

| *JMR*

JUNIOR MEDICAL RESEARCH JOURNAL

A QUARTERLY JOURNAL FOR YOUNG AND TALENTED

VOLUME 2 NUMBER 2

2019



Editorial

Non-emergency applications

Dr Mahmut Firat Kaynak, Dr Mary Emeliene Timajo

Overcrowding in emergency departments (ED) could delay and alter the quality of critical services provided. Despite the generalization of developed triage system, the rate of nonurgent applicants is still considerable worldwide. This usually leads to long waiting patients lists, healthcare practitioners over stress, and patients unsatisfaction. A recent literature review reported that between 4.8% to 90% of ED patients were potentially nonurgent cases and the sudden death cases reported in ED should be simply urgent; long waiting unmanaged cases [1]. Among the leading reasons for unsuitable use of ED for "nonurgent complaints."; patients related factors are most frequent. Elderly patients with heavy chronic conditions and lack of familial support are frequent ED users. Some patients prefer the ED due to the easy access and availability of all investigation tools. Ed is always convenient providing nonstop care by trained specialized team. According to some studies; it has been proved that a higher rate of nonemergency application is noticed in case of unavailability of primary health care centers access and during off-clinic hours [2]. The delayed appointments, and the lack of access to outpatient clinics on evenings and weekends is usually influencing the patient's attitude. Interestingly, some other reports showed that most of the patients admitted to the ED with mild and simple complaints are well educated, have good social status and do not have

chronic diseases [3]. For these cases, wrong perception could be bilateral. The patient is always considering his personal case as extremely urgent; and the health practitioner could not inform the emergency before the investigations. This risk-averse patient risk-averse doctor relationship could explain the major part of non-emergency applications [4]. With these overwhelmed available resources, the increase of nonurgent visits results in risks for patient safety. This problematic has been recognized long time ago. Since early 90^s many triage systems were implemented. However only five level triage instruments are significantly correlated with resource utilization, rate of admission for inpatient treatment, duration of emergency management, and frequency of transfer to intensive care or mortality. Unfortunately, these instruments could not be generalized to all ED [5]. Several other solutions have been proposed. Gatekeeping; redirecting patient systems, or health services cost sharing were not enough and difficult to implement. The benefit a financial penalty for patients categorized as nonurgent after the consultation or targeting frequent users by case management approach is still unclear [6]. In our point of view; the solution to decrease the rate of nonurgent visits is outside of emergency room and not inside. The only valuable option is to provide an alternative to ED by improving the outpatient departments and primary healthcare centers services quality. With patient large sensibilization, the benefit should be perceptible.

References:

- [1] Van den Heede k, Carine Van de Voorde C. Interventions to reduce emergency department utilisation: A review of reviews. Health Policy.2016; 120: 1337-49.
- [2] Huang LC, Chung WF, Liu SW, Wu JC, Chen LF, Chen YC. Characteristics of Non-Emergent Visits in Emergency Departments: Profiles and Longitudinal Pattern Changes in Taiwan, 2000-2010.Int J Environ Res Public Health. 2019; 16: 1999.
- [3] Enrique Pino-Moya E, Mónica Ortega-Moreno M, Juan Gómez-Salgado J, Carlos Ruiz-Frutos C. Determining factors for the increase in self-referrals to the Emergency Department of a rural hospital in Huelva (Spain). PLoS One. 2018; 13: e0207199.
- [4] Chiu Y, Racine-Hemmings F, Dufour I, Vanasse A, Chouinard MC, Bisson M, et al. Statistical tools used for analyses of frequent users of emergency department: a scoping review. BMJ Open. 2019; 9: e027750.
- [5] Michael Christ M, Florian Grossmann F, Winter D, Bingisser R, Platz E. Modern Triage in the Emergency Department. Dtsch Arztebl Int. 2010; 107: 892-898.



Original Article

Effectiveness and applicability of low FODMAP diet in the irritable bowel syndrome: Preliminary results of a prospective study

Sabbah Meriem^{1,2*}, Trad Dorra^{1,2}, Maazoun Hajer^{1,2}, Tmessek Aroua^{1,2}, Bibani Norsaf^{1,2}, Elloumi Hela^{1,2}, Ouakaa Ama^{1,2}, Gargouri Dalila^{1,2}.

1: Department of gastroenterology Habib Thameur Hospital Tunis Tunisia
2: College of medicine Tunis Tunisia
***Corresponding author**
Correspondence to:
sabbah_meriem@yahoo.fr
Publication data:
Submitted: July 15 ,2019
Accepted: September 26,2019
Online: October 15 ,2019

This article was subject to full peer-review.

This is an open access article distributed under the terms of the Creative Commons Attribution Non-Commercial License 4.0 (CCBY-NC) allowing to share and adapt.
Share: copy and redistribute the material in any medium or format.
Adapt: remix, transform, and build upon the licensed material.
the work provided must be properly cited and cannot be used for commercial purpose.

Abstract:

Introduction:

Irritable bowel syndrome (IBS) is a very common entity that alters patient's life quality worldwide. Several therapeutic modalities are available with variable results. Recently, the low-FODMAP diet effect on IBS symptoms has been proven.

The aim of our study was to study the efficiency of this diet and to assess its applicability in a Tunisian IBS group of patients.

Methods:

A longitudinal, prospective study including 34 patients with IBS was conducted. Patients responded to a food frequency survey and had to follow a low FODMAP diet with a dietary guide education for 3 weeks. After the diet, a telephone questionnaire was conducted to evaluate adherence and treatment efficiency.

Results:

Mean of the population age was 56.5 (21 - 83 years) with a sex ratio of almost ¼. The initial food survey showed a large consumption of white bread and fruits. Tolerance to rich in FODMAP foods was variable among patients. Up to 97% of patients adhered to the low FODMAP diet. A decrease in abdominal pain in 88% of cases and in bloating in 64.7% of cases ($p = 0.007$) were noted after the diet.

Conclusion:

In our patients, the low FODMAP diet showed satisfactory results with good adherence, and improvement of IBS symptoms. However, it is important to note the difficulty of a long-term diet in a population with a variable alimentary habit.

Key words: low FODMAP diet; irritable bowel syndrome, applicability, Tunisia

Introduction

Prevalence of irritable bowel syndrome (IBS) is high in the general population, estimated between 10-15% and around 21% in Tunisia [1]. The treatment is mostly based on medical prescription. However, more than two-thirds of patients make the link between symptoms and diets and claim the exclusion of some foods themselves. Several diets have been tried like gluten or lactose free diet but no study to date has demonstrated their definite effectiveness [2]. Recently, low fermentable oligosaccharide disaccharide monosaccharide and polyols (FODMAP) diet has been considered in the management of this disease. Our aim was to study the effectiveness of the poor FODMAP diet on IBS symptoms and to assess the adherence in Tunisian patients.

Patients and methods

A prospective longitudinal study involving 34 Tunisian patients with irritable bowel syndrome was conducted. All Patients presenting an IBS (according to Rome IV criteria) with total normal colonoscopy who gave informed consent for the enrollment were included. The Patients with history of diabetes, celiac disease, abdominal surgery, diverticulitis, food allergies, or taking medicines that can cause intestinal functional disorders were not included in the study. All Patients withdrawing their consents for the study or those unreachable by phone for the control questionnaire were excluded from the study. The study was done in several steps. An objective initial evaluation of the patient's symptoms was performed by visual analog scale for pain (VAS) and Bristol scale for stool consistency. Biological assessment (cell blood count, C reactive protein, glucose random, thyroid function and serology of celiac disease) was performed and the colonoscopy results were collected. Patients then answered to a qualitative and quantitative food questionnaire. A food education was then carried out with an explanation of the FODMAP poor diet protocol and distribution of a summary manual including authorized foods, foods to be weighed, and prohibited foods as well as examples of FODMAP-poor dishes to be prepared. The recommended duration of the diet was three weeks. The following health and dietary advice were also recommended: Maintain good hydration (drink minimum 1.5L of water per day), regular physical activity, a recommendation to eat slowly and chew the food, prohibit chewing gums that increase the flatulence, avoid fatty and spicy foods, and avoid snacking.

A follow up was performed during the diet and patients noted if they presented an improvement of their symptoms.

Three weeks after initiation of the diet, patients were contacted by phone to respond to a second questionnaire to assess the diet adherence and efficiency on IBS symptoms with a re-evaluation of the VAS and Bristol scales. For the third phase of adaptation of diet, patients were also contacted to evaluate the improvement of their symptoms.

A descriptive and analytical study were conducted (SPSS 23 software). The comparison among the quantitative variables were made using the Student's test, and in case of non-validity the non-parametric Mann-Whitney test.

Comparison among the qualitative variables were made by Pearson's X² (chi-square) test and, in case of non-validity of this test, by Fisher's exact bilateral test. For all statistical tests, a value of $p < 0.05$ was considered statistically significant. Informed consent (in Arabic or French) was obtained from each patient before the inclusion. The ethics committee of Habib Thameur Hospital agreed all patient enrollment and the study conduction.

Results

During the study period, 34 patients with IBS were enrolled.

Two patients were excluded after the diet (unreachable by phone for the control questionnaire).

- *Characteristics of the population*

Mean age was 56.5 years (21- 83) and 74% of our patients were female. Up to 26 % of cases were overweight while 29% were morbidly obese. IBS was evolving for more than 5 years in 44.1%. Before the diet, 23 of the patients had VAS values between 7 and 10/10 while 11 had values between 5 and 7/10. Over 58.8% of patients had type 1 stools according to the Bristol scale, 26.5% type 2 and 8.8% type 3. Thirty-three patients had abdominal bloating and distention while the other 30 patients presented dyspepsia before diet.

- *Results of the food survey*

Sixty percent of the patients did not consume gaseous water, 14.7% consumed it once a week, 8.8% consumed it twice a week and 8.8% very rarely. Sixty percent of patients consumed pasta once a week, 76.4% of patients ate white bread daily. Thirty percent of patients did not consume oleaginous grains, 20.5% consumed it twice a week and 14% consumed rarely.

Table 1: Foods tolerance

Foods	Tolerance (%)
Pasta	26.9
Fruits	29.4
Milk	32.4
Spicy	29.4
Pizza	26.5
Raw onion	76.5

- *Results of low FODMAP diet*

Adherence to low FODMAP diet was good in 97% of cases. More than 94% of patients reported feeling better overall after following the diet. The table 2 summarizes the comparison of IBS symptoms before and after low FODMAP diet.

Table 2: symptoms before and after low FODMAP diet

symptoms	Before diet n=34	After diet n=32	P
Abdominal pain (EVA) (mean±SD)	3,18±0,716	1,16±0,628	<0.0001
Bloating			
Yes	34	3	0.007
No	0	29	
Stools (Bristol scale)			
Type1	23	0	0.097
Type2	8	11	
Type3	3	16	
Type4	0	4	
Type5	0	1	
Dyspepsia			
Yes	30	1	<0.0001
No	4	31	
Distension			
Yes	70	52	0.007
No	22	2	

Discussion

The reduction in FODMAP sugar intake induces a reduction in the fermentation inside the bowel. That decreases the liquids arriving at the intestinal lumen by osmotic effect and colonic bacterial fermentation responsible of gas and volatile fatty acids production. The first study evaluating low FODMAP diet was Australian, conducted by Shepherd et al [3]. In our study, patients responded first to a food survey. They indicated that they ate bread (consumed by 60% at an average of one and a half sticks 2 to 3 times per day) and pasta (consumed by 60% once a week). They had no issues

with cabbages, onions and fruits, but around 80% of patients avoided oilseeds and 60% indicated they had intolerance for vegetables because of bloating and distension. In the literature, patients often report a relationship between diet and IBS symptoms [4,5]. Several carbohydrates cannot be digested or absorbed by the human gut. In fact, the intestine does not contain the required enzymes for oligosaccharides decomposition. This causes their fermentation in the intestine and becoming source of nutrients for colon bacteria and this could explain the immediate effect of some foods on the symptom's onset. In a Swedish, 51% of patients reported that symptoms are directly related to some homemade meals. These foods are summarized in Table 3 [5].

The diet duration and adherence were variable in the previous studies but most of the authors preferred shorter periods. In Halmos's study, 80% of patients followed the diet correctly for 21 days [6]. The diet was prescribed for 15 months in another observational study from New Zealand [7]. In our study, adherence to low FODMAP diet was good at 97% for a period of 3 weeks. More than 90% of patients noted an overall improvement with decreased symptoms. In fact, 80% of patients had a change in stool consistency and 70% of patients had a VAS decrease of at least 2mm. In a randomized controlled cross-over American study, Chumtazi and al. demonstrated a reduction in pain episodes after low FODMAP diet [8]. In another randomized, crossover-controlled Australian study, the symptom score was significantly better with the FODMAP-poor diet than that of a typical Australian diet with a decrease in EVA pain value. The analysis demonstrated as well a significant decrease in diarrhea [9]. Staudacher and al. also found a decrease in bloating in the group following the low FODMAP diet (82% vs 49%) that confirmed the findings of many other studies [10]. More recently, a meta-analysis demonstrated a significant reduction in IBS symptoms specially the bloating in low FODMAP diet [11]. Confronting the low FODMAP diet and the usual IBS diet that consist in removing legumes, cauliflower, onions, over-spicy and over-fatty foods, some studies proved that the control of the symptoms was significantly superior in the low FODMAP groups [12,13]. A comparative study found similar results for gluten-free and low FODMAP diets and 71% of patients

Table 3: IBS symptoms related foods

Food	%	Symptoms
Cream	37%	Diarrhea
Milk	30%	Bloating
Peas and beans	46%	Bloating /pain
Fried food	45%	Dyspepsia /pain
Pizza	44%	Dyspepsia/pain /diarrhea
Coffee	39%	GERD/ dyspepsia /diarrhea

claimed an objective decrease of IBS symptoms in the gluten-free diet [14]. Others interfering factors have been quickly considered in the management of IBS diet. The stress, the regularity of meal timing, the quality of food sources, and the underlying psychological status are affecting IBS symptoms considerably. Some other authors found out in a recent randomized study that the hypnosis is as efficient as the low-FODMAP diet in IBS symptoms control [15]. It remains to highlight the necessity of correct IBS diagnosis. Some IBS symptoms are close to celiac disease presentation and severe restrictions may lead to deficiencies and metabolic disorders [16-18]. The low FODMAP diet seems to be balanced and safe. The caloric intake from carbohydrates, fats and proteins for patients following low FODMAP diet was equivalent and enough as well as for folate, vitamin C and riboflavin [19,20]. The results depend usually more on the adherence to the dietary advice and the lifestyle management. In our study, 97% of patients adhered well to the diet. Some elements could however explain the low compliance. The lack of motivation in some patient not convinced by the effectiveness of the diet in the treatment [21,22]. According to them, drug treatment is always easier to follow. The busy lifestyle and multiple daily tasks beside the financial constraints may limit also the efficiency of the diet [22-24]. The usually undiagnosed altered psychological patient's status can major IBS symptoms and reduce the acceptance of alimentary restrictions. Paduano and al. proposed a balanced diet for IBS and showed that it improves quality of life as well as pain scales [25]. A recent metanalysis including 1726 IBS cases showed a mild superiority of the low FODMAP diet. That was partially explained by the variety of foods allowed in this diet [26]. The Tunisian alimentary habits are different and characterized by large consumption of white bread, pasta, fruits and legumes and fat. The low FODMAP first seemed to be difficult to implement in our patients. The education, patient's selection and progressive approach should be the keys to ensure best adherence. The low FODMAP diet appears to improve IBS symptoms such as bloating and transit disorders.

However, the support of a specialized dietitian and psychologist remains more than mandatory. The applicability of this diet has been studied in several countries with various gastronomic cultures. In Tunisia, the short-term results are satisfactory. However, long-term applicability needs to be worked out. Our results must be approved on a larger population study.

Conclusions:

The low FODMAP diet is becoming increasingly important in the treatment of IBS and appears to be very effective in the improvement of the IBS symptoms. This diet could support the therapeutic management and reduce the need to conventional drug treatments. However, it remains a food plan to ease symptoms for the patients and trigger responsible foods. The interference of multiple IBS related factors should be ruled out to assess properly the real value of the low FODMAP in patient's quality of life improvement.

Conflict of interest: none

References

- [1] Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Miller-Lissner SA. Function bowel disorders and functional abdominal pain. *Gut* 1999; 45:43-47.
- [2] Biesiekierski JR, Newnham ED, Irving PM, Barrett JS, Haines M, Doecke JD, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol*. 2011; 106: 508-14.
- [3] Shepherd SJ, Parker FC, Muir JG, Gibson PR. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. *ClinGastroenterolHepatol*.2008; 6: 765-71.
- [4] Heizer WD, Southern S, McGovern S. The role of diet in symptoms of irritable bowel syndrome in adults: a narrative review. *J Am Diet Assoc*. 2009; 109:1204-14.
- [5] Simren M, Mansson A, Langkilde AM, Svedlund J, Abrahamsson H, Bengtsson U, Bjornsson ES. Food-related gastrointestinal symptoms in the irritable bowel syndrome. *Digestion*.2001; 63:108-15.
- [6] Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology*.2014; 146: 67-75.
- [7] De Roest RH, Dobbs BR, Chapman BA, Batman B, O'Brien LA, Leeper JA, et al. The low FODMAP diet improves gastrointestinal symptoms in patients with irritable bowel syndrome: a prospective study. *Int J Clin Pract*.2013; 67: 895-903.
- [8] Chumpitazi BP, Cope JL, Hollister EB, Tsai CM, McMeans AR, Luna RA, and al. Randomised clinical trial: Gut microbiome biomarkers are associated with clinical response to a low FODMAP diet in children with the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2015; 42:418-27.
- [9] Pedersen N, Andersen NN, Végh Z, Jensen L, Ankersen DV, Felding M1, et al. E health: low FODMAP diet vs Lactobacillus rhamnosus GG in irritable bowel syndrome. *World J Gastroenterol* .2014; 20:16215-26.

- [10] Staudacher HM, Whelan K, Irving PM, Lomer MC. Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome. *J Hum Nutr Diet.*2011; 24:487-95.
- [11] Marsh A, Eslick EM, Eslick GD. Does a diet low in FODMAPs reduce symptoms associated with functional gastrointestinal disorders? A comprehensive systematic review and meta-analysis. *Eur J Nutr.* 2016; 55:897-906.
- [12] Trott N, Aziz I, Rej A, Surendran Sanders D. How Patients with IBS use low FODMAP dietary information provided by general practitioners and gastroenterologists: A Qualitative Study. *Nutrients.* 2019;11: E1313.
- [13] Böhn L, Störsrud S, LiJebo T, Collin L, Lindfors P, Törnblom H, et al. A multi-center, randomized, controlled, single-blind, comparative trial: low-FODMAP diet versus traditional dietary advice in IBS. *United Eur Gastroenterol J.*2014; 2: A1-A131.
- [14] Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR. No effects of gluten in patients with self-reported nonceliac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, shortchain carbohydrates. *Gastroenterology.*2013;145:320-8.
- [15] Peters SL, Muir JG, Gibson PR. Review article: gut-directed hypnotherapy in the management of irritable bowel syndrome and inflammatory bowel disease. *Aliment Pharmacol Ther.* 2015; 41:1104-15.
- [16] Aziz I, Trott N, Briggs R, North JR, Hadjivassiliou M, Sanders DS. Efficacy of a gluten-free diet in subjects with irritable bowel syndrome-diarrhea unaware of their HLA-DQ2/8 genotype. *Clin Gastroenterol Hepatol.* 2016;14(5):696-703.
- [17] Peters SL, Yao CK, Philpott H, Yelland GW, Muir JG, Gibson PR. Randomized clinical trial: the efficacy of gut-directed hypnotherapy is similar to that of the low FODMAP diet for the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther.* 2016; 44:447-59.
- [18] De Giorgio R, Volta U, Gibson PR. Sensitivity to wheat, gluten and FODMAPs in IBS: facts or fiction? *Gut.* 2016; 65:169-178.
- [19] Zar S, Mincher L, Benson MJ, Kumar D. Food specific IgG4 antibody-guided exclusion diet improves symptoms and rectal compliance in irritable bowel syndrome. *Scand J Gastroenterol.*2005; 40:800-7.
- [20] Whorwell PJ, Prior A, Faragher EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable bowel syndrome. *Lancet.*1984; 2:1232-4.
- [21] Eswaran SL, Chey WD, Han-Markey T, Ball S, Jackson K. A Randomized Controlled Trial Comparing the Low FODMAP Diet vs. Modified NICE Guidelines in US Adults with IBS-D. *Am J Gastroenterol.* 2016; 111:1824-32.
- [22] Mazzawi T, Hausken T, Gundersen D, El-Salhy M. Effects of dietary guidance on the symptoms, quality of life and habitual dietary intake of patients with irritable bowel syndrome. *Mol Med Rep* 2013; 8:845-52.
- [23] Staudacher HM, Lomer MC, Anderson JL, Barrett JS, Muir JG, Irving PM, et al. Fermentable carbohydrate restriction reduces luminal bifido bacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. *J Nutr.*2012; 142:1510-8.
- [24] Ong DK, Mitchell SB, Barrett JS, Shepherd SJ, Irving PM, Biesiekierski JR, and al. Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. *J Gastroenterol Hepatol.*2010;25:1366-73.
- [25] Paduano D, Cingolani A, Tanda E, Usai P. Effect of Three Diets (Low-FODMAP, Gluten-free and Balanced) on Irritable Bowel Syndrome Symptoms and Health-Related Quality of Life. *Nutrients.* 2019;11: E1566.
- [26] Dionne J, Ford AC, Yuan Y, Chey WD, Lacy BE, Saito YA, and al. A Systematic Review and Meta-Analysis Evaluating the Efficacy of a Gluten-Free Diet and a Low FODMAPs Diet in Treating Symptoms of Irritable Bowel Syndrome. *Am J Gastroenterol.* 2018; 113:1290-1300.

Appendix: literature review

Study	n	Type	Diet duration	Results
Paduano 2019 Italy [25]	42	Prospective	4 weeks	3% of preference for low-FODMAP diet, 11% for the gluten-free and 86% for the balanced diet $p < 0.01$
Eswaran 2016 USA [21]	42	Randomized controlled trial	4 weeks	40-50% of relief of IBS-D symptoms Greater improvement than mNICE diet
Chumtazi 2015 USA [8]	33	Randomized double blind crossing over	1 week	Less abdominal pain with low FODMAP diet vs. traditional diet [1.1 ± 0.2 (SEM) episodes/day vs. 1.7 ± 0.4 , $p < 0.05$]
Pederson 2014 Danemark [12]	44	Crossing-over single blind	6 weeks	Réduction significative à l'échelle visuelle analogique de la douleur
Mazzawi 2013 Norway [22]	17	Case study	12 weeks	Improvement of life quality lower IBS score ($41,47 \pm 1.62/ 35,71 \pm 1.12$) $p=0,001$
Staudacher 2012 UK [23]	41	Randomized controlled trial	4 weeks	adequate control of symptoms in intervention group (13/19, 68%) compared with controls (5/22, 23%; $p= 0.005$)
Ong 2010 Australia[24]	30	Crossing-over single blind	2 days Low FODMAP (9g per day instead of 50g)	Higher levels of breath hydrogen produced Increased Gastrointestinal symptoms
Shepherd 2008 Australia [3]	25	Randomized double blind placebo controlled	22 weeks mixtures of FODMAPs	symptoms not well controlled with fructose (70%), fructans (77%), and mixture (79%) compared with 14% for glucose $p = 0.002$
Our study 2019 Tunisia	34	Longitudinal prospective	3 weeks	FODMAP applicable good adherence



Case report

Isolated right adrenal metastasis from an invasive ductal breast carcinoma.

Taha Mohammed Hassan 1*, Al Emadi Mohammed Abdullah 1, Lotfy Mohammed 1, Mustafa Mohamed Naser 2, Omar Amany Mohammed Rabie 3, El Mahdi Hoda Saleh 3.

1: Department of surgery
2: Department of radiology
3: Department of pathology
Al Emadi Hospital Doha, Qatar.

*Corresponding author

Correspondence to:

Dr.taha@alemadihospital.com.qa

Publication data:

Submitted: April 23,2019
Accepted: June 27,2019
Online: October 15,2019

This article was subject to full peer-review.

This is an open access article distributed under the terms of the Creative Commons Attribution Non-Commercial License 4.0 (CCBY-NC) allowing to share and adapt.
Share: copy and redistribute the material in any medium or format.
Adapt: remix, transform, and build upon the licensed material.
the work provided must be properly cited and cannot be used for commercial purpose.

Introduction

Invasive ductal carcinoma (IDC) is the most common histopathological type of breast cancer, accounting for up to 85% of all invasive breast carcinomas [1]. It spreads usually to the bone first. Solitary metastasis is commonly located in the lung, liver or brain [2]. Adrenal glands locations are extremely rare [3]. We report a case of isolated metachronous right adrenal metastasis, diagnosed four years after breast IDC management. The aim is to highlight clinical, diagnostic and therapeutic characteristics of this entity.

Case presentation

We report a case of 53 years old female referred to surgery for right adrenal mass. On her history we noted a previous tumorectomy followed by chemo and radiotherapy for right breast invasive ductal carcinoma moderately differentiated Not Otherwise Specified (IDC-NOS). The TNM staging of the tumor was T2 NX M0. On the four-year follow-up consultation, an incidental right suprarenal tumor was detected by abdominal ultrasound. CT and MRI scan (Figure 1), confirmed the presence of a 5x7 cm right adrenal gland mass. Endocrinological workup revealed that the tumor was not secreting. The patient underwent Laparoscopic Adrenalectomy which had to be converted to open, from which the patient made uneventful recovery. Gross examination revealed firm capsulated right adrenal mass, measuring 9 x 7 x 3 cm and about 123.5 grams in weight with cut sections showed heterogenous cystic appearance. Microscopic examination revealed infiltration by sheets, clusters and cords of malignant cells (figure 2a) with enlarged nuclei, prominent nucleoli and frequent mitosis. The tumor reached the surrounding fat with focal vascular invasion (figure 2b). Immunohistochemical staining revealed that tumor cells expressed diffuse positive staining with ER (2+ in 80% of tumor cells) (figure 4a), PR (2+ in 2% of tumor cells), GATA3 (figure 4b), E-cadherin, BCL-2, HER-2 is equivocal (2+) and Ki67 proliferation index was 30%. Histopathological confrontation of both adrenal and breast specimens revealed identical morphological and immunohistochemical features and was consistent with metastatic mammary carcinoma. Thereafter, the patient received 6 cycles of chemotherapy followed by hormonal therapy and kept a regular follow up until now.

Isolated right adrenal metastasis from an invasive ductal breast carcinoma.

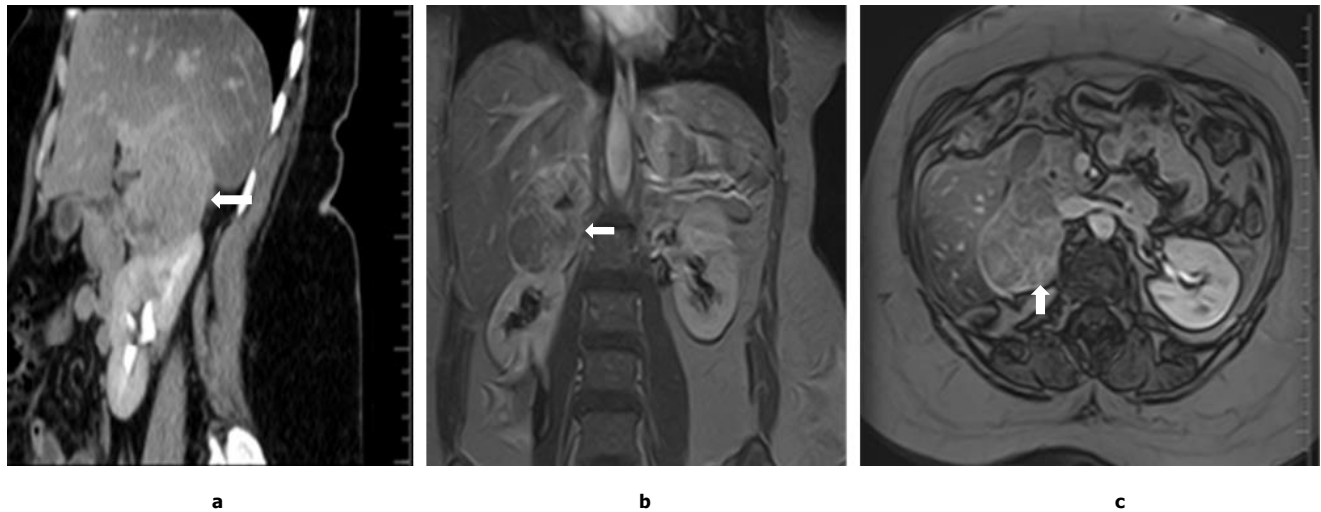


Figure 1: Imaging features of the right incidentaloma.

(a) CT scan showed 5x7x4 heterogeneous mass of the right suprarenal region. (b,c) right adrenal origin confirmed by MRI out phases showed a well-defined tumor arising from the adrenal gland with mass effect behavior on the right kidney

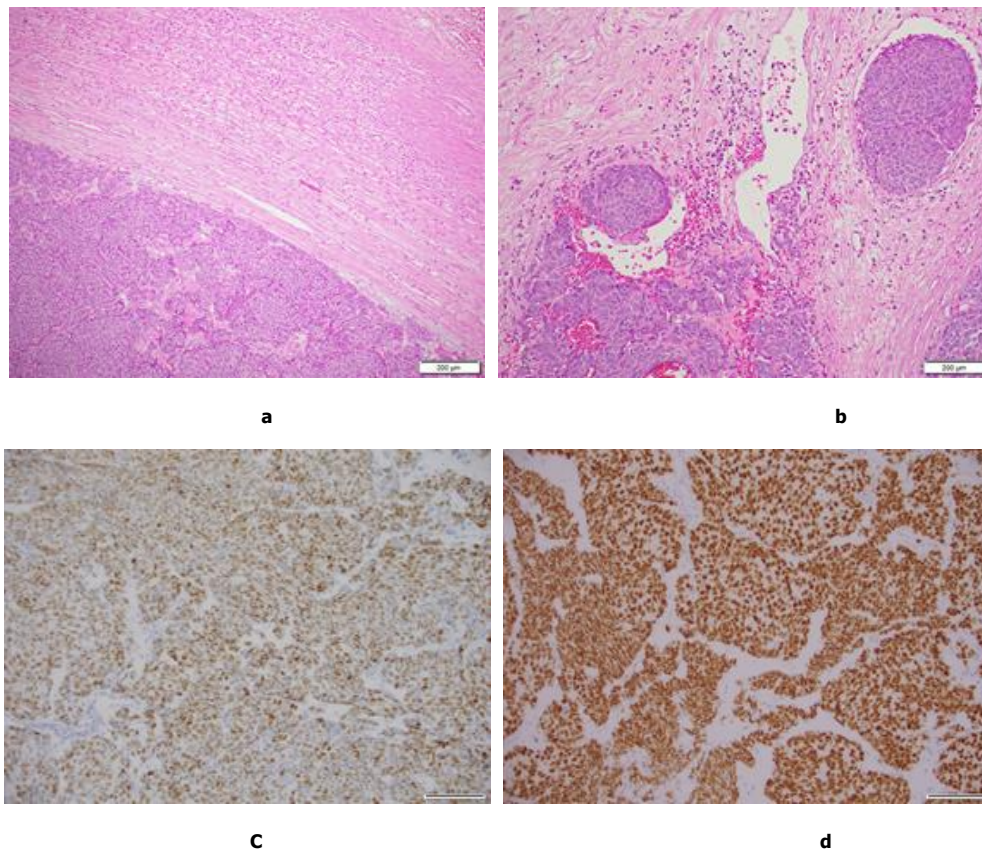


Figure 2: pathological examination

(a) Histology section shows adrenal tissue infiltrated by sheets of malignant cells (H and E, x200). (b) Histology section shows vascular invasion (H and E, x200). (c) Diffuse positive nuclear staining for ER (ER immunostaining, x200). (d) Diffuse positive nuclear staining for GATA3 (GATA3 immunostaining, x400).

Discussion

The first published case of breast metastasis at adrenal gland was by Liu et al in 2010 [1]. Only eight cases of adrenal metastases from invasive breast carcinoma not otherwise specified were published up to date [2]. In six cases the metastasis was to the left adrenal gland [1,2] and in only two cases metastasis was to the right adrenal gland [3] as our case. We have reported an incidental right adrenal metastasis which originated from moderately differentiated invasive ductal carcinoma managed four year before. Adrenal metastatic tumors are often misdiagnosed as primary adrenal tumors. CT scan and MRI are suitable methods for distinguishing between a metastatic and primary adrenal tumor [4,5]. Additionally, immunoassaying of tissue sections can confirm the primary site [6]. In our case immunoassaying confirmed the breast origin. Patients with adrenal metastasis usually are asymptomatic and start to express suprarenal gland dysfunction only when most of the adrenal gland is replaced or destroyed [7,8]. Our patient underwent Laparoscopic Right Adrenalectomy which was converted to open due to the large size of the tumor. In eight published cases, one case was treated by Lapatinib® [9] and the remaining cases was treated by open or laparoscopic Adrenalectomy [9]. The ideal treatment options of this condition are still unclear because of the rarity of solitary adrenal metastases from mammary carcinoma. Metastatic breast cancer is often fatal and the treatment in most of the cases is mainly limited to palliation chemotherapy or hormonal treatment. However, laparoscopic adrenalectomy for solitary adrenal metastasis is considered convenient, and could lead to a longer survival in some patients [10,11]. Even though it is important to avoid port-site metastasis and carcinomatosis which may happen after the procedure. Laparoscopic adrenalectomy is widely applied to adrenal gland tumors. However, the gold standardization in adrenal cancer metastasis remains controversial [12].

Conclusions

Although adrenal metastasis of an IDC is very rare, the present case is the ninth reported breast cancer metastatic to the adrenal gland. Definite diagnosis can be established by CT, MRI and histopathological examination. Early recognition and complete adrenalectomy may lead to survival benefit.

Conflict of interest: none

References

- [1]Liu XJ1, Shen P, Wang XF, Sun K, Sun FF. Solitary adrenal metastasis from invasive ductal breast cancer: an uncommon finding. *World J Surg Oncol.* 2010; 8:7.
- [2]Akhtar K, Sherwani R, Kahkhashan E. Carcinoma breast metastasis to the suprarenal gland: an unusual presentation. *Pol J Pathol.* 2012 ; 63: 284-5.
- [3]Barros N.A, Ferreira, A., Rocha, M.J., et al. Unusual Breast Cancer Metastasis. *BMJ Case Reports.* 2015; 43-45.
- [4]Toikkanen S, Pykkänen L, Joensuu H. Invasive lobular carcinoma of the breast has better short- and long-term survival than invasive ductal carcinoma. *Br J Cancer.* 1997; 76:1234-40.
- [5]Fassnacht M, Kenn W, Allolio B. Adrenal tumors. How to establish malignancy. *J Endocrinol Invest.* 2004; 27:387-99.
- [6]Takeda Y, Tsuta K, Shibuki Y. Analysis of expression patterns of breast cancer-specific markers (mammaglobin and gross cystic disease fluid protein 15) in lung and pleural tumors. *Arch Pathol Lab Med.* 2008; 132:239-43.
- [7]He T, Liu J, Li Y, Jin LU, Sun S, Ni L, et al. Left adrenal gland metastasis of breast invasive ductal carcinoma: A case report. *Mol Clin Oncol.* 2016; 4:859-62.
- [8]Suzuki H. Laparoscopic adrenalectomy for adrenal gland carcinoma and metastases. *Curr Opin Urol.* 2006; 16:47-53.
- [9]Shamoun S, Shamout A. A Case Report of Two Primary Cancers, Breast Cancer with Adrenal Gland Metastatic and Second Primary Neuroendocrine Tumor in Colon, a Rare Case in Al-Bashir Hospital. *Case Reports in Clinical Medicine.* 2018; 7: 306-13.
- [10]Tanvetyanon T, Robinson LA, Schell MJ. Outcomes of adrenalectomy for isolated synchronous versus metachronous adrenal metastases in non-small cell lung cancer: a systematic review and pooled analysis. *J Clin Oncol.* 2008; 26:1142-47.
- [11]Zografos GN, Perysinakis I, Kyrodinou E, Kassi E, Kaltsas G. Surgical treatment of potentially primary malignant adrenal gland tumors: An unresolved issue. *Hormones.* 2015; 14:47-58.
- [12]Shoji S, Usui Y, Nakano M, Hanai K, Sato H, Uchida T, et al. Surgical management of metastatic adrenal gland tumors: Decision-making factors in imaging. *Oncol Lett.* 2010; 1:967-71.



Case report

Une autre variante anatomique du tronc cœliaque. One more anatomic variant of the celiac trunk.

Ferjaoui Wael ^{1,2*}, Talbi Ghofrane ^{1,2}, Karouia Souhail ^{1,2}, Omrani Sahir^{1,2}, Hajri Mohamed ^{1,2}.

1: Department of surgery Mongi Slim Hospital Tunis Tunisia
2: College of medicine Tunis Tunisia
***Corresponding author**

Correspondence to:
Ferjaouiwael4@gmail.com

Publication data:
Submitted: August 8, 2019
Accepted: September 15, 2019
Online: October 15, 2019

This article was subject to full peer-review.

Abstract:

Anatomical variations of the celiac trunk are numerous. Variants of the hepatic artery are important to consider especially in the bilio-pancreatic procedures. Unusual arterial anatomy increases the risk of postoperative specific complications. We report a case of a rare anatomic variant of the celiac trunk that gives rise to a left and right hepatic artery separately. It is an exceptional variant found in a patient with a pancreatic head tumor and candidate for duodenopancreatectomy.

Key words: celiac trunk, right hepatic artery, anatomic variant.

Introduction :

Le tronc cœliaque a classiquement 3 branches qui sont l'artère gastrique gauche, l'artère splénique et l'artère hépatique commune. De nombreuses études, notamment sur les cadavres, ont montré des nombreuses variantes anatomiques. Environ 15% de la population présente des variations dans les branches du tronc cœliaque [1]. Une connaissance parfaite de ces variations anatomiques est essentielle afin d'éviter des nombreuses complications parfois mortelles qui peuvent survenir surtout en cas de chirurgie hépatobiliaire et pancréatique.

Nous rapportons ici une variante rare à propos d'une quadrifurcation du tronc cœliaque qui donne naissance à une artère hépatique droite, une artère hépatique gauche, une artère splénique et une artère gastrique gauche chez un patient atteint d'une tumeur de la tête du pancréas.

Observation :

Il s'agissait d'un patient âgé de 42 ans, sans antécédents, qui consulte pour un ictère généralisé évoluant d'un seul tenant depuis 1 mois. L'examen a montré un ictère cutanéomuqueux avec des lésions de grattage mais pas de vésicule biliaire palpable. La bilirubine totale était à 99 $\mu\text{mol/l}$ à prédominance conjuguée et l'antigène carbohydre 19-9 (CA 19-9) était élevé à 205 U/ml. L'échographie abdominale a révélé une masse hypoéchogène de 2 cm de la tête du pancréas et responsable d'une dilatation des voies biliaires intra et extra hépatiques et du canal de Wirsung. Un scanner-thoraco-abdomino-pelvien a montré une lésion tissulaire de la tête du pancréas de 35 mm venant au contact de la veine mésentérique supérieure avec une dilatation bicanalaire des voies biliaires et du canal du Wirsung (figure 1). Il existait un envahissement de la lame rétro-portale ; mais pas de lésions secondaires à distance. Par ailleurs, une variante anatomique du tronc cœliaque à type de quadrifurcation avec naissance de façon séparée de l'artère splénique, de l'artère gastrique gauche, de l'artère hépatique gauche et de l'artère hépatique droite était objectivée (figure 2A et 2B). Une échodoppler avec des biopsies avaient révélé un adénocarcinome moyennement différencié du pancréas. Le patient était adressé pour une chimiothérapie néoadjuvante après mise en place d'une prothèse biliaire.

This article is an open access article distributed under the terms of the Creative Commons Attribution Non-Commercial License 4.0 (CCBY-NC) allowing to share and adapt. Share: copy and redistribute the material in any medium or format. Adapt: remix, transform, and build upon the licensed material. The work provided must be properly cited and cannot be used for commercial purpose.

Une autre variante anatomique du tronc cœliaque.

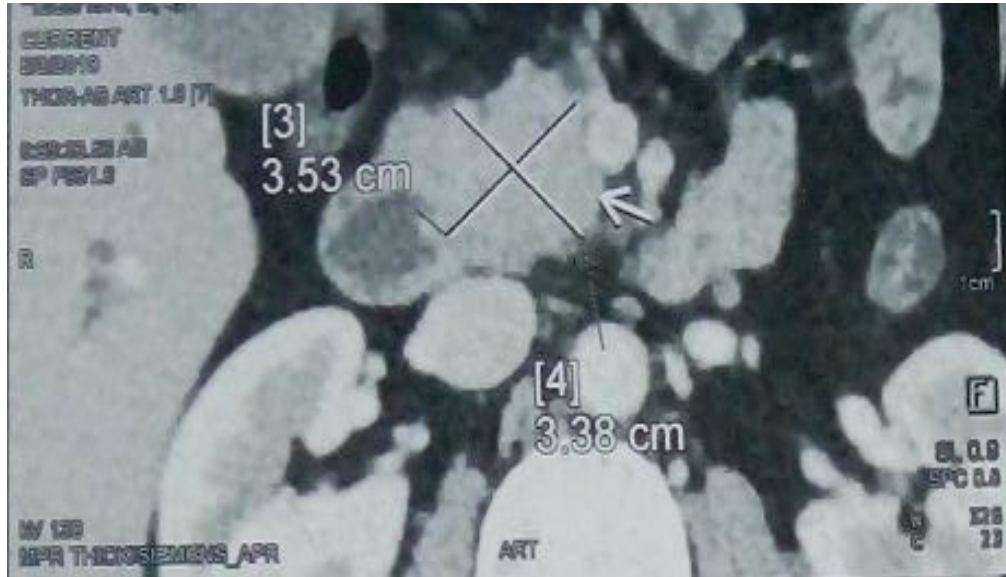


Figure 1 : coupe scanographique montrant une tumeur de la tête de pancréas venant au contact de la veine mésentérique supérieure.

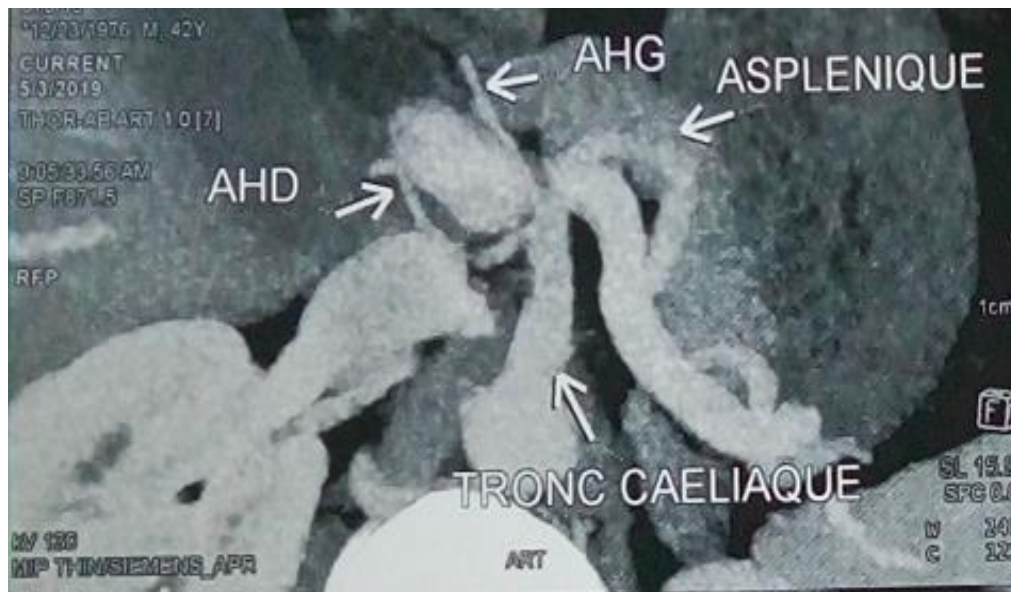


Figure 2A : Une coupe transversale montrant une naissance séparée de l'artère hépatique droite (AHD) et de l'artère hépatique gauche (AHG) et de l'artère splénique du tronc cœliaque.

Une autre variante anatomique du tronc coeliaque.

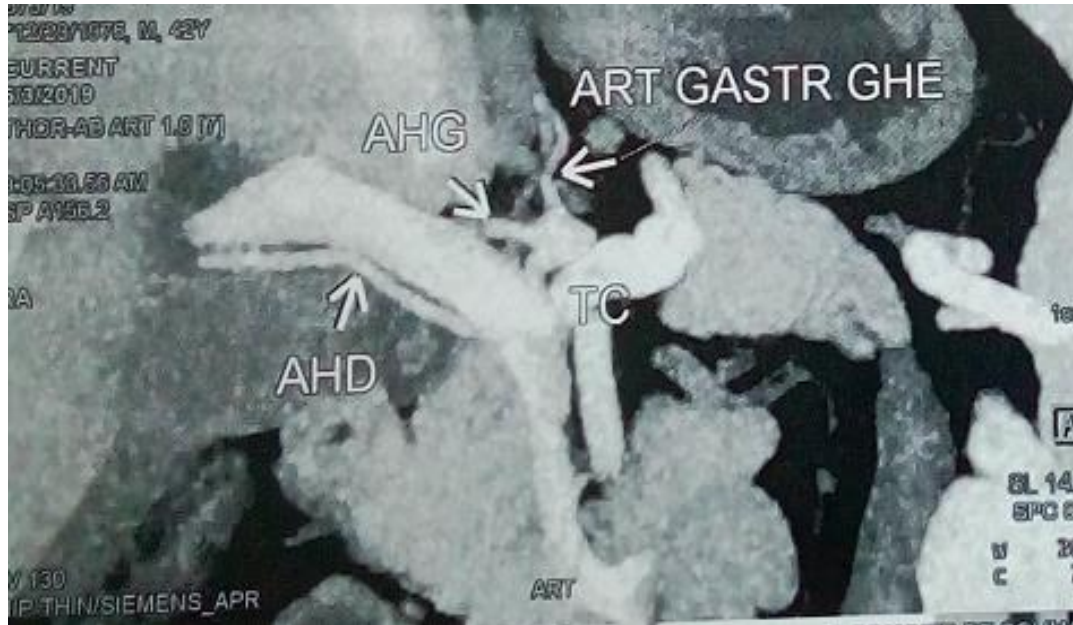


Figure 2B : une coupe frontale montrant une naissance séparée de l'artère hépatique droite (AHD) et de l'artère hépatique gauche (AHG) et de l'artère gastrique gauche du tronc coeliaque.

Discussion :

Le tronc coeliaque donne classiquement, après un trajet court, 3 branches qui sont : l'artère gastrique gauche, l'artère splénique et l'artère hépatique commune. Cette trifurcation est présente dans 72 % à 90 % de la population [1]. L'artère hépatique commune bifurque en artère gastro duodénale et une artère hépatique propre qui donne à son tour 2 branches : gauche et droite. Cette disposition dans la vascularisation hépatique, dite modale, est présente seulement dans 52% à 80 % [1,2]. Ainsi, on décrit plusieurs variantes anatomiques de l'artère hépatique qui ont été détaillés dans plusieurs études et classifications. La classification de Michel est la plus connue et la plus utilisée. Elle décrit 10 variantes du système artériel hépatique. La variante la plus fréquente était la naissance de l'artère hépatique droite de l'artère mésentérique supérieure [2]. L'importance de notre observation c'est qu'elle rapporte une variation non décrite dans la classification de Michel où le tronc coeliaque donne naissance de façon séparée à une artère hépatique droite et une artère hépatique gauche. La deuxième particularité de notre observation c'est sa présence chez un patient atteint d'une tumeur de la tête du pancréas. Cependant, une connaissance parfaite des variantes anatomique est indispensable avant toute chirurgie hépatobiliaire ou pancréatique afin d'éviter plusieurs complications parfois mortelles à type d'ischémie hépatique, hémorragie, abcès de foie et surtout des fistules biliaires [3]. En effet, la partie proximale de la voie biliaire principale est vascularisée par un plexus artériel anastomotique provenant de l'artère hépatique droite et de l'artère gastroduodénale [4]. Durant la duodéno pancréatectomie céphalique, l'artère gastroduodénale est généralement ligaturée, d'où l'importance de l'artère hépatique droite dans la vascularisation de l'anastomose hépato jéjunale qui nous permet d'éviter les fistules biliaires. L'angioscanner abdominal réalisé en pré opératoire permet d'avoir une idée sur la présence d'une artère hépatique droite aberrante ou accessoire et sur son trajet. Le but était ainsi de la préserver. Cela nous permet de diminuer le risque de complication per et post opératoire.

Conclusions :

Les variantes anatomiques du tronc coeliaque et de l'artère hépatique sont fréquentes. Leur connaissance en préopératoire est primordiale afin de diminuer le taux de morbimortalité liée à l'intervention.

Une autre variante anatomique du tronc cœliaque.

Conflit d'intérêt : aucun

References:

[1]Ugurel MS, Battal B, Bozlar U, Nural MS, Tasar M, Ors F, et al. Anatomical variations of hepatic arterial system, coeliac trunk and renal arteries: an analysis with multidetector CT angiography. *Br J Radiol.* 2010; 83:661-67.

[2]Ye Z, Ye S, Zhou D, Zheng S, Wang W. A rare variation of celiac trunk and hepatic artery complicating pancreaticoduodenectomy: A case report and literature review. *Medicine (Baltimore).* 2017;96: e8969.

[3]Shukla PJ, Barreto SG, Kulkarni A, Nagarajan G, Fingerhut A. Vascular Anomalies Encountered During Pancreatoduodenectomy: Do They Influence Outcomes? *Ann Surg Oncol.* 2010; 17:186-93.

[4]Stauffer JA, Bridges MD, Turan N, Nguyen JH, Martin JK. Aberrant right hepatic arterial anatomy and pancreaticoduodenectomy: recognition, prevalence and management. *HPB.* 2009; 11:161-5.



Mini Review

Vitamin D: The black knight.

Jlalia Zied^{1,3*}, Chaabene Helmi²

1:Orthopedic pediatric department, Kassab Institute Tunis Tunisia.

2:Sports Performance Optimization Laboratory, National Center of Medicine and Science in Sports (CNMSS)Tunis Tunisia.

3:College of medicine Tunis Tunisia
***Corresponding author**

Correspondence to:
zied-j@yahoo.fr

Publication data:
Submitted: August 8,2019
Accepted: September 15 ,2019
Online: October 15,2019

This article was subject to full peer review.

This article is an open access article distributed under the terms of the Creative Commons Attribution Non-Commercial License 4.0 (CCBY-NC) allowing to share and adapt.
Share: copy and redistribute the material in any medium or format.
Adapt: remix, transform, and build upon the licensed material.
the work provided must be properly cited and cannot be used for commercial purpose.

The group of vitamin D (VD) consists of 2 molecules, vitamin D2 or ergocalciferol and vitamin D3 called cholecalciferol. The synthesis of these two molecules is a chain reaction. Vit D is a secosteroid produced in the skin under the influence of ultraviolet B (UVB) radiation. Cholecalciferol is classified as a vitamin, but several aspects bring it closer to steroid hormones [1]. VD has been always supposed to play a crucial role in the prevention and treatment of various diseases. Additionally, to its control on calcium and phosphate equilibria, VD is an important modulator of cellular differentiation and proliferation in numerous normal and malignant processes [2]. VD deficiency leads to impaired growth in children. The supplementation before the age of 3 years is significantly associated with the increase of the overall height and the rate of height development. In 1975 Earnest proposed that 25(OH)D, presumably via a specific receptor, was directly stimulating the synthesis of protein, ATP and inorganic phosphate in the rat diaphragm muscle. However, an independent role of vitamin D on skeletal muscle mass and function development during growth remains unclear [1-3]. Some diseases such colorectal cancer, cardiovascular disease, multiple sclerosis, type I diabetes, osteoarthritis, high blood pressure, and allergies have a pathological distribution corresponding to zones of VD deficiency [4].

The lack of sunlight exposure leads to VD deficiency. Higher latitude countries have a high incidence of deficiency. However, despite high exposure to the sunlight, Vitamin D deficiency is well recognized in middle eastern woman, elite gymnasts in Australia, Hawaiian skateboarders, and adolescent girls in England [5,6]. Norman made a major advance in 1969 by discovering vitamin D receptor (VDR), identified on 37 organs of the human body including the dendritic cells. In 2010, he published the first map on the scale of the genome of vitamin D. He revealed that this vitamin is involved in the expression of 229 genes. The VDR gene located on chromosome 12 (12q 13.11) is known to have various polymorphisms including Bsm 1, Fok 1, Apa 1, and Taq 1, which have been associated with various functional outcomes [7]. Vitamin D acts on the immune system by stimulating the synthesis of tumor growth factor (TGF), upon expressing on the surface of macrophages, Lymphocytes T, B, monocytes Toll-like receptor 2, VDR and 1 Alpha hydroxylase particularly during bacillus exposure. That could explain the relationship between tuberculosis and VD deficiency [8].

This interference with immune system reactions made the VD low serum level an independent factor to study in several disease. Recent study has confirmed the association of vitamin D deficiency with hypothyroidism, thyroid autoimmunity, increased volume, nodularity, and vascularity of thyroid gland in hypothyroid patients as well as increased HOMA-IR. However, no association between VDR polymorphisms (Fok1 and Apa1) with TSH levels was found [9]. Similar findings were observed in a group of glaucoma patients [10]. VD can regulate proliferation, apoptosis, and cell adhesion at the tumor cell level. It also interferes with tumor angiogenesis, decreases oxidative DNA damage, and limits invasion and metastasis.

Vitamin D: The black knight.

According to some studies VD inhibits RCC cell proliferation, angiogenesis, clonogenicity, and metastasis. A preventive role has been also cited in several malignancies. Recent reports found that the homozygous genotype (aa) of the VDR SNP Apa I correlates with total VD serum level in the serum of colorectal cancer patients and that the heterozygous genotype (Tt) of the VDR SNP Taq I significantly associates with serum Ca levels. That may suggest that VD supply would be an easy economical and safe factor in cancer prevention [11,12].

It was also suggested that D-binding protein (DBP) may have a direct impact on carcinogenesis including macrophage activation, apoptosis, and angiogenesis. Prostate cancer cells can express VD metabolizing enzymes and the VDR. Moreover, it is proven that VD3 affects prostate cell differentiation and proliferation. Preclinical and epidemiologic data suggest that VD deficiency may be of great impact in the pathogenesis and progression of prostate cancer (PCa). Furthermore, the protective role of VD in PCa was greater with high-grade than with low-grade PCa [13,14].

Various studies have examined Bladder Cancer (Bc) incidence and serum level of VD. Afzal et al proved that lower plasma VD was associated with higher risk of tobacco-related cancers, including BC [15]. Superficial transitional cell carcinoma of the bladder expresses VDRs, and their polymorphisms were examined in BC. Mittal et al reported that BC risk is higher among patients with VDR rs10735810 polymorphism ('Fok1'), which is known to decrease the receptor's activity [16-18]. Significant antiproliferative VD3 effect on TGCT cells was proven in in-vitro studies [19]. Some other reports ruled out enticing evidence that VD regulates multiple cancer risk and prognosis-relevant pathways, including tumorigenesis in ovarian and breast carcinoma [20]. These results still need to be worked out to get consistency.

Higher VD levels have been associated with lower level of biomarkers of inflammation and oxidative stress in children [21]. VD should have an influence on airway inflammation. The optimal VD status for the prevention of allergic disease is unclear. Based on skeletal health, the institute of medicine recommends 25(OH)VD concentration of > 50 nmol/l and more to be enough [21,22]. However, it is argued that observed associations between VD deficiency and cardiometabolic risks are mediated by underlying adiposity, since 25(OH)D is fat-soluble and its level is lower with greater adiposity [22].

Only few studies have used direct methods such as dual X-ray absorptiometry to measure adiposity or the hyperinsulinaemic-euglycaemic clamp to accurately assess cardiometabolic risk. A meta-analysis demonstrated an almost cross-sectional association between vitamin D levels and cardiometabolic factors [23]. Measurements of serum VD levels (25(OH)VD) show that populations with higher VD levels are less likely to have high blood pressure, cardiovascular or cerebrovascular disease [24]. Over 45 clinical trials have been started to study VD supplementation as a treatment for high blood pressure. Another meta-analysis had highlighted the possibility of a VD induced reduction of systolic blood pressure [25]. The first description of vitamin D independent UV driven-nitrate reduction and vasodilatation mechanism was made by Robert Furchgott for his description of endothelial "Derived Relaxant Factor" that led to his Nobel price award. Today it is known to be the nitric oxide generated by the endothelial cells [26]. The role of vitamin D levels at different stages of pregnancy and different clinical outcomes has been the subject of interest for a long time. It was proven that VD low serum levels is associated with complicated pregnancy and neonatal courses [27].

Key takeaways:

- VD is not only a modulator of the calcium-phosphate metabolism but also an important factor controlling several human processes. This make it probably closer to hormones more than vitamins.
- It is evident that regular cellular proliferation and differentiation depend on VD. The deficiency leads to impaired growth and only early supplementation can make the damage reversible.
- The direct interference of VD low levels or the variation of VDR distribution and polymorphism on malignant process promotion and extension is no more to be ignored. This could be useful in the diagnostic, follow up and prevention of some malignancies.
- The large interference of VD with cardiovascular system should be ruled out in order to open new perspectives in the treatment of related diseases.

Vitamin D: The black knight.

Conflict of interest: none

References:

- [1]Hazell TJ, Deguire JR, Weiler HA. Vitamin D an overview of its role in skeletal muscle physiology in children and adolescents. *Nutrition Reviews*.2012; 7:520-33.
- [2]Birge SJ, Haddad J. 25 Hydroxycholecalciferol stimulation of muscle metabolism. *J Clin Invest*. 1975 ;56 :1100-107.
- [3]Simpson R, Thomas G, Arnold A. Identification of 1.25 dihydroxy Vit D3 receptors and activities in muscle. *J Biol Chem*.1985 ;260 :8882-91.
- [4]Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary intakes for calcium and vitamin D from the institute of medicine: What clinicians need to know. *J Clin endocrinol Metab*.2011;96:53-58.
- [5]Seo MW, Song JK, Jung HC, Kim SW, Kim JH, Lee JM. The Associations of Vitamin D Status with Athletic Performance and Blood-borne Markers in Adolescent Athletes: A Cross-Sectional Study. *Int J Environ Res Public Health*. 2019;16: E3422.
- [6]Raza A, Syed JG, Muhammad Ali F, Danish Khan M, Ali Khan M, Haleem F, et al. Incidence of Vitamin D Deficiency in Different Seasons in the Adult Karachi Population Presenting in the Medical Outpatient Department with Generalized Body Ache. *Cureus*. 2019 ;11 : e5167.
- [7]Binkley N, Novotny R, Krueger D, Kawahara T, Daida Y, Lensmeyer G, et al. Low vitamin D status despite abundant sun exposure. *J Clin End Met*.2007 ;92 :2130-35.
- [8]Bertrand K, Giovannucci E, Liu Y, Malspeis S, Eliassen H, Wu K, et al. Determinants of plasma 25-hydroxyvitamin D and development of prediction models in three U.S. cohorts. *Br J Nut*.2012 ;108 :1889-96.
- [9]ElRawi HA, Ghanem NS, ElSayed NM, Ali HM, Rashed LA, Mansour MM. Study of Vitamin D Level and Vitamin D Receptor Polymorphism in Hypothyroid Egyptian Patients. *J Thyroid Res*. 2019; 2019:3583250.
- [10]Ayyagari R, Chen YI, Zangwill LM, Holman M, Dirkes K, Hai Y, et al. Association of severity of primary open-angle glaucoma with serum vitamin D levels in patients of African descent. *Mol Vis*. 2019; 25:438-45.
- [11]Al-Ghafari AB, Balamash KS, Al Doghaither HA. Relationship between Serum Vitamin D and Calcium Levels and Vitamin D Receptor Gene Polymorphisms in Colorectal Cancer. *Biomed Res Int*. 2019; 2019:8571541
- [12]Fleet JC, Desmet M, Johnson R, Li Y. Vitamin D and cancer : a review of molecular mechanisms. *Biochem J*.2012; 441:61-76.
- [13]Krajewski W, Dziegala M, Kołodziej A, Dembowski J, Zdrojowy R. Vitamin D and urological cancers. *Cent European J Urol*.2016; 69:139-47.
- [14]Swami S, Krishnan AV, Feldman D. Vitamin D metabolism and action in the prostate: implications for health and disease. *Mol Ccell Endocrinol*.2011 ;347 :61-69.
- [15]Afzal S, Bojesen SE, Nordestgaard Bg. Low plasma 25-hydroxyvitamin D and risk of tobacco-related cancer. *Clin Chem*. 2013 ;59 :771-780.
- [16]Sahin MO, Canda AE, Yorukoglu K, Mungan MU, Sade M, Kirkali Z. 1.25 dihydroxyvitamin D(3) receptor expression in superficial transitional cell carcinoma of the bladder. A possible prognostic factor? *Eur Urol*.2005 ;47 :52-57.
- [17]Mittal RD, Manchanda PK, Bhat S, Bid HK. Association of vitamin-D receptor (fok-I) gene polymorphism with bladder cancer in an Indian population. *BJU Int*.2007 ;99 :933-37.
- [18]Bremmer F, Thelen P, Pottek T, Behnes CL, Radzun HJ, Schweyer S. Expression and function of the vitamin D receptor in malignant germ cell tumour of the testis. *Anticancer.Res* 2012 ;32 :341-49.
- [19]Krusinska B, Wadolowska L, Biernacki M, Slowinska MA, Drozdowski M. Serum 'Vitamin-Mineral' profiles: Associations with postmenopausal breast cancer risk including dietary patterns and supplementation. A case-control study. *Nutrients*. 2019;11: E2244.
- [20]Reyman M, Verrijin Stuart AA, Van Summeren M, Rakhshandehroo M, Nubor R, De Boer FK, et al. Vitamin D deficiency in childhood obesity is associated with high levels of circulating inflammatory mediators and low insulin sensitivity. *Int J Obes*.2014 ;38 :46-52.
- [21]Hussain Gilani SY, Bibi S, Siddiqui A, Ali Shah SR, Akram F, Rehman MU. Obesity And Diabetes As Determinants Of Vitamin D Deficiency. *J Ayub Med Coll Abbottabad*. 2019; 31:432-35.
- [22]Arunabh S, Pollack S, Yeh J, Aloia JF. Body fat content and 25-hydroxyvitamin D levels in healthy women. *J Clin endocrinol Metab*.2003 ;88 :157-61.
- [23]Parker J, Hashmi O, Dutton D, Mavrodaris A, Stranges S, Kandala NB, et al. Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. *Maturitas*.2010;65 :222-36.
- [24]Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis J. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *BMJ* 2014 ;348 :g2035.
- [25]Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K. Systematic review: Vitamin D and cardiometabolic outcomes. *Ann Intern Med*.2010 ;152 :307-14.
- [26]Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987 ;327 :524-26.
- [27]Aghajafari F, Nagulesapillai T, Ronksley PE, Tough SC, O'Beirne M, Rabi DM. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. *BMJ* 2013 ;346: f1169.

JUNIOR MEDICAL RESEARCH JOURNAL

JUNIOR MEDICAL RESEARCH JOURNAL

