INVESTIGATION INTO THE ASSOCIATION OF BIOCHEMICAL PARAMETERS AND GENE POLYMORPHISM WITH OBESITY IN PATIENTS UNDERGOING BARIATRIC SURGERY

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LIST OF CONTENTS

Sr .No	Title		Page No.
A	LIST OF TABLES		I
B	LIST OF FIGURES		II
1	ABSTRACT		1
2	INTRODUCTION		4
3	REVIEW OF LITERATURE		10-32
	3.1	Introduction	
	3.2	Epidemiology	
	3.3	Comorbidities and Weight	
	3.4	Classification of Obesity	
	3.5	Treatment for Obesity	
	3.6	Bariatric Surgery	
	3.7	Ghrelin	
	3.8	Glucagon Like Peptide-1	
	3.9	Polymorphism and Bariatric surgery	
4		METHODOLOGY	33-42
	4.1	Study Design	
	4.2	Ethical Consideration	
	4.3	Study Population	
	4.4	Study Methodology	
	4.5	Study Evaluation Criteria	
	4.6	Statistical Analysis	
5	RESULT		43
6	DISCUSSION		74
7	CONCLUSION		80
8	REFERENCE		81

LIST OF TABLE

Table No	Table Title	Page No
5.1.1	Sample size and Gender	43
5.1.2	Gender and ager distribution	44
5.2.1	Surgeries in Diabetic and non-diabetic patients	46
5.3.1.1	Effect of Bariatric surgery in mean HbA1c levels in Diabetic and non-diabetic patients	47
5.3.1.2	Distribution of Diabetic according to %HbA1c	47
5.3.2.1	Effect of bariatric surgery on mean BMI levels in Diabetic and non-diabetic patients	49
5.3.2.2	Distribution of non-diabetic and diabetic patients according to BMI	50
5.3.3.1	Effect of bariatric surgery on mean total cholesterol levels in Diabetic and non-diabetic patients	52
5.3.3.2	Distribution of non-diabetic and diabetic patients according to cholesterol	53
5.3.4.1	Effect of Bariatricsurgery on mean Triglycerides level in Diabetic and non-diabetic patients	55
5.3.4.2	Distribution of non-diabetic and diabetic according to % Triglycerides	56
5.3.5.1	Effect of Bariatric surgery on mean HDL levels in Diabetic an non-diabetic patients	58
5.3.5.2	Distribution of non-diabetic and diabetic according to % HDL	59
5.3.6.1	Effect of Bariatric surgery on mean LDL levels in Diabetic an non-diabetic patients	61
5.3.6.2	Distribution of non-diabetic and diabetic according to % LDL	62

B

Table No	Table Title	Page No
5.4.1	Distribution of gender	65
5.4.2	Occupation	66
5.4.3	Marital Status	67
5.5	Medical History	68
5.6	Type of surgery	69

I

LIST OF FIGURES

A

Table No	Table Title	Page No
5.1.1	Sample size and Gender	43
5.1.2	Gender and ager distribution	45
5.2.1 A & B	Surgeries in Diabetic and non-diabetic patients	46
5.3.1.1	Effect of Bariatric surgery in mean HbA1c levels in Diabetic and non-diabetic patients	48
5.3.1.2 a & b	Distribution of Diabetic according to %HbA1c	48
5.3.2.1	Effect of bariatric surgery on mean BMI levels in Diabetic and non-diabetic patients	50
5.3.2.2 a & b	Distribution of non-diabetic and diabetic patients according to BMI	51
5.3.3.1	Effect of bariatric surgery on mean total cholesterol levels in Diabetic and non-diabetic patients	53
5.3.3.2 a & b	Distribution of non-diabetic and diabetic patients according to cholesterol	54
5.3.4.1	Effect of Bariatricsurgery on mean Triglycerides level in Diabetic and non-diabetic patients	56
5.3.4.2 a & B	Distribution of non-diabetic and diabetic according to % Triglycerides	57
5.3.5.1	Effect of Bariatric surgery on mean HDL levels in Diabetic an non-diabetic patients	59
5.3.5.2 a & b	Distribution of non-diabetic and diabetic according to % HDL	60
5.3.6.1	Effect of Bariatric surgery on mean LDL levels in Diabetic an non-diabetic patients	62
5.3.6.2 a & b	Distribution of non-diabetic and diabetic according to % LDL	63

II

Table No	Table Title	Page No
5.4.1	Distribution of gender	65
5.4.2	Occupation	66
5.4.3	Marital Status	67
5.5	Medical History	68
5.6	Type of surgery	69
5.7.1	Quality Of DNA	70
5.7.2	Optimization of PCR	71
5.7.3	Presence of amplification confirmation	72
5.7.4	Genotype of rs9819506	73

B

II

Abstract:

Background and Objective

Obesity is growing worldwide and become a major issue in the society. It has doubled since 1980. According to world health organization, people suffering from overweight in 2014 were 1.9 billion and amongst them 600 million people are obese. Obesity can be prevented by adapting certain lifestyle modification, exercise, pharmacological treatment and surgical options. Bariatric surgery is carried out on stomach and/or intestine to facilitate the weight loss. This surgery is suitable for those whose BMI is 25 or more. There are mainly 3 types of surgeries: Restrictive, Malabsorptive and combination of both. Bariatric surgery has been proven to treat complications related to obesity like type II diabetes, hypertension, PCOS, arthritis, sleep apnoea etc. According to certain studies many complications can be treated by bariatric surgery. There are certain biochemical parameters which gets changed after bariatric surgery like cardiovascular parameters, renal parameters, diabetic parameters, Thyroid parameters etc. With reference to certain study weight loss after bariatric surgery is related to genetic polymorphism. Certain genes are identified like *GHSR and GLP-1*. These genes are associated with weight loss after bariatric surgery. There are two main objectives in the study first is related to changes in biochemical changes after bariatric surgery and the second objective is change in the polymorphism of *GHSR gene.* There are very few studies carried out in India with respect to bariatric surgery and biochemical changes after bariatric surgery.

Study Methodology:

A. Retrospective study included diabetic and non-diabetic patients registered at Asian Bariatric Pvt. Ltd. From the available data, patients were selected according to inclusion and exclusion criteria. Medical records of 107 patients were obtained from their respective case files. The study was purely retrospective and as such only analysis of available data was carried out. The study does not involve any interaction with the subjects, nor did it require any intervention in the management of patients.

B. In the second, prospective study included diabetic and non diabetic patients registered at Asian Bariatric Pvt.Ltd. Diabetic and non-diabetic patients those

who were willing to give written informed consent, were enrolled in the study. Patients were enrolled according to the inclusion and exclusion criteria. Every patient had all the right to refuse to give the consent. Blood collection of the patients was done and their lab investigation data were collected.. The small portion of stomach was cut and taken with the help of the surgeon. The stomach was stored in PBS at -80^{0}C. From the stomach portion, DNA was isolated from 40 tissues. The sequencing of the DNA was carried out after DNA isolation.

Result:

A.

1. Demographics:

In the present study, 52were male and 55 were females. In non-diabetic group, 28 were male and 36 were females. In non-diabetic group, 24 were male and 19 were females. There 6 types of surgeries done on both diabetic and non-diabetic patients. In Diabetic group, sleeve gasterectomy was carried out in 16 patients, Gsatric bypass in 21, mini gastric bypass in 1, banded sleeve in 4 and revision in 1 patient. In non-diabetic group, sleeve was carried out in 37 patients, gastric bypass in 15, mini gastric bypass in 2 , banded sleeve in 7, revision in 1 and gastric balloon in 2 patients.

2. HbA1c:

There was significant ($P<0.001$) reduction in mean HbA1c levels after 3 months and 6 months of bariatric surgery as compared to baseline levels in diabetic patients. It shows significant($P<0.001$) reduction in mean HbA1c levels after 6 months of bariatric surgery as compared to baseline levels in non-diabetic patients

3. Body mass index:

There was a significant ($P<0.001$) reduction in mean BMI levels after 3 and 6 months of bariatric surgery as compared to baseline in diabetic patients. There was a significant ($P<0.001$) reduction in mean BMI levels after 3 and 6 months of bariatric surgery as compared to baseline in non-diabetic patients.

4. Cholesterol:

There was no significant reduction in mean total cholesterol levels after 3 months and 6 months of bariatric surgery as compared to baseline levels in non-

diabetic patients while there was no significant($P<0.05$) reduction in total cholesterol levels after 3 months of bariatric surgery, but after 6 months there was significant($P<0.05$) reduction in Total cholesterol after bariatric surgery in diabetic patients.

5. Triglycerides:

There was significant ($P<0.05$) reduction in mean triglycerides levels after 3 months and after 6 months there was significant($P<0.01$) reduction after 6 months after bariatric surgery as compared to baseline in diabetic patients. There was no significant reduction in non-diabetic patients after 3 months of bariatric surgery but after 6 months, there was significant($P<0.05$) reduction observed after bariatric surgery

Other biochemical parameters were also observed like HDL, LDL, VLDL, Creatinine, Alkaline phosphate etc.

Conclusion:

In our study, it was observed that after bariatric surgery, in certain biochemical parameters significant change was observed like HDL, LDL, HbA1c, BMI, total cholesterol, Triglycerides. While some of the parameters were not significantly changed like alkaline phosphate, creatinine, bilirubin, SGPT, SGOT etc. In another objective, 7 polymorphism were reported in the patients which suggests that after bariatric surgery weight loss is achieved differently in the patients having polymorphism than those who have no polymorphism reported.

Introduction:

Obesity is growing worldwide and has become major issue in the society. It has doubled since 1980. As per World Health Organization; a person is termed as an obese when his/her Body Mass Index is greater than or equal to 30 and overweight when BMI is more than or equal to 25 but less than 30 (World Health Organization). People suffering from overweight in 2014 were 1.9 billion and amongst them, 600 million people were obese. Prevalence of obesity in India is increasing. In India 2.8% of women are overweight. 1.3 % of men are overweight. The prevalence is increasing in young generation i.e. girls classified in overweight are 18% and boys are 20.6% respectively. (World Health Organization) In Gujarat one study showed that out of 900 overweight people, 120 adults found overweight (13.3%) and 49 found obese (5.4%) (Brahmbhatt and Oza, 2012). Obesity is associated with various other diseases like type II diabetes, hypertension, polycystic ovarian syndrome (PCOS), apnoea, joint pain etc.

Obesity can be prevented by adapting to certain life style modification, exercise, pharmacological treatment and surgical options. Life style modification includes programming the diet and exercise. Dietary interventions demand low calorie diet and liquid meal (Melanson et al, 2002). Physical activity has a role in decreasing weight, programme of walking 45-60 minutes can make some difference but without calorie restriction, weight loss cannot be achieved (Pronk and Wing, 1994). Pharmacological treatment involves use of drugs like: Orlistat, Rimonnabant and Sibutramine. Orlistat is approved by Food and Drug administration (FDA) and inhibits the pancreatic lipase so reduces fat absorption by 30% (Borgstrom , 1988). Side effects reported are changes in bowel function because of the unabsorbed fat, fatty/oily stool, persistent nausea vomiting, severe stomach-ache, dark urine etc. (Broom et al., 2002) Rimonabant is a diet pill, works by blocking the binding of endogenous cannabinoid to CB1 neuronal receptors. This drug has cause GI problems, skin problems, musculoskeletal problems and CNS problems. Moreover it was not effective in the patients for losing the weight and was not approved in US because of its side effects (Scheen et al, 2006). Sibutramine, serotonin norepinephrine reuptake inhibitor, is associated with the feeling of fullness i.e. satiation. Side effects caused by Sibutramine are dizziness, dry mouth, inflammation of nose, nervousness, abnormal liver functions etc. (McNeely and Goa, 1998). Despite these approaches, obesity does not seem to be controlled in many

individuals. Hence, an approach which has been in use since last few years is surgical approach. The surgery is suitable for those who are having BMI (body mass index) greater than 35 or 40 and with or without co-morbidities like cardiovascular or metabolic

Bariatric surgery is carried out on stomach and/or intestine to facilitate the weight loss. This surgery is suitable for those whose BMI is 25 or more. There are mainly 3 types of surgeries: Restrictive, Malabsorptive and combination of both. The restrictive is used to restrict the food which will decrease the consumption of food by the patient. Vertical banded gastroplasty (VBG) and adjustable gastric banding are example of restrictive surgery Malabsorptive is a surgery in which small portion of the stomach is removed and then stapled. Biliopancreatic diversion and sleeve gsterectomy are the types of malabsorptive surgeries. This will not allow a patient to consume more amount of food, this will favour weight loss. (American Society for metabolic and Bariatric Surgery). Roux en Y Gastric bypass is the combination of both i.e. malabsorptive and restrictive. (American Society for metabolic and Bariatric Surgery) As bariatric surgery improves other co-morbid conditons, it is very popular in people to opt for bariatric surgery even if they are not morbidly obese (WebMD, Benefits of bariatric surgery). Bariatric surgery improve many co-morbid conditions like hypertension, Type II diabetes Mellitus, lipid disturbance (Sjstrom et al, 1999)PCOS, arthritis, sleep apnoea, asthma, venous statis, urinary incontienence (Sjstrom et al, 2006) and some cancers (Adams et Al, 2010).

Cardiovascular complication is a major complication in obese patients. Obese population is more prone to have heart disease than lean population. Because bariatric surgery can reduce weight up to 40% in patients, this can enhance the working condition of heart (Colquitt et Al, 2005). One meta- analysis done by Buchwald et al (2004) reported that patients having hypertension experienced improvement up to 61.7% after bariatric surgery. One Swedish study also showed that cardiovascular complications have reduced in the patients and maintained normal even after 10 years of bariatric surgery. (Sjostorm et al, 2004)

Atherosclerosis is one of the co-morbid conditions related to heart disease and risk factor for heart dysfunction. It is reported that bariatric surgery reduces. (Karason et al, 1999). Bariatric Surgery can inhibit some of the markers related to atheroma. It

lowers the amount of inflammatory markers like C- reactive protein, sialic acid, plasminogen etc. (Vazquez et al, 2005)(Uzun et al, 2004). There were many patients who had to go for heart transplantation because of cardiomyopathy but because of bariatric surgery these numbers have been decreased. (Ristow et al., 2008) It has been reported that bariatric surgery leads to increase in life span up to 15 % in patients having cardiovascular problems. (Sjostrom L et al, 2007)

Bariatric surgery also affects renal functions. After losing weight due to bariatric surgery, patients get relief from microalbuminuria and proteinuria.(Navarro et al, 2006) There is decline in creatinine clearance after bariatric surgery. (Afshinnia et al. 2010) Bariatric surgery is also reported to alter glomerular filtration rate. One study reported that BMI and blood pressure decreased after bariatric surgery and mean GFR increased from 47.9 to 61.6 mL/min/1.73m^2 (Navaneethan and Yehnert , 2009).

From above mentioned facts, it is evident that bariatric surgery produced improvement in co-morbid conditions of obesity like cardiovascular diseases, thyroid functions and renal disorders. However there is dearth of reports, with respect to Indian population. There are very few data available in Indian population and it is important to carry out such studies because obesity of Indian population is different from other countries. Obesity in Asian population is different from other countries. Asian population has less BMI and has more total and central adiposity when it is compared with other white population (Alberti ea al, 2006). Percentage of body fat is higher amongst Asian population which might be one of the factors in insulin resistance. According to survey of England and International Day for the evaluation and abdominal obesity in Asian Region, abdominal obesity is highly prevalent in South Asia (58% and 78% in men and women respectively).(European Society of Cardiology, 2006) Therefore obesity in Indian population is different from other countries. This points out towards the investigating effect of bariatric surgery on cardiovascular, renal thyroid functioning in Indian population.

Diabetes is a metabolic disease and has a prevalence of around 9% of the total population in the world. The data suggests that around 387 million people suffer from diabetes and it is expected that about 210 million more people will have diabetes by 2035 (National Health Federation). Diabetes is increasing day by day in India with more than 62 million diabetic individuals. (Kaveeshwar & Cornwall 2014) The drugs

available are biguanides, thiozolidinediones, sulfonyl urea, meglitinides, alpha glucosidase inhibitors, DPP-4 inhibitors and GLP-1 analogues. However, despite enormous amount of research being carried out in the field of new drug discovery for diabetes, it still remains to be "untreated" disorder and the drugs can only control sugar levels without providing complete cure of the diseases. Given the fact that diabetes is associated with microvascular and macrovascular long term complications, patients with uncontrolled diabetes often opt for surgical interventions like bariatric surgery.

Ghrelin is an endogenous agonist that has effect via growth hormone secretogogue receptor. It contains 28 amino acids residue peptide. (Chanoine et al. 2009) Ghrelin is secreted from stomach. The primary site of production of ghrelin is fundus of stomach and proximal intestine. Ghrelin is found in neuroendocrine cells of stomach. (X/A like cells in rodents and P/D cells in humans) ghrelin is present in two forms in body i.e. Acylated and des-acylated. (Akio et. al, 2004) Acylated ghrelin is in active form in body and acts through GHSR-1a. des-acylated ghrelin is degradation product of acylated ghrelin. Ghrelin is acylated by Ghelin-O-acyl transferase enzyme.

Incretins are hormones that enhances nsulin secretion after meals. Glucagon Like Peptide-1 and Glucose dependent Insulinotropic Polypeptide (GIP) are main two important hormones of incretin. GLP-1 is composed of 30 amino acid and it is a peptide hormone. It is produced in intestinal L-cells processed by proglucagon. (Holst, 2006) GLP-1 is insulin secretogogue and is produced from distal ileum. When a person consumes food, in response to that GLP-1 is secreted. It activates adenylated cyclase and stimulates glucose dependent secretion of insulin. It is also useful in emptying of GI, this will help in delayed digestion (Flint A et Al, 2001) Moreover it has action on CNS which produces feeling of satiety as well as less food intake.

It is reported that after bariatric surgery GLP-1 increases three folds. This may be because of rerouting of food which is undigested from stomach. Food which is bypassed directly goes into distal part of the ileum after RYGB. This will stimulate enteroendocrine cells. Also changes in Gut endocrinology plays role in increasing GLP-1 levels by secreting GLP-1. (Knop & Taylor, 2013) Rapid delivery of nutrients might be a factor for increased level of GLP-1. (Rubino et Al, 2006) Additionally, in RYBG, proximal small intestine is excluded which leads to decrease in anti-incretin hormones.

This leads to increase in GLP-1 and stimulates the glucagon and blood glucose control (Rubino et al. 2006)

There are some reports which suggest that the diabetes may or may not be remitted after the bariatric surgery. Study by Buchwald et al in 2009 reported that there was 80% of the remission occurs in the patients who opted for the bariatric surgery. Study done in American population reported that from 89% of the diabetic population, 57% experienced remission in diabetes after Gastric bypass.(Buchwald et al, 2009)(Keidar , 2007). A systemic review by Schauer et al was done which reported that 78.1 % of the patients experienced complete remission of diabetes. The data increased to 86.6 % when they considered the glycaemic control and diabetes resolved in the patients after the surgery. The hypoglycaemia is observed in the patients having type II diabetes. The data is not available why the hypoglycaemia is reported. Scorpinaro et al reported in one case series reported that out of 312 patients. 303 (97%) experienced remission after bariatric surgry. Another study done by Pories et al. showed that patients who had type II diabetes mellitus experienced complete remission in 83% while patients who had impaired glucose tolerance showed that 99% had resolved this situation. This remission was observed in the patients who opted for roux en Y gastric bypass. One case control study done by Pontlroll et al. (2002) showed that there was only 45% of resolution of diabetes was observed, while one prospective study by Sjstrom et al (2004) reported that 72 % patients who went for Vertical banded gastroplastuy and 36% of LABG surgeries experiend diabetes remission. Pronce et al (2004) and Dixon et al (2008) also showed remission of diabetes in 66% and 73% of patients after restrictive kind of surgeries. These data suggests that bariatric surgery exerts differential effect in terms of remission of diabetes. These variations needed to be investigated.

Genetic polymorphism is associated with different weight loss outcomes in patients undergoing bariatric surgery. One study was carried out for seeing marker's association for eleven obesity related genes in which maximum weight loss and maximum weight gain was observed after the bariatric surgery. The variation in diabetic patients might be related to the polymorphism of the gene which encodes for the ghrelin and GLP-1. There are data available for the variation in the gene with respect to the weight loss i.e. in some patients the weight loss is fast and in some patients the weight loss is slow. These variations are thought to be related due to polymorphism of the

particular gene. Single nucleotide polymorphism in the promoter region of its receptor gene has some correlation with weight loss. Association between the genotype for SNP rs9819506 and rs490683 in the promoter region of the GHSR gene was performed and weight loss outcomes was recorded for 30 months. Three models were taken: additive, recessive and dominant. Patients with homozygous for rs490683 C/C genotype showed most weight loss in additive models. People with this polymorphism lost higher weight loss than others. (Tymiz et al, 2011)(De Luis et Al, 2014) As this gene is related to weight loss we hypothesise that the GHSR gene might be associated with the diabetes or any metabolic disorder. The GLP-1R gene polymorphism is associated with weight loss after bariatric surgery. The Single nucleotide polymorphism of rs6923761 GLP-1R gene and its outcomes after biliopancreatic surgery is reported to be associated with the weight loss. 137 patients were taken and polymorphism was checked for SNP rs6923761. The weight loss was observed between non A allele carrier and A allele carriers. It was found that initial weight loss was higher in the patients with GG genotype than allele carriers. (De Luis, Pacheco D, Aller R, Izaola O, 2014) Although reports are available with respect to association of polymorphism in *GHSR* & *GLP-1* gene and weight loss, no data is available depicting co-relation of these genes' polymorphism and diabetes remission.

- To study the alteration in biochemical parameters in patients undergoing bariatric surgery
- To study genetic polymorphism in patients undergoing bariatric surgery

3.1 INTRODUCTION

Obesity is a major health issue now a days and does not get easily eliminated. In the world, having 7 billion people, around 2.8 million people die because of the overweight problem and 35.8 million people who are extremely obese die because of the obesity. Therefore it is a very crucial problem and it has to be solved. A parameter which states whether a person is obese or not is termed as Body mass index. It is classified in different categories like underweight, normal, pre overweight, overweight and obese. A person is considered as an obese when his or her Body Mass index is more than 35 and he or she is considered as an overweight when the BMI is more than 25. (World Health Organization).

3.2 EPIDEMIOLOGY

Globally United states has 33.9% of obese people, Canada has 23.1 % obese people and India has 0.7% obese people. The ratio of obese people is quite less in India than any developed countries.(World Health Organization)Every year at least 2.8 million people die because of obesity and the percentage is increasing day by day. 2.3% of people are obese or overweight worldwide. In 2008 35% of adults were overweight i.e. 34% men and 35% women. The obesity prevalence's has doubled between 1980 to 2008. (World health organization).

3.2.1 PREVALENCE IN INDIA:

The survey was done in the rural and urben areas of India and the states taken are Tamilnad(TN), Maharashtra(MH), Jharkhand(JH) union territories and Chandigarh(CH). The prevalence of generalised obesity was 24.6%, 16.6%, 11.8 %, 31.1% for TN, MH, JH and CH respectively. The combined obesity was found 19.3%, 13.0%, 9.8% and 26.6 % respectively for the above states. The prevalence for the overweight was found to be 15.2%, 11.3%, 7.8% and 15.9 % for the above respective states. (Praddepa R et al, 2015) Indian population is becoming obese faster and faster than it is expected. The prevalence is around 0.7% in India for the obese people.

3.3 COMORBIDITIES AND OBESITY:

As body weight increases, comorbid conditions may also increase. The prevalence of obesity is increasing progressively and as they are steadily increasing, many people are facing co-morbid conditions like cardiovascular diseases, diabetes, osteoarthritis, stroke, Hyperuricemia, gallbladder diseases, PCOS, sleep apnoea, etc. Moreover there are some cancers which can also be caused because of obesity viz. colorectal cancer and prostate cancer in men and endometrial, breast and gallbladder cancers in women. Obese patients might also have risk of impaired psychological and physical functioning which may impact negatively in the life. (Khaodhiar, McCowen, & Blackburn, 1999). This may decrease the life span of a person and might increase the risk of death in the early age of the patients. Obesity is impaired with the glucose intolerance or type II diabetes mellitus. The mechanism is thought to be due to insulin resistance. (Keskin M et al, 2005). Hypertension has an association with obesity. The weight gain is directly related to hypertension. (Huang Z et al, 1998). Waist circumference and BMI are good parameters for assessing the obesity and risk of hypertension. (Janssen I, 2004) The evidences suggest that coronary artery disease (CAD) is also associated with obesity. Risk of heart failure was found two fold higher in obese patients than non-obese patients. (Kenchaiah S, 2002) Dyslipidaemia is also associated with obesity. In this insulin resistance is considered as a cause of dyslipidaemia. The insulin resistance is associated with higher levels of VLDL and impairment of lipoprotein lipase. (Despres JP et al., 1991)(Pouliot MC et al., 1991)(Despres JP, 1990) The risk of haemorrhage and stroke increases if the person is obese. In women the risk of haemorrhage is there but not stroke. (Song YM et al, 2004) Obstructive sleep apnea and obesity has link according to the study conducetd by Wisconsin Sleep. (Young T, 1993) asthma is an another complication which occurs because of obesity. The prevalence of asthma increases in the patients who are obese. Mechanism is associated with increased airway hyper responsiveness and decreased functional and tidal volume plus increased inflammatory cytokines. (Shore SA, Fredberg JJ, 2005). Gastrointestinal abnormalities also increases because of obesity and the maily observed abnormality is GORD(Gastroesophagal reflux disease). (Hampel H, Abraham NS, El-Serag HB, 2005). PCOS is very common in obese women. In men the obesity is relate to impotence and infertility. The sexual dysfunctions improves after the BMI has decreased. (Ehrmann

DA,2005)(Espostio K, 2004) There are other complications occur because of obesity like gestational diabetes, macrosomia, dystocia and increased rate of caesarean section. (Dietl J, 2005)

Psychosocial problems are found in girls because of obesity in them. In one study of 294 female obese people, psychiatric evaluation was performed. They found out that people were suffering from somatization, phobia, hypochondriasis amd obsessive compulsive disorders. (Rosik CH, 2005) There are evidence available that obesity has a role to play in cancer. These all include the cancer of gall bladder, esophagus, thyroid, kidney, uterus, colon and breast.(Renehan AG, 2008)

Obesity is classified according to WHO and they are classified in various categories like under-weight, normal, overweight and obese.

3.4 CLASSIFICATION OF OBESITY:

Body mass index(BMI) kg/m^2	Classification
18.5-24.9	Normal
25.0-29.9	Overweight
30.0-34.9	Obesity(type I)
35.0-39.9	Obesity(type II)
>= 40	Morbid Obesity
>= 50	Super Obesity

3.5 TREATMENTS FOR OBESITY:

The treatments are available for eradicating obesity but they are not that much at success. The diet plans are hard to follow and people do not go for exercise regularly. Thus obesity is a big problem and should be addressed. The main cause of obesity is energy imbalance with increased intake of food. Moreover it is caused by lethargic lifestyle. People do not give attention to their daily life and have become inactive. The workload of an individual has increased but the physical activity has decreased. This may result in obesity. Some people have genetic factors which increases the weight without any reason.

NON-PHARMACOLOGICA TREATMENT:

Obesity can be prevented by adapting to certain life style modification, exercise, pharmacological treatment and surgical options. Life style modification includes programming the diet and exercise. Dietary interventions demand low calorie diet and liquid meal (Melanson K., 2002). Physical activity has a role in decreasing weight, programme of walking 45-60 minutes can make some difference but without calorie restriction, weight loss cannot be achieved. (Pronk NP, Wing RR, 1994).

PHARMACOLOGICAL TREATMENT:

Pharmacological treatment involves use of drugs like: Orlistat , Rimonnabant and Sibutramine . Orlistat is approved by FDA(Food and Drug administration) and inhibits the pancreatic lipase so reduces fat absorption by 30%(Borgstrom B. 1988). Side effects reported are changes in bowel function because of the unabsorbed fat, fatty/oily stool, persistent nausea vomiting, severe stomach-ache, dark urine etc('orlistat oral', n.d.). Rimonabant is a diet pill, works by blocking the binding of endogenous cannabinoid to CB1 neuronal receptors. This drug has cause GI problems, skin problems, musculoskeletal problems and CNS problems. Moreover it was not effective in the patients for losing the weight and was not approved in US because of its side effects('Dangerous Side Effects of Rimonabant (Acomplia)', n.d.). Sibutramine, serotonin norepinephrine reuptake inhibitor, is associated with the feeling of fullness i.e. satiation. Side effects caused by Sibutramine are dizziness, dry mouth, inflammation of nose, nervousness, abnormal liver functions etc('Common and Rare Side Effects for sibutramine oral', n.d.) (Lean MEJ, 1997). Combination of orlisat and sibutramine are available in the market and reduces the triglyceride digestion in the GIT. But the data suggests that it does not have synergistic effects on the person takin combination of both. Benzphetamine might be used for the weight reduction but can be used for short term. Many other drugs are available for the obesity reduction. They are Diethyl propion, phentermine etc. The sympathomimetic drugs like benzphetamine, diethylpropion, phendimetrazine and phentermine are used with different mechanisms and it blocks the norepinephrine reuptake from syneptic granules. Weight loss with phentermine and diethylpropion have good efficacy and suggests that it does not have that much tolerance after taking the drug for a long period of time. If tolerance was observed the efficacy of the drug decreases drastically. The safety measures are good

with these drugs. The side effects are insomnia, dry mouth, asthenia and constipation. There are some drugs which are useful for decreasing the obesity but not approved for the same purpose. Fluoxetine and sertraline are seretonine reuptake inhibitors and can be useful in reducing the food intake. In a two week placebo control trial, it was found that the dose of 60mg/day of fluoxetine can reduce the amount of food taken by the patient. They are approved for the purpose of depression but can be useful for decreasing the weight in the patients having obesity. (Lawton CL et al, 1995)

3.6 BARIATRIC SURGERY

Bariatric surgery is a surgery done on the stomach and/or intestine to reduce the weight of the patients who are overweight or obese. All the candidates are eligible to go for the bariatric surgery but mainly the age group is between 18 to 60. However old people may also go for bariatric surgery with careful caring of the patient. There are some criteria for the surgery like prior attempts have been mate to reduce the weight and has failed. BMI more than 30, p0atient should tell all the comorbid condition he or she has. Person should know that the bariatric surgery is not the quick fix for the patient. It takes time to reduce the weight and requires patience from the person who is going for the bariatric surgery. (Buchwald H et al., 2004)(Christou NVet al., 2004) Bariatric surgeries can be classified according to the mechanism of action of the surgery. They are restrictive, malabsorptive and combination of both.

3.6.1TYPES OF BARIATRIC SURGERY:

3.6.1 2Restrictive Surgery:

In this surgery the surgeon creates a pouch in the stomach and it will narrow the outlet of the stomach. This will restrict the patient to take more amount of the food after surgery. There are mainly two types of restrictive procedures ie.e vertical banded gastroplasty and laparoscopic adjustable gastric banding. Verical banded gastroplasty is not performed that much by surgeons now a days. This surgery might have long term complications and the patient might come for the another operation. The long term weight reduction is not that much at success. (Kim CH, Sarr MG, 1992)(Nightengle ML et al, 1991)(Maclean LD, Rhode BM, Forse RA, 1990)(Ramsey Stewart G, 1995)(Balsiger BM et al. 2000) Laparoscopic adjustable gastric banding has an advantage that the band allows to adjust the collar and then it allows one tune of the size of the outlet which minimize the side effects as well as maximises the weight reduction.

3.6.1.2 Malabsorptive Surgery:

This surgery bypasses a major portion of stomach and intestine such that the food absorption is less. Biliopancreatic diversion, Duodenal switch are the example of malabsorptive bariatric surgery. These both the surgeries are quite difficult to perform and then it causes complications like nutritional deficiency. (Coucoulas A et al, 2003)

Another procedure which is combination of both is used i.e. Roux-en Y gastric bypass. This can be performed by doing laparoscopic or by doing open surgery. Food intake is restricted by creating the small pouch of 30 mL of the upper part of the stomach. The absorption is decreased because the proximal intestine is also bypassed. The standard limb is around 75 to 150 cm long and it bypasses the distal stomach, duodenum and small portion of jejunum. The small intestine is almost intact which will decrease the risk of diarrhoea and protein malabsorption.(Nguyen NT et al, 2004)

3.6.3 TYPES OF BARIATRIC SURGERIES:

3.6.3.1Gastric Bypass:

It is called Roux-en-Y Gastric Bypass and is very useful surgry for the obese patients.

METHOD: Small pouch is formed from the upper part of the stomach of about 30 milliliters. The proximal part of the small intestine is divided and the latter part of intestine will be attached to the newly formed part of the stomach. Then the top portion of divided stomach will be connected to the proximal part of the intestine. This portion will give the shape of 'Y'. The reason behind this is because the bypassed portion of the stomach and intestine still make the gastric acid and enzymes which are necessary for the digestion of the food.

MECHANISM: The newly created stomach is small and it does not allow the patient to consume more amount of the stomach in the body. This will facilitates the less amount of the calories consumed. The digestion of the food is also less because of the small amount of the stomach. This will make less nutrients to reach to the small intestine and probably less amount of the absorption of calories and nutrients.

Advantages:

1. It produces long amount of weight loss and then 60 – 80 % of the loss.
2. Less amount of the food consumed.
3. May increase the energy expenditure

4. Make change in the gut hormone and then it reduces the amount of the food consumed.

Disadvantages:

1. Complex surgery than Adjustable Gastric Banding and Laparoscopic sleeve gasterectomy.
2. Long term vitamin and mineral defeciencies.
3. Longer hospital stay
4. Go for the dietary recommendations for longer period of time

3.6.3.2 Sleeve Gastrectomy:

It is performed by removing almost 80% part of the stomach and then the remaining part of the stomach is joined with the intestine portion of the GI tract. It gives the banana like shape of the stomach.

PROCEDURE: It works by several mechanisms. The smaller part of the stomach cannot hold more amount of the food ant this will decrease the amount of the food consumed by the patient. It has action on the gut hormones and because of that the factors are induced which will have impact on the hunger and blood sugar control. The studies have shown that sleeve gastretomy is more effective than the RYGB.

Advantages:

1. Restrict the amount of the stomach can be consumed.
2. Rapid and effective weight loss.
3. Requires more foreign objects and no re-routing are required.

Dis-advantages:

1. We cannot reversible the procedure
2. Patient ay develop long term vitamin and minerals deficiencies
3. More complication rate than others

3.6.3.3 Adjustable Gastric Band:

Also Called Band. In this surgery, the inflatable band is placed around the upper portion of the stomach which will create a small pouch above the band which will decrease the amount of food to be taken by the person. This will part the stomach in two portion i.e. upper paet and the lower part.

PROCEDURE:

The procedure is same as RYGB. In this kind of surgery the stomach is converted into a small pouch with the help of band which does not allow a person to take more amount of food and make him feel full. The feeling of fullness depends on the size of the opening of the pouch and remainder of the stomach created by gastric band.

Advantages:

1. Reduce the intake of food by an individual
2. Weight loss I approximately 40-50 %
3. No removal or re-routing is done
4. Less days in the hospital
5. It is reversible and Adjustable
6. It has rare complications and mortality
7. The lower level of vitamin and mineral deficiency.

Disadvantages:

1. The weight loss is slower than other surgeries.
2. 50% weight loss is not achieved in this kind of surgery
3. It is difficult because the body contains the foreign substance in the body

3.6.3.4 Biliopancreatic Diversion:

It has mainly two components. On the first place the most of the stomach's portion is removed and then large portion of small intestine is bypassed.

PROCEDURE:

The Duodenum is divided just past the outlet of the stomach The portion of the small intestine is then brought up and connected to the new portion of the stomach created. This will make the food to go directly in the newly created pouch and it directly goes in the small intestine. The portion of the small intestine which is bypassed is then joined with the newly formed small intestine segment because it contains certain pancreatic enzymes and bile which is useful for the breaking down the food and absorption of the protein and fat. This surgery on the first place will reduce the amount of the food to be taken by the patient but as the time passes a person can take normal food. Moreover the food will get mixed with the bile and enzymes far down in the small intestine. This will

not allow the absorption of most of the part of the food which will result in lack of nutrients in the body.

Advantages:

1. More weight loss than othe surgeries i.e. RYGB, Sleeve and Adjustable gastric Banding.
2. A patient can eventually eat normal food
3. Fat absorption reduces upto 70 %
4. Appetite hormones are changes after the surgery so reduces the appetite and absorption of the food.
5. It has more effect on diabetes than others

Disadvantages:

1. More risk than other surgeries.
2. Longer hospital stay in after surgery
3. More deficiencies of protein than any other surgery
4. Complicated procedure
5. Follow up is quite necessary because the guidelines of the diet and supplements must be followed by the patients. (American Society for metabolic and Bariatric Surery)

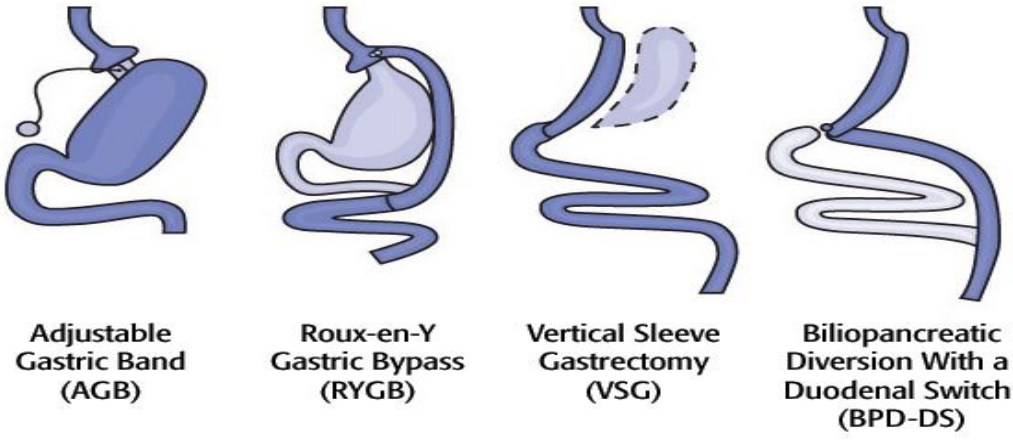


Fig-1.Different Kind Of Bariatric Surgeries(ASMBS)

3.6.4 Benefits of Bariatric Surgery:

Weight Loss:

Diabetes Remission

Heart disease Improvement

Improvement in Cholesterol levels

Sleep Apnoea disappearance

Decrease the depression

Self-esteem improvemant

Improved Mobility

3.6.5 RISK ASSOCIATED WITH BARIATRIC SURGERY:

3.6.5.1 Open V/s Laparoscopic Roux-en Y gastric bypass:

Open surgery causes more amount of pain. Patient needs more time to recover from the surgery and it will be difficult for the patient to do normal activity. Moreover there are chances of iatrogenic splenectomy and abdominal wall complications i.e. upto 20%. Where as in Laparoscopic one, the pain is less and recovery is faster than the open surgery. The wound complication is also less in the open surgery. (Podnos YD et al, 2003)

Complications:

The complications are late and earle. The early complictaions are wound problems and incisional hernias done by Podnos et al in 2003. Small bowel obstructions(2.1%), anastomotic stenosis(0.7%) GI haemorrhage(0.6%) leaks(1.2%), pulmonary embolus(<1%) and pneumonia(0.1-0.3%) are the complications caused by Gstric bypass. Late complictaoions include disorders of GI tract functioning. Nutritional defeciencies and protein-calorie malnutrition. (Podnos et al, 2003)

Bleeding: The bleeding occurs only upto 4% in the patients. The post operative bleeding can be from the staple line and which is harmless. The bleeding in the staple can be diagnosed by endoscopy. The prevention can be achieved by oversewing or buttressing the staple lines.

Anastomotic Leak: The tachycardia is the sign of anastomotic leak. It is a very rare complication but if it occurs the mortality increases upto 30%. The incidence after laparoscopic RYGB this rate has decreased to 4.4%.

Wound Infection: It occurs in 5% of the patient who undergo RYGB. The infection is not that much difficult to manage. Applying antibiotics on the wound would be sufficient to stop the infection.

Thromboembolism: The chances of forming thrombus during RYGB are 0-1.3 %. And rate of pulmonary embolism is 0-1.1%. Pulmonary embolism and anastomotic leak are major reason for the mortality in the bariatric surgery patients. (Nguyen NT et al, 2003)

Anastomotic Strictures: The anastomotic may develop jejunostomy after LRYGB. The occurrence of the complication is about 2-16%. The complication depends on the experience of the surgeon.

Marginal Ulcers: This occurs after the surgery is over. Usually the ulcer occurs at gastrojejunal anastomosis. It is related to the ischemia and tension at the base because of the staples. This can be treated by depressing the acid.

Cholelithiasis: The gall stones are common after the bariatric surgery when patient starts losnig the weight. The incidence is 38-52% and the stones are developed within 1 year of the surgery.

Nutritional Deficiencies: The stomach and intestine are bypassed, it may cause deficiencies of different nutritions like iron, vitamin $B_{12,}$ and other micronutrients. The diet shld be based on the nutrion deficiencies and it can be achieved by taking multivitamintablets as well as taking supplementation of irons as well. (Stacy AB, 2006) { the article of bariatric surgery and its safety and complications whole review article taken }

Perioperative mortality: The risk of death increases if the age is more otherwise the chances of death is nill.

3.6.5.2 Complication of Laparoscopic Adjustable Gastric Banding:

The risk of death is least with adjustable Gastric banding. Postoperative complications occur in 0.8-12% of the patients (Belachew M, Belwa PH, Desaive C, 2002). Bleeding is very rare after Gastric banding i.e. 0.1% (Biertho L et al, 2003)

3.6.6 EFFECT OF BARIATRIC SURGERY ON COMORBID CONDITIONS:

Bariatric Surgery shows a great result in decreasing the weight and thereafter there are many comorbid conditions which can get benefits because of bariatric surgery.

Long term follow up of the bariatric surgery shows less number of mortality rates because the chances of heart diseases, diabetes mellitus and cancer decreases. Mortality is decreased upto 40% after bariatric surgery. (Christou NVet al, 2004)(Sjostorm L et al, 2007)(Adams TD et al, 2006). Obesity can cause many diseases and which some diseases can be harmful at the later stage of the life. Health problems like metabolic disorders, cardiovascular complications, arthritis, cancer and dyslipidaemia are some of the examples which are caused by obesity. (Thomas CB, Cohen BH, 1955) Bariatric surgery is beneficial for the diabetic patients. The surgery gives a great result for the patients suffering from type II diabetes. The highest impact of bariatric surgery is noticeable in the patients having Type II diabetes. Modification in the insulin level is a noticeable parameter after bariatric Surgery. The insulin level increases 2 to 3 times after the surgery. The data suggests that around 76.8% surgical patients experience the resolution of diabetes. The mechanism is not known but it is weight loss independent. Bariatric surgery is also opted for those who are having type II diabetes. The patients having a hypertension also opt for the bariatric surgery and in addition the cholesterol levels are also affected by the bariatric surgery. One study conducted in 182 patients and their cardiovascular parameters were checked after the bariatric surgery. From them 57 patients remained and other did not co-operate. But the data suggests that after bariatric surgery, cholesterol levels reduced to 174 from 184 after the surgery. HDL rose to 40 and LDL cholesterol also improved. Triglycerides declined by 55%. The C - reactive protein, which is a marker of inflammation and a risk factor for heart attack also, reduced upto 80%. Moreover the patients who were taking the statins stopped taking the drug after the surgery. (Bariatric Surgery Cuts Heart Risk for Years, WebMed)

Bariatric Surgery is also beneficial for arthritic patients. The patients having arthritic pain can have great effects after the bariatric surgery. The improvement was noted not only in the RA but also in the inflammatory markers. Moreover the patient has to take less amount of medicines after bariatric surgery for Rheumatoid Arthritis. In one study 57% of the 53 patients had RA and they reported that the bariatric surgery can cure RA

after 3 to 9 years of the surgery. According to one study done in the patients suffering from RA, 12 months follow up was taken after the bariatric surgery. The follow up of 6 months and 12 months showed that 72% and 68% patients experienced remission of diabetes respectively. 62% of the patients were on disease modifying ant rheumatic drugs(DMARDS), compared to 93 % at baseline. 23 % were at complete remission and were not taking any kind of DMARDS after the surgery. (Study: Weight Loss after Bariatric Surgery Improves RA, MEDPAGE TODAY)

The epidemics suggest that type II diabetes is related to obesity. It has been noted that the type II diabetes is resolved for more than 10 years. The mortality rate is decreased after the surgery is performed on diabetic patients. The biliopancreatic and Bypass surgeries are more effective in the diabetic patients. It is also seen that the diabetic related mortality has decreased significantly after going under bariatric surgery. There are some mechanisms which are proposed for the remission. The only weight loss is not responsible for the diabetes remission. This can be said because the glycaemic level is achieved after only few days of the surgery. Some mechanisms which can be suggested are decrease in the food intake, partial malabsorption of nutrients and anatomical changes in the GI tract. This will make changes in the incretin levels and this will change the levels of glucose in the body.

Reduced Cancer Death Biggest Win from Bariatric Surgery: The obese patients have the risk of developing cancer and it can be avoided by doing the surgery.

3.6.7 EFFECT OF BARIATRIC SURGERY ON TYPE II DIABETES:

3.6.7.1 Remission of Diabetes After bariatric Surgery:

A systemic review and meta-analysis was done which showed that complete resolution was achieved in 78.1% of the cases. This number increased to 86.6% when glycaemic control was added in the study. (Buchwald H et al, 2009) Two large case series by Pories et al. and Achauer et al focused on diabetes remission after RYGB. In the former studies the mean fasting blood glucose decreased noticeably after the surgery. (Pories WJ et al, 1995)(Schauer PR, 2003) A meta-analysis of 136 bariatric surgery studies including 22094 individuals confirmed that around 84% of the patients experienced complete cure of diabetes after RYGB. (Buchwald H et al., 2004). Two prospective, controlled studies have shown good glycaemic control after the surgery. The multicentre

SOS study compared bariatric surgery with weight loss. This results in 16.1% average weight loss in the patients. Mean Fasting Blood sugar increased in the patients without the surgery and in the patients who opted for the surgery, the mean FBG decreased after the surgery. The risk of developing diabetes was three times lower in surgical patients than the non-surgical patients. (Sjostrom L et al., 2004) One study conducted by Dixon et al. did a randomised trial on the patients who were having mild diabetes and they went for LABG(Laparoscopic adjustable gastric band). They observed the significant decrease in the fasting blood sugar, HbA1c and medication of diabetes. (Dixon JB , 2008). Scopinaro et al. showed that 97% of the patients experienced euglycaemia in 268 diabetic patients after 10 years of the surgery (Scopinaro et al., 2006). This effect on the diabetes is long lasting and long term glucaemic control is observed in the patients after the surgery. Bariatric surgeries are meant for decrease the weight whose BMI is more than 35 or 50. But after the reports, many people are going for the surgery for remission of type II diabetes Mellitus. People with BMI <35kg/m^2 have reported complete remission of diabetes. The reports suggest that the remission is observed in the patients going for RYGB. (Cohen R et al, 2006)(Lee JW et al. 2008) The RYGB has best result amongst them and gives remission of diabetes up to 16 years. (Schauer et al. 2003) There are now enough evidence that the mortality is decreased in the diabetic patients after bariatric surgery. Adams et al. showed that the death rate was decreased up to 92 %.

Data is not available for the Indian populations.

The mechanism by which the bariatric surgery is remitting diabetes is related to two important parameters i.e. Ghrelin and Glucagon like peptide-1. The former one is an appetite inducer and the later one is stimulator of insulin.

3.6.7.2 Bariatric and Other GI operations in Type II Diabetic Patients :

The data suggests that bariatric surgery is beneficial for those who are moderately obese or non-obese and suffering from diabetes. The most importantly, nowadays non obese diabetic patients also opt for the bariatric surgery because they experience the remission for a longer period of time. A study done by De Paula et al reported that patients with BMI 29.7 and have diabetes since last 3 years plus insulin therapy and the HbA1c near 8.8 went for the sleeve gasterectomy. They observed that the postprandial glucose level decreased from 262 to 136 after the surgery.

Possible Mechanisms:

There are certain mechanisms which are proposed and they are:

1. Higher secretion of L-cells peptides which are Glucagon like peptides
2. Exclusion of proximal small intestine from nutrient flow which are responsible for decreasing the level of incretin factors.
3. Ghrelin secretion is impaired.
4. Changes in the nutrient sensing mechanisms regulation the insulin sensitivity.
5. Bile acid perturbations
6. Alterations in the GIT factors, mainly in duodenum.(Rubino F et al., 2006)

The main mechanism is still not found and people have given the hypothesis why diabetes is remitted.

3.7.GHRELIN:

Ghrelin is a 28 amino acid peptide hormone which is secreted by the epithelial cells of fundus of the stomach. It is an appetite inducer and it has effect on the food intake and food regulations. (Leonetti F et al, 2003)(Cummings DE et al, 2001) (Lee H et al., 2006)(Lin e et al, 2004) It is released form stomach and upper intestine(Cummings DE, 2004) Ghrelin's levels increases before meal and it decreases after the meal. (Callahan HS, et al, 2004) It is synthesized by X/A like endocrine cells and it is present in the mucosa of the fundus. It is a natural ligand for the growth hormone secretogogue receptor. The ghrelin present in two forms which are acylated and dys-acylated. While the ghrelin is in the systemic circulation, 90% is in the form of Dys-acylated and 10% is in the acylated form. The acyl groiup is required for the ghrelin to bind with the GHS-R which will activate the further pathways. (Kojima M et al. 1999)(Kojima M, Hosoda H, Kangawa K, 2001)Ghrelin's levels are associated with the diabetes remission and some mechanisms are also proposed by some of the scientists. The data is provided in the following paragraph about the ghrelin levels and bariatric surgery.

3.7.1 Ghrelin and RYGB:

RYGB is most common surgery done worldwide and is quite successful. A study done by Cummings et al. in 2002 showed decrease in the levels of the ghrelin after RYGB.

Though these studies are not conclusive and various studies showed that the ghrelin levels are not consistent for the RYGB. Some of them showed decrease in fasting as well as postprandial ghrelin levels(Geloneze B et al, 2003), some of them showed no change in the fasting and postprandial levels of ghrelin (Le Roux CW et al, 2006) and increase in the levels of ghrelin i.e. fasting (Vendrell J et al., 2004) The mechanisms are proposed but none of them are accepted widely. The increase in the levels of Ghrelin in the diet induced weight loss is much more than the ghrelin levels increased because of the surgery. (Korner J et al. 2005) The investigation was done why ghrelin level is different after the surgery. They came up with the hypothesis that the intraoperative changes in the in ghrelin levels during the surgery. The vertical pouch formation after the surgery might be the reason of the which is responsible for the decline in the level of ghrelin. (Lin E et al. 2003) In the surgery, ghrelin producing portion of the stomach is excluded and this may cause the decrease in the amount of ghrelin in the circulation after the surgery. (McLaughlin T et al, 2004) Technical difference is also reported. The vagus nerve is required for the appetite effect. The vagus dysfunction caused intraoperatively might also play role. The study showed that the decrease in the level of ghrelin on the first day after the surgery and increase after one month and further increase after 12 months. (Sundbom M et al, 2007)

3.7.2 Ghrelin and Biliopancreatic diversion:

The study showed that initially the levels of ghrelin decreased in the fasting condition and then it returned to the normal levels. When the food consumption resumed to normal, the ghrelin level also resumed to normal. (Adami GF et al, 2003) more studies also show the increased level of ghrelin after bariatric surgery(Garcia-Unzueta MT et al., 2006) and no change in the ghrelin level after bariatric surgery.(Gracia-Fuentes E et al. 2008)

3.7.3 Ghrelin and Gastric banding:

Schindler et al.in 2002 showed that the fasting ghrelin level is increased. Further studies showed that the ghrelin level is increased at fasted state (Stoeckli r et al., 2004) and the suppression is also observed in the LABG surgery.(Le Roux CE et al, 2006)

3.7.4 Ghrelin and Sleeve Gasterectony:

The fundus is excluded in the sleeve gasterectomy, the levels of ghrelin varies in the body. The suppression of ghrelin is observed in the patients who opt for the sleeve rather than the RYGB according to one study. (Wang Y and Liu J, 2009)

Ghrelin plays important role in diabetes remission.

3.8 GLUCAGON LIKE PEPTIDE-1:

Glucagon like peptide is one of the gastrointestinal hormones which is located at jejunum, ileum and colon. (Buffa et al., 1975)(Buchan et al., 1978) It has action on regulation on glycaemia, stimukation of glucose dependent insulin secretion, pro-insulingene expression and β-cell proliferative anf anti-apoptotic pathways. It also inhibits the glucagon release, gastric emptying and food intake. (Drucker DJ, 2006). The GLP-1 receptor agonists are also available in the market for the diabetes type II treatment. (Exenatide for type II diabetes, 2005) the proglucagon is located in the eneteroendocrine L-cells and pancreatic cells, GLP-1 is synthesized by posttranslational processing of proglucagon in the intestine. (Eissele R et al., 1992) The GLP-1 is degradable and it gets degraded quite fast by the enzyme called dipeptidyl peptidase IV and it has a very short half-life of 2 minutes. (Holst JJ, 2006)

3.8.1 Action of GLP-1:

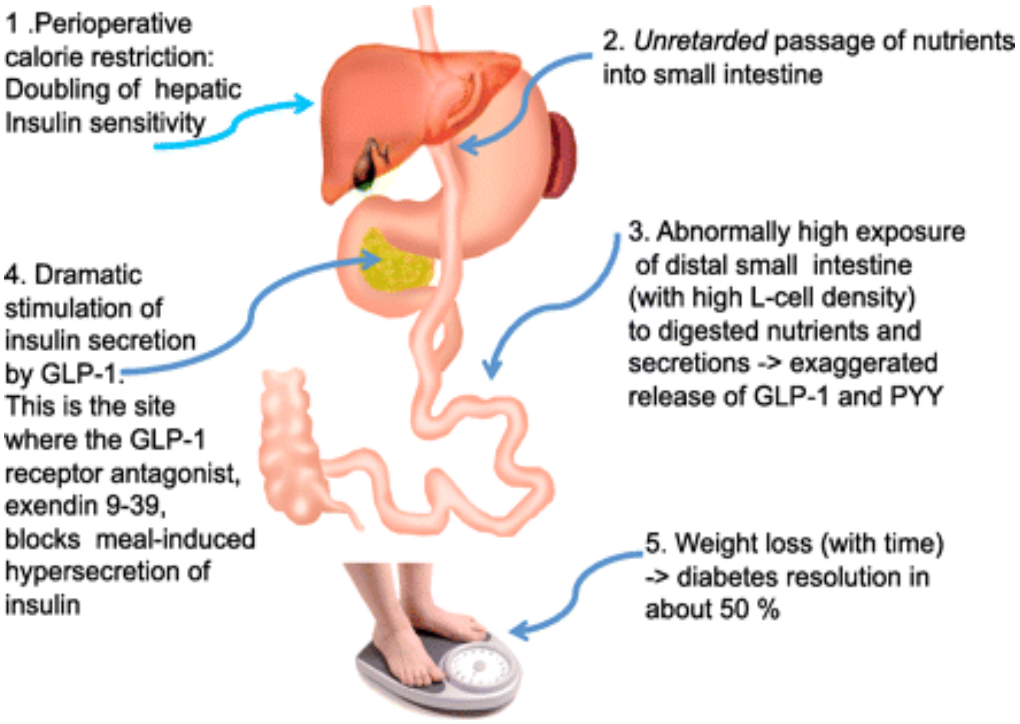
1. GLp-1 is a major contributor for the ilial break mechanism of the upper GI tract, this will stimulate the gastric emptying nad acid secretion in the stomach which will break the food and will help in the digestion of food.(Naslund E et al., 1999).
2. GLP-1 also have effect on the glucose homeostasis by its insulinotropic effect plus its glucagonostatic effects. (Orskov C, 1992)
3. The Action of GLP-1 is to slows down the gastric emptying of the food i.e. solid as well as liquid, the requirement of the insulin decreases.

GLP-1 is expressed by β-cells. The GLP-1 stimulated the insulin gene transcription, islets cell growth and neogenesis.

3.8.2 GLP-1 and Bariatric Surgery:

GLP-1 is associated with Bariatric surgery as well. The levrls of GLP-1 is increased after the bariatric surgery is reported. Studies have supported htat the increased levels are there after the surgery and the effect is both on weight loss as well as diabetes.

(Ziegler O et al., 2009) The remission of diabetes is obsereved in the patients who are undergoin the RYGB surgery. The exaggerated secretion is observed in this kind of the surgery. This will enhance the insulin secretion and might be responsible for the diabetic remission. (Goldfine AB et al., 2007)



Mechanism of GLP-1 and Diabetes Remission

Postprandial GLP-1 releases might have two mechanisms of action in which the one will affect the food intake and one will affect the satiety.

The reports suggest that the remission of diabetes is observed in the patiets undergouing bariatric surgery i.e. sleeve and Gastric bypass. (Madsbad S, Diarksen C, Holst JJ, 2014) The mechanisms are not that much clear and the widely accepted byt some of the scients have suggested the hypothesis about the correlation of GLP_1 and diabetes remission after bariatric surgery. Several studies have shown that the blockade of the GLP-1 receptor which will increase the levels of glucagon levels during the meal test. Taking all the studies together we can say that GLP-1 will induce the beta cell function

and which will improve the glucose tolerance from the first day of the surgery. (Bojsen-Moller KN et al., 2014)

These are two main parameters which suggest that the diabetes remission is related to Ghrelin and GLP-1.

3.9.POLYMORPHISM AND BARIATRIC SURGERY:

There are some people who undergo the bariatric surgery and experience the diabetes remission while some of them do not experience the remission. There must be some reason why the remission does not occur in some patients. A systemic review and meta-analysis of English literature reported that the complete resolution is achieved in 78.1% of the patients. This percentage increased to 86.6% when patients' glycaemic control was taken in the consideration. Two case series studied by Pories et al and Schauer et al presented the data on glycaemic control and RYGB patients. The HbA1c remained 6.6% without the diabetic medications. (Schauer PR et al, 2003)(Pories et al., 1995) The prospective controlled studies showed changes in the glycaemic control after RYGB. Dixon et al. in 2008 reported that patients going for laparoscopic adjustable gastric bypass promoted more reduction in the fasting blood sugar and HbA1c as well as less medication for the diabetes. The Scorpinaro et al in 2006 showed that in 268 patients 975 of the patients had euglycaemic levels even after the 10 years of the surgery. The remaining patients who did not experience the diabetes remission, there must be some reason behind it.

The reason for the variation in diabetes remission and no remission might be polymorphism. Polymorphism is the change in the sequencing of DNA in one person or in a large amount of people (Maggert KA and Maggert KA, 2012). Sources of genetic polymorphism include single nucleotide polymorphism, replication in the sequence, deletion and recombination. The genetic polymorphism is the result of the chance processes or may have been induced by the external agents such as virus and radiations (Functional Genomics and Proteomics, Feb 2002). The weight loss is observed in all the patients but variation occurs surgery to surgery. In some of the patients weight loss occurs fast and in some the weight loss is slow. This can be explained by the polymorphism. Lot of research is carried out on identification of genes in which the polymorphism has been observed. Several SNPs are reported which are responsible for

variation in the weight loss even after the bariatric surgery. The data are not available for the diabetes remission, bariatric surgery and genetic polymorphism.

Some of the genes are related to the genetic polymorphism and bariatric surgeries. The weight loss is having an association with the genetic polymorphism. The data are available for the GHSR gene and GLP-1 R gene. The former one is Growth Hormone secretogogue receptor which is responsible for the the coding of the ghrelin and the later one is responsible for the glucagon like peptide-1 coding.

Genetic polymorphism and weight loss in bariatric surgery:

Genetic polymorphism is associated with different weight loss outcomes in patients undergoing bariatric surgery. One study was carried out for seeing marker's association for eleven obesity related genes in which maximum weight loss and maximum weight gain was observed after the bariatric surgery. In this study 11 genes were taken i.e. ADIPOQ, BDNF, FTO, GNB3, LEP, LEPR, MC4R, NR3C1, PPARG, PPARGC1A and TNF. After the study, it was found that the minor allele at the FTO rs16945088 locus is associated with maximum weight reduction after banding surgery. An allele of FTO single nucleotide polymorphism rs8050136 was correlated with higher Body mass index and high chances of obesity. None of the other genotype was related to the weight gain or loss after bariatric surgery. [17] Table 3 describes about the summery of gene variations in the bariatric surgery. Details of several genetic polymorphism associated with different types of bariatric surgeries are provided in the following section.

Genetic polymorphism in Gastric bypass:

PGC-1:

Peroxisome proliferator activated receptor gamma co-activator (PGC)-1α is a co-activator in the body responsible for the transcription involved in the metabolic and non-metabolic disorders' regulations. The hypothesis was made that Gly482Ser polymorphism of the ppargc1a (peroxisome proliferator activated receptor gamma co-activator 1 alpha) gene would predict differently after bariatric surgery than other genes. The association was found between the ppargc1a (gene coding for PGC1 α) polymorphism and bariatric surgery. The two groups were selected i.e Gly/Gly and

Gly/Ser + Ser/Ser. The inflammatory parameters, anthropometric, C-IMT and metabolic parameters were performed in the interval of at 1, 6 and 12 months. The polymerase chain reaction restriction fragment length polymorphism assay was performed for the primers Gly482Ser sense and Gly482Ser antisense. It was found that Gly482Ser might be an important marker for the complications and amelioration of the disease. The waist ratio was the anthropometric parameter which was significantly reduced The Gly/Ser + Ser/ Ser group had more reduction in hip/Waist ratio than the Gly/Gly group. It was concluded that Gly482Ser polymorphism may improve the metabolic and inflammatory outcomes which leads to reduction in the structural marker of atherosclerosis in obese patients undergoing gastric bypass surgery. Bariatric surgery showed improvement in the various outcomes like metabolic, inflammatory and vascular in the patients having polymorphism in the PGC1α gene Gly482Ser.[18]

Amide hydrolase gene, Leptin, GLP-1 and Biliopancreatic Surgery:

Amide hydrolase :

Fatty acid amide hydrolase is a member of serine hydrolase family of enzymes. This enzyme is responsible for the hydrolysis of anandamide, an endocannabinoid. In biliopencriatic surgery the polymorphism was checked for C358A of the fatty acid amide hydrolase gene on the clinical outcomes for one year. It was noted that the allele A358C of the fatty acid amide hydrolase was associated with a better initial percentage of excess weight loss 9 and 12 months after biliopencriatic diversion.[20]

Leptin:

Leptin is a hormone and have a major role in the energy balancec . It is a mediator for the long term regulation of energy, it suppresses the food intake and so decrease the weight . The leptin is strongly associated with the with the bariatric surgery because the BMI levels are the indicator of the decrease or increase in the leptin levels. Two groups were taken for the study i.e. mutant group and wild group. Patients with Lyc656/Asn656 and Asn6566/Asn656 genotype were included in the mutant group and patients with Lys656/Lys656 genotype were included in the wild group. After the bariatric surgery, the influence was checked for Lys656Asn polymorphism of leptin

receptor gene in biliopancreatic diversion. The study concluded that weight loss was higher in mutant group i.e. Lys656Asn and Asn656Asn higher than the wild type Lys656Lys group after the surgery. [21]

Genetic polymorphism in Adjustable gastric banding:

174 G>C IL-6:

In laparoscopic adjustable gastric banding the polymorphism was checked in the 174G>C IL-6 for the bioelectrical parameters in the obese subjects. It was thought that 174G>C IL-6 polymorphism may play role in the differences in therapeutic response to the LAGB surgery. The C allele frequency was 35% and the GG, GC, and CC genotype frequency were 45%, 40%, and 15% respectively for IL-6. The two carriers were selected i.e. C(-) and C(+) carriers. The weight loss and BMI was more reduced in the C(-) carrier than C(+ carrier)[23]

UCP2 gene:

Mitochondrial uncoupling proteins (UCP2) are the members of larger family of mitochondrial anion carrier proteins. They separate the oxidative phosphorylation from ATP synthesis with energy dissipated as heat. This is expressed highly in the skeletal muscles. It plays a role in the thermogenesis, obesity and diabetes.[24]. One study selected four SNPs i.e. rs660339, -866G/A, rs17132534 and rs643064. It is associated with diabetes and the Ala55Val polymorphism on the UCP2 gene may predict the greater weight loss in morbidly obese patients who undergo the Gastric banding. All the subjects were genotyped for four SNPs on the gene. The SNPs associated with the obesity are the markers of the weight change. rs660339 on exon 4 was associated with the morbid obesity. Patients with TT or CT genotypes had experienced more weight loss compared to CC after the laparoscopic adjustable Gastric Banding (LABG). [25]

3.9.1 Ghrelin and Genetic Polymorphism:

Ghrelin is a hormone which is having major influence on energy balance, it is a natural ligand of the growth hormone secretogogue receptor thus stimulates growth hormone

secretion and has a role of appetite inducer. The genetic co-relation has been found between the ghrelin gene and bariatric surgery. Single nucleotide polymorphism in the promoter region of its receptor gene has some correlation with weight loss. Association between the genotypes for single nucleotide polymorphisms (SNPs) rs9819506 and rs490683 in the promoter region of the Growth hormone secretogogue receptor(GHSR) gene and weight loss outcome was performed for 30 months. Three models were taken: additive, recessive and dominant. Patients with homozygous for rs490683 (GHSR194) C/C genotype showed most weight loss in additive model. The study suggested that patients with C/C genotype lost 5% more weight than those who does not have this genotype. (Obesity Surgery, 2012)

3.9.2 GLP-1 and Polymorphism:

Glucagon like peptide-1 is a 30 amino acid peptide hormone. GLP- 1 stimulates the insulin secretion (i.e. to act like incretin hormone) and to inhibit the glucagon secretion. GLP-1 also has a role in the regulation of the appetite and food intake. Studies of Glucagon like peptide-1(GLP-1) receptor (GLP-1R) have been done to identify the relation between the polymorphism of the gene GLP-1R and pathogenesis of the obesity. Investigation was made on the polymorphism of rs6923761 GLP-1R gene and its outcome after the biliopancreatic diversion. 137 patients were taken. Parameters like weight, blood pressure basal glucose and lipid profiles were measured at basal visit and each following visit i.e. 3, 9, 12 and 18 months. The BMI, weight and waist circumference were lower in the non-A allele carrier than A carriers after 18 months. The initial weight loss was higher in patients with GG genotype than allele carriers. (De Luis DA et al.,2014)

4. Methodology:

The study was carried out in two parts to meet the two objectives.

A. To investigate the biochemical parameters of patients undergoing bariatric surgery for diabetic and no-diabetic patients.

4.1 Study Design:

Retrospective, single centric study involving diabetic and non-diabetic patients

4.2 Site Of Study

Asian Bariatrics, S.G. Highway, Ahmedabad

4.3 Ethical Consideration:

Study protocol was approved by the ethics committee of Asian Bariatrics Pvt. Ltd.

4.4 Study Population:

Sample size: 107

4.4.1 Inclusion Criteria

- Patients with diabetes or without diabetes having BMI more than 25 and undergoing bariatric surgery
- Age of patient should be more than 18
- Patients who are willing to provide consent for the study.

4.4.2 Exclusion Criteria

- Patients who are coming for second time for the surgery
- Patients with chronic renal failure
- Patients with chronic hepatic failure

4.5 Study Methodology

4.5.1

Bariatric patients registered at Asian Bariatrics , Ahmedabad were included in the study. Medical records of 107 patients were obtained from their respective files from May 2015 to December 2015. From the available records 107 patients were selected according to inclusion and exclusion criteria. The data of lipid profile, blood tests, hepatic parameters, calcium, iron, thyroid parameters, pre-existing diabetes, and hypertension were collected from the records. The study was purely retrospective. The data at baseline(before Surgery) was compared with the data after first follow up (3 months) and second follow up (6 months) of surgery.

4.6 Study Evaluation criteria

4.6.1 Baseline Characteristics

- Age
- Gender
- Hypertension
- Diabetes

4.6.2 Laboratory investigations:

- CBC(Complete blood Count)
- S. Iron
- S. Calcium
- FBS
- PP2BS
- HbA1c
- Insulin
- Cholesterol
- Triglycerides
- HDL
- LDL
- VLDL
- Bilirubin
- Alkaline Phosphate
- SGPT
- TSH
- T_3
- T_4
- Vitamin B_{12}
- Vitamin D_3
- S. Creatinine
- B. Urea
- Sodium
- Potassium
- Chloride

4.7. Statistical Analysis:

Analysis was performed by using ANOVA. Two way ANOVA was used to compare the variables. A valueof $P<0.05$ will be considered significant: quantitative results were expressed as mean±SD.

B. To determine GHSR gene polymorphism and its correlation with obese patients undergoing bariatric surgery.

4.7 Study Design: Prospective, single centric study involving bariatric patients.

4.8 Site Of Study

Asian Bariatrics, S.G. Highway, Ahmedabad

4.9 Ethical Consideration:

Study protocol was approved by the ethics committee of Asian Bariatrics Pvt. Ltd.

4.10 Study Population:

Sample Size: 40

4.10.1 Inclusion Criteria

- Patients with diabetes or without diabetes having BMI more than 25 and undergoing bariatric surgery
- Age of patient should be more than 18
- Patients who are willing to provide consent for the study.

4.10.2 Exclusion Criteria

- Patients who are coming for second time for the surgery
- Patients with chronic renal failure
- Patients with chronic hepatic failure

4.11 Study Methodology:

4.11.1

Diabetic and non-diabetic patients those who were willing to give written informed consent, were enrolled in the study. Patients were enrolled according to the inclusion and exclusion criteria. Every patient had all the right to refuse to give the consent. Blood collection of the patients was done and their lab investigation data were collected.. The small portion of stomach was cut and taken with the help of the surgeon. The stomach was stored in PBS at -80^{0}C. From the stomach portion, DNA was isolated from 40 tissues.

4.12 Study Evaluation Criteria:

a. Basic Characteristics:

- Gender
- Weight
- Height
- BMI

b. **Demographic Details**

- Age
- Socio Economic Status
- Location
- Occupation
- Lifestyle
- Marital Status

c. Medical History

- Other Complications
- Allergy
- Infertility
- Joint pain
- Breathing Problems
- PCOS

d. Biochemical Tests:

- Blood Tests
- Sugar test
- Lipid Profile
- Renal Test
- Cardiovascular test
- Vitamin b_{12}

- Vitamin D

5. RESULTS

A: Retrospective Study

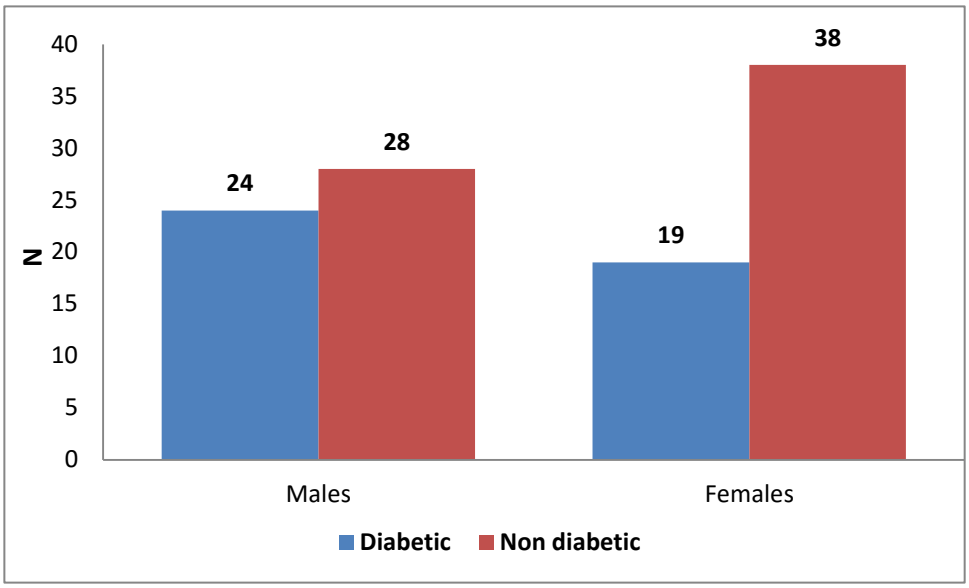
5.1 Demographic Profile:

5.1.1Sample Size and Gender:

In the present study, there were total 107 patients out of which 64 were non diabetic and 43 were non diabetic. Among the non-diabetic 28 were males and 34 were females. In diabetic 24 were males and 19 were females.

Table 5.1.1: Sample size and gender

Gender	Non-Diabetic	Diabetic
Male	28(43.75%)	24(55.81%)
Female	36(56.25%)	19(44.18%)
Total	64 (100%)	43(100%)
Mean	33	21.5



5.1.1 Sample Size and Gender

5.1.2 Distribution according to Age:

The table 5.1.2 shows age and gender distribution for the Diabetic as well as the Non-diabetic group. It was observed that 4.65% of subjects under diabetic group belonged to the age group of < 30 years, 13.95% belonged to the age group of 31-40 years, 27.9% belonged to age group of 41-50 years, 32.55% belonged to the age group of 51-60 years

and the remaining about 20.93% were older than 60 years. It was observed that 37.5% of patients under non-diabetic group belonged to the age group of < 30 years, 23.43% belonged to the age group of 31-40 years, 21.87% belonged to age group of 41-50 years, 14.06% belonged to the age group of 51-60 years and the remaining about 3.125% were older than 60 years.

Table 5.1.2: Gender and age distribution

Age Group	Diabetic Group				Non-Diabetic Group			
	Gender		Total(N)	Percent(%)	Gender		Total(N)	Percent(%)
	Male	Female			Male	Female		
<=30	2	0	2	4.65	11	13	24	37.5
31-40	2	4	6	13.95	6	9	15	23.43
41-50	7	5	12	27.9	6	8	14	21.87
51-60	6	8	14	32.55	4	5	9	14.06
61-70	7	2	9	20.93	1	1	2	3.125
Total	24	19	43	99.98	28	36	64	99.985

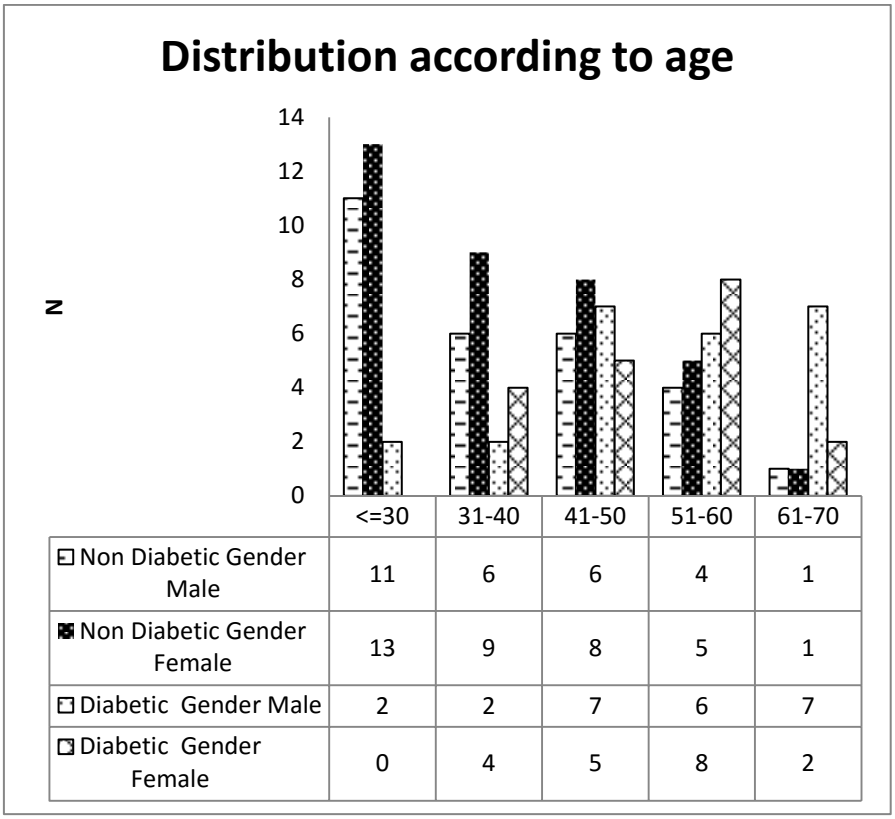


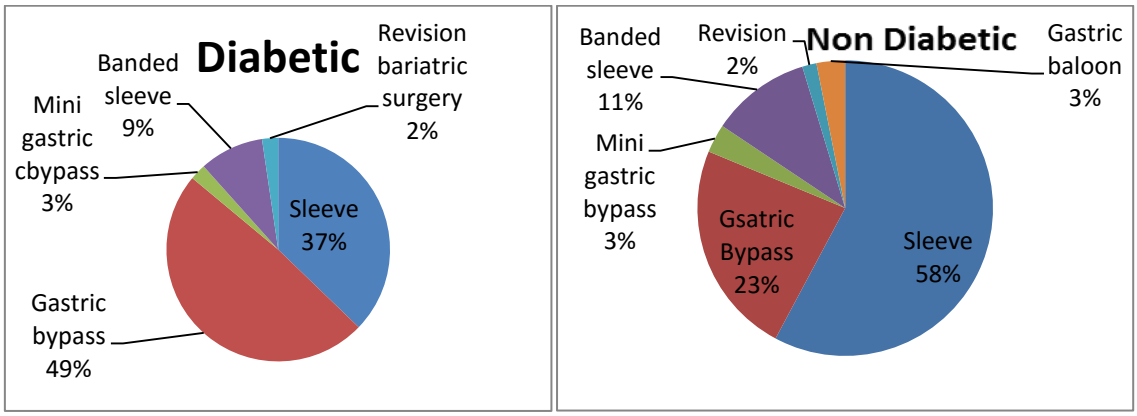
Figure5.1.2: Gender and Age Distribution

Types of Surgery:

Figure and table 5.2.1.A and B shows the surgeries performed in diabetic and non-diabetic patients. Amongst diabetic patients, gastric bypass was carried out in 21 patients, sleeve gasterectomy in 16 patients and banded sleeve in 1 patient, mini gastric bypass in 1 patient and revision in 1 patients. Amongst non-diabetic patients, gastric bypass was performed in 15 patients, sleeve gasterectomy eas performed in 37 , mini gastric bypass in 2, banded sleeve in 7 and revision was in 1 patient.

Table: 5.2.1: Surgeries in Diabetic and Non-Diabetic patients

Type of surgery	Sleeve Gasterectomy	Gastric bypass	Mini gastric bypass	Banded sleeve	Revision bariatric surgery	Gastric Balloon	Total
Diabetic Patients	16	21	1	4	1	0	43
Per cent(%)	37.20	48.83	2.32	9.30	2.32	0	100
Non Diabetic	37	15	2	7	1	2	64
Percentage (%)	57.81	23.43	3.125	10.93	1.56	3.125	100%



A **B**

Figure 5.2.1: Types of Bariatric Surgeries

5.3 BIOCHEMICAL PAMETERS

5.3.1 HbA1C:

Table 5.3.1.1 and 5.3.1.2 shows that there was significant ($p<0.001$) reduction in mean HbA1c levels after 3 months and 6 months of bariatric surgery as compared to baseline levels in diabetic patients. In non-diabetic patients also, there was a significant ($p<0.001$) reduction in mean HbA1c levels after 6 months of bariatric surgery as compared to baseline levels. In Diabetic Patients, at baseline there were 2.32% patients with HbA1c less than 6, 27.99% with 6-7.5%, 27.99% with 7.6-8.5 and 41.86% with more than 8.5% HbA1c. After 3 months, 37.2% had HbA1c <6 and after 6 months 51.16% had HbA1c< 6 indicating complete remission of diabetes of diabetes after bariatric surgery. In non-diabetic patients the levels of HbA1c was normal before and after bariatric surgery.

5.3.1.1 Effect of Bariatric surgery in mean HbA1c levels in Diabetic and Non-Diabetic Patients

	% HbA1c			
	N	**Baseline**	**3 months**	**6 months**
Diabetic	**43**	8.42±1.88	6.5 ±0.89***	6.10 ±0.997***
Non-Diabetic	**64**	6.35 ±1.17	5.37 ±0.48	5.48 ±0.48***

Each value represents Mean±SD

***significantly different from baseline ($p<0.001$)

Table 5.3.1.2: Distribution of Diabetic and Non-diabetic according to % HbA1c

HbA1c	%BL	%F-1	%F-2
<6	2.32	37.2	51.16
6-7.5	27.99	55.81	48.83
7.6-8.5	27.99	6.97	0
>8.5	41.86	0	0

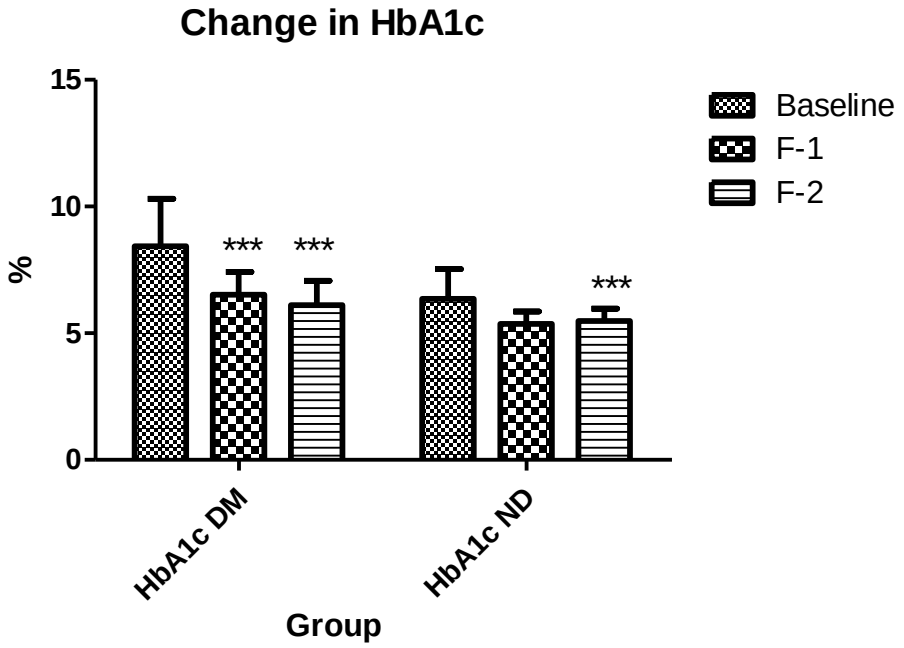
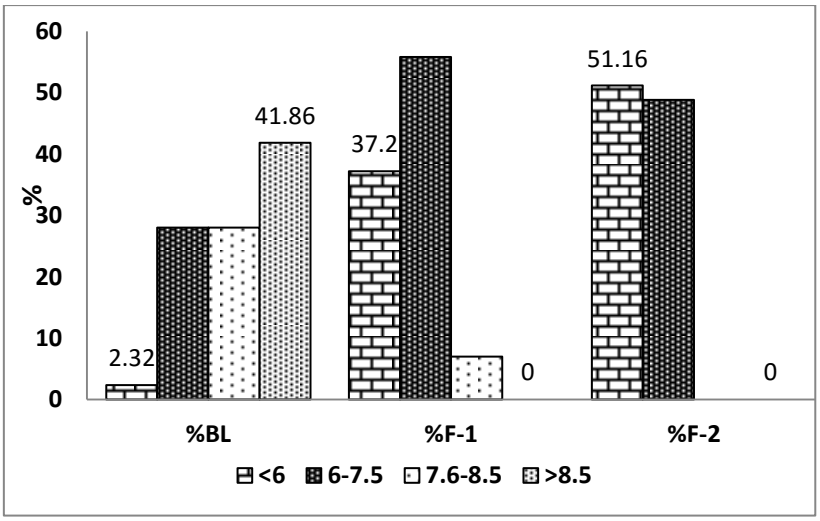


Figure 5.3.1.1 Effect of Bariatric surgery in mean HbA1c levels in Diabetic and non-diabetic patients

Each value represents Mean±SD

***significantly different from baseline ($p<0.001$)



5.3.1.2 Distribution of patients according to %Hba1c

5.3.2 Body Mass Index (BMI):

BMI in Non-diabetic and Diabetic Patients:

Table 5.3.2.1 shows the mean change in diabetic and non-diabetic patients. There was a significant ($p<0.001$) reduction in mean BMI levels after 3 and 6 months of bariatric surgery as compared to baseline in diabetic patients. There was a significant ($p<0.001$) reduction in mean BMI levels after 3 and 6 months of bariatric surgery as compared to baseline in non-diabetic patients also.

Table 5.3.2.2 represents distribution pattern of BMI of diabetic and non-diabetic patients. Out of 64 non-diabetic patients, there were 1.75% patients with BMI 25-29.9, 7.017% patients with BMI 30-34.9, 22.8% patients with BMI 35-39.9, 56.14% patients with 40-49.9 and 10.52% patients with BMI more than 50 kg/m^2. After 3 months it was found 3.5%, 1.75%, 35.087%, 26.07%, 28.07% and 5.26 respectively for BMI. After 6 months it was 5.26%, 28.07%, 24.56%, 22.8%, 19.29% and 0% respectively.

Out of 43 diabetic patients, at baseline, there were 0% patients with BMI 25-29.9, 16.27% patients with BMI 30-34.9, 20.93% patients with BMI 35-39.9, 48.83% patients with 40-49.9 and 13.95% patients with BMI more than 50 kg/m^2. After 3 months BMI per cent change was found 3.5%, 1.75%, 35.087%, 26.07%, 28.07% and 5.26 respectively for BMI. After 6 months it was 5.26%, 28.07%, 24.56%, 22.8%,19.29% and 0% respectively

5.3.2.1 Effect of Bariatric surgery on mean BMI levels in Diabetic an non-diabetic patients

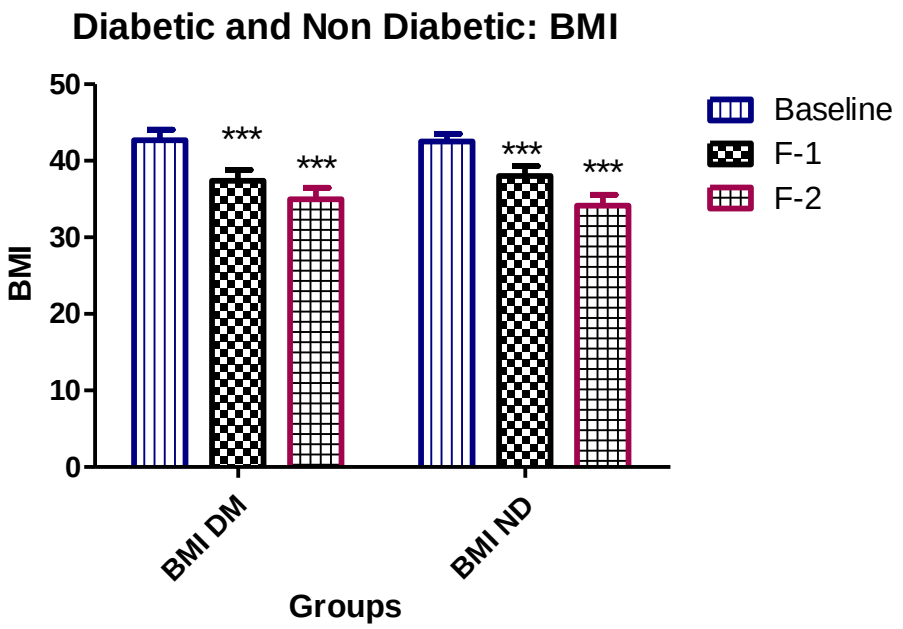
Body Mass Index(kg/m^2)				
	N	**Baseline**	**3 months**	**6 months**
Diabetic	**43**	42.67±7.40	37.40±6.82***	34.96±7.71***
Non-Diabetic	**64**	42.5311±7.29	38.0314±7.66***	34.16105±6.74***

Each value represents Mean±SD

***significantly different from baseline ($p<0.001$)

5.3.2.2 Distribution of non-diabetic and diabetic patients according to BMI

Non -diabetic			
BMI Kg/m^2	**Baseline**	**3 months**	**6 months**
18.5-24.9	1.75	3.5	5.26
25-29.9	1.75	1.75	28.07
30-34.9	7.017	35.087	24.56
35-39.9	22.8	26.31	22.8
40-49.9	56.14	28.07	19.29
>=50	10.52	5.26	0
Diabetic			
BMI kg/m^2	**%baseline**	**3 months**	**6 months**
18.5-24.9	0	0	4.65
25-29.9	0	13.95	20.93
30-34.9	16.27	27.9	32.55
35-39.9	20.93	25.58	20.93
40-49.9	48.83	30.23	18.6
>=50	13.95	2.32	2.32



5.3.2.1 Effect of bariatric surgery on mean BMI levels in Diabetic and non-diabetic patients

Each bar represents Mean±SD

***significantly different from baseline ($p<0.001$)

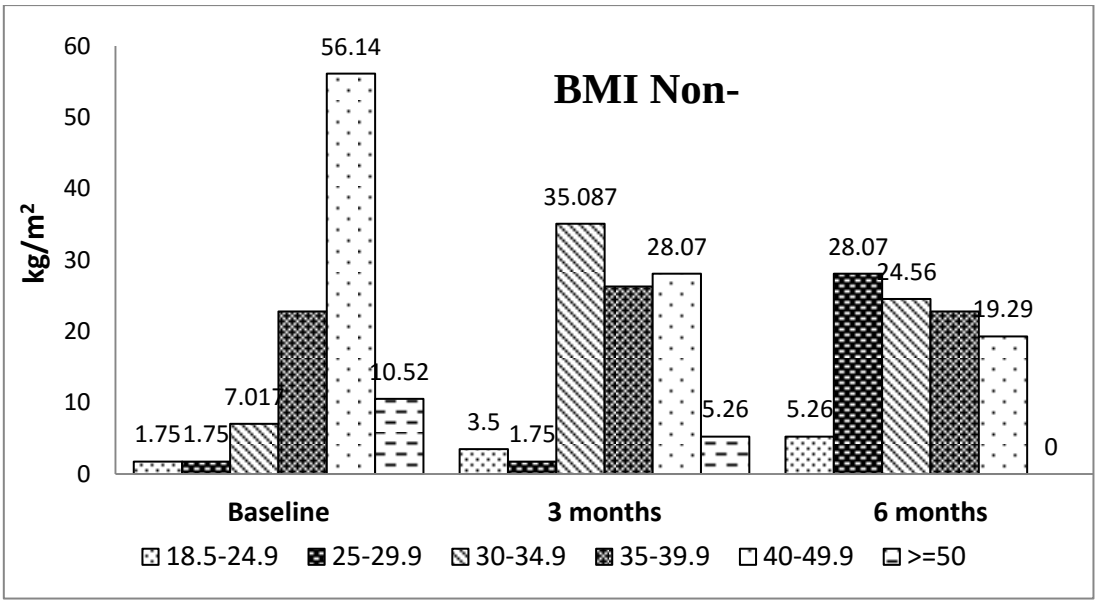


Figure 5.3.2.2 a: Distribution of non-diabetic according to % BMI

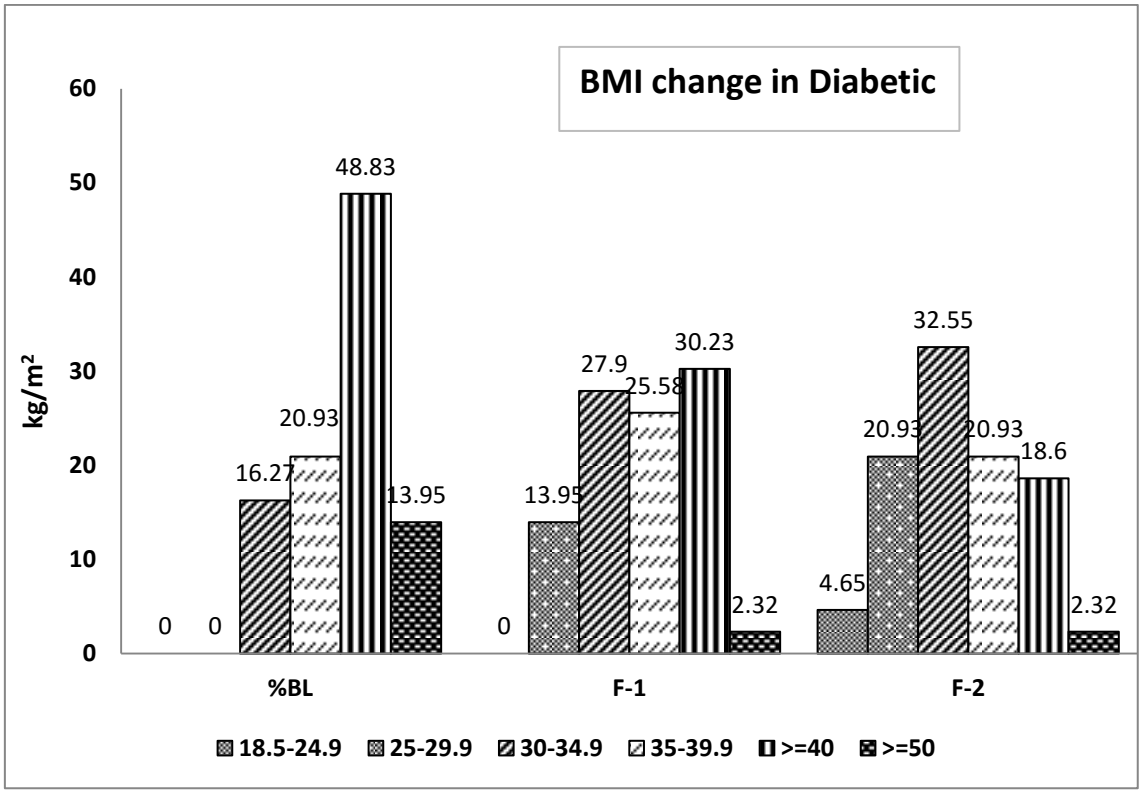


Figure 5.3.2.2 b Distribution of non-diabetic according to % BMI

5.3.3 Cholesterol:

Table 5.3.3.1 shows the effect of bariatric surgery on mean total cholesterol in diabetic an non diabetic patients. There was no significant reduction in mean total cholesterol levels after 3 months and 6 months of bariatric surgery as compared to baseline levels in non-diabetic patients while in diabetic patients there was no significant ($p<0.05$) reduction in total cholesterol levels after 3 months of bariatric surgery, but after 6 months there was significant($p<0.05$) reduction in Total cholesterol after bariatric surgery.

At baseline in out of 64 non Diabetic patients, there were 29.23% patients with cholesterol between 101-150 mg/dL, 53.84% patients with cholesterol between 151 to 200mg/dL and 16.92 % patients with cholesterol more than 200. After 3 months, the percentage were o%,43.07%, 41.53% and 15 38% respectively. After 6 months the change in percentage was 0%, 53.84%, 33.84%, 12.31% respectively.

At baseline out of 43 diabetic patients, there were 51.16% patients with cholesterol between 101-150 mg/dL, 32.55% patients with cholesterol between 151 to 200mg/dL and 16.27 % patients with cholesterol more than 200. After 3 months, the

percentage were o%,67.44%, 25.58% and 6.97% respectively. After 6 months the change in percentage was 0%, 74.41, 23.25, 2.32respectively.

5.3.3.1 Effect of Bariatric surgery on mean Total Cholesterol levels in Diabetic an non-diabetic patients

Total Cholesterol(mg/dL)				
	N	**Baseline**	**3 months**	**6 months**
Diabetic	**43**	162.80±21.45	151.53±44	142.24±40*
Non-Diabetic	**64**	167.01±42	161.28±34	161.28±36

Each value represents Mean±SD

*significantly different from baseline ($p<0.01$)

Table 5.3.3.2: Distribution of non-diabetic and diabetic patients according to Cholesterol

Cholesterol(mg/dL)	**Baseline%**	**3 months%**	**6 months%**
Non-Diabetic			
101-150	29.23	43.07	53.84
151-200	53.84	41.53	33.84
>200	16.92	15.38	12.31
Diabetic			
100-150	51.16	67.44	74.41
151-200	32.55	25.58	23.25
201-250	16.27	6.97	2.32

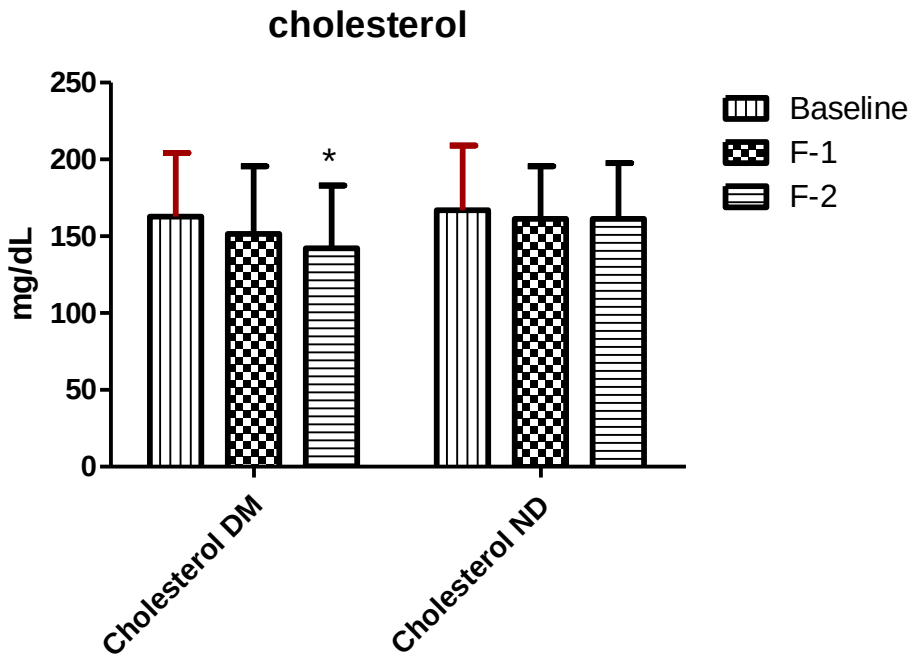


Figure 5.3.3.1 Effect of bariatric surgery on mean total cholesterol levels in Diabetic and non-diabetic patients

Each bar represents Mean±SD

*significantly different from baseline ($p<0.01$)

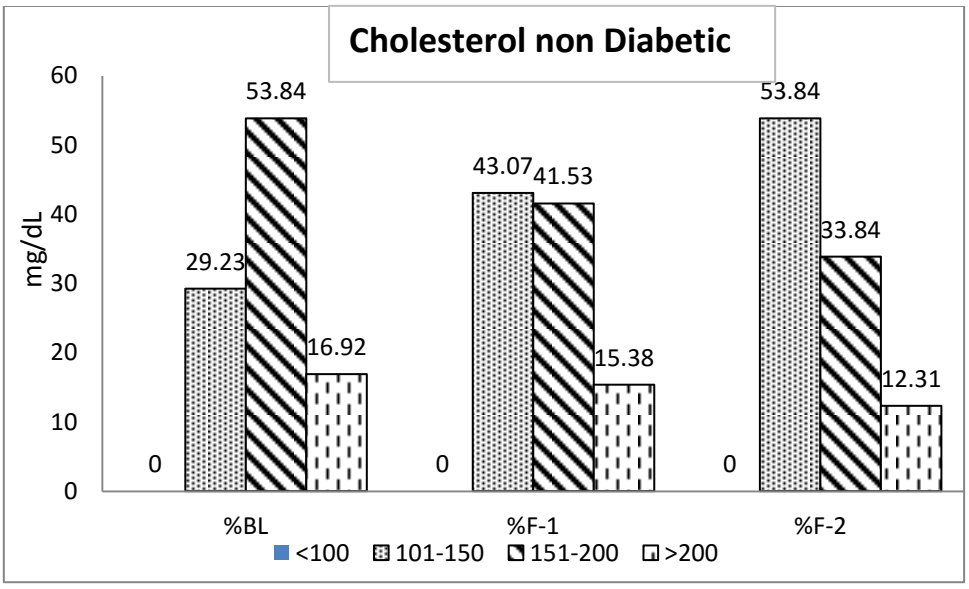
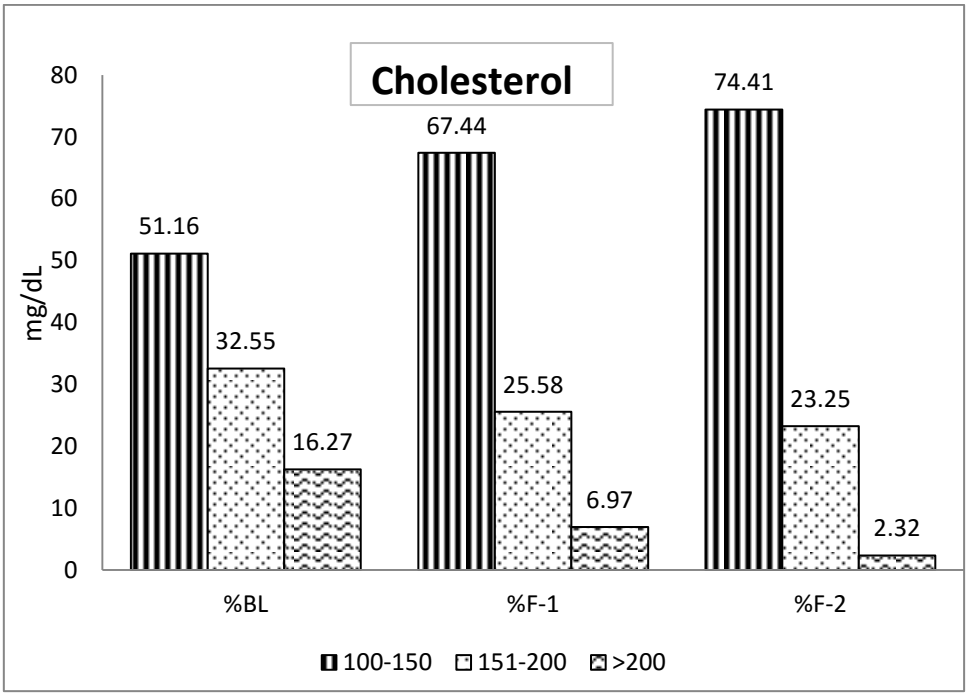


Figure 5.3.3.2 a: Distribution of non-diabetic according to %cholesterol



5.3.3.2 b Distribution of diabetic according to % cholesterol

5.3.4 Triglycerides:

Table 5.3.4.1 depicts change in diabetic and non-diabetic patients undergoing bariatric surgery. There was significant ($p<0.05$) reduction in mean triglycerides levels after 3 months and after 6 months there was significant($p<0.01$) reduction after 6 months after bariatric surgery as compared to baseline in diabetic patients. There was no significant reduction in non-diabetic patients after 3 months of bariatric surgery but after 6 months, there was significant ($p<0.05$) reduction observed after bariatric surgery.

Table 5.3.4.2a and b represents distribution pattern of triglycerides of diabetic and non-diabetic patients.Out of 64 non-diabetic patients, at baseline there were 46.15% patients with triglycerides less than 150, 36.92% patients with triglycerides between 151-199 mg/dL, 16.92% patients with triglycerides more than 200mg/dL in non-diabetic group. After 3 months 56.92% of the patients had triglycerides levels normal and after 6 months 69.235 patients had normal levels of Triglycerides.(<105mg/dL)

In diabetic patients, at baseline there were 43.9% patients with triglycerides less than 150, 31.7% patients with triglycerides between 151-199 mg/dL, 24.39% patients with triglycerides more than 200mg/dL in non-diabetic group. After 3 months 47.5%

ahd norma triglycerides level and 52.55 patients had normal triglycerides after 6 months.

5.3.4.1 Effect of Bariatric surgery on mean Triglycerides levels in Diabetic an non-diabetic patients

Triglycerides (mg/dL)				
	N	**Baseline**	**3 months**	**6 months**
Diabetic	**43**	162.42 ±77.50	131.25 ±47.86*	116.12 ±48.90***
Non-Diabetic	**64**	135.03±70.04	125.25±62.12	109.657±52.69*

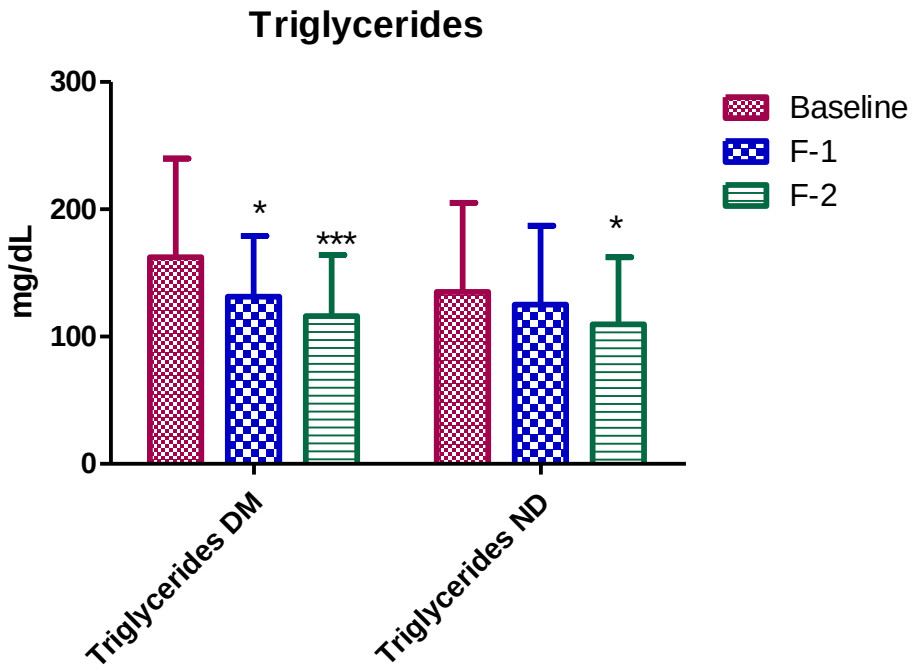
Each value represents Mean±SD

* Significantly different from baseline (P<0.05)

***significantly different from baseline (P<0.001)

5.3.4.2 Distribution of non-diabetic and diabetic according to % Triglycerides

Non Diabetic			
Triglycerides(mg/dL)	**%Baseline**	**%3 months**	**%6 months**
<150	46.15	56.92	69.23
151-199	36.92	32.32	26.15
>200	16.92	10.76	4.61
Diabetic			
Triglycerides (mg/dL)			
<150	43.9	47.5	52.5
150-199	31.7	30	35
>200	24.39	22.5	12.5



5.3.4.1. Effect of Bariatric surgery on mean Triglycerides level in Diabetic and non-diabetic patients

Each bar represents Mean±SD

*significantly different from baseline (P<0.01)

***significantly different from baseline (P<0.001)

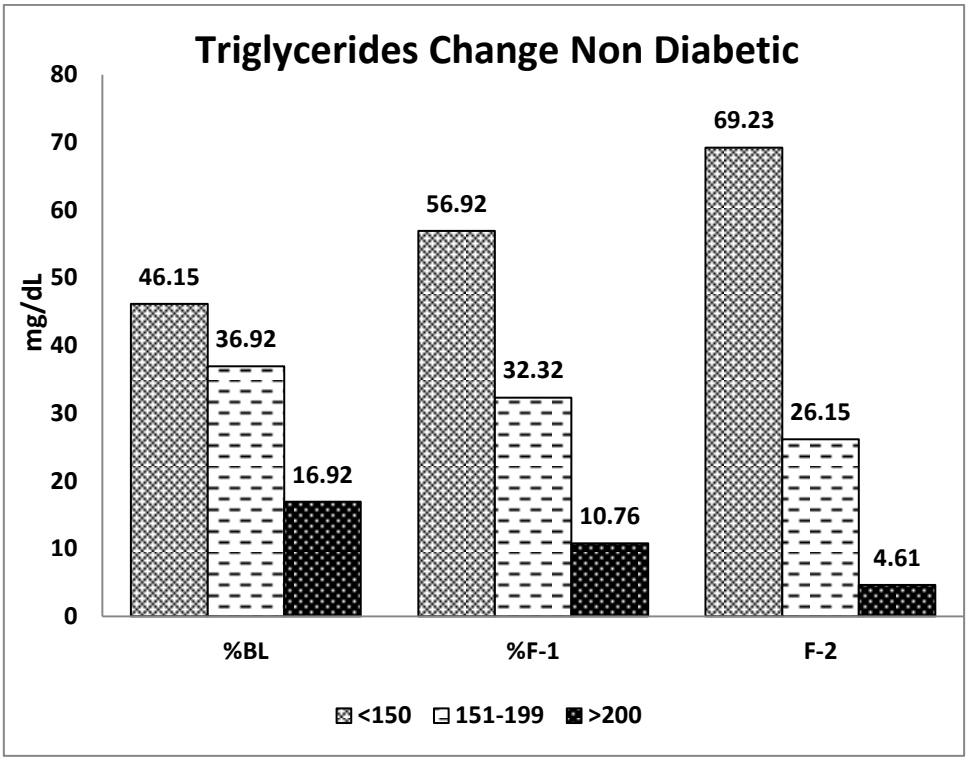


Figure 5.3.4.2a Distribution of non-diabetic according to %Triglyccerides

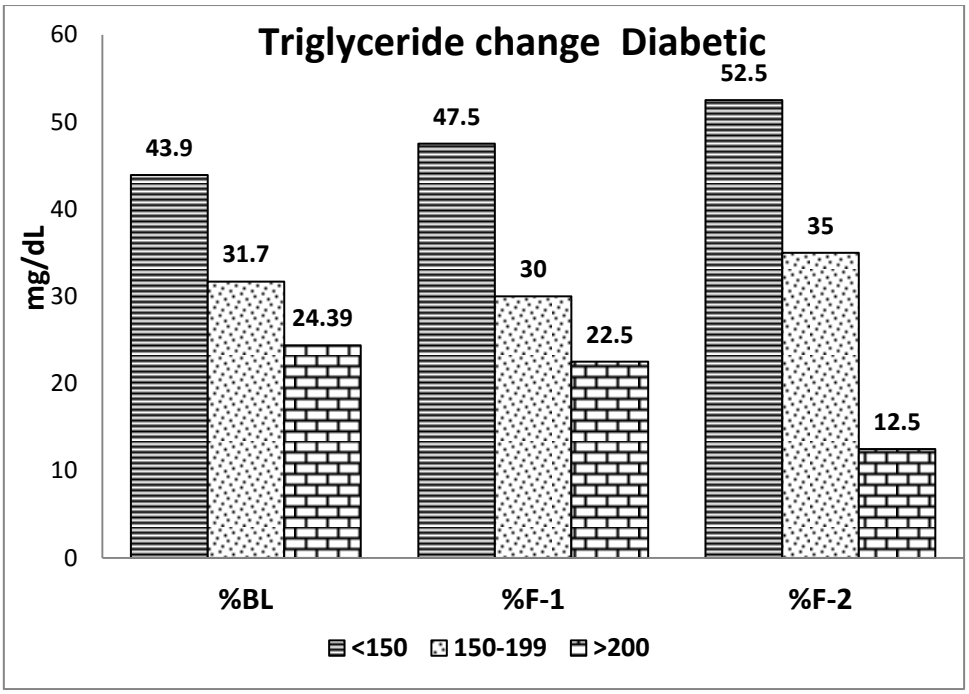


Figure 5.3.4.2b Distribution of diabetic according to %Triglycerides

5.3.5 HDL:

Table 5.3.5.1 shows the mean change in diabetic and non-diabetic patients undergoing bariatric surgery **.**There was no significant increase after 3 months after bariatric surgery compared to baseline after bariatric surgery in diabetic patients while after 6 months there was significant($p<0.01$) increase after bariatric surgery compared to baseline. While in non-diabetic patients there was no significant difference observed after bariatric surgery compared to baseline.

Table 5.3.5.1 represents distribution pattern of HDL of diabetic and non-diabetic patients. Out of 64 non-diabetic patients at baseline, there were 37.48% patients with HDL less than 40mg/dL, 64.51% patients with HDL between 40-100 mg/dL and 0% patients with HDL more tahn100mg.After 3 months 82.25 % patients had HDL between 40-100 and after 6 months 88.7% patients had normal range of HDL i.e. 40-100 mg/dL.

At baseline in diabetic group, there were 37.2% patients with HDL less than 40mg/dL, 58.13% patients with HDL between 40-100 mg/dL and 4.65% patients with HDL more tahn100mg.After 3 months 62.79 % patients had HDL between 40-100 and after 6 months65.11% patients had normal range of HDL i.e. 40-100 mg/dL.

5.3.5.1 Effect of Bariatric surgery on mean HDL levels in Diabetic an non-diabetic patients

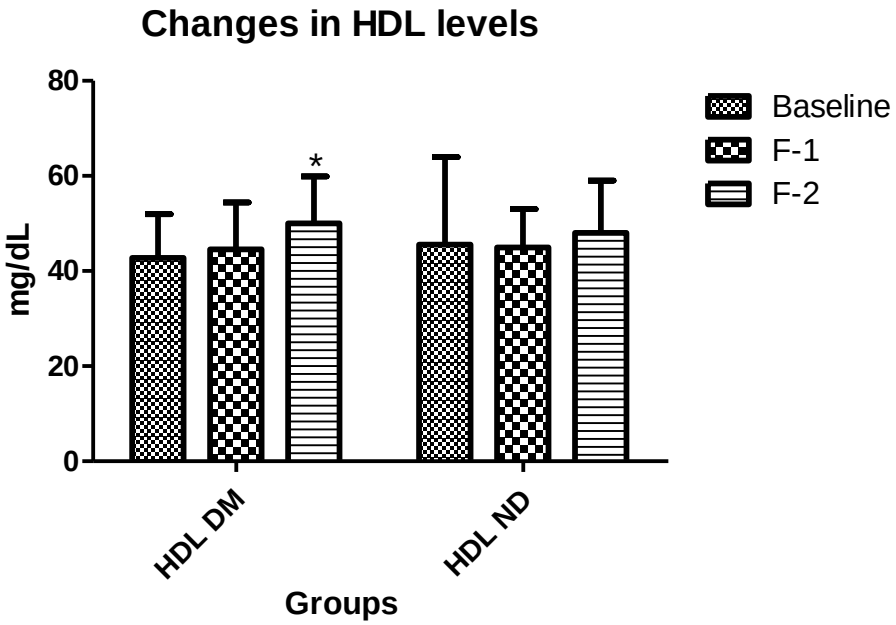
HDL (mg/dL)				
	N	**Baseline**	**3 months**	**6 months**
Diabetic	**43**	42.78±9.17	44.54 ±9.87	50.45 ±11.50*
Non-Diabetic	**64**	45.54±18.43	44.94±8.07	48.99±11.10

Each value represents Mean±SD

*significantly different from baseline ($P<0.01$)

5.3.5.2 Distribution of non-diabetic and diabetic according to % HDL

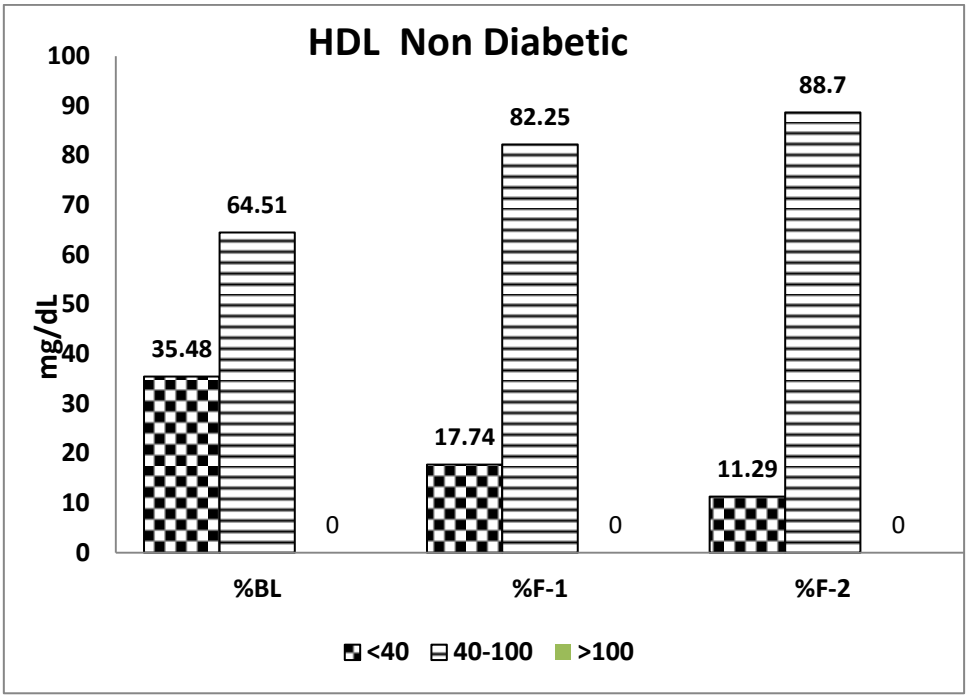
Non Diabetic(%)			
HDL(mg/dL)	**Baseline**	**3 months**	**6 months**
<40	35.48	17.74	11.29
40-100	64.51	82.25	88.7
>100	0	0	0
Diabetic(%)			
HDL			
<40	37.2	34.88	32.55
40-100	58.13	62.79	65.11
>100	4.65	2.32	2.32



5.3.5.1 Effect of Bariatric surgery on mean HDL levels in Diabetic an non-diabetic patients

Each value represents Mean±SD

*significantly different from baseline ($p<0.01$)



5.3.5.2.a Distribution of non-diabetic according to % HDL

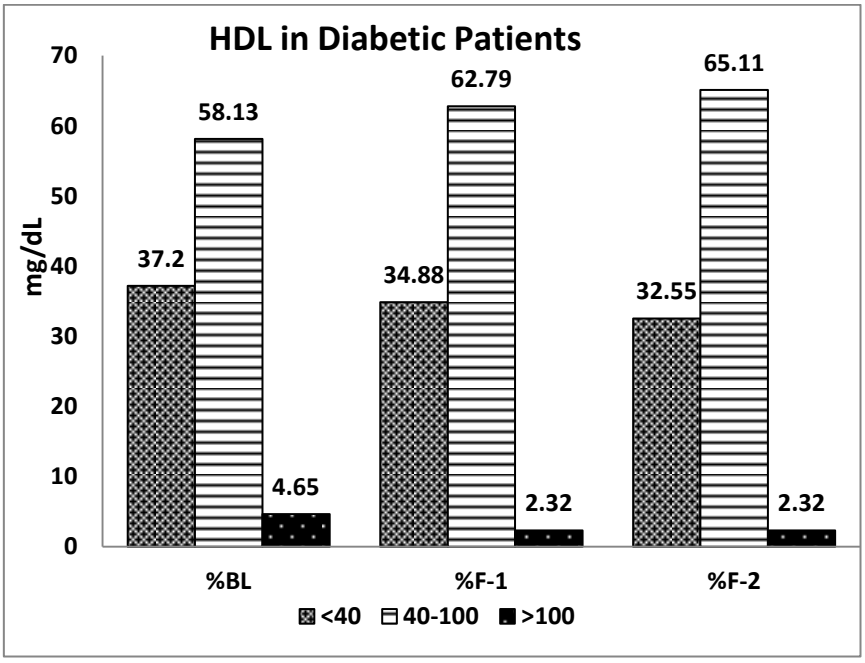


Figure 5.3.5.2.b: Distribution of non-diabetic according to % HDL

5.3.6 LDL:

Table 5.3.6.1 shows the mean changes in diabetic and non-diabetic patients undergoing bariatric surgery. There was no significant change in LDL levels after 3 months but there was significant ($p<0.05$) increase in LDL levels after 6 months of bariatric surgery in diabetic patients. In non-diabetic patients there was significant ($p<0.001$) increase after 3 months and significant ($P<0.05$) increase after 6 months after bariatric surgery.

Table and graph 5.3.6.2 a gives information of change in LDL levels in non-diabetic individuals. The level of LDL decreased to normal levels after follow up 1 and follow up 2. The per cent of LDL increased from 60% to 76% after 6 months.

Table and figure 5.3.6.2b depict the changes in LDL levels after bariatric surgery in diabetic group. In diabetic group, LDL level went to normal (100mg/dL) in 92.3 %. The levels which were risky decreased to 2.56%. After follow up, LDL levels decreased gradually in follow up 1 and follow up 2.

5.3.6.1 Effect of Bariatric surgery on mean LDL levels in Diabetic an non-diabetic patients

LDL(mg/dL)				
	N	**Baseline**	**3 months**	**6 months**
Diabetic	**43**	86.4578 ±7.80	84.38 ±8.23	94.78±5,70**
Non-Diabetic	**64**	94.68±3.84	101.32±9.49***	106.39±4.070**

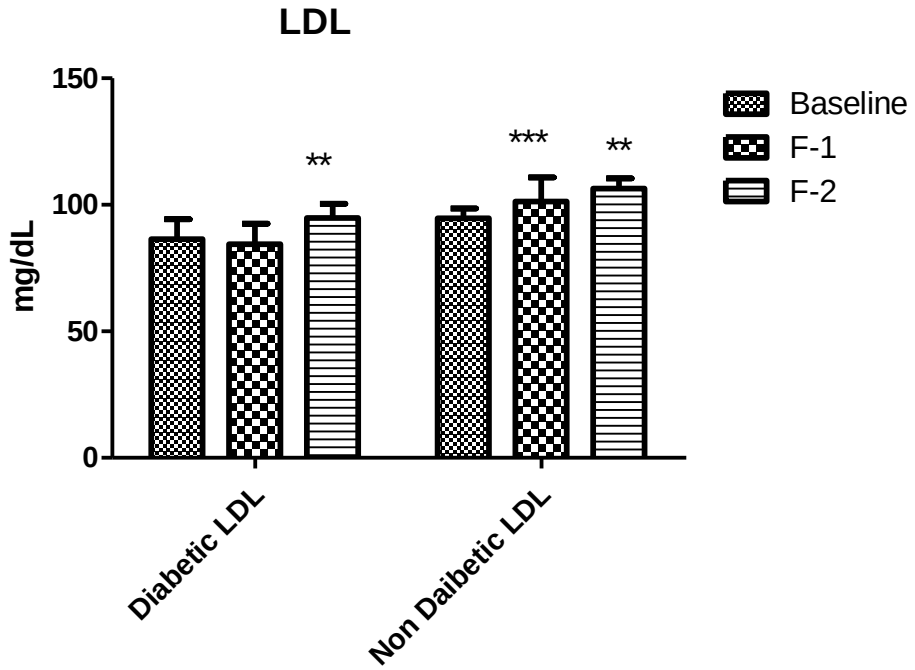
Each value represents Mean±SD

** significantly different from baseline ($p<0.05$)

***significantly different from baseline ($p<0.001$)

5.3.6.2 Distribution of non-diabetic and diabetic according to % LDL

LDL Non Diabetic	**Baseline%**	**3 months%**	**6 months%**
<100 mg/dL	60.31	73.77	76.92
100-129	28.57	19.67	15.38
130-159	6.34	4.91	3.07
>160	4.76	1.63	4.61
LDL Diabetic			
<100	74.35	79.48	92.3
100-129	17.94	15.38	5.12
130-159	7.69	5.12	2.56

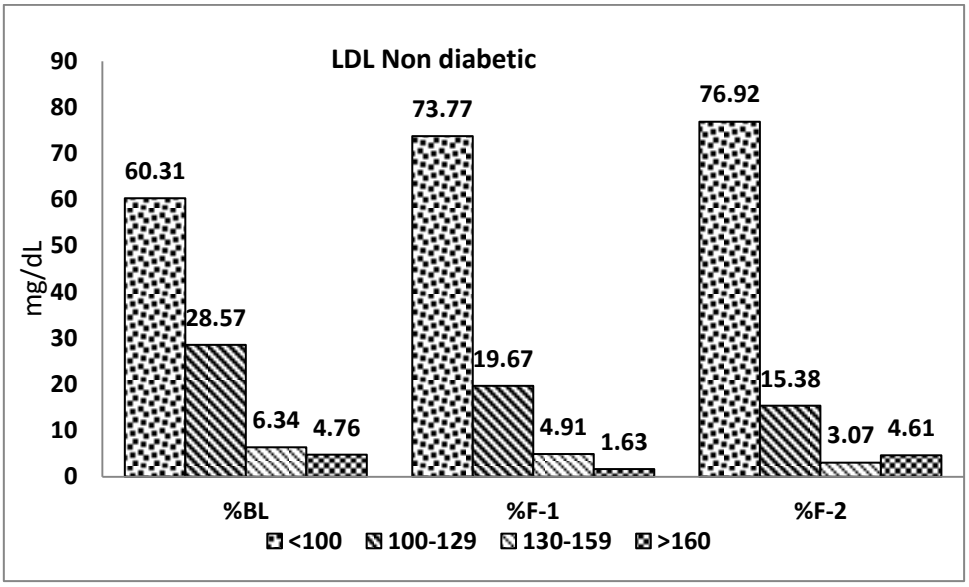


5.3.6.1 Effect of Bariatric surgery on mean LDL levels in Diabetic an non-diabetic patients

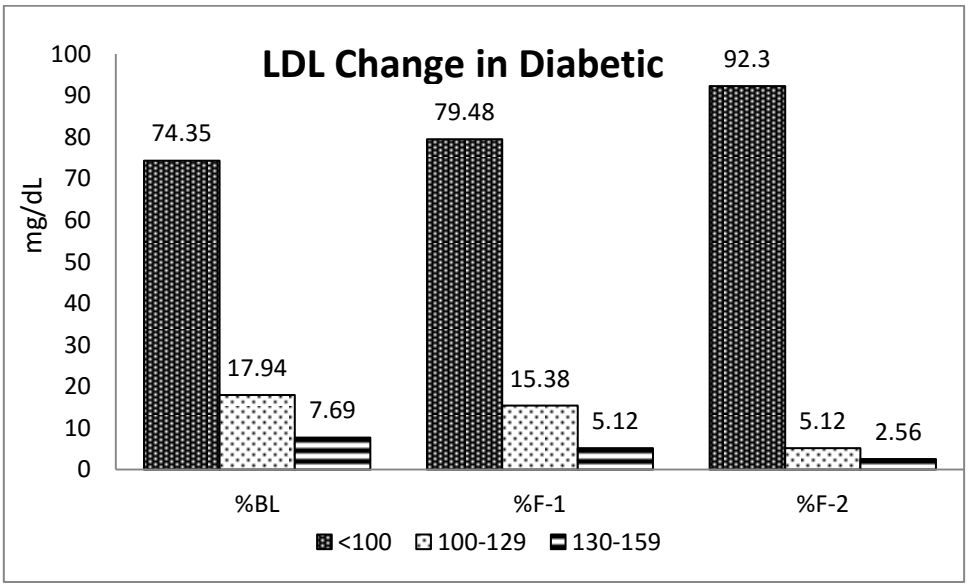
Each bar represents Mean±SD

** Significantly different from baseline ($p<0.05$)

***significantly different from baseline ($p<0.001$)



5.3.6.2a Distribution of non-diabetic patients according %LDL

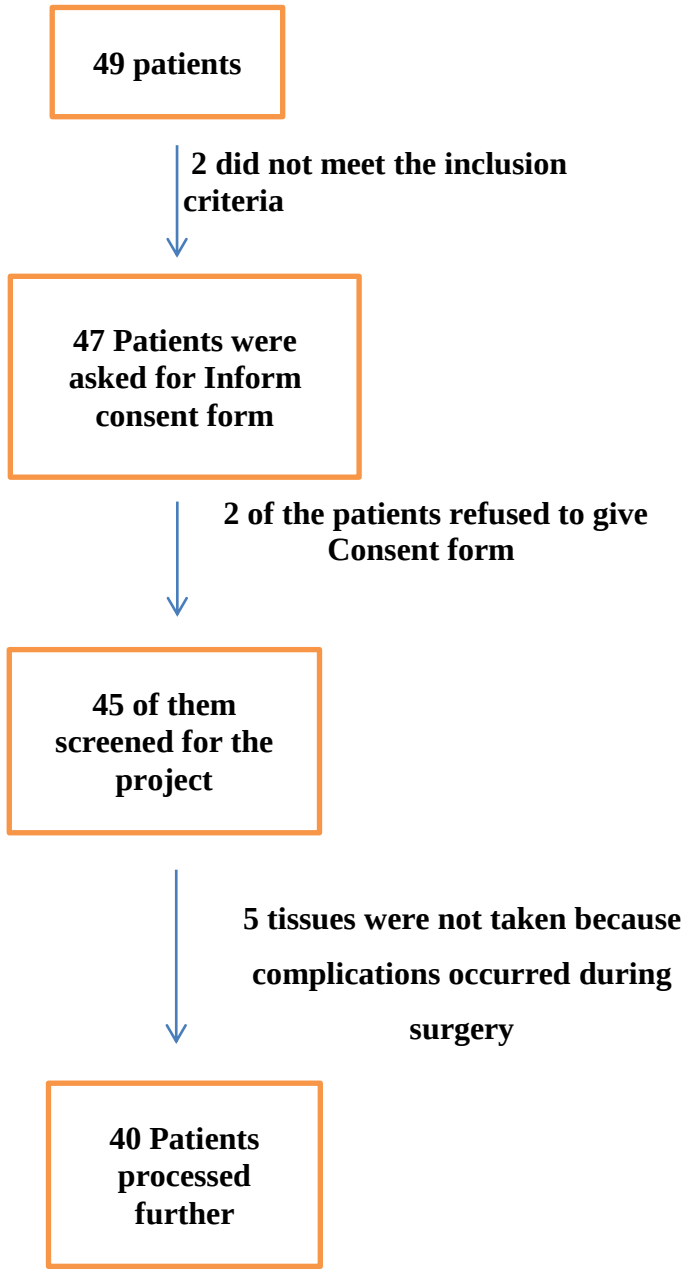


5.3.6.2b Distribution of diabetic patients according to %LDL

B: Prospective Study:

Result:

49 patients underwent bariatric surgery from January 2016 to March 2016. On enrolment, 2 did not meet the inclusion criteria;hence 47 patients were asked to give their consent. 2 patients refused to provide consent and hence 45 patients were enrolled in the study. Out of these 45, 5 tissuessamples could not be taken since they developed some complications during the surgery. Hence 40 patients were finally recruited in the study. (Figure 5.1B)



5.4 Demographic Details:

5.4.1 Sample size and Gender:

Table 5.4.1 shows that there were 40 patients enrolled in the study. There were 15 diabetic and 25 non diabetic patients.

Table 5.4.1 Distribution of gender

Gender	Diabetic(N)	Non-Diabetic(N)
Male	10(66.66%)	10(25%)
Female	5(33.33%)	15(75%)
Total	15(100%)	25(100%)

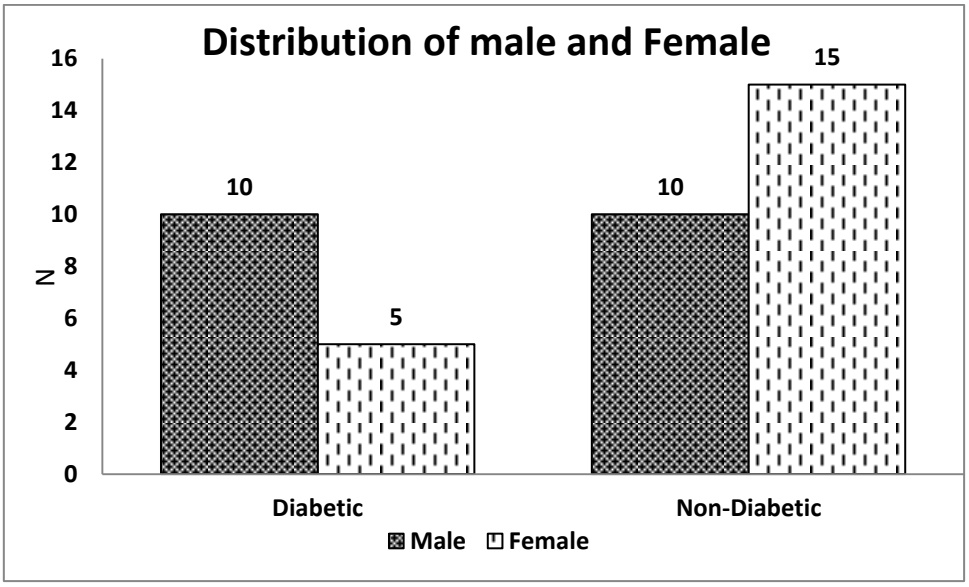


Figure 5.4.1 Distribution of gende

5.4.2 Occupation:

There were 40 patients and table 5.4.2 shows that from them 7.31% were retired, 4.87% were students, 24.39% were doing job, 34.14% were house maker, 24.39% were having business and 4.87% were farmer.

Table 5.4.2 Occupation

Occupation	N
Retired	3(7.31%)
Student	2(4.87%)
Job	10(24.39%)
Housewife	14(34.14%)
Business	10(24.39%)
Farmer	2(4.87%)
Total	41(100%)

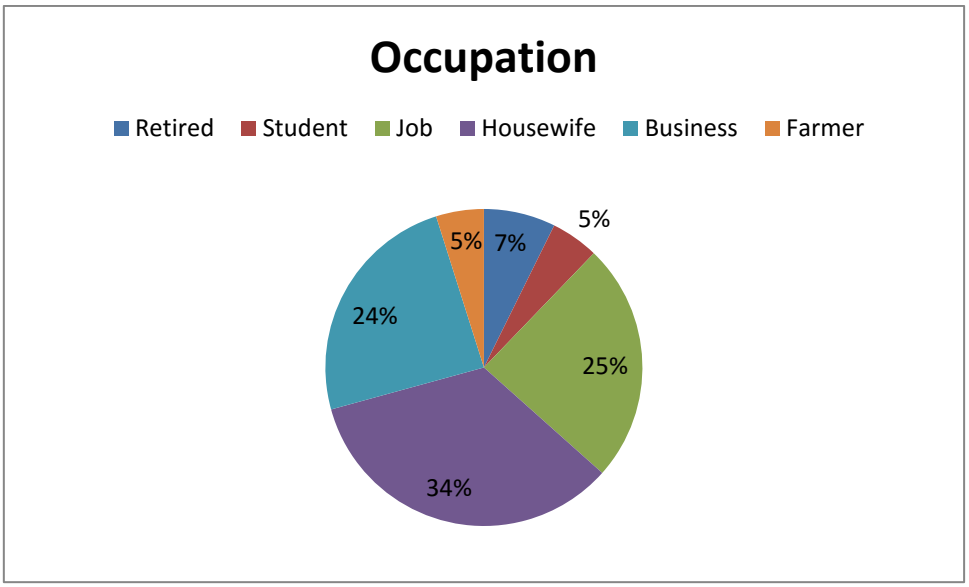


Figure 5.4.2 Occupation

5.4.3 Marital Status :

Table 5.4.3 shows that out of 40 patients, 34 were married and 6 were unmarried.

Table 5.4.3 Marital Status

Marital Status	N (%)
Married	34(85%)
Unmarried	6(15%)
Total	40(100%)

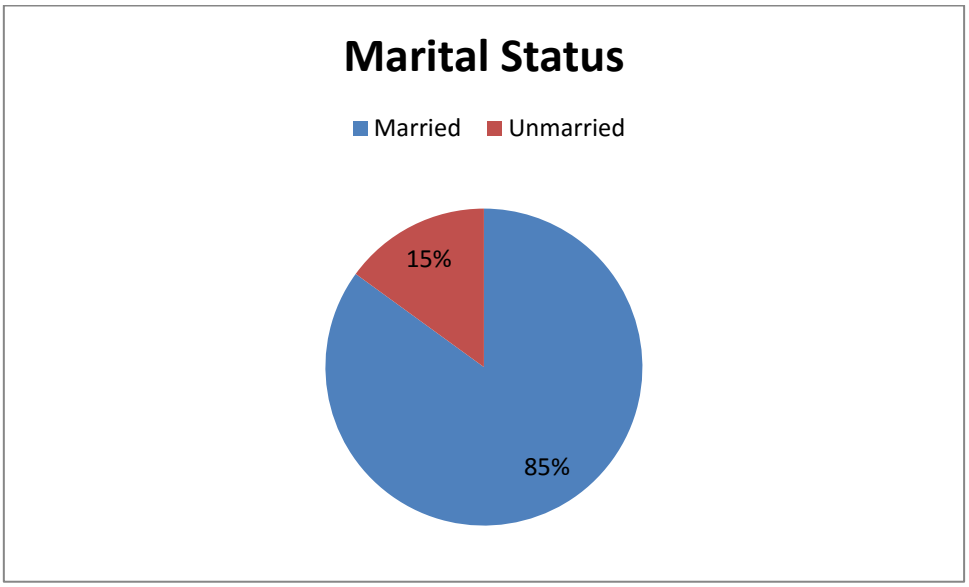


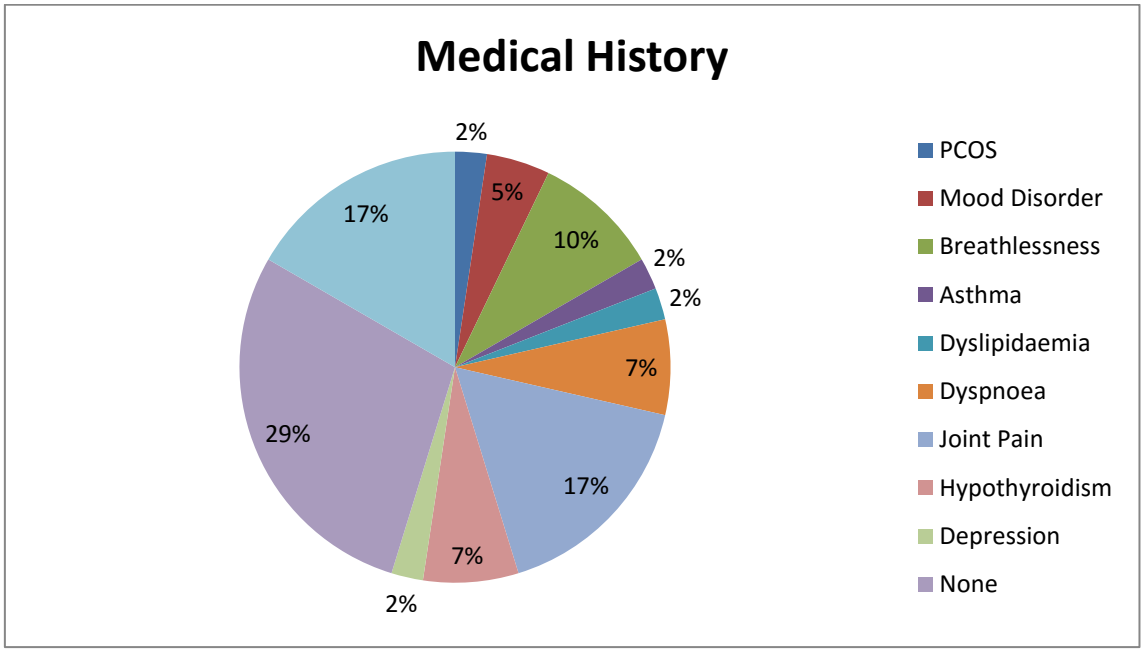
Figure 5.4.3 Marital Status

5.5 Medical History:

Table and graph 5.5 show Medical history of 40 patients. 1 patients was having PCOS, 2 were having mood disorder, 4 were having breathlessness. Asthma and dyslipidaemia was in one patients each and dyspnoea was in 3 patients. 7 patients were having joint pain and 3 were having hypothyroidism. Depression was observed in 1 patient. 7 patiets had some kind of allergies and 12 had none of them.

Table 5.5 Medical History

PCOS	1
Mood Disorder	2
Breathlessness	4
Asthma	1
Dyslipidaemia	1
Dyspnoea	3
Joint Pain	7
Hypothyroidism	3
Depression	1
None	12
Allergy	7



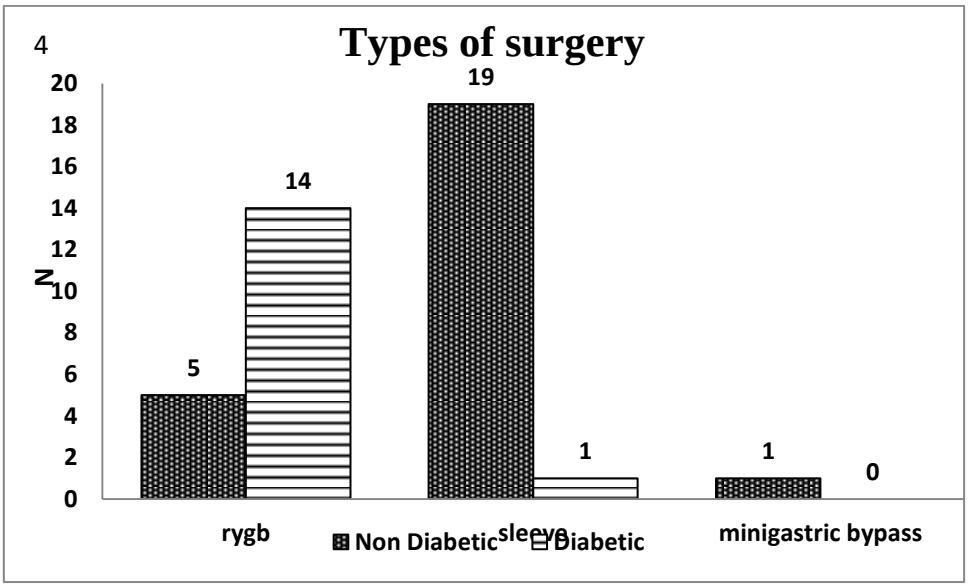
5.5 Medical History

5.6 Type of Surgery:

Diabetic Patients: Table 5.6 shows that out of 14 diabetic patients, RYGB was carried out in 14 patients and 1 patient was operated with sleeve gasterectomy. Out of 25 non diabetic patients, Sleeve gasterectomy was carried out in 19 patients, RYGB was performed in 5 patients and mini gastric bypass was performed in 1 patient.

5.6 Type of Surgery

Surgery	rygb	sleeve	minigastric bypass	Total
Non Diabetic	5	19	1	25
Diabetic	14	1	0	15



5.6 Types of surgery

Discussion:

Present study was carried out to determine alterations in biochemical parameters in the patients undergoing bariatric surgery and determine gene polymorphism. The study has two sections: First section involves retrospective data analysis of patients undergoing bariatric surgery between May 2015 to December 2015. In the present study, 64 patients were non diabetic and 43 patients were diabetic making it to 107 patients.

It was observed that in non-diabetic patients, sleeve gasterectomy (58%) was preferred and in Diabetic patients, Roux en Y Gastric bypass was preferred (51%) Sleeve gasterectomy is now a days popular surgery for the obese patients. It is observed that sleeve decreases the weight faster than other surgeries. This is more preferable because half of the weight loss is achieved because of reduction in stomach volume and another is thought to be reduced because of change in the levels of Ghrelin-the hunger hormone. (Mehmet et al, 2015) Sleeve gasterectomy offeres advantages on other surgeries like easy procedure, rapid weight reduction and relatively short stay in hospital.RYGB is a combination of restrictive and malabsorpive surgery. It is proposed that changing in the engineering of the stomach and intestine might change the levels of hormones in the stomach and gut-mind communication. This may result in blood sugar control. (Saeidi et al., 2013). Despite of the hypothetical mechanisms, RYGB is most recommended surgery. RYGB offers some advantages like significant long term weight reduction, increase inenergy depletion, diabetes remission, more than 50% weight loss and some dis-advantages like it is a complicated procedure, certain vitamin deficiencies occurs after RYGB. ('Bariatric Surgery Procedures - ASMBS', n.d.)(Thomas et al, 2012 It has some disadvantages like it is not reversible procedure and might cause long term vitamin deficiencies.

As per World Health Organization, weight is classified as normal [18.5-24.9]l, overweight[25-29.9], obesity (Type 1) [30-34.9], Obesity(Type II)[35-39.9], Morbid Obesity [>=40]- and super obesity[>=50]. BMI is a parameter which determines the obesity and overweight. Thus it is an important parameter to classify obesity. Moreover if a person is obese, he/she might get other complications like diabetes mellitus, hypertension, joint pain, polycystic ovarian syndrome, and certain cancers. In current study, Weight loss was observed in both groups i.e. diabetic and non-diabetic. In both non-diabetic and diabetic patients, BMI decreased significantly after 3 months ($P<0.01$)

and after 6 months ($P<0.01$). However there was no statistically significant reduction in BMI in diabetic patients between 3 and 6 months after the surgery while in non-diabetic patients, there was significant reduction in BMI between 3 and 6 months. Thus we can say that in non-diabetic patients, weight loss is consistent than in diabetic patients. A study reported that bariatric surgery decreases weight loss significantly compared to other obesity treatments in non diabetic patients. (James et al, 2012) Another study carried out in patients who were diabetic and bariatric surgery was performed in them. It was observed that BMI decreased from preoperative mean 137 kg to 87 kg by 1 year. (Pories et al, 1995) Our study is consistent with other studies done on diabetic as well as non-diabetic patients. It is proposed that control might occur in weight loss because the caloric intake has decreased after bariatric surgery and food intake is also decreased after bariatric surgery which promotes weight loss. (Long et al, 1994)

Diabetes is characterised by increase in fasting blood sugar levels. Normal range of fasting blood sugar is less than 100. In our study fasting blood sugar decreased significantly and it was reported normal after the second follow up i.e. 6 months in Diabetic patients. It was noticed that in non-diabetic patients fasting blood sugar decreased significantly after 3 months and remained normal after 6 months. One study showed the same result that patients FBS returned to normal range after 3 months of the bariatric surgery. (An et al. 2013) Another study showed that after bariatric surgery, fasting blood glucose decreased from clearly diabetic value to normal levels. (Dixon et al, 2008) Some of the hypotheses given are: 1. Increased postprandial secretion of L-cell peptides like GLP-1 2. Exclusion of proximal small intestine form nutrient flow which down regulates the anti-incretin factors 3. Impaired ghrelin secretion. 4. Changes in intestinal nutrient-sensing mechanisms regulating insulin sensitivity. (Rubino et al, 2006)

Glucose levels in diabetic patients are important factor to look after. HbA1c is an important biomarker which gives an idea to the clinician about average blood sugar have been over a period of weeks or months. (Diabetes CO UK) HbA1c is important to observe in diabetic patients because higher the HbA1c, higher would be the complications in the patients. (Glycated Haemoglobin, Patient info). In the present study, the mean of HbA1c in diabetic patients was found 8.42 at baseline which reduced significantly after 3 months and 6 months. It indicates the remission of diabetes in the

patients. In our study, after 3 months 37.2% patients had good control, 55.81% of the patients had fair control after the surgery. After 6 months, it was found that 51.16 % of the population had experienced complete diabetes remission i.e. HbA1c<6.0%. 48.83% had fair control i.e HbA1c 6-6.7%. It has been reported in one meta-analysis done by Buchwald et al in 2009 in The United States of America that 89% of the patients reported complete remission of type II diabetes mellitus. (Buchwald et al, 2009). Another study conducted by Sjstrom et al(2014) in Sweden reported that in non-surgical patients the remission was 16.4% while in bariatric patients the remission was 72.3% within 2 years of the bariatric surgery. (Sjstrom et al., 2014) This indicates that there is difference in terms of diabetes remission in Indian population. This different might be attributes to the fact that diabetes in Indian population is quite different than American and European (Unjali et al, 2012). South Asians are shown to be shown to be more insulin resistant than Caucasian populations even at younger ages and lower levels of BMI. Some of this increased propensity for insulin resistance in South Asians might be attributed to greater deposition of visceral fat in South Asians as compared to Caucasians (Gujral et al 2013). Thus, the this might be possible mechanism behind lesser percentage of patients experiencing complete remission of diabetes in present study. In India, certain studies have been performed to see the effect of bariatric surgery on diabetic patients. Study carried out by Chowbey et al (2010) showed that after sleeve gasterectomy, 73.9% of the patients experienced diabetic remission. A study done by Raj et al (2010) showed that after sleeve gasterectomy, 63% of the patients experienced remission. Another study showed that after RYGB, 80 of the patients observed diabetes remission after 3 months and after 6 months it was 100%. (Shah et al, 2010) In our study, we found complete remission in 51.16% of patients. The reason behind difference in terms of less number of patients getting complete remission might be because we have studied the effect till 6 months. It is possible that on long term, more patients may be remitted completely. There are difference between Indiana and other population. Prevalence of Type II diabetes is higher in south Asians and is rising rapidly. There are many differences in the populations like physical activity, diet and other behaviours. (Gujaral et al, 2012) Our results are not that similar to the reports available.

Lipid profile is an important factor which is useful for broad medical screening of abnormalities in lipids, such as cholesterol, triglycerides, HDL, VLDL and LDL. The result of this test can be useful for determining the risk of cardiovascular diseases. (Cardiovascular Risk reduction guidelines- NHLBI, NIH) Cholesterol is an essential lipid component of cell membrane. High cholesterol levels may promote atherosclerosis and heart disorders. It is an important biomarker for cardiovascular disorders. (Cholesterol Metabolism). In the present study, cholesterol levels were significantly reduced in diabetic group after 6 months but in non-diabetic patients the significant difference was not observed. After bariatric surgery, it is observed that the cholesterol levels decline and improves the cardiovascular functioning. Our study was in contrast with a study performed by Brolin et al (2011), Nguyen et al (2007) and Dixon et al (2009). They all have reported that after bariatric surgery the level of cholesterol reduced significantly in non-diabetic patients. These differences might be attributed to types of surgery being carried out. One study carried out on diabetic patients showed reduction in total cholesterol levels after bariatric surgery (Alberto et al, 2013). Also, reduction in cholesterol levels were seen after 6 months in study by Bela et al. (2010). Thus, in diabetic patients, our data are in consistence with other reports.

Low density lipoprotein is negatively co-related with heart functioning. More LDL, higher will be the risk of cardiovascular problems. Obese people are having increased risk of having metabolic disorders, coronary heart diseases and LDL and VLDL plays a role in these diseases. In our study, there was significant change in LDL levels after 6 months in diabetic patients and in non diabetic patients there was significant change after bariatric surgery. The LDL levels reports is available in accordance with our result in which one study showed decreased level of LDL after bariatric surgery (Alberto et al, 2013). In contrast to this, studies carried out by Dixon et al.(2009) and Hanusch et al.(2004) showed that after bariatric surgery there was no change observed in the level of LDL. It was in contrast with our result, which might be due to difference in obesity pattern in Indian population.

Triglycerides are fat in the blood and is useful for providing energy to the body when needed. They are stored in different places in the body and released whenever it is needed. Higher levels of triglycerides may lead to heart diseases. (WebMD, Cholesterol and Triglycerides Health Center). In the present study, in both diabetic and non-diabetic

patients, triglycerides decreased significantly after 6 months. One study showed that triglyceride levels constantly reduced after the weight loss surgery (Buchwald et al, 2004). Greater impact was seen with RYGB surgery. Mechanism is may be because of gut microbacteria alteration which occurs after exogenous changes in diet and altered luminal pH. (Zhang et al, 2009) Another study done by Nguyen et al (2006) also showed the same result with triglycerides. One study showed that after bariatric surgery, triglycerides reduced after 3 months in non-diabetic patients. i.e. 53%. (Carswell et al, 2015) Another study carried out on diabetic patient showed that after 1 year triglycerides levels decreased subsequently to 100mg/dL and 80.6% had normal range of triglycerides. (Pedro et al, 2013)

In the present study, high density lipoprotein increased significantly in diabetic patients after 6 months of bariatric surgery. However in non-diabetic patients, there was no statistical significance found between baseline and 3 months follow up as well as at 6 months follow up. A study done by Griffo et al (2012) in 19 obese diabetic patients showed that, HDL level increased after bariatric surgery. This was in consistent with our study. One study done by Buchwald et al (2004) and Sjatrom et al(2004) showed increased amount of HDL after bariatric surgery in non-diabetic patients.. It increased from 13% to 47% after weight loss surgery. Therefore, we can say that our data is in contrast with other studies with respect to non-diabetic patients. It is reported that South Asians not only have lower HDL levels but also have a higher concentration of small, less-protective HDL particles (Bhalodkar et al 2004). Asian Indian males have a higher prevalence of low HDL2b than non-Asian Indians, which suggests impaired reverse cholesterol transport (Superko et al 2005). Thus, these difference in terms of HDL may be responsible for contrasting results in present study.

The data were analysed for other biochemical parameters like creatinine levels, alkaline phosphate levels, TSH levels, Urea levels, vitamin B_{12} and Vitamin D_3 . In present study, there was no significant change observed after 3 and 6 months compared to baseline after bariatric surgery.

It is observed that iron deficiencies occur after bariatric surgery. However, because patients are prescribed supplements after the surgery, deficiencies are not observed in the present study.

The limitations of the study are that we could obtain the data upto six months post-surgery. Long term studies might give better results and more predictive indicators of response to bariatric surgery. Also, we do not have the data with respect to the anti-diabetic medications been taken by the patients which might act as confounders for the study. For gene polymorphism, we could carry out the SNP study of only 7 patients. More number of sample analysis is required to confirm the variation data.

Conclusions:

In conclusion our study suggests that obesity leads to many complications and bariatric surgery is useful in treating those complications. In the retrospective study, one major effect observed in the study was complete remission of diabetes after bariatric surgery in 51.16% of the patients.

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