Review Article

# Thiamine deficiency in diabetes, obesity and bariatric surgery: Recipes for diabetic ketoacidosis

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## Abstract

Diabetic ketoacidosis (DKA) is a life-threatening condition affecting individuals with diabetes characterised by hyperglycaemia, metabolic acidosis and ketonemia. The incidence and financial burden of DKA is still high. Thiamine deficiency is well documented in patients with DKA and could be associated with cardiac dysfunction in those patients. Thiamine deficiency leads to cardiac dysfunction, neuronal death and worsens the prognosis of DKA. There is an existing metabolic relationship between thiamine deficiency in diabetes, obesity and bariatric surgery. Careful monitoring of thiamine, along with other vitamins, is essential for diabetic patients, obese individuals and postbariatric surgery. Further research and clinical studies are urgently needed to assess the following: (1) Whether diabetes, obesity and bariatric surgery make individuals more prone to have DKA related to thiamine deficiency and (2) Whether supplementation of thiamine can protect diabetic patients, obese subjects and individuals undergoing bariatric surgery from DKA. This review summarises the biochemistry of thiamine and the existing metabolic relationships between thiamine deficiency in DKA, diabetes, obesity and bariatric surgery. Primary and family physicians have an important role in ensuring adequate replacement of thiamine in individuals with diabetes, obesity and bariatric surgery.

**Keywords:** Bariatric surgery, diabetes, diabetic ketoacidosis, obesity, thiamine deficiency

## Introduction

Diabetic ketoacidosis (DKA) is a life-threatening condition. Although the mortality rate of DKA decreased over recent decades, the incidence and financial burden of this condition are still high. The cases of DKA account for four to eight of every thousand admissions for diabetes, or about 100,000 hospital admissions per year. The annual cost of medical expenditures of DKA is about one billion dollars per year.[1,2] Thiamine deficiency is well documented in patients with DKA and could be associated with cardiac dysfunction.[3] Thiamine or Vitamin B1 is a water-soluble essential vitamin found in foods including bread cereals, nuts, and meats.[4]

Thiamine is a co-factor for enzymes that are not only crucial in glucose metabolism and ATP production, but also key players

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**Received:** 26-08-2023 **Revised:** 23-09-2023
**Accepted:** 10-11-2023 **Published:** 24-05-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1413_23

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**How to cite this article:** Panda A, Heidari A, Borumand M, Ahmed M, Hassan A, Ahmed MH. Thiamine deficiency in diabetes, obesity and bariatric surgery: Recipes for diabetic ketoacidosis. J Family Med Prim Care 2024;13:1620-7.

in the synthesis of RNA and DNA.[5] Thiamine deficiency leads to cardiac dysfunction and neuronal death.[6] Malnutrition and alcoholism are known aetiological factors of thiamine deficiency.[7] Thiamine deficiency has a strong metabolic relationship with diabetes, obesity, and bariatric surgery. It is known to cause conditions like wet and dry Beriberi and also worsens Diabetic Ketoacidosis (DKA) outcomes.[8,9] Thiamine, unlike lipid-soluble vitamins, cannot be stored in substantial amounts.[10] This issue becomes significant when vitamin B1 requirements are raised in states of increased energy demands such as surgery, pregnancy and sepsis.[11] Vitamin B1 is particularly important in highly metabolically active tissues, including neurons, cardiac myocytes and erythrocytes which rely on glucose as their main source of energy.[12] Thiamine deficiency primarily affects the cardiovascular and nervous systems. 'Wet Beriberi' refers to the resultant cardiovascular dysfunction, whereas 'Dry Beriberi' and 'Wernicke-Korsakoff syndromes' are manifestations of neuronal dysfunction. Wet Beriberi is characterised by high output heart failure, dyspnoea, oedema and dysrhythmias, whilst dry Beriberi is characterised by peripheral neuropathy. Wernicke–Korsakoff syndrome manifestations include ataxia, nystagmus and ophthalmoplegia and later progresses to confusion, retrograde amnesia and general cognitive decline.[13] This review summarises the biochemistry of thiamine and the existing metabolic relationships between thiamine deficiency in DKA, diabetes, obesity and bariatric surgery.

## Methods

This research project was conducted as a narrative review article. The authors searched the literature using the following databases: PubMed, Medline, Scopus and Google scholar. These databases were searched using the keywords: thiamine, DKA, thiamine deficiency, diabetes, obesity and bariatric surgery. The authors searched also using a combination of the following terms [thiamine deficiency) AND (diabetes) AND (obesity) AND (bariatric surgery)] OR [(Diabetic Ketoacidosis) AND (thiamine deficiency) AND (clinical trials)]. The search was based on studies published in the English language from 1991 to 2023; the abstracts and the articles were then screened. Articles were scanned and read; further relevant references in the reference lists are also included. Please see Figure 1 for the PRISMA diagram.

## Biochemistry of thiamine

Thiamine occurs in the human body as free thiamine and as various phosphorylated forms, such as thiamine triphosphate (TPP). TPP is the active form of thiamine that serves as a cofactor for several enzymes in energy metabolism.[14] There are three central enzymes of metabolism that require TPP. These enzymes are pyruvate dehydrogenase (PDH), alpha-ketoglutarate dehydrogenase and transketolase.[15] Mitochondrial aerobic metabolism, namely the linking of glycolysis to oxidative phosphorylation, is thiamine dependent. TPP is required for the production of acetyl coenzyme

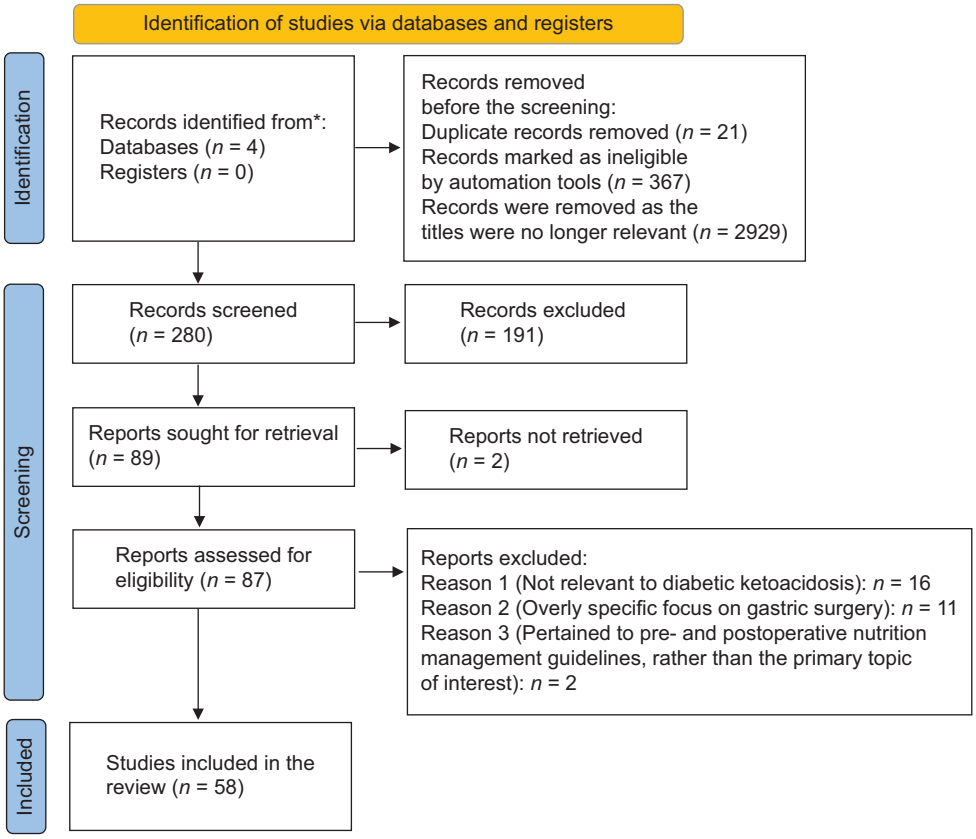


**Figure 1:** PRISMA flow diagram illustrating the systematic search and selection process undertaken for this review spanning from 1991 to 2023

A (CoA) through the oxidative decarboxylation of pyruvate by PDH.[16] In thiamine deficiency, acetyl CoA cannot be utilised in the Krebs cycle and is thus converted to lactate by lactate dehydrogenase. This would in turn result in reduced adenosine triphosphate (ATP) availability and increased concentrations of lactic acid, as shown in Figure 2. These changes would render cells incapable of maintaining cellular electrochemical gradients, cellular metabolism and actin–myosin interactions.[17] The lactic acidosis and the reduction in ATP can cause both neuronal necrosis and apoptosis due to mitochondrial dysfunction.

As erythrocytes rely on the pentose phosphate pathway to metabolise glucose, thiamine deficiency would result in a reduction in transketolase enzyme activity. This metabolic pathway in erythrocytes produces reduced nicotinamide adenine dinucleotide phosphate which is required for the maintenance of the erythrocyte's cytoskeleton.[18] The downregulation of transketolase in thiamine deficiency results in reduced oxygen delivery to vital organs which produces further lactic acidosis and hypoxia, ultimately leading to organ dysfunction.[19]

Moreover, the neurotransmitter acetylcholine is synthesised from choline and acetyl CoA. Therefore, the outcome of thiamine deficiency is neurotransmitter imbalance in the nervous system.[20] *In vitro* studies have shown that the cardiovascular[21] and neuronal dysfunctions[13,22] are attributed to the acidotic, oxidised and ATP lacking environment described above causing wet Beriberi, dry Beriberi and Wernicke–Korsakoff syndrome.

## Thiamine deficiency and DKA

Thiamine deficiency is associated with the worsening prognosis of DKA due to its critical role as a cofactor in glucose metabolism. This mainly occurs through the production of lactic acid. Diabetes mellitus has been linked to the predisposition of thiamine deficiency due to the increased renal clearance of thiamine that occurs in osmotic diuresis and hyperglycaemia.[8] During the treatment of DKA, pre-existing thiamine deficiency is thought to be exacerbated by insulin and dextrose fluid therapy due to the rapid increase of thiamine utilisation.[23] Many studies have explored the relationship between diabetes mellitus and thiamine deficiency; however. there is limited research regarding DKA and thiamine deficiency. For instance, the prospective observational cohort study by Moskowitz *et al.* investigated 32 patients above 18 years of age who presented with DKA in Nashville, USA. This study showed that 25% of patients with DKA had thiamine deficiency. The study also found a statistically significant inverse relationship between thiamine and lactic acid levels ($P = 0.02$).[9] A prospective observational pilot study conducted by Rosner *et al.* was the first study in children to demonstrate a link between DKA and thiamine deficiency. A total of 22 patients aged 2–18 years with DKA were admitted to the ICU in Michigan, USA and enrolled in the study. Their study showed that 24% of patients had thiamine deficiency before commencing insulin therapy. After 8 h of insulin therapy, 35% of patients had thiamine deficiency and 68% of patients had a median decrease of 10 nmol/L in thiamine levels ($P = 0.014$). This study showed the significant prevalence of thiamine deficiency in DKA patients and showed that thiamine levels decreased following insulin therapy.[24]

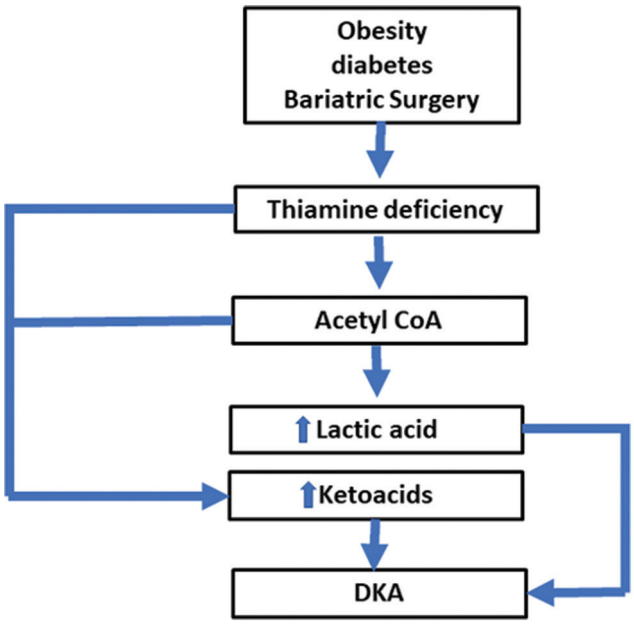


**Figure 2:** The role of thiamine in glucose metabolism and the complex relationship between thiamine deficiency, obesity, diabetes and bariatric surgery and how this can lead to DKA

The impact of thiamine supplementation was shown in few case report studies. For instance, Clark *et al.* discussed a case report in which a 13-year-old female presented with severe DKA. The patient's serum thiamine level was low at 22.4 ng/L (normal reference value was 74–222 nmol/L). Accordingly, 100 mg of IV thiamine hydrochloride was given and within 4 h the patient improved with reduced insulin requirements, and her urine was negative for ketones.[25] In another case, a 16-year-old male presented with lactic acidosis in DKA with a lactate level of 11.9 mmol. In this patient, thiamine deficiency was suspected, and an IV 100 mg thiamine supplement was given which resulted in lactate levels decreasing to 6.7 mmol within four hours.[23] Moreover, Moseley *et al.* showed in another case report that thiamine deficiency can lead to DKA following bariatric surgery in an individual with type 1 diabetes.[26] Interestingly, an ongoing randomised control trial (RCT) looked at the impact of thiamine replacement on recovery from acidosis due to DKA. They will also investigate the relationship between thiamine and cellular oxygen consumption in addition to the effects of thiamine on intensive care and hospital stays.[27]

## Thiamine deficiency and diabetes

The mechanism behind thiamine deficiency in patients with diabetes mellitus is still not completely understood. Studies have found that insulin deficiency is associated with a reduction in thiamine transportation in the small intestine.[28] Thiamine deficiency can also lead to a decrease in insulin synthesis, indicating that both deficiencies can concurrently have an

**Table 1: Summary of the impact of thiamine in DKA, diabetes, obesity, and bariatric surgery**

| Role of thiamine in | Summary of action | References |
|---|---|---|
| Diabetic ketoacidosis | • Thiamine deficiency can precipitate DKA<br>• Thiamine deficiency linked to high lactic acid<br>• Thiamine deficiency can precipitate DKA with bariatric surgery<br>• DKA treatment may lead to thiamine deficiency<br>• An ongoing randomised control trial (RCT), looking at the impact of thiamine replacement on recovery from acidosis due to DKA, and whether this can decrease the need for intensive care and hospital stays | 8, 24–27 |
| Diabetes | • Diabetes can be associated with thiamine deficiency in type 1 and type 2<br>• Thiamine deficiency can lead to decreased insulin synthesis<br>• Thiamine replacement can be associated with a reduction in glucose and HbA1c levels and an increase in insulin.<br>• Thiamine may also modulate the level of advanced glycation end products (AGEs)<br>• Thiamine may have potential benefits in the treatment of microalbuminuria and fasting blood glucose | 8, 28–33 |
| Obesity | • Obesity can be associated with thiamine deficiency in proportion to high BMI<br>• Risk factors leading to thiamine deficiency were carbohydrate intake derived mainly from simple sugars and processed foods high in fat but low in essential vitamins and minerals<br>• Genetic or acquired changes in cellular transporters may be responsible for thiamine deficiency. The organic cation transporter 1 (OCT1) may be responsible for mediating thiamine uptake into the liver | 34–38 |
| Bariatric surgery | • Bariatric surgery can be associated with thiamine deficiency | 39–45 |
| In animal rat models | • Thiamine therapy prevented diabetic dyslipidaemia, diabetic nephropathy, vascular damage and improved insulin sensitivity in diabetic rats | 46–49 |

impact on each other.[28] Studies undertaken in rat species have demonstrated the positive effects of thiamine therapy on diabetes and diabetic complications. A summary of these studies is shown in Table 1.

The prevalence of thiamine deficiency in patients with diabetes mellitus has been shown to be increased compared to the general population.[29] A literature review has found that in type 1 and type 2 diabetes; thiamine deficiency can range from 17% to 79%.[28] A cohort study conducted by Thornalley *et al.* in Essex, United Kingdom showed that plasma thiamine levels were reduced by 76% in type 1 diabetic patients and 75% in type 2 diabetic patients when compared to healthy volunteers ($P < 0.001$).[8] Additionally, a study from Saudi Arabia demonstrated that there is a strong association between blood thiamine levels and type 1 diabetes mellitus, with thiamine levels being reduced in these patients.[29]

Several studies have been conducted which look at the effect of thiamine or benfotiamine supplementation on diabetes mellitus and its complications. Karkabounas *et al.* performed an RCT which showed the effects of α-lipoic acid (ALA), carnosine and thiamine supplementation in obese patients with type 2 diabetes mellitus. Their study concluded that patients given a thiamine supplementation of 1 mg/kg, ALA and carnosine had a reduction in glucose and HbA1c levels and an increase in insulin.[30] Because the study participants had received multiple supplementations simultaneously, it is difficult to determine the direct effects of thiamine. Another study linked advanced glycation end products (AGEs) levels to benfotiamine treatment in type 2 diabetes. This study showed that the basal values of AGEs in patients who had benfotiamine decreased from 7.2 to 4.1 ng/mL, compared to the placebo group whose values increased.[31] Conversely, an RCT conducted by Alkhalaf *et al.* showed no reduction of AGEs following supplementation.[32] It is important to note the variation in sample size with the first study having 41 subjects whilst the second has 86 subjects. Importantly, an RCT conducted in Pakistan demonstrated the effects of high-dose thiamine therapy on risk factors of type 2 diabetes mellitus including microalbuminuria. The study showed that following 300 mg/day of thiamine therapy for three months, there was a decrease in fasting blood glucose in the 2-month washout period.[33] The decrease was 20.83% in the patients with thiamine and 18.9% in the placebo group, which was statistically significant ($P < 0.05$).[33] Recent findings from a systematic review and meta-analysis by Ziegler *et al.* (2023) shed further light on this association. The study pointed to an association between diabetes and reduced systemic thiamine markers, such as thiamine, thiamine monophosphate and total thiamine compounds. Individuals with diabetes and albuminuria seem to be at a higher risk of having reduced thiamine concentrations. The systematic review concludes that individuals with diabetes might require more thiamine than those without the condition. This study emphasises, thus, on the potential benefits of thiamine treatment and prevention in diabetes-associated microvascular complications.[34]

## Thiamine deficiency and obesity

In 2006, a survey of almost 4000 obese subjects in Thailand found that deficiencies of multiple nutrients are more common in people with obesity than in normal-weight participants.[35] One such deficiency is vitamin B1 or thiamine. This was in support of an earlier study by Carrodeguas *et al.*, (2005) who evaluated the degree of thiamine deficiency in adults with an average BMI of 60 kg/m$^2$, and concluded that 15.5% had low thiamine levels.[36] More recently, Densupsoontorn *et al.* (2019)[37] investigated the prevalence of factors associated with thiamine deficiency in obese Thai children aged 7–15 years old, almost 42% had thiamine deficiency.

Vitamin B complex is involved in the metabolism of carbohydrates and amino acids. The total organic reserve of vitamin B1, mainly as thiamine pyrophosphate, is approximately 30 mg, with a half-life of 9–18 days.[37] Therefore, adults who have a high carbohydrate intake derived mainly from simple sugars are at risk of developing thiamine deficiency. This is evidenced by the fact that replenishment of carbohydrates, without vitamin B1, specifically in refeeding syndrome or alcoholic liver disease[37,38] precipitates thiamine deficiency. An additional causative factor for thiamine deficiency is that processed foods are high in fat but low in essential vitamins and minerals, hence contributing to weight gain, however, leave the individual deficient in important micronutrients.

Additionally, increased excretion, driven using diuretics for weight loss or managing comorbidities in individuals with medically complicated obesity, can potentially lead to clinical thiamine deficiency by escalating thiamine loss in urine. This can create a cycle of fluid overload, necessitating more diuretics, and thus, exacerbating thiamine deficiency further.[7,39]

Alternatively, genetic or acquired changes in cellular transporters may be responsible for thiamine deficiency. The organic cation transporter 1 (OCT1) may be responsible for mediating thiamine uptake into the liver.[40] Deletion of *Oct1* gene in mice or feeding wild-type mice a thiamine-deficient diet led to reduced activity of thiamine-dependent enzyme PDH, the key enzyme involved in linking glycolysis to the Krebs Cycle and, hence, energy production. This resulted in a reduction in glucose utilisation and, thus, increased adiposity. Information on the micronutrient quality of weight-loss diets is limited, so it is not clear whether they meet the recommended dietary allowance (RDA) for thiamine of 1.1 mg/d in women and 1.2 mg/d in men, and specifically in obese individuals. In fact, the American National Research Council reported that >80% of people eat a diet that is below the RDA for vitamins and mineral.[41] It is plausible to suggest the need for further studies to further characterise the thiamine deficiency with obesity and to assess whether thiamine supplementation is needed during weight loss and whether this weight loss is achieved by dieting through bariatric surgery.

## Thiamine deficiency and bariatric surgery

Bariatric surgery is widely performed across the globe due to the high prevalence of the epidemic of obesity. Deficiency of micronutrients can also occur after bariatric surgery. For instance, a systematic review of the literature reported 84 cases of Wernicke encephalopathy (WE) within 6 months of bariatrics surgery[42] Roux-en-Y Gastric bypass (RYGB) or a restrictive procedure had been performed in 95% of the cases. RYGB is still the most performed procedure. According to Lakhani SV *et al.*, (2008), since RYGB bypasses the duodenum and more than 30 cm of jejunum, it reduces the absorption of thiamine. In addition, small intestinal bacterial overgrowth can occur, leading to further thiamine deficiency.[43]

There are also more recently published cases of WE, presenting with progressive neurologic symptoms (nystagmus, irritability, ataxia) and frequent vomiting, following bariatric surgery.[44,45] The case reported by Henrique da Silva *et al.* also had evident wet Beriberi symptoms.[45] The patients reported underwent RYGB and gastroplasty, respectively. Another clinical manifestation of thiamine deficiency, Korsakoff syndrome, has not been associated with bariatric surgery. However, a case of isolated ascending sensory neuropathy was seen with mildly low thiamine levels, 4 months after Roux-en-Y gastric bypass surgery.[46] Nutritional deficiency is more common in patients who are noncompliant with dietary recommendations following bariatric surgery. In fact, in all the cases published, patients improved significantly within a few days after nutrient replenishment. NICE guidelines recommend regular monitoring of a person's micronutrient status[47] but do not specify what 'regular' refers to.

A study conducted by Inge *et al.* (2004) revealed that the majority of patients undergoing bariatric procedures do not receive adequate and appropriate nutrition supplements, before and/or after the operation.[48] In support of this, a study of thiamine levels in perioperative patients found 15% to have low thiamine levels,[49] so adequate assessment of nutritional status in patients prior to bariatric surgery is also important. The number of bariatric procedures carried out is dramatically increasing and thiamine deficiency must be considered as a long-term complication, especially as 'Bariatric Beriberi' has 20% mortality and is considered a neurological emergency.[50,51] It can be avoided by careful monitoring of vitamin B1, along with other vitamins, notably vitamin B12, and vitamin D, and attention to neurological symptoms.[52] In addition, patients may be advised to restrict their intake of tea, coffee and alcohol, as these can break down the vitamin.[49,53]

## Will diabetes, obesity and bariatric surgery make the individual more prone to have DKA related to thiamine deficiency?

Thiamine deficiency is reported in patients with DKA and could be associated with cardiac dysfunction in those patients.[3] Although the mechanism of thiamine deficiency in patients with diabetes mellitus is not fully elucidated, it is well established that insulin deficiency is associated with a reduction in the transport of thiamine in the small intestine.[28] Preclinical studies demonstrated positive effects of thiamine therapy on diabetes and diabetic complications.[54-57] In children with DKA, thiamine deficiency is prevalent, and treatments involving insulin administration, rehydration and hypovolemia correction can further decrease serum thiamine levels. Persistent acidosis, increasing insulin requirements and ongoing encephalopathy in patients receiving appropriate therapy indicate a potential thiamine deficiency.[58] It is also proposed that thiamine can be used as an adjunct in DKA treatment in the paediatric population.[59] In the same direction, a clinical study showed that the administration of thiamine alone caused a decrease in fasting blood glucose[33] or in combination with ALA and carnosine caused a reduction in glucose and

HbA1c levels and an increase in insulin level.[30] Obesity can be associated with diabetes and insulin resistance. Obese individuals have an existing nutritional deficiency.[60] Several studies demonstrated thiamine deficiency in obese subjects.[35,37,49] However, it is still not clear at what level of obesity thiamine deficiency presents. The number of bariatric surgeries carried out is dramatically increasing. Thiamine deficiency is expected to be a long-term complication of bariatric surgery. Patients with diabetes, obesity and those undergoing bariatric surgery could be more prone to develop DKA related to thiamine deficiency because there is an existing metabolic relationship between these conditions and thiamine deficiency.[56-60] Therefore, further research and clinical studies are urgently needed to establish whether diabetes, obesity and bariatric surgery make individuals more prone to have DKA [Figure 1].

## Limitations

One of the salient limitations is the variability in defining the threshold of obesity that results in thiamine deficiency, which is seen across multiple studies. This variance introduces a confounding factor and poses challenges to the accurate identification and treatment of thiamine deficiency in individuals with obesity and those undergoing bariatric surgery. Regarding the breadth of the literature, the review encompasses a selection of 58 studies, a sample size that may not capture the entire scope and diversity of available research on the subject. This limitation, in turn, affects the generalisability of the results and conclusions drawn from the review. The findings primarily reflect short-term outcomes and immediate postsurgical scenarios, with a paucity of data on the long-term ramifications of thiamine deficiency postbariatric surgery. Furthermore, the review highlights a relationship between insulin deficiency and diminished thiamine transport in the small intestine. However, the depth of exploration into the mechanistic intricacies of this association is somewhat limited in the studies cited. This lack of detailed examination particularly pertains to the interaction between insulin administration, rehydration, hypovolemia correction and thiamine levels in paediatric patients with DKA.

Potential biases in the included studies also warrant consideration. Variations in study design, participant selection criteria and data analysis methodologies across the reviewed papers could introduce bias, thereby influencing the interpretability and applicability of the findings. Moreover, the diversity of the study populations and the geographic locations of the studies could impact the external validity of the results. Finally, despite the inclusion of studies up to 2023, there remains a discernible gap in recent, in-depth research exploring the multifaceted relationship between thiamine deficiency, DKA, diabetes, obesity, and bariatric surgery.

# Conclusion

DKA is a life-threatening condition. Thiamine deficiency is well documented in patients with DKA and could worsen the prognosis of DKA. There is an existing metabolic relationship between thiamine deficiency in diabetes, obesity and bariatric surgery. Further research and clinical studies are urgently needed to establish whether diabetes, obesity and bariatric surgery make individuals more prone to develop DKA related to thiamine deficiency; and whether supplementation of thiamine can protect diabetic patients, obese subjects and individuals undergoing bariatric surgery from DKA.

## Key points

- Diabetes, obesity and bariatric surgery can be associated with thiamine deficiency.
- Thiamine deficiency can be associated with DKA.
- In clinical settings, proactive thiamine supplementation in patients at high risk is advisable over waiting for biochemical confirmation of thiamine deficiency.

## Take home message

Family and primary care physicians can start thiamine replacement (100 mg twice per day) in high-risk patients without the need for plasma measurement of thiamine level.

## Ethics approval and consent to participate

This review article and no need for ethical approval.

## Consent for publication

Not needed.

## Availability of data and materials

Not needed.

## Authors' contributions

(I) Conception and design: MH Ahmed; (II) administrative support: MH Ahmed; (III) provision of study materials or patients: all authors; (IV) collection and assembly of data: all authors; (V) data analysis and interpretation: all authors; (VI) manuscript writing: all authors; (VII) final approval of manuscript: all authors.

## Acknowledgements

We would like to acknowledge our families for their support and encouragement during the writing of this review article.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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