Study the effects of sleeve gastroectomy on IL-8, IL-18, and vitamin D3 deficiencies

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Abstract

Bariatric surgery is the most successful therapy for weight loss, Sleeve gastrectomy; part of the stomach is removed, reducing its capacity by about 85%. Reducing stomach size decreases the consumption of food. Obesity is measured based on their BMI, an estimate of body fat based on weight and height is to study the association between sleeve gastroectomy and some immune marker by estimation level of interleukin-8 (IL-8), interleukin-18 (IL-18), and vitamin D3 in sera patient and control groups, to determination the correlation between in markers; Body mass index (BMI) and their parameters. A total of thirty blood samples were obtained from obese patients with pre and post gastrectomy operative compared with healthy during more than 6 months, the samples preoperative were obtained from the Medical City/Baghdad Teaching Hospital and postoperative for more than 6 months after surgery, taken at home to be the result of pre and post of the sleeve gasterectomy, the age of patients range between (20-46) years for obese patients and similar age group (20-46) year in a healthy person. Then the serum samples were tested to screen the interleukin-8, interleukin-18, and vitamin D by the ELISA method. The study reported that increasing levels of BMI pre-operation, IL-8 pre-operation, and IL-18 pre-operation were increased relative to post-operation. The study reported high BMI, IL-8 and IL-18 pre-operative. The mean value was poor in vitamin D3 preoperation relative to post-operation. The relationships between IL-18, and IL-8 is positive while negative correlation with vitamin D3. The highest mean value of BMI, IL-8, and IL-18 was recorded in preoperation, while the lowest mean was at post-operation. BMI showed a high sensitivity when compared with IL-8, IL-18, vitamin D3.

Keyword: Sleeve gastrectomy, Overweight, vitamin D3.

دراسة تاثير قص المعدة على انترلوكين 8 وانترلوكين 18 ونقص فيتامين د3

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الخلاصة

جراحة علاج السمنة هو العلاج الاكثر نجاحا لاجل فقد الوزن . قص المعدة هو از الة جزء من المعدة و اختز ال سعتها بحوالي 28% . اختز ال حجم المعدة هو قلة استهلاك الطعام . السمنة تتم قياسها بمؤشر كتلة الجسم وذلك بوزن دهن الجسم اعتمادا على قياس الوزن و الطول . لدر اسة العلاقة بين قص المعدة وبعض المعلمات المناعية بو اسطة قياس مستوى الانترلوكين 8 وانتلوكين 8 وفيتامين د3 في سيرم المصابين ومجموعة السيطرة لتحديد العلاقة بين معلمات مؤشر كتلة الجسم ومعاملاته . جمعت 30 نموذج وفيتامين د3 في سيرم المصابين ومجموعة السيطرة لتحديد العلاقة بين معلمات مؤشر كتلة الجسم ومعاملاته . جمعت 30 نموذج معنة من الشخاص يعانون السمنة و اخذت العينات قبل وبعد عملية قص المعدة جراحيا وقور نت باشخاص لا يعانون من السمنة عينة دم من اشخاص يعانون السمنة و اخذت العينات قبل وبعد عملية قص المعدة جراحيا وقور نت باشخاص لا يعانون من السمنة العينات قبل وبعد عملية قص المعدة جراحيا وقور نت باشخاص لا يعانون من السمنة الاصحاء خلال اكثر من ستة اشهر . النماذج قبل العملية اخذت من مستشفى مدينة الطب / مستشفى بغداد التعليمي و النماذج بعد العملية اخذت بعد ستة الشهر من اجراء عملية قص المعدة من المنزل للحصول على العينات قبل وبعد اجراء العملية . معل العملية اخذت من مستشفى مدينة الطب / مستشفى بغداد التعليمي و النماذج بعد المصابين بين 20-46 سنة المصابين و نفس المعد تم اخذه للاصحاء 20- 40 سنة بعدها نماذج السيرم فحصت الكشف عن المصابين بين 20-46 سنة المصابين و نفس العمر تم اخذه للاصحاء 20- 40 سنة بعدها نماذج السيرم فحصت للكشف عن المولين 8 و انترلوكين 30 و كانت الزيادة نسبية بمقار نتها بتائج بعد عملية قص المعدة . معدل القيم كانت قليلة بالنسبة لفيتامين د3 و انترلوكين 8 وانترلوكين 8 و انترلوكين 8 و انترلوكي 8 و انترلوكين 8 و انترلوكين 8 و انترلوكين 8 وانترلو

الكلمات المفتاحية : تكميم المعدة، زيادة الوزن وفيتامين د3.

Introduction

Obesity is one of the main critical health issues in the world. There is an important indication that obesity is associated with many cardiovascular, endocrine, neurological, and diabetes disorders [1]. Obesity is a health disorder that occurs when the BMI is bigger than or equal to 30 kg of the body weight per m2 of height. It is caused by the production of overweight that can supply to cardiovascular disease, type 2 diabetes mellitus, osteoarticular system disorders, stroke, metabolic syndrome, and cancer [2]. Bariatric procedures are related to several micronutrient deficiencies, including vitamin D deficiency [3]. Vitamin D is necessary for the homeostasis of calcium and bone metabolism. There are concerns that bone health may be adversely impacted by bariatric health [4]. Lymphocytes play a vital function in the immune system due to their effect on the immune response to infectious micro-organisms and other substances of foreign origin [5]. They have a required response to an attack by invasive micro-organisms [6]. Cytokines are a cell- signaling community

of low molecular weight cellular polypeptides/glycoproteins produced by several immune cells, predominantly T cells, macrophages, and neutrophils, which are responsible for promoting and regulating the immune response [7]. Interleukin-18 is a cytokine that activates and has pleiotropic functions for various cell retypes IL-18 precursors are mainly current in monocytes, macrophages, dendritic cells of healthy subjects [8]. Inflammatory mediators and cytokines closely linked to obesity and insulin resistance are predicted to regularly decrease following bariatric surgery, in research published in 2006 [9], the monocyte chemoattractant protein1(MCP-1) decreased significantly (more than 50%) following by bariatric surgery, the result was also noted in 2012, six months after the Roux-en-Y gastric bypass(RYGB) operation. Lipid and cytokine mediators are the primary inflammatory response modulators in arthritis, both of which are known to the development of joint inflammation plays an especially critical role, and contributes significantly to the production of pro-inflammatory cytokines and potent chemokines, such as IL-8, responsible for joint inflammation [10].

Materials and methods

Patient's: This study was performed during the period from December 2019 to September 2020, for this purpose 30 patient's Obesity with BMI >40 were selected from people attended the Baghdad hospital at Medical City during the period. Their age was ranged between 20-46 years. All planned investigation was carried out on 30 patients compared to 20 sample control group subjects, their age ranged between 20-46 years for each subject, five ml of blood sample has been collected from each patient's obesity with BMI more than 40, and also from apparently healthy persons, which were not undergoing any disease.

Methods

IL-8 and IL-18 detected by enzyme immune sorbent assay (ELISA): the method was all samples and reagents were brought to room temperature before use. The study sample was centrifuged again after freezing before the assay: One hundred microliters of sample and standard per well have been added. Covered with the supplied adhesive strip and incubated for 2 hours at 37 C. The liquid was removed from each well. One hundred microliters biotin antibodies (1x) were added to each well. Covered with a new adhesive strip for protection and incubated at 37 C for 1 hour. Each well was aspirated and washed, repeating the process twice for a total of three washes. Washed by filling each well with an auto washer or washing buffer 200µl, and let it stand for 2 min, complete liquid removal at each step is important to good performance. After the last cleaning, any remaining wash buffer by aspirating or decanting was removed. The plate was inverted on clean towels made of paper. One

hundred microliters of HRP-avidin (1x) added to each well, the plate was covered with a new adhesive strip for protection and incubated at 37C for 1 hour.

The wash/aspiration process was repeated 5 times. Ninety microliters substrates of TMB were added to each well, and it was incubated at 37 C for 30 min. Fifty microliters of the stop solution have been added to each well. The optical density of each well has been determining within 5 minutes, operating a microplate reader to correct for optical imperfections in the plate. Read immediately by use ELISA reader.

Calculation of the results

The sample results were calculated by interpolation. From a standard curve that was performed in the same assay as that of the sample. The standard curve was drawn by plotting the IL–8 concentrations of standards on the horizontal axis and their corresponding absorbance was plotted on the vertical axis. The absorbance for each sample was located on the vertical axis, the corresponding IL–8 concentrations were reading off on the horizontal axis (shows the IL-8 ELISA kit contents.).

25 (OH) vitamin D3 by ELISA technique: The techniques were carried by the instruction manual of the company (Accubind, USA): The required reagents have been removed from the refrigerator and allowed to reach room temperature for at least 30 minutes. The controls, calibrators, and samples for analysis are diluted with 1:26 in biotin working strength. Biotin working strength was added and mixed carefully (vortex) and incubated at room temperature for at least 10 minutes. For wells of controls and calibrators: original density calibrators were added as follows: set up 6 calibrator points include: 0 ng/ml, 4 ng/ml, 10 ng/ml, 25 ng/ml, 60 ng/ml, 120 ng/ml, control 1, and control 2. About 200µl of sample required diluted in each of the microplate wells in the biotin buffer, incubated at room temperature for 2 hours. Reagent wells were washed three times by an automated washer with 450µl of working strength wash buffer, the washing buffer was left for 30 to 60 seconds per washing cycle in each well, and then the wells were washed. After washing all solution was disposed carefully of the microplate by tapping it on absorbent clean towels paper with the opening facing downwards to remove all residual wash buffers. About 100µl of the conjugate enzyme (streptavidin-peroxidase) was pipetted into each of the microplate wells and incubated at room temperature for 30 minutes. The wells were emptied and subsequently washed by an automatic washer three times using 450µl of working strength wash buffer. Approximately 100µl of solution chromogen/substrate was pipetted into all of the microplate wells and incubated at room temperature for 15 minutes protected from direct sunlight. Approximately 100µl of stop solution was pipetted into all of the microplate wells in the same order and at the same speed as chromogen/substrate solution. Colormetric measurement of

the colour influence made at a wavelength of 450 nm and reference wavelength among 620 nm and 650 nm with the stop solution added in 30 minutes. Before measuring, we checked the microplate slightly to ensure a homogenous solution distribution.

The normal value of 25-OH Vitamin D Total: Vitamin D levels were classified into 3major groups according to the classification of the Institute of Medicine (IOM) as follows; sufficient (30-100 ng/mL), insufficient (20–29 ng/mL) and deficient (<20ng/mL) [11].

Statistical analysis: Data of the current study were analyzed by using Chi-square (X^2) test to compare percentages. ROC curve is used to measure the sensitivity and specificity of diagnostic tests (detection the best test for diagnosis). Numeric dates were described by (Mean ± SD). T-test was used to compare between two numeric variables, while F-test (ANOVA) was used to compare between three numeric variables or more. Also, used LSD to compare among means. Pearson correlation (r) accounted to explain the type and strength of relationship among variables. A level of significance of α =0.05 was applied to the test. (SPSS v.22 and excel 2013) programs used to analyze current data

Results and Discussion

Thirty samples of obese patients were collected from Baghdad medical city in Baghdad hospital, the result was compared with 20 healthy individuals as a control.

Mean value of BMI, IL-8, IL-18, and vitamin D3 among studies groups: the result of the present study showed the highest mean value of BMI was at pre-operation (48.00 ± 9.99), while the lowest mean value was at controls (25.79 ± 6.69) with high significant different (P<0.05). The highest mean value of IL-8 and IL-18 recorded at pre-operation (105.74 ± 34.66) and (214.19 ± 88.15) respectively, while the lowest mean value was at post-operation (15.07 ± 12.65) and (17.68 ± 10.36) respectively with high significant different (P<0.05). In contrast, the highest mean value of vitamin D3 was at controls (37.75 ± 14.39), while the lowest mean value was at pre-operation (9.76 ± 7.29) with a highly significant difference (P<0.05) among studied groups the result is shown in "Table1 and Fig1".

Parameters		Ν	Mean	SD	P value
Body mass index	Pre-operation	30	48.00	9.99	0.001*
	Post-operation	30	32.06	5.31	LSD=9.08
	Controls	20	25.79	6.69	
Interlukin-8	Pre-operation	30	105.74	34.66	0.002
	Post-operation	30	15.07	12.65	**LSD=88.21
	Controls	20	17.80	9.06	
Interlukin- 18	Pre-operation	30	214.19	88.15	0.001
	Post-operation	30	17.68	10.63	LSD=140.82
	Controls	20	21.04	12.60	
Vitamin D3	Pre-operation	30	9.76	7.29	0.003
	Post-operation	30	17.02	6.58	LSD=13.21
	Controls	20	37.75	14.39	

Table (1): mean levels of BMI, IL-8, IL-18 and vitamin D3 among study groups compared by using

 F test

N: number, SD: standard deviation, LSD: Least Significant Difference, *highly significant

The findings of our analysis showed that the highest mean value of BMI was pre-operative (48.00 ± 9.99) while the mean value after laparoscopic sleeve gastrectomy surgery (32.06 ± 5.31) with a highly significant difference (P<0.05). These findings were very consistent with the results of [12] which suggested that BMI levels decreased after laparoscopic sleeve gastrostomy. Obesity, identified as a BMI of >30 kg/m2, is a chronic, severe and costly condition. It is linked with an increased incidence of co-morbidities, including cardiovascular disease, type-2 diabetes mellitus, and certain forms of cancer [13]. Various international recommendations recommend that applicants for bariatric and metabolic surgery are only those patients with BMI over 40 (morbid obesity) or BMI over 35 (severe obesity) and at least two obese-related comorbidities and failure to maintain a stable weight loss applicants for at least one year with previous weight loss attempts [14]. Also, bariatric surgery is safe and successful in patients [15]. Besides, BMI obesity greater than 40 is associated with increased levels of all-cause mortality [16]. The basic reason for SG was to start losing weight in super-obese clinicians with BMI >60 to reach the second stage of biliopancreatic diversion-duodenal switch safely (BPD-DS).

The only scientific proof of clinically significant and maintainable weight loss in patients with severe obesity class II or III is medical treatment [17]. In our analysis, Interleukin-8 observed the highest pre-operative value (105.74±34.66) and the lowest post-operative value (15.07±12.65) with a highly significant difference (P<0.01). These findings were very consistent with the results of [18]. The recorded levels of IL-8 decline after laparoscopic sleeve gastrostomy. Obesity may cause physiological changes that are potentially linked to a reduced inflammatory process disorder due to elevated expression of cytokines, such as CRP, IL-6, IL-8, and TNF- α [19]. In constant, significant changes in serum concentrations of IL-8 occurred following twelve months of sleeve gastrectomy [18]. Inflammation is a defensive tissue reaction to tissue damage or degradation that is used to kill or sweeten both the harmful agent and the wounded tissue [20]. Obesity a hallmark characteristic of metabolic syndrome [21]. Obesity, a characteristic of metabolic syndrome, has been associated with chronic inflammation in obese subjects [22]. Represents studies explain that hs-CRP, IL-1Ra, IL-6, TNF- α , and adiponectin are correlated (p<0.0001) with obesity markers [23].

In our research, Interleukin-18 observed a high pre-operative value (214.19±88.15) and the lowest post-operative value (17.68±10.36) with a highly significant difference (P<0.01). These findings were very consistent with the results of [24] recorded lowering of IL-18 levels after laparoscopic sleeve gastrostomy surgery. Obesity is characterized by chronic low-grade inflammatory drugs caused by increased systemic levels of inflammatory factors like CRP, IL-6, IL-18 TNF- α [25]. Oddly, the plasma level of IL-6, IL-18, and TNF5-007 remained unchanged following gastric bypass, but the level of CRP declined 18 months after the surgery [24].



Fig (1): mean levels of BMI, IL-8, IL-18, and vitaminD3 among studies groups.

IL-18 increases in obesity, metabolic syndrome, and type 2 diabetes (T2D) as part of the chronically low inflammatory phase [26]. [27] presented a summary of the increased IL-18 rates in obese diabetic patients. This IL-18 resistance refers to the combination of obesity and diabetes with higher serum IL-18 concentrations near hyperinsulinemia and hyperleptinemia. Many other pro-inflammatory cytokines were shown to be increased in tandem with a growing number of parts of the disorder, while the anti-inflammatory and adipocyte-specific material adiponectin is significantly lower [28]. Adipokines are involved in several biochemical functions, involving inflammation, thrombosis, insulin levels, and energy balance [29]. However, a growing body of research indicates that IL-18 is closely related to metabolic syndrome and its effects. Oddly, clinical hyperglycemia was shown to raise the expression of IL-18 in adjocytes, an effect that was even more prominent in the presence of sporadic hyperglycemia [30]. However, other studies have suggested that non-adipocytes are the major sources of IL-18 in adipose tissue [31]. Vitamin D3 in our study observed the highest value in control groups (37.75±14.39) and lowest at pre-operation (9.76±7.29) with a highly significant different (P < 0.05). These results were quite compatible with the results [32] who reported the levels of Vitamin-D3 are increasing after laparoscopic sleeve gastrostomy. The frequency of vitamin D deficiency decreased from 96.7 percent preoperatively to 3.3 percent after 1-year postoperative follow-up. [33] indicated that vitamin D deficiency following bariatric surgery, including SG; is due

to decreased food intake. The authors recommended a daily supplementation of 2,000 IU of vitamin D3 and 1,500 mg of calcium citrate; they considered this regimen to be effective in reducing the incidence of vitamin D deficiency from 54.5 % preoperatively to 27.4 % three months after SG. Vitamin D deficiency is extremely common in obese patients, and several reports have shown a major effect of calcitriol on adipose tissue [34]. Genetic experiments have created an ability to determine which proteins relate vitamin D to obese pathology, include vitamin D receptors, toll-like receptors, renin-angiotensin, apolipoprotein E, vascular endothelial growth factor, and polymerase-1 (ADPribose) polymerase-1 [35]. Vitamin D also is capable of working through a variety of non-genomic pathways, including protein expression, oxidative stress, inflammation, and cell metabolism, which indicates that vitamin D plays a role in obesity [36]. Vitamin D deficiency and obesity are pandemic diseases and they are associated with cardiovascular disease, metabolic syndrome and type 2 diabetes mellitus, and other diseases. Concentrations of 25-hydroxyvitamin D 25(OH) are considered as the best indicator of total body vitamin D stores [37]. Low vitamin D status and obesity have concomitantly reached epidemic levels worldwide. Up to now the direction of the association between low vitamin D status and obesity, the exact mechanisms responsible for this association and the clinical usefulness to increase vitamin D status for reducing adiposity still warrant further evaluation [38]. Refer study the BMI≥2.5 SD) and does not significantly change by season, ethnicity, nutrient intake, or cardiovascular disease risk parameters [39].

ROC curve (sensitivity and specificity) of BMI, vitamin D3, and interleukins (IL-8 and IL-18)

As shown in table (2) and Fig (2), BMI showed a high sensitivity when compared with IL-8, IL-18, and vitamin D3 (90% vs. 56%, 73%, and 23%) respectively. So, the BMI showed a highly specificity when compared with IL-8, IL-18, and vitamin D3 (100% vs. 50%, 70%, and 90%) respectively.

Parameters	AUC	Sensitivity	Specificity
Body mass index	0.882	90%	100%
Interlukin-8	0.591	56%	50%
Interlukin-18	0.673	73%	70%
Vitamin-D3	0.126	23%	90%

AUC= area under curve



Fig (2): ROC curve of Body mass index, vitamin D3 and interleukins 8 and 18.

The Body Mass Index is a widely recognized anthropometric system for the classification of overweight and obesity [40]. BMI is the most commonly used indicator for the diagnosis of obesity (41). Centered on the Centers for Disease Control (CDC) guidelines, the BMI of 95th percentile or more and below 85 to 95th percentile are classified as obese and overweight, respectively. According to the World Health Organization study, extra body fat in childhood is associated with a rise in body fat in adulthood and the prevalence of illness diseases. Taking into consideration that body fat can be calculated using various methods such as dual X-ray absorption, bioelectric impedance analysis, and caliper, it seems important to calculate body fat in addition to BMI throughout childhood [42].

It is therefore important to take into account body fat mass when assessing obesity to predict obesity outcomes, which are mainly due to a rise in body fat mass [43]. Diagnosis of BMI in elderly individuals may not be accurate due to changes in body structure. Latest research aiming at analyzing the accuracy of BMI thresholds by the World Health Organization and the Diet Screening Initiative to detect obesity in aged patients on hemodialysis [44]. Several pro-inflammatory cytokines have been shown to increase in tandem with an increasing number of parts of the disease, while adiponectin, the anti-inflammatory and adipocyte-specific component is always lower, [45]. IL-8 is a chemokine used in systemic immunity, penetration, and activation of macrophages in adipose tissue and can play a significant role in the pathogenesis of type 2 diabetes mellitus and atherosclerosis [46]. Obesity is associated with an increased risk of cardiovascular disease, heart disease, and obesity [47].Vitamin D deficiency is a common issue among the overweight community [48]. It is currently

being discussed whether the administration of vitamin D will boost glucose homeostasis by interacting with insulin sensitivity modulators such as adiponectin and its oligomers [49].

Correlation pre- and post-operation BMI with other parameters

Depending on per-operation BMI, findings of our study show a positive correlation between BMI and IL-8, a negative correlation between BMI and IL-18, and a strong negative with vitamin D3. Also, in post-operation BMI is a positive correlation with IL-8, negative with IL-18 and strong negative with vitamin D3 (Table 3).

Table (3): Correlation relationship between pre and post-operation BMI and IL-8, IL-18, and vitaminD3 parameters by using Pearson Correlation.

	Mean ± SE				
Studied Groups	IL-6	TNF-α			
Chronic group	26.26 ±1.48	92.96 ± 1.80			
Control group	13.02 ±0.34	66.55 ±0.45			
P-value	0.0001**	0.0001**			
** (P≤0.01) Highly Significant, IL-6= interleukin 6, TNF-α= Tumor necrosis factor, SE=Standard Error					

r: regression, p: pearson corrlation

Rising incidence of reduced systemic inflammation was reported in overweight and obese persons relative to normal-weight persons. Depending on the per-operation and post-operation of BMI, the findings of our research indicate a positive link between BMI and IL-8 and these results are consistent with the [50] results, (2020) showed a positive association between BMI and IL-8 due to IL-8 pro-inflammatory cytokines associated with obesity. On the other hand, BMI is negatively correlated with IL-18 and vitamin D3 and these findings are consistent with the results of [51]; [52]and [53] of the separate association between BMI and IL-18 and vitamin D3. But at the other hand, another recent study in 144 men unexpectedly recorded a major association of IL-18 with fat-free weight [54]. Analysis of the genotype distributions showed that IL-18 – 607 C/A polymorphism was correlated with a rise in body mass index in obese people in the Korean population [55]. Coupled with an elevated low-grade inflammatory condition (which tends to be most pronounced in women), this results in higher vitamin D requirements for obesity [56]. Although an increase in body weight can have a protective impact on bone fractures, the scientific rationale has shown some possible

explanations that associate obesity with increased risk of fracture with reduced concentrations of vitamin D [57]. Besides, the degree to which serum concentrations are susceptible to change despite the weight reduction has still not been established [48]. Decreased concentration of vitamin D may be due to its connection to muscle metabolism, recommending special attention to supplementation in postmenopausal overweight women who perform physical activity [58].

Conclusions

Positive correlation between chronic diseases with obesity in an obese person. The highest mean value of BMI, IL-8, and IL-18 was recorded in pre-operation, while the lowest mean was at post-operation. On the other hand, vitamin D3 was higher in control compared with pre-operation and post-operation. The BMI showed a high sensitivity when compared with IL-8, IL-18, and vitamin D3.

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