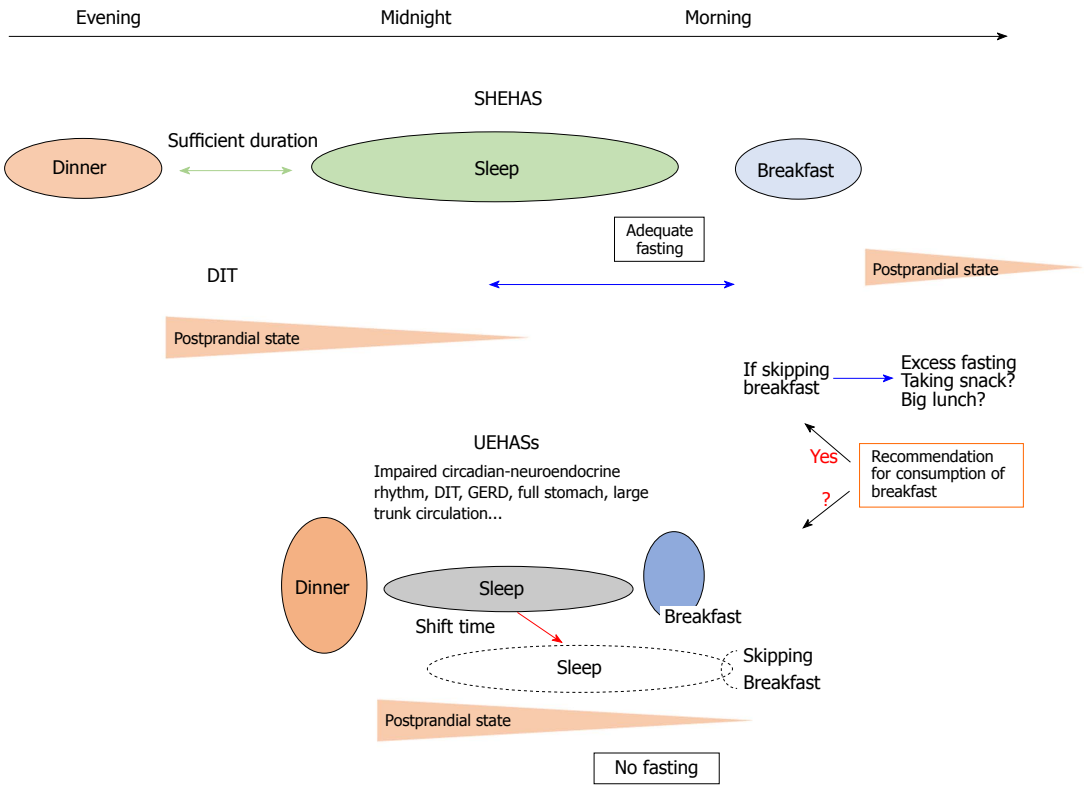

Figure 1 Comparison between unhealthy eating-habits around sleep and short sleep and sleep and healthy eating-habits around sleep. Sufficient time periods exist around sleep and sufficient fasting occurs before the breakfast meal in sleep and healthy eating-habits around sleep (SHEHAS), but not in unhealthy eating-habits around sleep and short sleep (UEHASs). If individuals with late-night dinner eating (LNDE) delay their bedtime to allow for a certain time period before sleep, or prolong the duration of sleep, the opportunity for taking a breakfast may be missed owing to delayed wakeup. DIT: Diet-induced thermogenesis; GERD: Gastroesophageal reflux disease.

of sleep is shorter. Therefore, it is best to refrain from LNDE for a healthy sleep and for optimal conditions in early morning. However, if it is impossible to prevent LNDE because of compulsory shift work or family/individual reasons, the dinner should have less energy and consist of a small amount of easy-to-digest ingredients. Alternatively, instead of completely skipping breakfast, consumption of a very low-calorie meal of less than 200 kcal including water, minimum minerals, and vitamins[46,47] may be an effective option for avoiding potential fasting and adverse reactions such as hypoglycemia and dehydration. Simultaneously, healthy sleep habits may be necessary for conditions the next morning.

Our previous UEHAS cross-sectional studies[11,12] have shown that BS without LNDE, *i.e.*, BS alone, was not associated with obesity or diabetes. Therefore, these results suggest a paradoxical possibility that BS or taking a very low energy breakfast might prevent obesity and diabetes in people with habitual LNDE. Otherwise, hunger, but not fasting, occurs throughout the day in individuals with LNDE. It is possible that BS or taking a smaller breakfast in children with LNDE[13] may be a natural physiological response that manages to avoid the sustained metabolic abnormalities such as hyperglycemia caused by LNDE.

Importantly, the timing of meals substantially affects peripheral clocks existing in multiple organs, including liver, adrenal gland, stomach, intestines, pancreas, kidney, heart, and lungs[48-50]. Therefore, UEHAS may disrupt the peripheral circadian rhythm and thereby affect the central circadian rhythm, regulated by a master circadian clock located in the suprachiasmatic nucleus of the anterior hypothalamus, *via* irregular secretion of hormones including cortisol, ghrelin, leptin, insulin, glucagon, and glucagon-like peptide-1[48]. This metabolic feedback can be mediated through so-called circadian-endocrine cross-talk[49]. In particular, LNDE may enhance the desynchrony between the peripheral and central circadian rhythms, possibly by shortening the duration of sleep, besides unfavorable effects of LNDE on the secretion of incretins. Intriguingly, plasma insulin has been reported to be fundamentally regulated by pancreatic autonomous circadian oscillators, independent of the suprachiasmatic nucleus[51]. In this regard, however, the composition of a meal, for instance the proportion of energy as carbohydrate, can also affect the peripheral circadian rhythm because insulin is usually secreted in in greater quantities following a carbohydrate rich meal. This topic therefore warrants further study.

In conclusion, taking a breakfast is recommended primarily for people without LNDE to take sufficient energy for intellectual and physical activities in the morning (Figure 1). In contrast, taking a breakfast, especially of a full amount, may not be recommended

for people with habitual LNDE to allow them to attain a fasting state for a certain period per day. However, a well-considered meal for late-night dinner or breakfast can ameliorate the conditions above and the metabolic abnormalities in people with LNDE and/or BS, in harmony with the autonomous circadian-endocrine system. Health professionals such as physicians and dieticians should carefully consider individuals' backgrounds and chrono-nutrition, and UEHASs. Further integrated studies are needed to elucidate the effects of eating behaviors and sleep on health and cardiometabolic diseases in view of scientific and public interests.

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FIELD OF VISION

Circadian rhythms of hormone secretion and obesity

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Abstract

The adipose tissue homeostasis is profoundly affected by circadian rhythms of corticosteroid secretion and chronic loss of hormonal oscillations is associated with obesity. How adipose tissue differentially responds to pulsatile *vs* continuous presence of glucocorticoids is poorly defined. To address this question, Bahrami-Nejad *et al* studied differentiation of pre-adipocytes, containing endogenously tagged CCAAT/enhancer binding protein and peroxisome proliferator-activated receptor (PPAR) γ (key regulators of adipocyte differentiation), in response to corticosteroids that were delivered either in an oscillatory fashion or continuously. The authors show that the bi-stable state of differentiation of pre-adipocytes and adipocytes was regulated by a combination of fast and slow positive feedback networks, that determined unique threshold of PPARγ in these cells. Evidently, pre-adipocytes used the fast feedback loop to reject differentiation cues of oscillating pulses of glucocorticoids and failed to differentiate into fat cells. In contrast, when glucocorticoids were delivered continuously, precursor cells exploited the slow feedback loop to embark on a path of maximal differentiation. This differential differentiation response of pre-adipocytes to pulsatile *vs* continuous exposure to glucocorticoids was corroborated *in vivo*. Thus, mice receiving non-oscillating doses of exogenous glucocorticoids, for 21 d, elicited excessive accumulation of visceral and subcutaneous fat. These data shed new light on the mechanisms of obesity caused by putative misalignment of circadian secretion of glucocorticoids or their persistently high levels due to chronic stress or Cushing's disease.

Key words: Circadian rhythms; Glucocorticoids; Adipose tissue; Pre-adipocytes; Stem cells; Terminal differentiation

Core tip: Bahrami-Nejad *et al* examined pre-adipocytes for their ability to differentiate into fat cells in response to hormonal stimuli that were presented either in a pulsatile manner, mimicking circadian rhythms, or delivered continuously. These experiments revealed that

adipocyte differentiation program, made up of slow and fast feedback circuits, was able to distinguish between the oscillating and continuous hormonal signals. The authors showed that pre-adipocytes apparently used the fast, positive feedback network to reject the oscillating hormonal cues. In contrast, if delivered continuously, similar strength glucocorticoids impinged on the slow positive feedback circuit to trigger maximal differentiation of pre-adipocytes into bone fide fat cells. The pulsatile *vs* continuous hormone stimuli were similarly discriminated *in vivo* since mice receiving glucocorticoids in a non-oscillating manner for 21 d elicited increased accumulation of subcutaneous and visceral fat. These data elucidate a potential mechanism underling the development of obesity associated with chronic stress or Cushing's disease.

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COMMENTARY ON HOT TOPICS

Disturbance of diurnal rhythms of day and night, as experienced by night-shift workers, has been linked to obesity and type 2 diabetes mellitus. However, the mechanistic connection between circadian misalignment and obesity are poorly defined. Persistent interruption of diurnal rhythms leads to dysfunctional patterns of secretion of hormones, including corticosteroids, which adversely affect many tissues that include the adipose tissue.

Circadian secretion of glucocorticoids is pivotally involved in the mechanisms of adipose tissue homeostasis[1]. Adipocyte stem cells, pre-adipocytes, embedded in the subcutaneous and visceral adipose tissues comprise about 20% of the cell population[2]. Although pre-adipocytes are exposed to diurnal pulses of glucocorticoids, their terminal differentiation occurs at a very slow rate. For instance, in healthy humans, on a given day, approximately 1% pre-adipocytes embark on the process of differentiation which is completed in about 12 d[3]. This behavior of pre-adipocytes is even more puzzling since these cells mount a robust, dose-dependent differentiation response to glucocorticoids *in vitro*. Sustained non-pulsatile exposure to glucocorticoids, as occurs during chronic stress or in patients with Cushing's disease, leads to the development of visceral obesity[4-6]. This raises an important mechanistic question: How does the machinery of adipocyte differentiation distinguish between the physiological (diurnal glucocorticoid oscillations) and pathological (persistently high glucocorticoid levels) presence of glucocorticoids? This question was recently addressed by Bahrami-Nejad *et al*[7] *via* a series of elegant *in vitro* and *in vivo* experiments. To further supplant brief methodological and conceptual description contained in my FOV commentary, motivated readers should consult the original publication and its' Graphical Abstract.

The cellular and molecular underpinnings of how pre-adipocytes differentiate into bona fide fat cells have been studied in model cell lines and in stem cells isolated from adipose[3]. These studies, facilitated by methods of molecular biology, quantitative mass spectrometry and single cell imaging, combined with computer modeling, indicate that differentiation of pre-adipocytes into adipocytes involves key cell-intrinsic elements and their interactions with hormones such as glucocorticoids, insulin, ghrelin, and others. It is also evident from these studies that unique gene expression signatures distinguish pre-adipocytes from bone fide fat cells; apparently, these bi-stable phenotypes are maintained by unique thresholds of CCAAT/enhancer binding protein α (CEBPA) and peroxisome proliferator-activated receptor γ (PPARG). A positive feedback loop between CEBPA and PPARG is thought to interact with additional feedback networks to induce adipocyte differentiation in response to different hormonal inputs[8]. Hierarchical interactions among putative gene regulatory networks and their temporal regulation during *de novo* adipogenesis are poorly defined.

Since unique thresholds of PPARG and CEBPA proteins are thought to distinguish pre-adipocytes from bona fide fat cells[8,9], Bahrami-Nejad *et al*[7], created a clone of murine pre-adipocytes (OP9 cells) that harbored fluorescently tagged *CEBPA* and *PPARG* genes. These model pre-adipocytes enabled the authors to simultaneously monitor the expression of *CEBPA* and *PPARG* and their relationship with a progressive emergence of canonical markers of adipocyte differentiation[10] in live cells, over a period of several days. When cultured in medium (DMI) containing a cocktail of differentiation inducing factors (1 μmol/L of dexamethasone, 250 μmol/L of IBMX and 1.75 nmol/L of insulin) OP9 cells (and stromal vascular fraction-associated primary pre-adipocytes) vigorously differentiated into mature fat cells. Progressively longer exposure to either dexamethasone (a synthetic glucocorticoid) or corticosterone (a physiological corticosteroid), for 12, 24, 36 and 48 h, induced a correspondingly larger fraction of pre-adipocytes to differentiate. However, when glucocorticoid-containing DMI was presented in oscillating pulses, only a small fraction of pre-adipocytes elicited terminal differentiation. Thus, the differentiation program seemed to reject the circadian rhythms of glucocorticoid treatment, but responded robustly to sustained presence of glucocorticoids in the DMI. In contrast, rosiglitazone (a direct activator of PPARG) induced adipocyte differentiation in a dose-dependent manner, regardless of the mode of temporal delivery. These data were interpreted to mean that filtering of temporal glucocorticoid signals occurred either prior to or simultaneously with the induction of PPARG gene expression.

To further explore the regulatory behavior of the putative bi-stable switch separating pre-adipocytes from adipocytes, Bahrami-Nejad *et al*[7], tracked the expression

of fluorescently tagged PPARG in OP9 cells continuously over a 4-d period. Interestingly, the abundance of nuclear PPARG in individual cells was positively correlated with their progressive phenotypic transformation into bona fide fat cells. When cells were exposed to glucocorticoids in repeated 12-h on/12-h off cycles, a small fraction of OP9 and primary pre-adipocytes (SVF cells) concomitantly traversed a high threshold of PPARG and underwent terminal differentiation. In contrast, if glucocorticoid stimuli of similar strength were applied in a sustained manner, a high proportion of pre-adipocytes differentiated into fat cells.

Since the of PPARG gene expression is known to be activated by the transcription factor CCAAT/enhancer binding protein β (CEBPB), the authors tracked expression of CEBPB in live cells while they were cultured in DMI. These experiments revealed that nuclear abundance of CEBPB was dynamically regulated, and even more importantly, temporal expression CEBPB closely mirrored the oscillations of glucocorticoids. Since CEBPB is known to have a rapid rate of turnover, the authors reasoned that CEBPB could potentially form a fast feedback loop with PPARG. In response to circadian glucocorticoid stimuli, such a fast responsive system will not allow nuclear levels of PPARG to reach the threshold needed to initiate differentiation. An additional feature of such regulation would be that the positive feedback loop will become independent of external differentiation stimuli once a certain threshold of PPARG was reached. Quantification of nuclear abundance of PPARG *via* continuous, live cell imaging of OP9 cells revealed that an irreversible PPARG threshold was indeed reached after 36-48 h exposure to DMI[7]. Although, an involvement of a fast feedback loop between CEBPB and PPARG was confirmed by experiments assessing differentiation of pre-adipocytes in response to diurnally oscillating glucocorticoids, such a fast feedback loop could not explain how a progressive build-up of PPARG occurred in response to continuous, days-long exposure to glucocorticoids.

The mode of differentiation of pre-adipocytes in response to prolonged, non-oscillating exposure to glucocorticoids predicted the existence of a slow positive feedback loop regulating nuclear abundance of PPARG. Such a slow positive feedback circuit would enable adipocyte precursors to discriminate between oscillating *vs* continuous signals and mount a differential differentiation response.

From a number of candidate genes that might be linked to PPARG in a slow positive feedback loop[8], the authors favored FABP4, a known regulator of PPARG with a long half-life[11]. It was noted that the rate of turnover of FABP4 was low, and even more importantly, accumulation of FABP4 in the cytoplasm and nuclear abundance of PPARG followed similar kinetics. Thus, authors posited that FABP4, *via* its ability to transport fatty acid ligands that activate PPARG, formed a slow positive feedback loop with PPARG; involvement of such a slow positive feedback regulatory loop would enable pre-adipocytes to mount a differential response to oscillatory *vs* continuous stimuli. Of course, these data did not rule out the existence of additional regulatory circuits that could further modulate the mechanisms of *de novo* adipogenesis.

Experimental findings derived from *in vitro* differentiation of pre-adipocyte cell lines were subjected to computer simulations. The authors used an ordinary differentiation equation model to test the predicted dynamics of nuclear abundance of PPAG, *via* actions of the combined fast and slow positive feedback circuits. Indeed, such simulations could explain the observed rejection of single and repetitive pulses of differentiation stimuli. However, this model failed to explain why a small fraction of cells still differentiated in response to oscillating signals and why prolonged pulses of < 12 h induced a larger fraction of cells to undergo differentiation. To reconcile these observations, the authors modified their theoretical model of combined fast and slow positive feedbacks by adding a factor of stochastic variation in PPARG levels in the population of pre-adipocytes. These analyses revealed that a regulatory system consisting of fast and slow positive feedback links, when combined with putative stochastic abundance of nuclear PPARG (a cell-intrinsic property), could not only explain the variable delay in cells reaching PPARG threshold but also why low differentiation rates were seen in response to daily oscillations of glucocorticoids.

To corroborate these *in vitro* findings *in vivo*, the authors implanted continuous release pellets of cortisone in 8-wk old C57BL/6J mice. Experimental flattening of circadian rhythms of cortisone secretion, for 21 d, led to enhanced accumulation of subcutaneous (inguinal) and epidydimal (visceral) fat in mice. Mice with cortisone implants had significantly larger adipocytes compared with animals containing sham implants. Moreover, the visceral adipose tissues of mice exposed to sustained high levels of cortisone had more numerous adipocytes. Thus, persistently high circulating levels of cortisone not only enhanced *de novo* adipogenesis but also led to increased volume of adipocytes

In summary, Bahrami-Nejad *et al*[7], have shown that adipocyte differentiation was underpinned by cell-autonomous factors and their differential interaction with cortisone, depending on whether it was delivered continuously or in a circadian manner. While low signal variability was a key stochastic determinant that prevented de-differentiation of bone fide adipocytes, a high cell-to-cell signal variability was needed to ensure that only a small fraction of pre-adipocytes underwent differentiation in response to circadian delivery of glucocorticoids. The results of Bahrami-Nejad *et al*[7], in addition to elucidating how circadian exposure to glucocorticoid affects adipocyte differentiation, have broader clinical implications. It was demonstrated in a recent study that misaligned circadian rhythms had adverse effects on insulin sensitivity and energy metabolism in the skeletal muscles of healthy young adults[12]. Since mechanisms of repair and regeneration,

via recruitment of stem cells and their differentiation *in situ,* are central to tissue homeostasis across the animal kingdom[13], a role of circadian secretion of growth and differentiation factors in these processes is warranted.

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MINIREVIEWS

Use of sodium bicarbonate and blood gas monitoring in diabetic ketoacidosis: A review

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Abstract

Diabetic ketoacidosis (DKA) is a severe and too-common complication of uncontrolled diabetes mellitus. Acidosis is one of the fundamental disruptions stemming from the disease process, the complications of which are potentially lethal. Hydration and insulin administration have been the cornerstones of DKA therapy; however, adjunctive treatments such as the use of sodium bicarbonate and protocols that include serial monitoring with blood gas analysis have been much more controversial. There is substantial literature available regarding the use of exogenous sodium bicarbonate in mild to moderately severe acidosis; the bulk of the data argue against significant benefit in important clinical outcomes and suggest possible adverse effects with the use of bicarbonate. However, there is scant data to support or refute the role of bicarbonate therapy in very severe acidosis. Arterial blood gas (ABG) assessment is an element of some treatment protocols, including society guidelines, for DKA. We review the evidence supporting these recommendations. In addition, we review the data supporting some less cumbersome tests, including venous blood gas assessment and routine chemistries. It remains unclear that measurement of blood gas pH, via arterial or venous sampling, impacts management of the patient substantially enough to warrant the testing, especially if sodium bicarbonate administration is not being considered. There are special circumstances when serial ABG monitoring and/or sodium bicarbonate infusion are necessary, which we also review. Additional studies are needed to determine the utility of these interventions in patients with severe DKA and pH less than 7.0.

Key words: Diabetic ketoacidosis; Sodium bicarbonate; Blood gas analysis; Acidosis; Ketosis; Ketone bodies; Hyperglycemia

Core tip: Serial arterial blood gas measurements and intravenous sodium bicarbonate are often used to assess and correct acidosis associated with diabetic ketoacidosis. The available literature, primarily in patients with mild to moderately severe acidosis, does not support the routine use of sodium bicarbonate. Additionally, arterial sampling for blood gas measurement may not be necessary, nor does it appear to substantially add to the care of these patients. While neither intervention may be needed on a routine basis, there are special circumstances when either, or both, of these modalities is indicated and useful.

Patel MP, Ahmed A, Gunapalan T, Hesselbacher SE. Use of sodium bicarbonate and blood gas monitoring in diabetic ketoacidosis: A review. *World J Diabetes* 2018; 9(11): 199-205 Available from: URL: http://www.wjgnet.com/1948-9358/full/v9/i11/199.htm DOI: http://dx.doi.org/10.4239/wjd.v9.i11.199

INTRODUCTION

Diabetic ketoacidosis (DKA) represents one of the most serious complications of uncontrolled diabetes mellitus (DM)[1]. It is responsible for more than 500000 hospital days per year and is estimated to generate $2.4 billion in healthcare costs per year[2]. Furthermore, epidemiological studies have shown that hospital admissions for DKA in the United States are increasing at a rate even faster than the overall rate of the diagnosis of DM[1]. Insulin and intravenous hydration are the mainstays of therapy in the management of DKA. For severe cases, adjunctive therapies such as bicarbonate administration and protocols that call for serial blood gas monitoring have been more controversial. This article will review the evidence regarding bicarbonate administration and the utility of arterial and venous blood gas (VBG) monitoring.

PATHOPHYSIOLOGY

Metabolic derangements during an episode of DKA, depicted in Figure 1, can lead to profound consequences if left untreated. A myriad of events can occur which can lead to hyperglycemia; insulin deficiency, peripheral insulin resistance, and increased counter-regulatory hormones such as cortisol, growth hormone and catecholamines, all contribute to deteriorating clinical status and underlie the pathophysiology of DKA[3]. Furthermore, these effects are compounded by increased gluconeogenesis, glycogenolysis and impaired glucose uptake by peripheral tissue. The unfavorable combination of insulin resistance and counter-regulatory hormones leads to the release of free fatty acids (FFA) from adipose tissue via lipolysis and decreased lipogenesis, which ultimately results in ketogenesis and the production of beta-hydryoxybutyrate and acetoacetate[4,5]. Overproduction of these strong ketoacids leads to excessive hydrogen ion production upon dissociation, overwhelming the human body's buffering capacity, depleting bicarbonate stores, and ultimately generating an anion gap metabolic acidosis[6]. In addition, this process generates glycerol and alanine, which serve as substrates in the production of glucose in the liver, which propagates the cycle of hyperglycemia. Unchecked, this can lead to an osmotic diuresis that leads to marked urinary losses of free water and derangement of electrolytes. Urinary ketone losses will drive excretion of both sodium and potassium[5]. Serum sodium may fall drastically due to natriuresis or rise due to large losses of free water. As a response to acidosis, potassium shifts to the extracellular space *via* the proton-potassium exchange channel, resulting in normal or elevated serum potassium concentrations despite a severe total body deficit. To counter these metabolic derangements, aggressive intravenous volume and electrolyte repletion along with parenteral insulin administration are implemented and represent the foundation of treatment of patients in DKA.

SODIUM BICARBONATE INFUSION IN DKA

The use of sodium bicarbonate infusion in the setting of DKA has been a controversial topic for many years. Early on, the administration of bicarbonate to patients in severe DKA had been largely empiric. As clinical and experimental data emerged that failed to demonstrate therapeutic value, concerns arose regarding the efficacy and safety of this treatment modality. Controversy regarding its use in severe DKA persists to this day, resulting in varied practice pattern.

The acidemia that plagues these patients is often quite severe and perhaps multifactorial. Ketone-generated acidosis may be compounded by lactate acidosis resulting from impaired tissue perfusion due to volume contraction and adrenergic response to the underlying precipitating illness, such as infection[7]. Tissue acidosis can lead to profound organ dysfunction, including reduced myocardial contractility and cardiac output[7]. Additionally, the oxyhemoglobin dissociation curve may shift via the Bohr Effect, with concurrently lowering levels of 2,3-diphosphoglycerate (2,3-DPG) increasing hemoglobin-oxygen affinity; thus, metabolic acidosis influences tissue oxygenation and inhibits key rate limiting intracellular enzymes which can alter metabolic pathways and result in vital organ dysfunction[8-10]. Furthermore, severe acidosis impairs the ability of insulin to utilize glucose, with a lower pH conferring high insulin resistance[11]. Table 1 outlines many of the known consequences of significant acidosis. The fate of bicarbonate in the body can be illustrated by the following equation: $H^+ + HCO3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$. Given that the direct observable end products of this pathway are benign, its implementation was thought to be non-harmful. As a result, the mainstay of therapy in the past

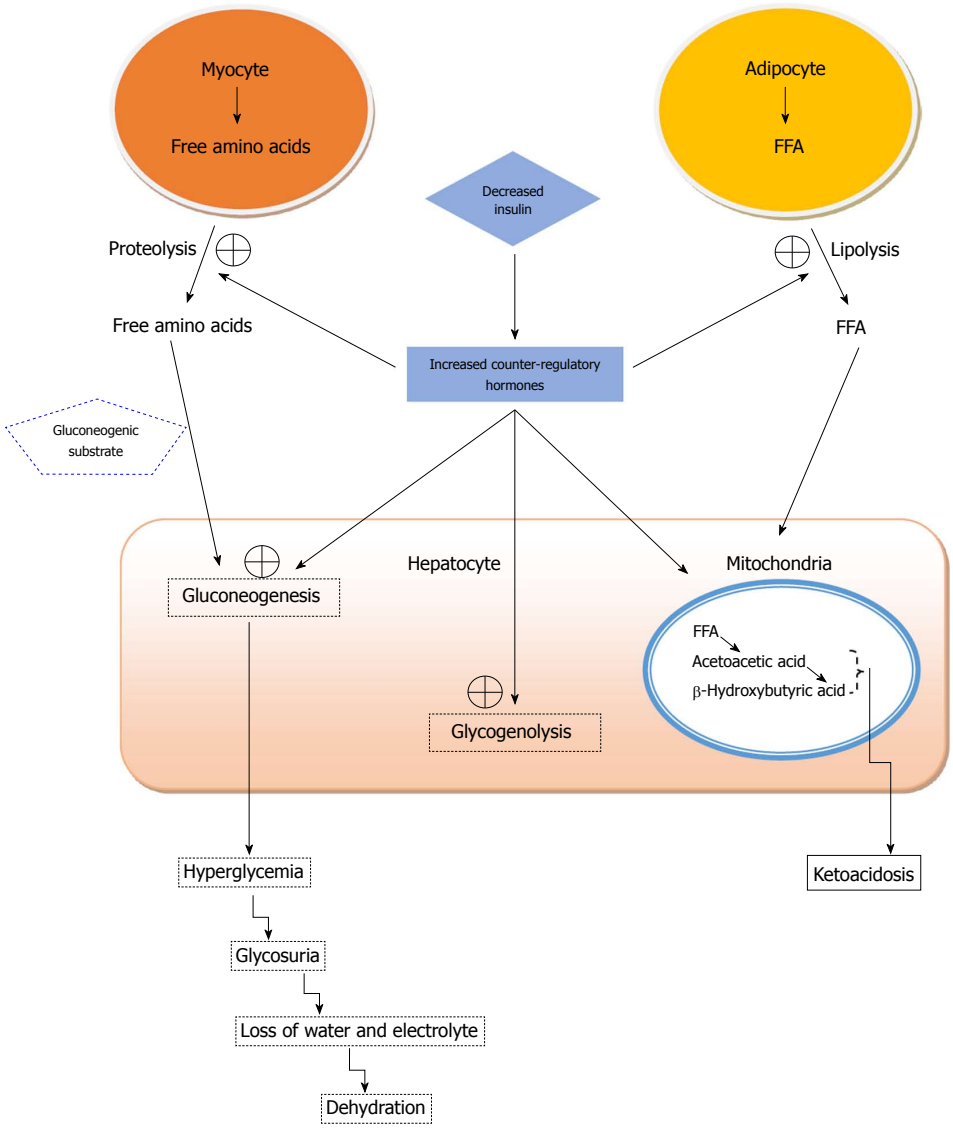

Figure 1 The pathophysiology of diabetic ketoacidosis. Decreased insulin sensitivity leads to increased concentrations of counter-regulatory hormones which promote catabolism of proteins and adipocytes. The production of free amino acids leads to the stimulation of gluconeogenesis and glycogenolysis leading to hyperglycemia. Free fatty acids undergo oxidation in the mitochondria and result in ketone production leading to acidosis. FFA: Free fatty acids.

placed great emphasis on the rapid reversal of acute acidemia in concordance with intravenous hydration and insulin administration. This physiological paradigm led to the widespread acceptance of intravenous bicarbonate administration in this setting.

There is robust data suggesting that the use of bicarbonate in patients with moderate DKA, in whom the pH is greater than 7.0, is not associated with improved outcomes as compared to saline-treated counterparts[12-15]. However, in patients with severe DKA (pH less than 7.0), there is a deficit of data that incorporates large, randomized controlled trial (RCT) designs. Several smaller studies failed to show benefit, albeit in only a handful of patients. Morris *et al*[15] showed in a randomized trial of 21 DKA patients with initial pH ranging between 6.90 to 7.14 that bicarbonate therapy did not improve morbidity or mortality. Additionally, the time to resolution of acidosis and bicarbonate regeneration was not significantly different. As of the writing of this review article, there have not been any results reported from prospective randomized trials concerning the use of bicarbonate in severe DKA with pH less than 6.90.

In a well-executed systematic review that included 44 articles including three RCTs, Chua *et al*[12] demonstrated a lack of consensus in pH threshold, time, concentration and amount of bicarbonate administration in various studies. There was no evidence of improved outcomes or glycemic control. Bicarbonate administration did not result in any significant benefit in duration of hospitalization, mortality, resolution of ketosis and/or acidosis, electrolyte imbalance, tissue oxygenation, or cerebrospinal fluid (CSF) acidosis[12]. It is worth noting that two adult RCTs demonstrated a shorter reversal time of acidosis at two hours after therapy in the bicarbonate arm[14,16], which was not sustained at 24 h

Table 1 Clinical effects of metabolic acidosis[27,28]

System	Clinical effects
Cardiovascular	Depressed myocardium contractility
	Changes in SVR
	Acidosis-aided catecholamine release opposes acidosis-mediated vasodilation.
	Net SVR depends on the sum of both effects
	Conduction defects and dysrhythmias
	Impaired response to exogenous vasopressors
Pulmonary	Increased work of breathing and respiratory failure
	Compensatory alveolar hyperventilation
	Dyspnea (Kussmaul's breathing)
	Acute decrease in hemoglobin oxygen affinity (Bohr Effect)
	Temporary: Affinity rises after 36 h due to depletion of RBC 2,3-DPG
Renal	Pseudo-hyperkalemia
	Hyperuricemia
	Hypercalcemia
Hematological effect	Impaired coagulation
	Thrombocytopenia
	Reduced fibrinogen and thrombin formation
	Impaired clotting factor function
	Factor Va
	Factor Ⅶa
	Factor Ⅶa/tissue factor complex
Endocrine	Insulin resistance
	Catecholamine, cortisol, PTH and aldosterone stimulation
	Bone demineralization
	Protein wasting
	Free radical formation
Musculoskeletal system	Anti-anabolic effect on the bone growth centers in chronic metabolic acidosis
	Muscle fatigue
Central nerve system	Cerebral edema
	Depressed sensorium
Immune system	Impaired leukocyte function
	Increased susceptibility to infections

SVR: Systemic vascular resistance; RBC: Red blood cell; 2,3-DPG: 2,3 diphosphoglycerate; PTH: Parathyroid hormone.

follow up mark[16] and led to no clinical difference. The vast majority of retrospective adult studies failed to show improvement in acidosis resolution[12]. A composite of nine small studies totaling 434 patients with DKA (217 treated with bicarbonate plus standard care and 178 with standard care) mirrors previous findings in a lack of benefit in outcomes[17].

There are several concerns that come into play when considering the role of bicarbonate infusion for DKA. Okuda *et al*[18] demonstrated a rise in serum ketoacid anion levels and a delay in ketosis resolution in patients treated with bicarbonate infusion. Animal data suggests acceleration in ketogenesis with bicarbonate administration[18]. In addition, if bicarbonate infusion is able to increase serum bicarbonate levels acutely, this may lead to a paradoxical worsening of acidosis in the central nervous system. Increased partial pressure of carbon dioxide (pCO_2) quickly and readily crosses the blood-brain barrier as compared to arterial bicarbonate, which can lead to a fall in cerebral pH and clinical neurological deterioration. In an RCT, adults receiving bicarbonate infusion had a non-significant trend toward a larger decline in CSF pH at 6-8 h compared with controls[15]. In the pediatric population, multiple non-randomized studies have implicated bicarbonate therapy as a risk factor for the development of cerebral edema[12] and retrospective evidence suggests that it is associated with prolonged hospitalization. Several studies, including one double-blinded adult RCT[16], identified a need for more aggressive potassium replacement in patients receiving bicarbonate infusion over 24 h. Given that patients in DKA are already at a total body deficit of potassium, implementation of bicarbonate may compound the problem and perhaps lead to fatal arrhythmia. These studies did not report any fatal outcomes secondary to hypokalemia; however, the theoretical risk is of substantial concern, especially when considering the widespread use of this intervention. Acute reversal of acidosis with bicarbonate has previously been linked to worsening tissue oxygenation. Acidosis will induce the Bohr effect and reduce total hemoglobin-oxygen affinity. However, it also lowers the concentration of 2,3-DPG in erythrocytes which leads to a counter-active increased hemoglobin-oxygen affinity. There exists a delicate balance in favor of the Bohr effect in the initial presentation of DKA, which theoretically can be pushed towards lower 2,3-DPG levels with bicarbonate administration and abrupt acidemia reversal. However, there is evidence to suggest that this may occur regardless of bicarbonate administration, and

Table 2 Key findings and conclusions regarding the use of sodium bicarbonate in diabetic ketoacidosis

Sodium bicarbonate use in mild to moderate acidemia (pH ⩾ 7.0) is associated with
No benefit in mortality or duration of hospitalization[12]
Possible transient benefit in reversal of acidosis[12,14,16]
Delay in resolution of ketosis[18]
Trend toward worsening of central nervous system acidosis[15]
Increased need for potassium supplementation[16]
Worsened tissue hypoxia[19]
Cerebral edema and prolonged hospitalization in pediatric patients[12]
Post-treatment metabolic alkalosis
Sodium bicarbonate use in severe acidemia (pH < 7.0) has not been well-studied
No improvement in morbidity or mortality in a small, randomized trial[15]
Routine use of sodium bicarbonate in diabetic ketoacidosis is not supported by the available literature
Several situations exist in which the use of sodium bicarbonate may be warranted
Severe acidosis
Life-threatening hyperkalemia
Recovery from saline-induced metabolic acidosis

levels of 2,3-DPG remain quite low for several days beyond the treatment of acidosis[19]. Finally, bicarbonate administration can lead to post-treatment metabolic alkalosis as insulin mediated ketoacid metabolism leads to both spontaneous bicarbonate generation and resolution of metabolic acidosis.

Although no prospective randomized trials have been conducted on patients with severe DKA, the American Diabetes Association recommends the administration of 100 mmol sodium bicarbonate in 400 mL sterile water with 20 mEq of KCl to patients with a pH of less than 6.90 until the pH rises above 7.00[5]. This is largely due to the concern of cardiovascular compromise in the setting of severe acidemia[8]. Additionally, bicarbonate administration is reasonable in the setting of life threatening hyperkalemia, since its administration may shift potassium into cells. Another potential setting in which bicarbonate therapy may be helpful is during the recovery phase. Intravenous hydration therapy with 0.9% sodium chloride, widely implemented in the treatment of DKA, contributes to the development of hyperchloremic metabolic acidosis. Also contributing to hyperchloremia is the preferential renal excretion of ketones over chloride anions. This may lead to reduced renal bicarbonate genesis in the setting of concomitant kidney injury and volume related hyperchloremic acidosis. This is perhaps the mechanism of the initial favorable physiologic outcome in the two previously discussed RCTs[14,16] with bicarbonate therapy as it may represent a reduced risk of hyperchloremic acidosis. However, the evidence is weak at best: the effect was transient and of uncertain clinical significance.

Taken in context of patient care, the theoretical benefits that provided the rational basis of rapid acidemia reversal with bicarbonate administration failed to provide any significant clinical differences or improved outcomes. This holds true for patients with severe DKA as well, albeit their sparse involvement in trials precludes any robust, evidence-based conclusion. Transient paradoxical worsening of ketosis and increased need for potassium replacement were the major clinical issues found to be of concern. In the pediatric population, retrospective analysis yielded evidence of clinical harm including increased risk of cerebral edema and prolonged hospitalization with bicarbonate administration. The findings and conclusions drawn from the available literature are summarized in Table 2.

ARTERIAL AND VBG MONITORING

Modern medicine has evolved to quite an extent so as to provide a wide complement of tools that are available for use in the diagnosis and management of any disease process. The most fundamental element upon which all else is built is a thorough history and physical exam. Patients who present with DKA characteristically develop a rapid onset of signs and symptoms that prompt initial evaluation. Classically, complaints of polyuria, polydipsia, weight loss, nausea and vomiting, abdominal pain and generalized weakness are among the most common symptoms. Physical findings can include dry mucus membranes and poor skin turgor, tachycardia, Kussmaul respirations, fruity odor, and diffuse abdominal tenderness to palpation[5]. Caution needs to be exercised to assess for infection, as it is the most common cause of DKA. Other factors such as medication compliance, changes in medications or dosages, myocardial infarction, and pancreatitis must be assessed as well.

The triad of hyperglycemia, anion gap metabolic acidosis and ketonemia are the hallmark findings that help establish the diagnosis. The American Diabetes Association have proposed diagnostic criteria which stratify DKA severity based on pH, bicarbonate levels, and anion gap in addition to mental status changes[5]. As such, the measurement of arterial pH in the diagnosis of DKA became an important aspect of the management of these patients. Many protocols for the management of these patients, including the guidelines set forth by the American Diabetes Association, call for the serial measurement of several laboratory parameters including serum chemistry and blood gases as often as every two hours[5].

Table 3 Key findings and conclusions regarding blood gas monitoring in diabetic ketoacidosis

Venous blood is similar to arterial sampling in measuring
pH[21-25]
Bicarbonate[21,24]
Lactate[21]
Base excess[21]
Venous blood gas measurement may be used in place of arterial blood for the purposes of stratifying disease severity in diabetic ketoacidosis
Blood gas measurement does not often change management of diabetic ketoacidosis, especially when routine chemistries (including bicarbonate level) and ketone body identification are available[25]
Routine use of arterial and/or venous blood gas measurement may not be necessary in the evaluation and management of diabetic ketoacidosis
Exceptions where blood gas analysis would likely alter management include
Abnormal baseline serum bicarbonate levels
Chronic respiratory failure
Renal tubular acidosis
Acute respiratory compromise
Adequacy of respiratory compensation for metabolic acidosis
Respiratory muscle fatigue and failure

As such, attention shifted to the possible role of VBG sampling in the monitoring of DKA in an effort to avoid the complications and patient discomfort that accompanies repeated arterial punctures. Multiple studies comparing arterial to venous blood gases parameters in a wide array of patient population and co-morbidities including DKA demonstrate a close agreement for the values of pH, bicarbonate, lactate, and base excess with an acceptably narrow 95% limits of agreement[20-25]. The authors universally agree that VBG analysis for pH and bicarbonate is an acceptable alternative of arterial blood gas (ABG) analysis. Despite strong data to support its use, many centers still engage in ABG usage for assessment of acid-base status.

An interesting and perhaps more thought-provoking element of management is to question the role of blood gas monitoring itself. While ABG and VBG may accurately measure the parameters in question, the impact on disease management is less clear, when taken in the context of the larger clinical picture and other available laboratory parameters. An interesting observational study by Ma *et al*[25], looked at two hundred consecutive patients who presented to the emergency department with suspected DKA and had ABG, VBG and a chemistry panel drawn before treatment. Attending physicians indicated a tentative treatment plan and disposition on a standardized form before and after reviewing results of the blood gases, and found that this additional information rarely led to a change in diagnosis, treatment, management, or disposition[26]. Additionally, they mirrored the data cited from previous studies regarding the correlation of venous to arterial pH and drew similar conclusions regarding its use as a substitute.

In most patients, routine measurement of pH may not necessarily add more information to the clinical picture, as the presence of metabolic acidosis can be established by routine measurement of venous bicarbonate level and identification of abnormal ketone bodies. Previously cited studies have demonstrated a strong correlation between pH and bicarbonate levels[21-25]; as such, information from a blood gas will add little, if any, diagnostic value to serum bicarbonate levels in both the initial presentation and subsequent management of DKA patients. Some exceptions may be found in patients with known or suspected abnormal baseline serum bicarbonate levels, as in chronic respiratory failure or renal tubular acidosis; a single measurement of arterial or VBG may confirm this abnormality. In select cases, measurement of an ABG may be of value in seeking information about the respiratory status of the patient. The value of pCO_2 may help assess the adequacy of respiratory compensation for the ongoing metabolic acidosis, and potentially identify those patients who may require mechanical ventilator support due to respiratory muscle fatigue[26]. However, perhaps the same information can be attained with serial physical examination and close clinical monitoring of the patient. The findings and conclusions drawn from the available literature are summarized in Table 3.

CONCLUSION

It is clear from the increasing rate of hospital admission for DKA, healthcare providers will need to be weary of following dogmatic policies of previous decades and turn to evidence-based practices to improve outcomes. The role of sodium bicarbonate administration has been fraught with controversy for many years now; however, an increasing volume of evidence reflects a lack of benefit in its role for the treatment of DKA. Some evidence suggests that the use of bicarbonate is associated with delayed ketone clearance and worsened hypokalemia. In children, bicarbonate has been associated with prolonged hospitalizations and a higher risk of cerebral edema. However, to draw more definitive conclusions, prospective RCTs that include severely acidotic patients need to be performed on a large scale. As far as blood gas sampling, a plethora of data is available that faithfully correlates VBG sampling, including pH and bicarbonate, to their corresponding arterial samples. However, the additional value that a blood gas sample may provide is questionable and, guidelines notwithstanding, may not be necessary in all patients who present with DKA.

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