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Association of vitamin D deficiency with diabetic gastroparesis and its intramuscular vitamin D treatment

Dr. Kanhiya Lal Talreja
Medical unit, Dr Ruth K M Pfau Civil Hospital Karachi
Corresponding author email: talrejakanhiyalal@yahoo.com

Dr. Haseeb Ahmed Bhatti
Dr. Ruth K M Pfau Civil Hospital Karachi

Dr Humaira Siddiqui
Dr. Ruth K M Pfau Civil Hospital Karachi

Dr. Saweeta Kumari
Dr. Ruth K.M pafu civil Hospital Karachi

Dr. Rakesh Panjwani
Senior Registrar in Medicine Department, Dow University Hospital Karachi

Dr. Maryam Mesud
Department of General Medicine, Northwest General Hospital and Research Center

Muhammad Farhan Siddiq Rao
Institute of Molecular Biology and Biotechnology (IMBB) Bahauddin Zakariya University Multan

Sudhair Abbas Bangash
Faculty of Life Science, Department of Pharmacy, Sarhad University of Science and Information Technology, Peshawar, Pakistan

Maryam Batool
Department of Life Sciences, School of Science, University of Management and Technology, Lahore, Pakistan

***Abstract*---**Introduction: Diabetic gastroparesis (DGp) is a component of autonomic neuropathy resulting from long-standing poorly controlled type 1 and type 2 diabetes. There are currently no approved vitamin D supplementation recommendations for people with DGp.

Objectives: To investigate the relationship between vitamin D insufficiency and DGp, as well as the efficacy of intramuscular vitamin D therapy. Methodology: 71 patients (18 DM Gp & 53 Non-DM Gp) seeking treatment for gastroparesis symptoms were studied. The blood levels of vitamin D, homocysteine, gastric emptying test (GET) at 1, 2, and 4 h were recorded. 25-OH vitamin D levels were detected by kit. Potential clinical and statistical correlations between all results, symptoms, and GET data were explored. Descriptive statistics were used to investigate etiologic differences at baseline while multiple linear regression models were employed to explore relationships of vitamin D deficiency with diabetic gastroparesis and its intramuscular vitamin D treatment. Results: Majority of DGp patients were older than 18 years (88%) and were non-smokers (83%). The majority of those with and without diabetes were married (11; 71% vs. 34; 64%). The majority of participants in the DM group had only completed elementary school (n=7/18; 38.8%). All patients' 25-OH vitamin D levels, at 89.69 nM/l 62.55, were below the anticipated range of 50-250 nM/l. However, by comparing the group variance of p = 0.211, the diabetic group had considerably greater mean 25-OH vitamin D levels, at 76.85 nM/l 32.42. All of the DGp patients were given intramuscular injections of 10-20 g of vitamin D daily (400-800 IU). Conclusion: Most individuals with diabetes and gastroparesis who were deficient in vitamin D (n=11) did not respond to intramuscular vitamin D therapy. Six people have reported feeling better after receiving the medication while only one patient has mentioned any unfavorable reactions to the therapy.

***Keywords*---**malnourishment, vitamin D deficiency, diabetic gastroparesis, vitamin D treatment.

Introduction

Gastroparesis (Gp) is a complicated, incapacitating illness with signs which include vomiting and post-prandial intestinal discomfort or fullness (Camilleri et al., 2013). Screening of dietary condition and treatment of malnourishment are essential components in the care of individuals with Gp. The symptoms of Gp may be very incapacitating, and the resulting nutritional abnormalities can be fatal (Parrish and Yoshida, 2005). Human Gp is shown in Figure 1 by many gastrointestinal pathophysiological abnormalities. Gp is difficult to diagnose since the GET is not routinely conducted, and the individuals that have been discovered represent merely the tip of the iceberg (Rey et al., 2012). It affects 1-2% of type 2 diabetics and 0.2-0.3% of those without diabetes mellitus (DM) and is more frequent in women than males (Choung et al., 2012).

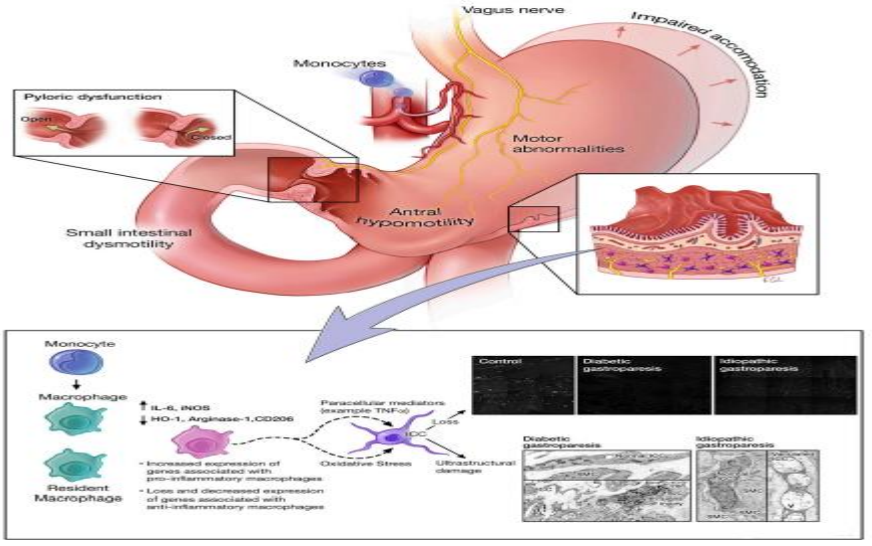

Figure 1: Gastrointestinal pathophysiological changes in human Gp (Source: Grover et al., 2019)

Since almost a century, the link between prolonged GE and diabetes has been recognised. First seen in diabetic patients, delayed GE was subsequently described by Boas in 1925. In 1958, Kassender created the word “Gp diabeticorum” to define asymptomatic gastric retention in diabetic individuals (Krishnasamy and Abell, 2018). In the absence of a mechanical blockage, DGp (DGp) refers to a significant consequence of diabetes characterised by delayed GE and upper gastrointestinal (GI) symptoms. The incidence of DGp is anticipated to increase as the prevalence of DM rises. A diabetic patient who also presents with nausea, diarrhoea, and poor glucose control may have an artificially low bmi because they are dehydrated. If a euvolemic true weight isn't used, a patient's apparent weight reduction with time may be greatly exaggerated, leading doctors to incorrectly diagnose severe malnutrition when they may only be dehydrated (Parrish and Yoshida, 2005).

Type 2 diabetes mellitus (T2DM) is a metabolic condition characterised by elevated blood glucose due to insulin resistance and ultimately insulin insufficiency. Extensive study is presently being conducted to better comprehend the origins of insulin resistance in the body. Numerous variables, including obesity, exposure to toxins, infections, and mental stress, all contribute to chronic inflammation and the development of this chronic illness and its numerous severe consequences. Literature indicates that patients with subtotal or complete gastrectomies may have faster bone loss, hence increasing their risk for osteoporosis. It is believed that reduced consumption of calcium, vit-D, and lactose-containing foods, together with impaired absorption and metabolism, contribute to bone disease in this group (Meyer, 1994). Patients with Gp may also benefit from an evaluation of 25-OH vit-D levels (not 1, 25-OH2 vit-D) and bone mineral density (Bernstein & Leslie, 2003).

It is recommended that a compensatory nutrition for reduced GE. This diet is low in fibre and fats, which might promote gastric retention in people with Gp (Parkma et al., 2011; Kedar et al., 2013). Increasing awareness in dietary consumption for Gp patients has resulted in a remarkable increase in their nutritional intake (Parkma et al., 2011), however nutritional effects on gastrointestinal motility for individuals with DM Gp remain understudied (Kedar et al., 2013). Although relationships of 25-OH vit-D with several disease conditions, such as hypertension control, have been widely researched (Reusch et al., 2009), data on stomach motility and low vit-D levels are scarce (Kedar et al., 2013). There are currently no approved vit-D supplementation recommendations for people with DGp. Multivitamin/mineral supplements offer variable levels of calcium and vit-D; hence, further supplementation is often necessary (McCray, 2003). The purpose of this research was to fill this knowledge gap by examining the association between vit-D deficiency and DGp and the effectiveness of vit-D treatment administered intramuscularly.

Materials and Methods

Study design

This study was carried out from March to October 2022 in the Dr Ruth K M Pfau Civil Hospital Karachi. A total of 71 patients pursuing treatment for Gp symptoms during their first appointment were studied. We recorded the baseline blood levels of vit-D and homocysteine; Standardized comparative data was used to measure GE at 1, 2, and 4 h. This was accompanied by "Total GET." The diagnosis of reduced 25-OH vit-D levels in patients was a variable of great interest. Potential clinical and statistical correlations between all results, symptoms, and GET data were explored.

Data collecting

We assessed 71 patients in all (18 DM Gp, 53 Non-DM Gp). At the first clinic appointment, the evaluator gathered patient-reported history information via patient interviews. In addition, a retrospective analysis of patient records was conducted to identify prescribed and nonprescription supplement use prior to collecting blood samples. Each patient reported Gp symptoms on a simple, 5-item Patient Reported Outcome (PRO) diary, which allowed for easy notation of the daily absence or presence and intensity of vomiting, nausea, anorexia/early satiety, bloating/distension, and abdominal pain. Symptom severity was reported on a 0-5 scale, with 0 representing no symptoms, 1 representing mild symptoms, 2 representing moderate symptoms, 3 representing severe symptoms, and 4 representing extremely severe (disabling) symptoms. The study staff added the 5 daily scores (1 each symptom) to generate the Total Symptoms Score for each subject (Daram et al., 2011).

Upon completion of the clinical evaluation by the attending physician, patient agreement for the research blood draw procedure was acquired so that micronutrient and macronutrient tests could be conducted. To test 25-OH vit-D, ELISA kit (ab213966), was used to conduct liquid chromatography and tandem mass spectrometry experiments. Utilization of a multicenter GET methodology. In

a normal egg beater meal, 1.0 mCi of technetium 99m sulphur colloid was administered to participants who had followed a “nothing by mouth” diet after midnight before to the test. A single head gamma camera was used to acquire anterior and posterior abdomen planar pictures of the patient in an upright posture at 1, 2, and 4 hours, with one minute of data collection per image. If more than sixty percent (60%) of the isotope remained in the stomach after two hours, and more than ten percent (10%) after four hours, the data were deemed delayed. Total GE times were computed for each patient by summing the gastric retention seen at 1, 2, and 4 h, and the results were interpreted by comparing them to normal values (160% in healthy subjects).

Descriptive statistics were generated and used to investigate etiologic differences at baseline. Multiple linear regression models were employed to explore the association of vit-D deficiency with diabetic gastroparesis and its intramuscular vit-D treatment. By studying nonparametric lowess smoothers, diagnostic tests for linearity assumptions were undertaken, and no violations were identified (Hastie et al., 1990; Kedar et al., 2016).

Results

Our retrospective analysis of clinical records for supplement usage indicated an expected disparity between groups in the data obtained: all diabetes patients (n = 18/71) had much more clinic visits and follow-up, and patients with DGp had a better-defined illness profile. Table 1 demonstrates that the majority of patients were older than 18 years (DM group = 16/18, or 88%, vs Non-DM group = 32/52, or 60%) The majority of those with and without diabetes were married (11; 71% vs. 34; 64%). 83% (n = 15/18) of the DM patients were non-smokers, compared to 74% (n = 39/53) of the non-diabetics, and 16% (n = 3) of the DM group had never smoked, compared to 26% (n = 14) of the non-diabetics. The majority of participants in the DM group had only completed elementary school (n=7/18; 38.8%), while the majority of patients in the non-DM group have completed high school (n=25/53; 55.5%) and beyond (n=20/53; 38.5%). The majority of individuals in both groups were employed (77% vs. 74%).

Table 1. Sociodemographic characteristics of the patients

Variables		Diabetics n(18)	%	Non-Diabetics n(53)	%	Total n(71)	%
Age	<18	2	11.11	21	40%	23	0.37
	>18	16	88.88	32	60%	48	0.78
Marital Status	Married	11	71.11	34	64%	45	0.74
	Unmarried	7	38.88	19	36%	26	0.42
Smoking Status	Yes	3	16.6	14	26%	17	0.27
	No	15	83.3	39	74%	54	0.88
Education	Primary or below	10	55.5	8	15%	18	0.29
	High School	7	38.8	25	47%	32	0.52
	Graduate or above	1	5.5	20	38%	21	0.34
Occupation	Unemployed	4	22.2	14	26%	18	0.29

	Employed	14	77.7	39	74%	53	0.86

Patients with diabetes were all receiving multivitamin treatments. All patients' vit-D levels, at 89.69 Nanomolar (nM)/l 62.55, were below the anticipated range of 50-250 nM/l. However, by comparing the group variance of p = 0.211, the diabetic group had considerably greater mean 25-OH vit-D levels, at 76.85 nM/l 32.42. (Table 2). All research participants had serum homocysteine levels within the predicted range, however those in the diabetes group had substantially higher levels (p = 0.077). The mean homocysteine level for diabetics was 11.02 mol/l 6.01, p = 0.077.

Similar to this, the diabetic group scored significantly higher for each of the following symptoms than the non-DM group: vomiting (1.9±1.52 vs. 1.71±1.42), nausea (3.23±2.03 vs. 2.77±1.14), bloating (3.06±1.51 vs. 2.39±1.35), and intestinal pain (3.37±0.79 vs. 2.50±1.36; Table 2). The non-DM With > 10% retention in all patients, overall GE at the fourth hour was considerably delayed (20.04%; 19.21). Individuals with diabetes experienced this delay a little more often (29.35% 27.87) than patients without diabetes (17.32%; 21.91). For all groups, gastric delay at the first and second hour assessments was almost the same (Table 2).

Table 2. Assessment of different variables of the participants in comparison to the normal range

Variables		Normal range	Diabetics Mean±SD	Total patients Mean±SD	P-value
Vit-D	25-OH D levels	50–250nM/l	76.85±32.42	89.69±62.55	0.21
Homocysteine	Serum levels	5–15µmol/l	11.02±6.01	8.93±4.40	0.07
Severity of Gp symptoms	Vomiting	0-5	1.9±1.52	1.71±1.42	0.53
	Nausea	0-5	3.23±2.03	2.77±1.14	0.29
	Anorexia	0-5	2.23±1.39	2.39±1.22	0.62
	Bloating	0-5	3.06±1.51	2.39±1.35	0.56
	Intestinal pain	0-5	3.37±0.79	2.50±1.36	0.11
	Total Score	0–20	12.63±3.41	11.75±4.62	0.38
Gastric emptying retention test	1 h	>90	60.71±23.49	60.51±23.52	0.97
	2 h	>60	39.27±29.25	38.82±25.76	0.93
	4 h	>10	29.35±27.87	20.04±19.21	0.27
	Total time	<160	124.08±79.95	118.13±70.26	0.70

Improvements in GE time and increases in micronutrient levels for almost all vitamins were measured in non-DM patients, with results showing mixed results. The first two hours of the four-hour GET test showed a marginal correlation with 25-OH vit-D levels (Table 3). At 4 hours, however, the correlation between higher 25-OH vit-D levels and better GET measures for these patients was close to statistical significance (0.13, CI:0.24, 0.01, p=0.06). However, The extent of these

results is limited by the fact that only around half of non-diabetic individuals received vitamin and mineral supplements, whereas all diabetes patients received supplements.

Table 3. Association of vit-D with the varying degrees of gastric emptying time (GET)

Nutritional parameters		GET 1h	GET 2h	GET 4h
25-OH Vit-D	Total patients	−0.13 (−0.24, 0.01), p = 0.05	−0.13 (−0.25, 0.02), p = 0.08	−0.13 (−0.25, 0.01), p = 0.05
	DGp patients	0.20 (−0.44, 0.86), p = 0.52	0.01 (−0.74, 0.76), p = 0.97	0.04 (−0.58, 0.81), p = 0.93

The dairy products are commonly supplemented with vit-D to help people with DGp deal with vit-D shortage. Vit-D is now considered a micronutrient. All of the patients with diabetes and Gp who were deficient in vit-D (n=18) were given intramuscular injections of 10-20 g of vit-D daily (400-800 IU). Measurement of plasma 25(OH)D3 is often used as an indicator of vit-D levels in the body. However, the biologically active component, 1,25(OH)2VD, is very unstable with a half-life that may be measured in hours rather than the weeks that 25(OH)D3 requires to degrade. Most individuals with diabetes and Gp who were deficient in vit-D (n=11) did not respond to intramuscular vit-D therapy. Six people have reported feeling better after receiving the medication. In any case, not even one patient has mentioned any unfavourable reactions to the therapy (figure 2).

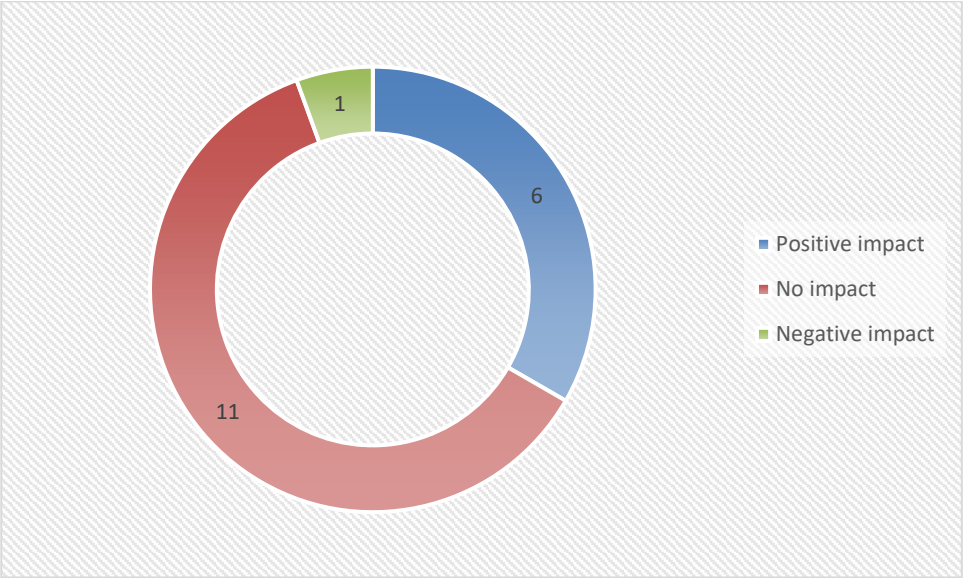

Figure 2: Effects of 10 –20 g/daily (400 – 800 IU) intramuscular vit-D treatment of DGp

Discussion

We analysed the vitamin levels of individuals with Gp and the time it took for their stomach to empty to see whether there was a correlation between the two. It has been noted that these individuals suffer from nutritional inadequacies, but the connection between these issues and GET has not been well explained. Impaired stomach motility was linked to vit-Deficiencies, which we were able to discover in our investigation. The low serum levels we observed could be the result of a lack of vit-D in the diet, or it could be the result of 25-OH vit-D being sequestered in obese conditions (Earthman et al., 2012), or it could be the result of volumetric dilution of this fat-soluble vitamin (Drincic et al., 2012), both of which suggest an increased risk of developing diabetes that might be mitigated by eating more whole grains (Kaline et al., 2007). Devaraj et al., (2011) reported that individuals' fasting glucose levels are rising with metabolic syndrome and low 25-hydroxyvit-D have been reported recently, suggesting a possible risk of developing diabetes.

According to some studies (Kedar et al., 2011; Kedar et al., 2013), it is possible that poor enteric neuronal function and pathology underpin the link between a low blood 25-OH level and Gp. Entire stomach biopsies taken from the body antral junction region have shown immune filtration of the myenteric plexus and the presence of inflammatory T cells (CD4, CD8, and CD68) in this area, all of which affect Finding the missing pieces of the jigsaw of non-DM Gp pathophysiology may also rely on determining the specific mechanism by which 25-OH vit-D improves gastric transit.

Large, high-caloric, fatty meals, dietary fibres, and any item that the particular patient recognises to increase postprandial symptoms are all still fair recommendations for people with Gp to avoid. These recommendations stem from pathophysiological thinking or sound common sense, but they have never been verified by proper research. Patients with DG who followed a diet composed of foods with tiny particle sizes had reductions in reflux symptoms, fullness, nausea, vomiting, and bloating, according to a randomised, controlled trial (Olausson et al., 2014). The majority of patients with Gp did not get nutritional counselling, and just 2% were really following dietary recommendations (Grover et al., 2019). Over 60% of patients reported caloric-deficient diets (defined as 60% of estimated daily total energy need) and had shortages in various vitamins and minerals, despite the rising prevalence of obesity among patients with Gp (Parkman et al., 2011). Therefore, these individuals need a focused history for calorie intake and nutritional counselling.

Different types of monocytes such as, T- and B-lymphocytes, and macrophages that not only express VDR receptors but also possess the necessary enzyme 25-hydroxyvit-D3-1hydroxylase, to synthesise 25-OH vit-D locally, have shown that 25-OH vit-D plays a role as a hormone with potent immunomodulatory effects (Kedar et al., 2013). It's possible that the improved stomach motility is due to the immunomodulatory effects of 25-OH vit-D on the enteric nervous system, which merits further investigation. Due to its favourable effects on enhancing B-cell activity and peripheral insulin sensitivity, new studies advocate high blood levels of 25-OH vit-D in all diabetics (Knekt et al., 2008; Blanton et al., 2011).

Treatment with high doses of 25-hydroxyvit-D has been shown to increase neurotrophic factors like glial cell line-derived neurotrophic factor (GDNF) and insulin-like growth factor-I (IGF-I), as well as improve the immune response via immunomodulation and reduce inflammation in the area surrounding the motor neurons (Karam & Scelsa, 2011; Mason, 2011). Our findings indicate that injectable vit-D therapy for DGp is effective for the vast majority of individuals who have vit-D insufficiency. However, therapeutic supplementation is strongly suggested in all diabetes patients with blood 25-OH vit-D levels below 50 nmols/l due to the significance of 25-OH vit-D and its favourable benefits in improving glycemic control. Our findings suggest that symptom improvement in chronic Gp may be achieved with the use of an adjuvant nutritional supplementation treatment consisting of a multivitamin complex, and particularly 25-OH vit-D.

Conclusion

There are currently no approved vit-D supplementation recommendations for people with DGp. In current researcy, majority of DGp patients were older than 18 years (88%) and were non-smokers (83%). The majority of those with and without diabetes were married (11; 71% vs. 34; 64%). The majority of participants in the DM group had only completed elementary school (n=7/18; 38.8%). All patients' 25-OH vit-D levels, at 89.69 nM/l 62.55, were below the anticipated range of 50-250 nM/l. However, by comparing the group variance of p = 0.201, the diabetic group had slightly higher mean 25-OH vit-D levels, at 76.85 nM/l 32.42. All of the DGp patients were given intramuscular injections of 10-20 g of vit-D daily (400-800 IU). Most individuals with diabetes and Gp who were deficient in vit-D (n=11) did not respond to intramuscular vit-D therapy. Six people have reported feeling better after receiving the medication. In any case, not even one patient has mentioned any unfavourable reactions to the therapy.

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