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REVIEW

Bariatric surgery and long-term nutritional issues

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Abstract

Bariatric surgery is recognized as a highly effective therapy for obesity since it accomplishes sustained weight loss, reduction of obesity-related comorbidities and mortality, and improvement of quality of life. Overall, bariatric surgery is associated with a 42% reduction of the cardiovascular risk and 30% reduction of all-cause mortality. This review focuses on some nutritional consequences that can occur in bariatric patients that could potentially hinder the clinical benefits of this therapeutic option. All bariatric procedures, to variable degrees, alter the anatomy and physiology of the gastrointestinal tract; this alteration makes these patients more susceptible to developing nutritional complications, namely, deficiencies of macro- and micro-nutrients, which could lead to disabling diseases such as anemia, osteoporosis, protein malnutrition. Of note is the evidence that most obese patients present a number of nutritional deficits already prior to surgery, the most important being vitamin D and iron deficiencies. This finding prompts the need for a complete nutritional assessment and, eventually, an adequate correction of pre-existing deficits before surgery. Another critical issue that follows bariatric surgery is post-operative weight regain, which is commonly associated with the relapse of obesity-related co-morbidities. Nu-tritional complications associated with bariatric surgery can be prevented by life-long nutritional monitoring with the administration of multi-vitamins and mineral supplements according to the patient's needs.

Key words: Bariatric surgery; Nutrient deficiency; Roux-en-Y gastric bypass; Sleeve gastrectomy; Pre-operative

deficit; Weight regain

Core tip: Bariatric surgery is increasingly and successfully applied for the treatment of morbid obesity. In spite of multiple clinical benefits, *i.e.*, durable weight loss and improvement/reversal of many comorbidities, a number of nutritional complications can develop especially in the long term, which could cause serious detriment to patients' health. We examine some important clinical conditions that are caused by the deficit of vitamins and micronutrients, such as anemia, osteoporosis, and malnutrition. We also discuss the importance of careful pre-operative assessments and the correction of pre-existing nutritional deficiencies, and present the current recommendations for an appropriate biochemical and nutritional monitoring in the long term.

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INTRODUCTION

Obesity has become an important public health priority because it increases the risk of comorbid conditions, including diabetes, cardiovascular disease and several types of cancers. In addition, it affects life quality and expectancy[1]. The impact of obesity on life expectancy has been well documented. Worldwide, over 2.5 million deaths annually can be attributed to obesity. Of particular concern is the growing economic burden that the care of obesity and its complications imposes on society and the health care system[2].

The increasing prevalence of obesity and comorbid conditions worldwide prompts for effective strategies for both treatment and prevention[1]. The treatment of obesity includes lifestyle changes (dietary restrictions and increased physical activity), the use of medications, and in some cases, surgery. Lifestyle changes can cause a 2%-6% weight loss; however, after 1-5 years, almost 90% of the patients have returned to their original weight or might even gain some weight. Drug treatment in general leads to a 5%-15% weight loss and should be considered only as an adjunct to lifestyle changes. Unfortunately, with respect to lifestyle intervention, medical treatment rarely yields satisfactory results in the long term[1,3].

Bariatric surgery has proven to achieve greater weight loss than non-surgical management and, most importantly, has proven to maintain it in the long term[4]. Thus, in patients with morbid obesity, *i.e.*, a body mass index of $\geqslant$ 40 or $\geqslant$ 35 kg/m^2 with co-morbidities, bariatric surgery is presently considered to be the only effective therapy for obesity. Extensive data demonstrate that surgery can improve or even reverse many comorbidities, such as type 2 diabetes, hypertension, obstructive sleep apnea and steatohepatitis[5-7]. With regard to type 2 diabetes, observational and randomized controlled trials with a follow-up duration of up to 5 years have established the superiority of bariatric surgery over medical therapy at achieving remission of the disease and improvement of the overall cardiovascular risk profile[8-10]. One of the longest weight-loss studies - the Swedish Obese Subjects - evaluated the long-term effects of different bariatric procedures and demonstrated significant reductions in cardiovascular and cancer-related mortality as well as significant improvement in the quality of life[11-13].

In spite of multiple clinical benefits, a number of surgical and gastrointestinal complications can occur following bariatric procedures, although the diffusion of the laparoscopic approach and the expansion of centers of excellence have greatly reduced the rate of post-operative mortality and adverse events[14]. The mean mortality rate is 0.3% for all procedures, which is comparable to those for hip replacement (0.3%) or laparoscopic cholecystectomy (0.3%-0.6%). Indeed, even lower mortality rates (0.04-0.13) are achieved in high-volume obesity centers[14]. Among the possible complications, nutritional deficiencies deserve careful consideration. They can develop as a consequence of reduced intake and/or malabsorption of nutrients and are more commonly seen after malabsorptive or mixed procedures in comparison to the restrictive procedures. Other causal factors include pre-operative deficiencies, post-surgery food intolerance, changes in taste and eating patterns and non-adherence to dietary and supplement recommendations. Nutritional deficiencies can present with a wide range of clinical manifestations, depending on the specific nutrients/micronutrients that are involved, the severity, and the duration of the deficiency states. Because they could cause serious detriment to patients' everyday lives and, in some instances, could result in life-threatening complications, a nutritional screening both before and after surgery is strongly recommended.

This review focuses on the main nutritional issues related to bariatric procedures by examining some important clinical conditions that are caused by the deficit of vitamins and micronutrients, such as anemia, osteoporosis, neurologic disorders, and malnutrition. We will also discuss the importance of careful pre-operative assessments and the correction of pre-existing nutritional deficiencies, which are quite common in obese patients. Last, recommendations for the prevention and treatment of nutritional deficiencies after bariatric surgery are presented.

CONVENTIONAL BARIATRIC SURGICAL PROCEDURES

Surgical procedures are generally classified into restrictive procedures, in which the stomach's capacity

is greatly reduced, malabsorptive procedures, in which malabsorption is the primary driver of the weight loss, or a combination of restrictive and malabsorptive elements (Figure 1). However, over the past few years, it has become clear that weight loss is not only due to reduced food intake and/or absorption induced by modification of gastrointestinal anatomy but also a consequence of changes in neural and gut hormonal signals that regulate hunger and satiety, gut microbiota, intestinal nutrient sensing, food preferences, and possibly energy expenditure[15]. These so-called weight-independent mechanisms contribute to a variable extent to weight loss and metabolic improvement, depending on the type of surgical technique.

***Laparoscopic adjustable gastric banding* (AGB)**

An adjustable silicone band is placed around the upper stomach, a few centimeters below the cardia, creating a 15 to 30 mL gastric pouch. The diameter of the outlet can be changed by injection of or removal of saline through a portal placed in the subcutaneous tissue that is connected to the band.

***Roux-en-Y gastric bypass* (RYGB)**

A small, vertically oriented gastric pouch is created, which remains attached to the esophagus at one end and, at the other end, is connected to a small section of the small intestine, thus bypassing the remaining stomach and the initial loop of the small intestine.

***Sleeve gastrectomy* (SG)**

The operation involves division of the stomach vertically, which reduces its size by 75%. The pyloric valve at the bottom of the stomach is preserved such that the stomach function and digestion remain unaltered. The procedure is not reversible and might be a first stage procedure to a RYGB or duodenal switch.

***Biliopancreatic diversion* (BPD)**

The operation consists of a distal horizontal gastrectomy that leaves a 200-250 mL of upper stomach. This remnant stomach is anastomosed to the distal 250 cm of small intestine (alimentary limb). The excluded small intestine (carrying bile and pancreatic secretion), called the biliopancreatic limb, is connected to the small bowel 50 cm proximal to the ileocecal valve. The 50-cm common limb is the only segment where digestive secretions and nutrients mix, which causes a marked malabsorption, especially for fat and protein.

A recent survey by the International Federation for the Surgery of Obesity showed that RYGB and SG account for the large majority of bariatric procedures (45% and 37%, respectively). The use of ABG has drastically fallen during the last decade and currently accounts for 10% of all procedures. BPD and its duodenal switch (BPD/DS)variant, which are truly malabsorptive procedures, are rarely used (< 2%) to date given the high risk of nutritional complications[16].

NUTRITIONAL ISSUES AFTER BARIATRIC SURGERY

Anemia

According to a recent report from the American Society of Hematology, people who have undergone bariatric procedures show the highest risk for anemia, with 33%-49% of operated patients presenting anemia within 2 years after surgery[17]. As expected, the average prevalence of anemia is lower following LSG (17%) and reaches 45%-50% after RYGB and BPD. It should be noted that, as underlined for other nutrient deficiencies, up to 10%-12% of obese patients already have anemia before surgery[18]; thus, baseline screening for anemia is recommended in all patients who are scheduled for bariatric procedures.

Patients with mild anemia are most likely asymptomatic; however, when the anemia worsens, the patients could present with symptoms, such as fatigue, pallor, and dyspnea on exertion. Of note, the presence of anemia increases by twofold the risk of hospitalizations as well as the length of the in-hospital stay[19].

Post-bariatric anemia is in most cases due to iron deficiency, along with vitamin B12 deficiency as a secondary cause. Iron deficiency, expressed by low serum ferritin, occurs in more than 30% of patients after 5 years from surgery, with a similar rate after RYGB and SG, as recently reported by Alexandrou *et al*[20]. Iron-deficiency can be attributed to several causes. Reduced iron absorption due to hypocloridria and the bypassing of the duodenum and proximal jejunum (which are the main sites of iron absorption) are the primary mechanisms that lead to iron deficiency. Post-operative reduction in food intake and changes in food preferences, such as intolerance for meat and dairy products, are important contributory factors.

Measurement of serum ferritin is the best diagnostic test for detecting iron deficiency since it is a more specific and earlier indicator of iron body capacity and becomes abnormal prior to a decrease in serum iron con-centration. For this reason, ferritin and hemoglobin should be periodically monitored in bariatric patients. Current guidelines[21] recommend oral iron supplementation in all operated patients for preventive purposes. However, for the correction of iron deficiency (when iron deficiency sets in), oral supplementation is not sufficient, and intravenous iron administration is required.

Vitamin B12 deficiency is a major cause of anemia in patients who undergo BPD and RYGB, with a prevalence of 19%-35% after 5 years[22]. Purely restrictive procedures are usually not associated with vitamin B12 deficiency. Vitamin B12 deficiency can result from inadequate secretion of intrinsic factor, limited gastric acidity and, above all, the bypassing of the duodenum, which is the main site of vitamin B12 absorption. Since the human body has substantial reserves of vitamin B12, clinical manifestations of a deficit can appear after

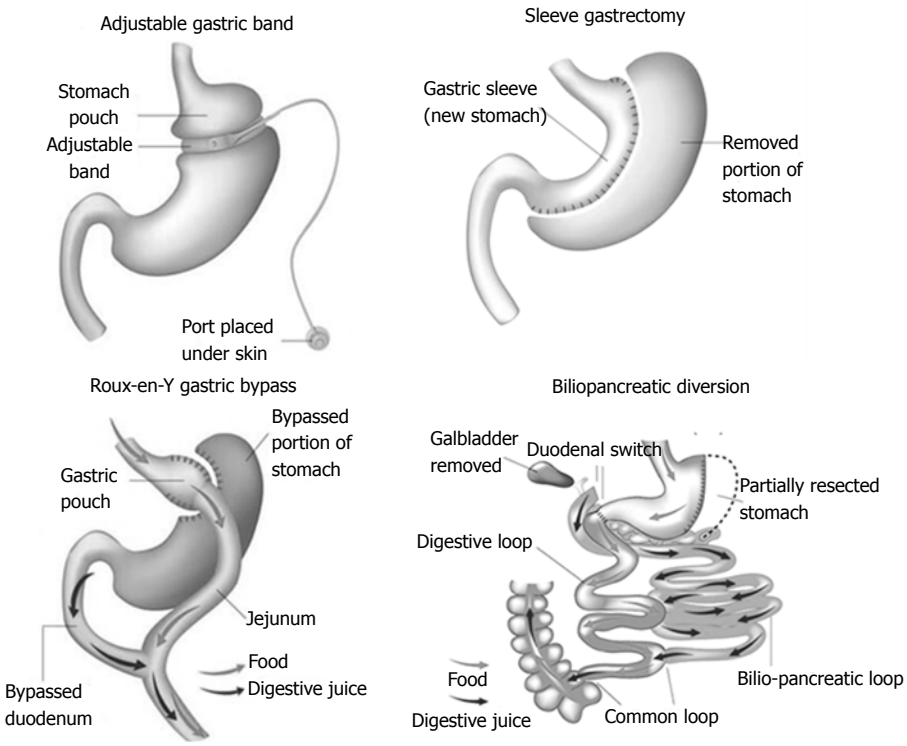

Figure 1 Commonly performed bariatric surgeries. Modified from http://www.bariatric-surgery-source.com/.

a certain time from surgery, when the body stores are depleted to as little as 5%-10%. In addition to anemia, a lack of vitamin B12 can lead to neurological and psychiatric symptoms, including paresthesia, numbness, disturbance of coordination, memory disturbance and, in some instances, dementia. Oral or intramuscular supplementation of vitamin B12 is recommended after malabsorptive procedures, while there is no evidence of benefits after restrictive surgery.

Folic acid deficiency is a potential complication of bariatric procedures that can contribute to anemia. The prevalence of this deficit after both restrictive and malabsorptive procedures ranges from 9% to 39%[23,24]. It can manifest as macrocytic anemia, piastrinopenia, leucopenia, or glossitis. It could cause growth retardation and, in pregnant women, congenital defects (neural tube). Since folate is absorbed throughout the small intestine, the deficiency is primarily induced by a shortage of dietary intake rather than malabsorption. Furthermore, folate deficiency can be aggravated by vitamin B12 deficiency since the latter is necessary for the conversion of inactive methyltetrahydrofolic acid to the active tetrahydrofolic acid. Folate deficiency can be easily corrected by oral supplementation.

Abnormalities of bone metabolism

Bariatric surgery could impact bone metabolism and induce significant changes, such as decreased mechanical loading, calcium/vitamin D malabsorption with secondary hyperparathyroidism, nutritional deprivations, changes in fat mass and alterations in fat- and gut-derived hormones[25-27].

In general, weight loss, achieved through dietary restriction, drugs or bariatric surgery, is associated with a significant reduction in bone mineral density (BMD) and increased bone turnover[28]. In particular, the bone loss reported after non-surgical weight loss is much lower (1%-2%)[29] than that found after bariatric procedures (8%-13%)[30,31] A recent meta-analysis of studies that compare bariatric vs a non-operated control group showed reduced BMD at the femoral neck but not at the lumbar spine[30]. However, it is important to note that the measurement error at the spine BMD is greater than at other sites, which could likely account for this discrepancy. In addition, there is high heterogeneity in the studies analyzed with regard to different surgery procedures, study design (most retrospective), and patient characteristics (ethnicity, sex, menopausal/postmenopausal stage, follow-up length), which could account for the differences between the two sites. Overall, the reductions in the BMD results are greater after malabsorptive or mixed than after restrictive procedures. Studies that compare RYGB and SG have shown a greater bone loss after RYBG than SG, especially at the hip and femoral neck[32]. Accordingly, bone turnover expressed by circulating markers such as CTX, PINP, TRAcP5b was significantly higher after RYGB than after SG[33]. The difference in the BMD between the two procedures could also be related to the different hormonal patterns induced by the two operations. Indeed, there is increasing evidence that many fat- and gut-derived hormones could affect bone health[25,33,34]. In particular, low levels of GIP, ghrelin, amylin, and insulin and high levels of PYY exert negative

effects on the bone mass. In contrast, low serotonin and high GLP-1 levels appear to positively influence the bone metabolism[25]. However, further studies are needed to better define the role of these hormones in the regulation of bone metabolism.

Bariatric surgery is associated with an increased risk of fractures[35,36]. In a population-based study, the cumulative incidence of any new fracture at 15 years was 58% in bariatric patients compared to 24% in non-operated men and women of similar age. The relative risk for any fracture was increased by 2.3-fold both at the traditional osteoporotic (hip, spine, wrist) and at non-osteoporotic sites[35].

Calcium and vitamin D deficiencies are the main factors that are responsible for the accelerated bone loss after bariatric surgery. The incidence of calcium deficiency after surgery is almost 10%[37] and is caused by reduced calcium absorption that results from bypassing the duodenum and proximal jejunum, which are the main sites of absorption. In some cases, calcium deficiency could be exacerbated by low calcium intake due to the intolerance/exclusion of milk products.

The prevalence of hypovitaminosis D after surgery varies between 25% and 73%, depending on the duration of the follow-up and its defining parameters (25-OH-vitamin D < 20 or < 30 ng/mL). It is important to note that hypovitaminosis D exists in a large proportion of patients prior to surgery, with reports that range from 25% to 80%. However, bariatric surgery *per se* affects the vitamin D status[38]. Indeed, similar to calcium deficiency, hypovitaminosis D could be a consequence of fat malabsorption, due to the bypass of the primary absorption sites of liposoluble vitamins in the small intestine[39,40]. In fact, a duodenal surgical bypass decreases cholecystokinin secretion, which results in a reduction in pancreatic lipolytic enzyme secretions and alteration in biliary salts, which in turn leads to an alteration in fat digestion and steatorrhea[24]. In addition, after both malabsorptive and restrictive procedures, reduced intake of dairy products, vomiting, and non-adherence to supplement recommendations could worsen the vitamin D status[39,40].

These are no clear recommendations for vitamin D doses following bariatric surgery, since individual patients could require larger or smaller doses according to the degree of deficit. Current recommendations[21] indicate that at least 5000 IU/d is required to maintain adequate vitamin D levels after RYGB, while higher doses (up to 50000 IU) are required after BPD. Recent studies have suggested that the vitamin D level should be maintained at over 25-30 ng/mL for the effective prevention of osteoporosis and fracture risk. Daily calcium supplementation (preferably as calcium citrate) from 1200 to 2000 mg daily is recommended. It must be considered that oral calcium could interfere with the absorption of some essential minerals such as iron, zinc and copper.

Deficiencies of other vitamins and minerals

Low serum levels of fat-soluble vitamins (vitamin A, K and E) have been found to occur after malabsorptive procedures (BPD and long limb RYGB). However, the available data are largely based on clinical reports and, therefore, are insufficient to estimate the real prevalence of these deficiencies. In two series of studies, the incidence of vitamin A deficiency was 61%-69% at 2-4 year after BPD, with or without duodenal switch[41,42]. In a third series, the incidence was as low as 5% by 4 year[43]. Clinical manifestation of vitamin A deficits are night blindness, xerophthalmia and dry hair.

Low levels of vitamin K have been reported in 50%-60%[42] of patients who underwent BPD or BPD/DS, but no clinical symptoms such as easy bruising, increased bleeding, or clotting alterations were reported.

With regard to the water-soluble vitamins, thiamine (vitamin B1) deficiency can occur in up to 49% of patients after surgery as a result of bypass of the jejunum, where it is primarily absorbed, or in the presence of impaired nutritional intake from persistent, severe vomiting[44]. The early symptoms of thiamine deficiency are nausea and constipation, followed by neurological and psychiatric complications known as Wernicke-Korsakoff syndrome. The prevalence of vitamin C deficiency ranges from 10%-50%[45,46], but it rarely results in manifest clinical signs (poor wound healing, petechiae, bleeding gums).

Although most of the literature focuses on calcium and iron, deficiencies of other essential minerals such as magnesium, zinc, copper, and selenium have been reported in bariatric patients[47]. Essential minerals act as enzymatic cofactors in several biochemical pathways, and therefore, their deficiency could cause variable clinical manifestations that involve neurological, cardiac and gastrointestinal systems. Mineral deficiencies are more common after BPD and RYGB; however, the real prevalence of these disturbances cannot be precisely estimated since most deficiencies can be present already before surgery (see the next paragraph). In addition, for some minerals such as copper and magnesium, the circulating concentrations might not reflect their total body stores, thus leading to underestimation of the real deficit.

Protein malnutrition

Protein malnutrition remains the most severe macronutrient complication associated with malabsorptive surgical procedures. It has been reported in 7%-21% of patients who underwent BPD and is a consequence of poor protein digestion and absorption secondary to altered biliary and pancreatic function[48]. Protein malnutrition can also occur after RYGB, where the Roux limb exceeds 150 cm, with an incidence of 13% at the 2-year follow-up. SG and AGB can lead to protein malnutrition in patients who present maladaptive eating behaviors after surgery, those who avoid protein food sources and those who have protracted vomiting. The clinical signs of protein malnutrition include edema, hearing loss and low serum albumin level (< 3.5 g/dL). Protein malnutrition associated with malabsorptive

procedures causes an annual hospitalization rate of 1% per year and leads to significant morbidity and poor outcomes[49,50]. Monitoring the serum albumin concentration is useful for the evaluation of the protein nutritional state, although the serum protein level often remains in the normal range until late. Measurement of lean body mass by means of dual X–ray absorptiometry or body bioimpedence assessment can be helpful for the evaluation of body composition, although their accuracy appears to be limited in bariatric patients.

According to consensus guidelines[21], the prevention of protein malnutrition requires an average daily protein intake of 60-120 g (1.1 g/kg of ideal body weight), which should be increased by 30% following BPD. Furthermore, great emphasis is posed on regular training and aerobic exercise as being essential to preserving lean mass and especially muscle mass. Patients with severe protein malnutrition should be managed with modular protein supplements that are rich in branch-chain amino acids and, eventually, enteral feeding.

Post-operative weight regain

The regain of the weight lost is one of the main concerns of bariatric patients over the long term. The incidence of this phenomenon is quite variable according to the type of procedure performed, the length of follow-up and, above all, the criteria to define weight regain. Among different definitions, the most widely accepted method refers to a regain of 25%-30% of the maximum weight lost, corresponding to the weight before surgery, with the subtraction of minimum weight or "nadir" after surgery[51-53]. A recent review has shown that the rates of weight regain for SG range from 5.7% at 2 years to 75.6% at 6 years[54]. For RYGB, the percentage of failure to maintain weight loss varies from 7% to 50% of the subjects and tends to be higher in superobese patients[55]. AGB is associated with the largest weight regain (35%-40% of the weight lost), as evidenced in several clinical studies[11,51].

The failure to maintain long-term weight loss has important consequences on the patients' health, including the relapse of obesity-related co-morbidities[56]. Furthermore, it has substantial economic repercussions for the recurrent costs associated with the management of on-going obesity. Therefore, there have been many efforts to understand the biological and psychologic/behavioral bases that underlie this important phenomenon.

One of the major factors responsible for weight regain is the reduction in energy expenditure (EE), which is generally paralleled by the simultaneous loss of lean body mass[57]. Recently, Tam *et al.*[57] showed that EE is significantly reduced 1 year after RYGB (-124 ± 42 kcal/die) as well as after SG (-155 ± 118 kcal/die) compared to the baseline. These findings extend what was already known with diet-induced weight loss and give support to the view that the reduction in EE is a homeostatic mechanism that counteracts a reduction in the caloric intake, which is aimed at preventing excessive weight loss; however, in some conditions, it could favor weight regain.

Another factor that contributes to weight regain is the changes in entero-hormone and appetite regulation[56]. As widely demonstrated, BS is associated with a recovery of the postprandial response of GLP-1, which increases by 3- to 6-fold compared to pre-surgery levels[58]. Interestingly, it has been shown[52] that in patients operated by RYGB, the post-meal response of GLP1 was significantly greater in individuals who maintained weight loss compared to individuals who failed, which suggests that this hormone plays a role in the maintenance of a favorable weight outcome. With regard to ghrelin, the results are quite controversial, with some but not all[59] studies showing greater and more sustained suppression of ghrelin levels in bariatric patients who maintained appropriate weight loss compared to those who regained weight[60,61].

Moreover, mental health disorders, such as depression, alcohol and drug use, and food urges are predictive factors of weight regain[62,63]. Although binge eating is more frequent among obese patients who make recourse to BS (10%-50%), there is no doubt that its persistence after surgery is associated with a minor weight loss and an early weight regain[64].

Beyond all of the above-mentioned factors, the success of bariatric surgery is strongly influenced by the patients' motivation to adhere to a healthier lifestyle, including controlled energy intake and physical activity[65]. In the Swedish Obese Subjects study[66], the reported mean energy intake was 2900 kcal/die before surgery, 1500 kcal/die 6 mo after surgery and approximately 2000 kcal/die 4-10 years after surgery, which demonstrates a progressive increase in calorie intake over the years. These data emphasize dietary counselling and the practice of physical exercise as fundamental measures to prevent weight recidivism.

PRE-OPERATIVE NUTRITIONAL STATE: A CRITICAL FACTOR

It is a common belief that nutritional deficiencies are rare in Western countries due to the availability of low cost and unlimited variety of food supply. However, obese subjects often adopt an unhealthy diet that is rich in high-calorie food with an unbalanced nutritional composition[67,68]. The concomitant presence of high calorie intake and nutrient deficiencies could impact the effectiveness of calorie utilization, which could determine a vicious cycle that leads to further weight gain, depression, eating disorders, metabolic syndrome, fatigue and more[67]. In support of these concepts, a growing number of studies in the literature attest to the frequent occurrence of nutrient and/or vitamin/mineral deficiencies in morbidly obese individuals prior

Table 1 Schedule of biochemical and nutritional assessments for the different bariatric procedures

Assessments	Pre-operative	1 mo	3 mo	6 mo	12 mo	18 mo	24 mo	Annually
MOC DEXA							AGB, SG, RYGB, BPD[1]	AGB3, SG, RYGB, BPD[1]
Calcium	AGB, SG, RYGB, BPD[2]	AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]
Magnesium	AGB, SG, RYGB, BPD[1]		AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]	RYGB, BPD[1]		RYGB, BPD[1]	RYGB, BPD[1]
Phosphorus	AGB, SG, RYGB, BPD[1]				AGB, SG, RYGB, BPD[1]		AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]
Zinc	AGB, SG, RYGB, BPD[2]		RYGB, BPD[1]	RYGB, BPD[2]	AGB, SG, RYGB, BPD[2]		AGB, SG, RYGB, BPD[2]	AGB, SG, RYGB, BPD[2]
Iron	AGB, SG, RYGB, BPD[2]		RYGB, BPD[1]	RYGB, BPD[1]	AGB, SG, RYGB, BPD[2]	RYGB, BPD[1]	AGB, SG, RYGB, BPD[2]	AGB, SG, RYGB, BPD[2]
Transferrin	AGB, SG, RYGB, BPD[2]		AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]		AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]
Ferritin	AGB, SG, RYGB, BPD[2]		AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]		AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]
Vitamin A	AGB, SG, RYGB, BPD[2]		RYGB, BPD[1]	RYGB, BPD[1]	RYGB, BPD[1]		RYGB, BPD[1]	RYGB, BPD[1]
Vitamin E	AGB, SG, RYGB, BPD[1]				AGB, SG, RYGB, BPD[1]			
Vitamin D	AGB, SG, RYGB, BPD[2]		RYGB, BPD[2]	RYGB, BPD[2]	AGB, SG, RYGB, BPD[2]		AGB, SG, RYGB, BPD[2]	AGB, SG, RYGB, BPD[2]
Vitamin B1	AGB, SG, RYGB, BPD[2]	AGB, SG, RYGB, BPD[2]	AGB, SG, RYGB, BPD[1]		AGB, SG, RYGB, BPD[1]		AGB, SG, RYGB, BPD[1]	AGB, SG, RYGB, BPD[1]
Vitamin B6	AGB, SG, RYGB, BPD[2]				AGB, SG, RYGB, BPD[1]			AGB[3], SG[3], RYGB[3], BPD[1,3]
Vitamin B12	AGB, SG, RYGB, BPD[1]			AGB, SG, RYGB, BPD[2]	AGB, SG, RYGB, BPD[2]	AGB, SG, RYGB, BPD[2]	AGB, SG, RYGB, BPD[2]	AGB, SG, RYGB, BPD[2]
Parathormone	AGB, SG, RYGB, BPD[2]			AGB, SG, RYGB, BPD[2]	AGB, SG, RYGB, BPD[2]		AGB, SG, RYGB, BPD[2]	AGB, SG, RYGB, BPD[2]

[1]Useful, including all contents in the space; [2]Recommended, including all contents in the space; [3]Every 2-5 years. AGB: Laparoscopic adjustable gastric banding; SG: Sleeve gastrectomy; RYGB: Roux-en-Y gastric bypass; BPD: Biliopancreatic diversion.

to bariatric surgery, before weight loss and possible surgical-related malabsorption set in.

With regard to the vitamin status, most evidence refers to a 25(OH)vitamin D deficit. Vitamin D insufficiency (< 30 ng/dL) has been reported in approximately 90% of different study populations, and ranges from 65%[69] to 100%[70], while vitamin D deficiency (< 20 ng/dL) is observed in approximately 60% of the patients, ranging from 22%[71] to 83%[72]. The prevalence of severe deficit (< 10 ng/dL) could reach 25%[73]. The degree of deficiency is predicted by the degree of obesity and race, with African Americans being at higher risk[74].

Obese individuals are more likely to be deficient in vitamin D because of the higher volumetric dilution and sequestration of this fat-soluble hormone in the adipose tissue[75]. As the fat mass increases, an individual will require greater amounts of vitamin D (*via* photoproduction from sun exposure, dietary intake, and/or supplementation). Moreover, although there is no difference in the vitamin D_3 production between obese and lean individuals, obese patients show an impaired release of vitamin D_3 from the skin[76]. Genetic variation in the function of the vitamin D binding protein and vitamin D receptor could also influence the 25(OH)D levels, with some studies suggesting a higher frequency of the poorer functioning forms in obesity[77,78].

The prevalence of vitamin B12 deficiency in patients scheduled for BS is reported in approximately 18% of patients. Similarly, low levels of vitamin B1 (thiamine) are reported in up to 20% of bariatric candidates. Few studies have assessed the vitamin C status in bariatric candidates, with a prevalence that ranges from 15%[69] to 33%[79]. With regard to vitamins A and E, their deficiencies are less frequent[69,73]. In particular, vitamin A has been found to be inversely associated with BMI, age and number of comorbidities[73]. This finding most likely occurs because low vitamin A levels are related to increased oxidative stress, insulin resistance, impaired glucose metabolism, cancers, and age-related macular degeneration[80], all of which are commonly associated with morbid obesity.

Among the minerals, iron deficiency is the most common and ranges from 20% to 47%[81]. Iron and ferritin deficiency and iron-deficiency anemia are more frequent in younger patients (< 25 years) than in older patients and in women than in men, although this finding is not confirmed in all studies[82]. Iron deficiency in obese patients is likely related to the negative impact that chronic inflammation exerts on iron homeostasis. In particular, there is evidence that cytokines (TNFα and

IFNγ) can induce the apoptosis of erythroid progenitor cells and increase hepcidin levels, which leads in turn, to reduced intestinal iron absorption and reduced bioavailability[83].

The prevalence of zinc deficiency prior to bariatric surgery amounts to 10.2%[84-86]. Interestingly, some studies have shown an inverse association of zinc levels, with C-reactive protein highlighting the adverse influence of systemic low-grade inflammation on the zinc status[84].

Overall, the high prevalence of pre-surgery nutritional deficiencies in bariatric candidates supports the need for a careful pre-operative evaluation of the nutritional status, to assess and adequately correct the pre-existing deficits.

CONCLUSION

Nutritional deficiencies represent a relevant long-term clinical problem in patients who underwent bariatric surgery as a result of modifications to the gastrointestinal anatomy and physiology, which could impact macro- and micro-nutrient absorption. Therefore, the best practices guidelines[21] highly recommend regular metabolic and nutritional monitoring after bariatric surgery, which frequency varies according to the type of procedure. In light of the high prevalence of nutrient deficiencies even prior to surgery, the current Guidelines also underscore the need for a complete pre-surgery nutritional assessment in all candidates for bariatric surgery. The schedule of the biochemical and nutritional monitoring for the different procedures is reported in Table 1. Although there are few studies with long-term nutritional follow-up, there is general agreement that nutritional assessments should be performed throughout life; furthermore, multivitamin and calcium supplementation with added vitamin D is recommended for all weight-loss surgery patients. In conclusion, nutritional surveillance is an essential component of the management of bariatric patients for the following reasons: (1) increases the patients' adherence to healthy dietary habits and appropriate supplementation regimens; (2) prevents the risk of weight regain; (3) facilitates the detection of possible nutritional deficiencies that could develop despite medical therapy; and (4) contributes to maintaining a good quality of life.

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ORIGINAL ARTICLE

Retrospective Study

Reproductive disturbances among Saudi adolescent girls and young women with type 1 diabetes mellitus

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Abstract

AIM

To identify reproductive disturbances among adolescent girls and young women with type 1 diabetes mellitus (T1DM) in Saudi Arabia.

METHODS

This cross sectional study was conducted among 102 female with T1DM, (aged 13-29 years) who attended the Diabetes Clinic at Diabetes Treatment Center, Prince Sultan Military Medical City, Saudi Arabia between April 2015 to March 2016. Clinical history, anthropometric characteristics and reproductive disturbance were collected through a questionnaire.

RESULTS

Of 102 patients included in this analysis, 26.5% (27/102) were reported that they experienced an irregular menses. Of these patients, when compared to whose diabetes was diagnosed before menarche (35.4%, 17/48), patients diagnosed with diabetes after menarche (18.5%, 10/54) showed significantly less irregular menses (difference 16.9%, $P = 0.04$). Similarly, compared to patients diagnosed with diabetes prior to menarche (mean age 12.9 years; $n = 48$), patients diagnosed with diabetes after menarche (mean

age 12.26 years; *n* = 54) were found to have 0.64 years delay in the age of menarche (*P* = 0.04). Among the studied patients, 15.7% (16/102) had polycystic ovary syndrome (PCOS). Of these PCOS patients, 37.5% (6/16) had irregular menses, 6.3% (1/16) had Celiac disease, 37.5% (6/16) had Hashimoto thyroiditis and 18.7% (3/16) had acne.

CONCLUSION

More than one fourth of the study population with T1DM experiencing an irregular menses. Adolescent girls and young women diagnosed with diabetes prior to menarche showed higher menstrual irregularity and a delay in the age of menarche.

Key words: Type 1 diabetes; Reproductive disturbances; Polycystic ovarian syndrome; Premature ovarian failure; Menarche; Saudi Arabia

Core tip: The present study found more than one fourth of the adolescent girls and young women with type 1 diabetes experiencing an irregular menses. Adolescent girls and young women diagnosed with diabetes prior to menarche reported 16.9% higher menstrual irregularity and 0.64 years delay in the age of menarche.

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INTRODUCTION

The last few decades have shown a trend of a steady increase in the incidence of type 1 diabetes mellitus (T1DM) patients in most parts of the world[1-3]. Research has shown a rise in the incidence of T1DM in Saudi Arabia in the preceding 30 years as well as in the prevalence of T1DM among the children and adolescents in the Kingdom to be 109.5 per 100000, a figure higher than that of several advanced countries[4-6].

T1DM is a chronic autoimmune disease that represents a multi-faceted challenge to normal reproductive function throughout life. Despite the improvements in diabetes therapy, adolescent girls and young women with T1DM still face frequent disturbances in the reproductive system including infertility, delayed onset of puberty and menarche, menstrual irregularities (especially oligomenorrhoea) and premature ovarian failure (POF)[7-9]. Such females show a tendency, on average, to attain menarche a little later in life than non-diabetic women[10]. At the other extreme, diabetic women tend to experience menopause marginally sooner[8,11]. Furthermore, women with T1DM exhibit a high degree of hyperandrogenic disorders, like polycystic ovary syndrome (PCOS) and hirsutism[12]. Despite the previous, PCOS is commonly linked with conditions driven by insulin resistance, such as type 2 diabetes mellitus (T2DM)[13]. However, several studies demonstrated that T1DM patients may also experience insulin resistance, especially in obese individuals, and even PCOS[12,14].

Compared to studies performed in the developed countries, limited literature are available in Saudi Arabia on reproductive disturbances among adolescent girls and young woman due to the lack of appropriate studies performed in these specific aspects. Therefore, the current work was done as a cross-sectional study to identify the reproductive disturbances among adolescent girls and young women with T1DM in a tertiary care center, specifically attempting to isolate the factors that can cause such abnormalities.

MATERIALS AND METHODS

Study design and setting

This cross sectional study was conducted among 102 female with T1DM (aged 13-29 years) who attended the Diabetes Clinic at Diabetes Treatment Center, Prince Sultan Military Medical City (PSMMC), Saudi Arabia between April 2015 to March 2016. The PSMMC is a 1200-bed, tertiary medical center in Riyadh, Saudi Arabia, with almost 40000 annual admissions (950000 active patients files) per year from different region of the country.

Criteria for selection of patients

The participants were conveniently selected according to their availability during their routine visit to the outpatient clinics. All patients provided written informed consent to participate the study, for adolescent patients consent form were collected from their parents/legal guardians.

Adolescent patients with T1DM and young women aged 13-29 years and Saudi nationals were included in the study, while patients with T2DM, double diabetes (expressing features resulting from both type 1 diabetes and type 2 diabetes), maturity onset diabetes of young (MODY), pregnant and patients using oral contraceptive pills were excluded. Also, patients with the other conditions with similar phenotypical characteristics to those associated with PCOS such as Hyperprolactinaemia states, Cushing's syndrome, Acromegaly, Congenital adrenal hyperplasia, thyroid disorders, adrenal tumors (adrenal carcinoma, adrenal adenoma), ovarian tumors, androblastomas (Sertoli–Leydig cell tumors), granulosa cell tumors, Sertoli cell tumors, Hilus cell tumors, primitive neuro-ectodermal tumors (PNET) and HAIR-AN syndrome were excluded.

Data collection and definitions

Anthropometric characteristics and a detailed clinical history were obtained through a questionnaire. A

complete physical examination was performed for all patients. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters (BMI; kg/m^2) and BMI z score (adjusted for child age and gender). The *z* score (or SD score) was calculated as per the formula (Xi-Mx)/SD, where Xi is the actual measurement, Mx is the mean value for that age and gender, and SD is the standard deviation corresponding to that age and gender [15].

History of recurrent diabetic ketoacidosis (RDKA) (defined as three or more episodes occurring within a period of four years as visiting the accident and emergency room or admitted in hospital), dyslipidemia, Hashimoto thyroiditis, Celiac disease and premature ovarian failure (POF) were also collected[16]. All patients were also screened for diabetic complications (neuropathy and retinopathy and nephropathy) if the duration of their diabetes 5 years or more.

Menstrual disturbances were recorded based on verbal information provided by the patients. Oligomenorrhea was defined by 3 or more cycles with a length of more than 36 d in the previous year, and amenorrhea was defined by lack of vaginal bleeding for the last 3 mo. Hirsutism was defined as excess terminal (thick pigmented) body hair in an androgen-dependent pattern, and which is commonly noted on the upper lip, chin, periareolar area, in the midsternum, and along the linea alba of the lower abdomen. It was estimated according to the modified Ferriman-Gallwey scale score of 8 or more, which was determined by a single experienced observer[17]. The presence of acne was also evaluated. The puberty was appreciated according to the Tanner Stage[18]. The POF was defined as the development of irregular menses or amenorrhea before the age of 40 years in association with follicle-stimulating hormone (FSH: IU/L) concentrations in the postmenopausal range (as defined by the measuring laboratory). Polycystic ovaries were diagnosed by pelvic or intravaginal sonography according to the Rotterdam consensus criteria. PCOS was defined by the presence of two out of three of the following criteria: (1) Oligo- and/or anovulation (irregular menses or amenorrhea); (2) Clinical and/or biochemical signs of hyperandrogenism; and (3) Polycystic ovaries (by pelvic ultrasound, include the presence of 12 or more follicles in each ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume (>10 mL; calculated using the formula 0.5 × length × width × thickness). One ovary fitting this definition is sufficient to define polycystic ovarian morphology (PCOM) and exclusion of other etiologies[19].

The glycosylated haemoglobin A1c (HbA1c) testing was performed in our laboratory using a method that is The National Glycohaemoglobin Standardization Program (NGSP), United States certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay[20]. Total testosterone level was done for all the patients (normal level 0.69 to 2.1 nmol/L). Plasma testosterone was analyzed using Elecsys Testosterone Ⅱ from Roche company where the electrochemiluminescence immunoassay "ECLIA" was intended for use on Elecsys and cobas e immunoassay analyzers. Regarding the testosterone level, 0.69 to 2.1 nmol/L considered as normal and testosterone > 2.1 mmol/L considered as high testosterone level.

In patients with irregular menses and no clinical or biochemical features of hyperandrogenism, we performed pelvic ultrasound to study the morphology of the ovaries. Pelvic ultrasound was also performed in patients with amenorrhea.

Statistical analysis

Data analysis was carried out using Microsoft Excel 2010 (Microsoft Corporation, Seattle, WA, United States) and Statistical Package for Social Sciences version 22 (SPSS Inc., Chicago, IL, United States). In addition to the descriptive analysis, χ^2 test (for categorical variables) and independent *t* test (for continuous variables) were also performed to identify variables associated with reproductive disturbances before and after diagnosis menarche and patients with PCOS and without PCOS. Continuous variables are represented as mean values ± SD, while categorical variables are expressed as frequencies and percentages. A *P*-value of < 0.05 was considered as statistically significant.

RESULTS

The overall mean of the clinical parameters of the study population were as follows: Age 18.26 ± 4.05 (range 13-29 years), age at diagnosis of diabetes 11.5 ± 3.96 (range 1-21 years), duration of T1DM 6.8 ± 5.35 years (range 1-28 years), age at menarche 12.56 ± 0.96 (range 9-16 years), BMI 23.54 ± 3.3 kg/m^2 (range 17.8-34.4) and HbA1c was 9.23 ± 1.92 (range 6-16).

Clinical and anthropometric characteristics of the study population are shown in Table 1. Among the studied population, 41.2% (42/102) possess family history of DM; 15.7% (16/102) had PCOS; 1% (1/102) had POF; and 2.95% (3/102) had amenorrhea. The study also found that 26.5% (27/102) of patients had irregular menses; 18.6% (19/102) had acne; 6.9% (7/102) had Celiac disease; 33.3% (34/102) had Hashimoto thyroiditis; 13.7% (14/102) had dyslipidemia, 24.5% (25/102) had hirsutism;12.7% (13/102) had RDKA and 11.8% (12/102) had diabetes complication (neuropathy and retinopathy and none of our patients had nephropathy).

Majority of the study population are in teen age group 13-19 (69.6%, 71/102; mean = 15.9). Among the 71 teenagers, 2.8% (2/71) underweight, 26.8% (19/71) overweight, 2.8% (2/71) obese and 67.6% (48/71) were normal. The mean age of the young women (20-29 years, *n* = 31) was 23.5 years. Among the young women, 3.2% (1/31) underweight, 48.4% (15/31) overweight, 3.2% (1/31) obese and 45.2% (14/31) were normal.

The factors associated with menarche before and after diagnosis of diabetes are shown in Table 2. A total

Table 1 Clinical and anthropometric characteristics of the study population

Variables	Frequency (n = 102)	%
Age (yr)		
13-19	71 (mean age 15.9 ± 2.72)	69.6
20-29	31 (mean age 23.5 ± 2.41)	30.4
Family History of diabetes		
No	60	58.8
Yes	42	41.2
Polycystic ovarian syndrome		
No	86	84.3
Yes	16	15.7
Recurrent diabetic ketoacidosis		
No	89	87.3
Yes	13	12.7
Complications of diabetes		
No	90	88.2
Yes	12	11.8
Age of diagnosis (yr)		
1-10	34 (mean 7.1 ± 2.85)	33.3
11-21	68 (mean 13.8 ± 1.99)	66.7
Age of menarche (yr)		
9-11	5	4.9
12	50	49
13-16	47	46.1
Menses		
Irregular	27	26.5
Regular	75	73.5
Premature ovarian failure		
No	101	99
Yes	1	1
Celiac disease		
No	95	93.1
Yes	7	6.9
Hashimoto thyroiditis		
No	68	66.7
Yes	34	33.3
Dyslipidemia		
No	88	86.3
Yes	14	13.7
Hirsutism		
No	77	75.5
Yes	25	24.5
Acne		
No	83	81.4
Yes	19	18.6
Pelvic ultrasound		
Not done	67	66.7
Small ovaries	3	2.9
Normal	11	10.8
PCOS	21	20.6
Testosterone level		
Normal	77	75.5
High	25	24.5
Hemoglobin A1C		
≤ 7%	13 (mean 6.67 ± 0.57)	12.7
> 7%	89 (mean 9.57 ± 1.78)	87.3

PCOS: Polycystic ovary syndrome.

of 47.1% (48/102) patients were diagnosed as having diabetes before menarche and 52.9% (54/102) were diagnosed as having diabetes after menarche. Age, duration of DM and acne showed statistically significant differences among the two groups. Similarly, when compared with those identified with diabetes before menarche (9.73%), the girls diagnosed with diabetes post menarche (8.78%) reported lower HbA1c levels (P = 0.007).

Figure 1 shows the percentage differences of irregular menses among patients diagnosed with diabetes before and after menarche. Compared to whose diabetes was diagnosed before menarche 35.4% (17/48), patients diagnosed with diabetes after menarche 18.5% (10/54) showed less irregular menses (differences 16.9%, P = 0.04). Similarly, compared with

Table 2 Factors associated with menarche before and after diagnosis of diabetes

Variables	Diabetes diagnosed before menarche (n = 48), n (%)	Diabetes diagnosed after menarche (n = 54), n (%)	P value
Age (yr)			
13-19 (n = 71)	38 (53.5)	33 (46.5)	0.038
20-29 (n = 31)	10 (32.3)	21 (67.7)	
Family history of diabetes			
No (n = 60)	28 (46.7)	32 (53.3)	0.542
Yes (n = 42)	20 (47.6)	22 (52.4)	
Polycystic ovarian syndrome			
No (n = 86)	42 (48.8)	44 (51.2)	0.289
Yes (n = 16)	6 (37.5)	10 (62.5)	
Recurrent diabetic ketoacidosis			
No (n = 89)	42 (47.2)	47 (52.8)	0.591
Yes (n = 13)	6 (46.2)	7 (53.8)	
Complications of diabetes			
No (n = 90)	41(45.6)	49 (54.4)	0.299
Yes (n = 12)	7 (58.3)	5 (41.7)	
Menses			
Irregular (n = 27)	17 (63)	10 (37)	0.04
Regular (n = 75)	31 (41.3)	44 (58.7)	
Premature ovarian failure			
No (n = 101)	48 (47.5)	53 (52.5)	
Yes (n = 1)	0	1 (100)	0.529
Celiac disease			
No (n = 95)	44 (46.3)	51(53.7)	0.434
Yes (n = 7)	4 (57.1)	3 (42.9)	
Hashimoto thyroiditis			
No (n = 68)	31 (45.6)	37 (54.4)	0.416
Yes (n = 34)	17 (50)	17 (50)	
Dyslipidemia			
No (n = 88)	42 (47.7)	46 (52.3)	0.482
Yes (n = 14)	6 (42.9)	8 (57.1)	
Hirsutism			
No (n = 77)	37 (48.1)	40 (51.9)	0.452
Yes (n = 25)	11 (44)	14 (56)	
Acne			
No (n = 83)	45 (54.2)	38 (45.8)	0.002
Yes (n = 19)	3 (15.8)	16 (84.2)	
Pelvic ultrasound			
Not done (n = 67)	31 (46.3)	36 (53.7)	0.103
Small ovaries (n = 3)	3 (100)	0	
Normal (n = 11)	7 (63.6)	4 (36.4)	
Polycystic ovary syndrome (n = 21)	7 (33.3)	14 (66.7)	
Testosterone level			
Normal (n = 77)	40 (51.9)	37 (48.1)	0.065
High (n = 25)	8 (32)	17 (68)	
Variables	mean ± SD	mean ± SD	P value
Body mass index	23.83 ± 0.5	23.28 ± 0.3	0.123
Duration of diabetes	9.13 ± 0.8	4.74 ± 0.5	0.011
Age at diabetes diagnosis	8.42 ± 0.4	14.3 ± 0.2	0
Insulin dose unit/kg	0.84 ± 0.23	0.88 ± 0.23	0.794
Hemoglobin A1c	9.73 ± 0.3	8.78 ± 0.2	0.007
Body mass index	23.83 ± 0.5	23.28 ± 0.3	0.123

Categorical variables analyzed by χ^2 test and the continuous variables analyzed by t-test. $P < 0.05$ considered as significant.

patients diagnosed with diabetes prior to menarche (mean age 12.9 years), patients diagnosed with diabetes post menarche (mean age 12.26 years) were found to have 0.64 years less in the age of menarche (P = 0.04) (Figure 2).

Results displayed as patients with PCOS (15.7%; 16/102) and without PCOS (84.3%; 86/102) are shown in Table 3. Out of 71 teenagers and out of 31 young women 15.5% (11/71) and 16.1% (5/31) had PCOS respectively. Of these PCOS patients, 37.5% (6/16) had irregular menses, 6.3% (1/16) had Celiac disease, 37.5% (6/16) had Hashimoto thyroiditis and 18.7% (3/16) had acne. There were no significant differences were observed among patients with PCOS and without PCOS except the variables family history (P = 0.001) and BMI (P = 0.008).

DISCUSSION

Reproductive disturbance has long been recognized

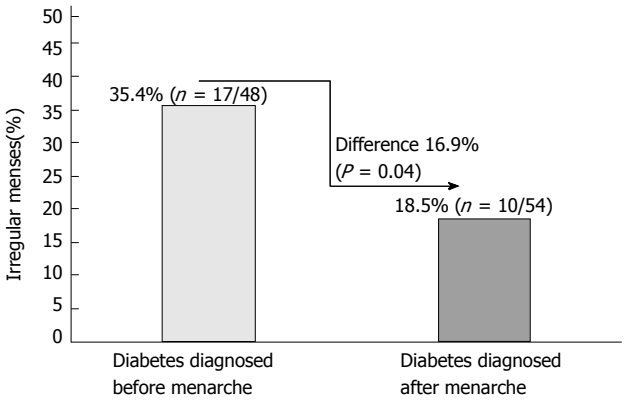

Figure 1 Irregular menses among girls/young women diagnoses with diabetes before (*n* = 48) and after menarche (*n* = 54).

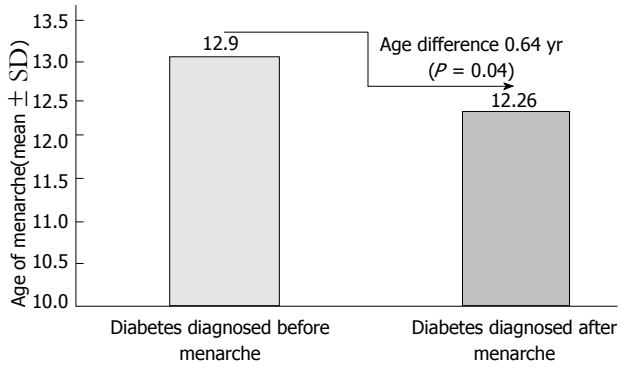

Figure 2 Mean age of menarche among girls/young women (*n* = 102) diagnoses with diabetes before and after menarche.

as a prevalent problem among girls and young women with T1DM[21]. In the present study, we found that approximately one fourth (26.5%) of the study population experiencing an irregular menses. An earlier study reported that approximately one third of young women with T1DM suffer some kind of menstrual dysfunction[21]. However, other studies reported that the rates of menstrual irregularity are 50% higher among patients with T1DM than those without T1DM[10,22]. Furthermore, it is well demonstrated that T1DM decreased physical, psychological well-being (depression and diabetes-related distress) and decreased the quality of life of adolescent girls and young women[23]. Such disturbances combined with other dysfunctions that could influence the reproductive system, are highly significant for type 1 diabetic adolescent girls and young women; in particular, those diagnosed prior to puberty often have peripubertal disturbances[25-27].

A growing number of studies have investigated that globally, a secular trend of younger age at menarche has been well recognized[28-30]. The mean age of menarche varies from about 12.5 years in the United States to 12.72 in Canada, 12.9 in the United Kingdom and 13.06 years in Iceland[28-30]. A study done on girls in Istanbul, Turkey, identified the median age at menarche to be 12.74 years[31]. In Saudi Arabia, the age of menarche shows considerable declining patterns. In the past decade, a study reported that the mean age at menarche among Saudis was 13.05[32]. However, more recent data from a study in 2015 indicated that the mean age of menarche for Saudi school going girls was 11.5 ± 1.48 years[33]. The present study revealed the mean age of menarche was 12.56 ± 0.96 among adolescent girls and young women with T1DM, which is higher than previous study findings (11.5 ± 1.48 years) among the normal school going girls in Saudi Arabia[33].

Similar to others, this study also identified delayed menarche among girls with T1DM[34,35]. The results from this present study demonstrated, that when those diagnosed with diabetes prior to menarche (12.26 years), experienced a delay (0.64 years) in the mean age of onset of menstruation compared with girls diagnosed after menarche. Other studies reported a delay of about one year in girls with T1DM at the age of menarche if diabetes mellitus onset was before puberty[25-27]. Kjaer, similar to the earlier findings of Bergqvist and Burkart, reported that should diabetes develop during childhood, menarche is often delayed[25]. However, age of menarche is comparable to that of the non-diabetic controls if diabetes mellitus onset occurred post puberty. This implies that menarche is not influenced by a genetic predisposition to diabetes but is possibly affected by the presence of clinical diabetes and diabetic metabolic disturbances, specifically the high HbA1c levels and duration of diabetes[26,27]. In the present study, when compared to patients who diagnosed as having diabetes after menarche (9.73 ± 0.3), patients who diagnosed as having diabetes before menarche (7.8 ± 0.2) had significantly lower HbA1c. Despite diagnostic and therapeutic advances of recent decades, delay at menarche and high prevalence of menstrual irregularity is still detected among adolescent females with T1DM[10,36]. The present study shows, that compared with those diagnosed with diabetes before menarche (35.4%), the girls diagnosed with diabetes after menarche (18.5%) experience less menstrual disturbance. Similarly, when compared with those identified with diabetes before menarche (9.73%), the girls diagnosed with diabetes post menarche (8.78%) had lower HbA1c levels. Studies also indicated that age at diabetes diagnosis and the HbA1c level were the risk factors for patients diagnosed prior menarche, which later in life resulted in the impairment of crucial life processes, including disturbances in menstruation and fertility, sexual and urinary tract dysfunctions[37]. An epidemiological study investigating menarche and menstrual disturbances, demonstrated menstrual dysfunction in 21.6% of women with T1DM compared with 10.8% in the nondiabetic controls, in 245 insulin-treated diabetic women and 253 healthy women. Therefore, it was evident that menstrual dysfunction occurred nearly twice as often in women with T1DM compared with the non-diabetic controls[26].

The fact that PCOS, which occurs quite frequently in women in the reproductive age, is related to reproductive and metabolic dysfunctions[38]. One of the

Table 3 Factors associated with polycystic ovarian syndrome *n* (%)

Variables	No PCOS (*n* = 86)	PCOS (*n* = 16)	*P* value
Age (yr)			
13-19 yr (*n* = 71)	60 (84.5)	11 (15.5)	0.574
20-29 yr (*n* = 31)	26 (83.9)	5 (16.1)	
Family History of diabetes			
No (*n* = 60)	57 (95)	3 (5)	0.001
Yes (*n* = 71)	29 (69)	13 (31)	
Recurrent diabetic ketoacidosis			
No (*n* = 89)	75 (84.3)	14 (15.7)	0.43
Yes (*n* = 13)	11 (84.6)	2 (15.4)	
Complications of diabetes			
No (*n* = 90)	79 (87.8)	11 (12.2)	0.092
Yes (*n* = 12)	7 (58.3)	5 (41.7)	
Menses			
Irregular (*n* = 27)	21 (78)	6 (16.7)	0.214
Regular (*n* = 75)	65 (87)	10 (15.4)	
Premature ovarian failure			
No (*n* = 101)	85 (84.2)	16 (15.8)	0.843
Yes (*n* = 1)	1 (100)	0	
Celiac disease			
No (*n* = 95)	80 (84.2)	15 (15.8)	0.698
Yes (*n* = 7)	6 (85.7)	1 (14.3)	
Hashimoto thyroiditis			
No (*n* = 68)	58 (85.3)	10 (14.7)	0.453
Yes (*n* = 34)	28 (82.4)	6 (17.6)	
Dyslipidemia			
No (*n* = 88)	76 (86.4)	12 (13.6)	0.15
Yes (*n* = 14)	10 (71.4)	4 (28.6)	
Hirsutism			
No (*n* = 77)	62 (80.5)	15 (19.5)	0.054
Yes (*n* = 25)	24 (96)	1 (4)	
Acne			
No (*n* = 83)	70 (84.3)	13 (15.7)	0.612
Yes (*n* = 19)	16 (84.2)	3 (15.8)	
Pelvic ultrasound			
Not done (*n* = 67)	54 (80.6)	13 (19.4)	0.317
Small ovaries (*n* = 3)	2 (66.7)	1 (33.3)	
Normal (*n* = 11)	10 (91)	1 (9)	
PCOS (*n* = 21)	20 (95.2)	1 (4.8)	
Testosterone level			
Normal (*n* = 77)	62 (80.5)	15 (19.5)	0.054
High (*n* = 25)	24 (96)	1 (4)	
Variables	mean ± SD	mean ± SD	*P* value
Body mass index	23.2 ± 2.86	25.3 ± 4.77	0.008
Duration of diabetes	6.59 ± 5.16	7.94 ± 6.45	0.53
Age at diabetes diagnosis	11.6 ± 3.82	10.8 ± 4.69	0.227
Age of menarche	12.5 ± 1	12.63 ± 0.69	0.118
Insulin dose unit/kg	0.8 ± 0.24	0.83 ± 0.20	0.493
Hemoglobin A1c	9.23 ± 1.98	9.19 ± 1.64	0.516

Categorical variables analyzed by χ^2 test and the continuous variables analyzed by *t*-test. $P < 0.05$ considered as significant. PCOS: Polycystic ovarian syndrome.

main characteristics of PCOS[39,40] is obesity, ranging from 12.5%[41] to 100%[42], with a total estimated prevalence of 49%[43], as reported in a recent meta-analysis[44]. Obesity may exacerbate the metabolic and reproductive disorders linked to this syndrome[45], like insulin resistance, dyslipidemia, and metabolic syndrome[38]. The meta-analysis revealed that women with PCOS exhibit higher levels of triglycerides (TG), LDL-cholesterol and total cholesterol (TC), and lower levels of HDL-cholesterol when compared with the controls, irrespective of BMI[46]. This present study showed a significant difference in the BMI between those with PCOS (mean BMI 25.3) and those without PCOS (mean BMI 23.2). Similarly, a family history of DM also revealed a significant difference between those with PCOS and those without the condition, a fact supported by earlier studies which recorded significantly increased numbers of women with a positive family history of diabetes among those with PCOS[47].

This study has few limitations, mainly, it was performed in a single center examining only a specified number of risk factors, there was no control group with which to compare the study population, patients were taking oral contraceptive pills were excluded which can

lead to underestimation of a reproductive disturbances proportion of female with T1DM especially PCOS and finally the details regarding the pelvic ultrasound report that in most cases does not include the measurement of the ovaries but defined only as small or normal. More research is necessary to address the limitation identified in this work. However, this study presents pertinent information on reproductive disturbance among Saudi adolescent girls and young women with T1DM.

In conclusion, more than one fourth of the study population with T1DM experiencing an irregular menses. Adolescent girls and young women diagnosed with diabetes prior to menarche reported higher menstrual irregularity and a delay in the age of menarche. More studies are required to confirm these findings among T1DM patients from different ethnic backgrounds.

COMMENTS

Background

Many studies have reported frequent disturbances in the reproductive system including infertility, delayed onset of menarche, menstrual irregularities and premature ovarian failure, in adolescent girls and young women with type 1 diabetes. Such females show a tendency, on average, to attain menarche a little later in life than non-diabetic women. Further, studies have found that there is a delay in the age of menarche and higher menstrual irregularity among type 1 diabetes if the onset of diabetes occurs before or near the onset of menarche and that this delay increases with poor glycemic control.

Research frontiers

Reproductive disturbance has long been recognized as a prevalent problem among girls and young women with type 1 diabetes mellitus (T1DM). However, compared to studies performed in the developed countries, limited literatures are available in Saudi Arabia on reproductive disturbances among adolescent girls and young woman due to the lack of appropriate studies performed in these specific aspects.

Innovations and breakthroughs

The authors found more than one fourth of the adolescent girls and young women with type 1 diabetes experiencing an irregular menses. Adolescent girls and young women diagnosed with diabetes prior to menarche reported 16.9% higher menstrual irregularity and 0.64 years delay in the age of menarche.

Applications

A better understanding of the nature, evolution and underlying mechanisms of the reproductive disturbances will help to develop the improved diagnostic and therapeutic strategies for an imperative set of co-morbidities disturbing the adolescent girls and young women with type 1 diabetes.

Peer-review

This is a well-written manuscript on an interesting and important clinical issue namely the frequency of irregular menstruation and amenorrhea in young women and teenagers with type 1 diabetes.

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