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Study of Correlation of Obesity Indices and Oral Hypoglycemic Drugs Response, in Patients of Type 2 Diabetes Mellitus

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The research work was planned to correlate the obesity parameters (i.e. body mass index (BMI), waist to hip (W/H) ratio and percentage body fat (%BF)) with dosages of oral hypoglycemic drugs for good control in type 2 diabetes mellitus patients. Out of all seventy patients (32 males and 38 females), of age group 32-65 years, 34 patients were classified as obese and 36 as non-obese on the basis of percentage body fat and no significant difference in W/H ratio, BMI, fasting and post prandial glucose levels. Age of 57 out of 70 diabetic patients was > 40 years, and half of them were seen to be obese. All obese patients > 40 years had significantly high BMI as compared to non-obese > 40 years. Forty four (63%) patients showed good control, 17 (24%) had bad-control while 9(13%) were of borderline control of diabetes. Among good control patients, non-obese patients showed significantly ($P < 0.01$) lower incident of increase W/H ratio and higher BMI while bad control and borderline patients showed non-significant distribution. Fasting and postprandial glucose levels (PGL and PPGL) of both good control-obese and bad control-obese patients were significantly higher as compared to good control-non-obese and bad control-non-obese patients. All the 70 patients in this investigation were on hypoglycemic drugs, 11 patients (4 obese and 7 non-obese) on sulfonylurea showed good control on low dosage, whereas good control was seen in 33 patients on high dosage of in metformin and combination therapy of sulfonylurea and metformin irrespective of obesity of the patients, indicates insulin resistance. Thus, insulin resistance may be due to some other factors rather than the obesity and failure of release of insulin.

Key words: Diabetes mellitus, obesity, hypoglycemic drugs, PGL, PPGL

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Introduction

Type 2 diabetes mellitus is a metabolic disease which is characterized by insulin resistance and hyperglycemia often associated with hypertension, lipid disturbance and obesity. The underlying pathology of type 2 diabetes mellitus appears to be increasing resistance either due to abnormal insulin structure, receptor defects, anti-insulin or anti-receptor antibodies or higher concentration of insulin antagonists (Ross., 1996). In type 2 diabetes mellitus, the most patients are over 40 years age and obese. Polyuria, polydipsia being common symptoms while ketonuria and weight loss generally are uncommon at the time of diagnosis (Frier *et al.*, 1999; Gorden, 1997).

It has been observed that obesity predisposes to type 2 diabetes mellitus, by causing insulin resistance (Walker, 1995). The obese type 2 diabetic patients, besides peripheral insulin resistance there are diminished pancreatic reserves or secretory defect in the pancreatic β cells, resulting in a failure to respond normally to alleviated glucose levels (Laker, 1996; James and Pearson, 1998).

Many oral drugs have been developed which either enhance the release of insulin from pancrease or act peripherally, reducing the level of blood glucose. Till 1997, FDA (Food and Drug administration) approved 4 classes of oral hypoglycemic drugs. These are: sulfonylurea (by stimulating pancrease to secrete more insulin), biguanides (by combined effect of reduced intestinal glucose absorption, decreased gluconeogenesis increased anaerobic glycolysis and enhanced muscle uptake of glucose), α glucosidase inhibitors (by delaying the digestion of complex carbohydrates) and insulin sensitizes (Thiazolidinediones) (by reducing insulin resistance in peripheral tissues) (Karam, 1998; Balfour and Tavish, 1993; Ten *et al.*, 2000). Obesity may be defined as a condition, in which there is excessive amount of fat. It is determined by measurement of body mass index (BMI), waist/hip ratio and percentage body fat (Baron, 1998). BMI is the body weight (Kg) divided by height (m^2). It has been reported that there is an international consensus that 20-24.9 is a desirable range, BMI > 25 is overweight or obese (Baron, 1998). Waist to hip ratio greater then 0.8 in women and greater than 0.9 in men indicated abnormal fat distribution and had greater risk of diabetes and obesity (Kissebah *et al.*, 1989; Lapidus *et al.*, 1984). Obesity is estimated by percentage body fat by measuring of skin fold thickness in different areas, particularly around triceps, biceps, subscapular and suprailliac. Percentage body fat can be determined from the standard nomogram. In males > 20% body and in females > 30% body fat is considered to be obese. However people might be over the weight limit for normal standards, but if they are muscular with low body fat they are non-obese. Therefore, it appears that percentage body fat may be the only reliable criteria of obesity. (Marley, 1982; Caro *et al.*, 1989). In the presence of insulin resistance requirement for hypoglycemic drugs for proper control of blood glucose levels is expected to be higher.

However, to the best of my knowledge, no study in Pakistan, on effect of obesity, on dose requirement of oral hypoglycemic drugs are available, nor any data about insulin resistance due to obesity has been reported. Thus this work was planned to correlate the dosage of oral hypoglycemic drugs needed for good control of type 2 diabetes mellitus with obesity parameters.

Materials and Methods

Seventy already diagnosed type 2 diabetic patients (32 males and 38 females) on oral hypoglycemic drugs were attending diabetic clinic of Shaikh Zayed Hospital, Lahore included in this investigation. Blood samples of each patient (fasting and postprandial (after two hours breakfast and oral drugs) were taken in EDTA (Ethyldiamine Tetra acetate) fluoride tubes and plasma pre-served for glucose estimation. Glucose was determined by enzymatic method, GOD-PAD method, (SERA-PAK Glucose KIT) (Trinder, 1969).

Twenty three (33%) patients were on sulfonylurea, 18 (26%) on metformin and 29 (41%) on combination of sulfonylurea and metformin. Patients on 1½ tablets of sulfonylurea or metformin and 1½ tablets sulfonylurea, one tablet of metformin were classified as low dosage. Patient having fasting glucose level of < 140mg dl^{-1} and PPGL< 200mg dl^{-1} were classified as good control of diabetes while patient showing both fasting PGL and PPGL above good control levels was taken as bad control, while patient showing one of the value above good control level were classified as bad control (Krall, 1978; Hill, 1987). Statistical applications were followed by using student's t test and chi square test (Walpole, 1999).

Results and Discussion

Out of total of 70 diabetic patients 34 were classified as obese and 36 as non obese on the basis % body fat. Mean age of non obese patients was significant (P> 0.01) higher as compared to obese group (Table 1). Out of obesity parameters only mean % body fat was significantly (P< 0.001) higher in non obese group while BMI only showed a non significant increase.

Table 1: Age, BMI, W/H, % BF, PGL and PPGL of obese and non-obese male and female diabetic patients were recorded. Mean and ± SE are given. Figures in parenthesis indicated the number of obese and non-obese patients.

Age Yrs.	BMI Kg m^{-2}	W/H Ratio	%BF	FGL mg dl^{-1}	PPGL mg dl^{-1}
		Obese (34)			
44	22	0.89	28.27	147	194
± 1.59	± 0.6	± 0.007	± 0.97	± 9.39	± 8.94
		Non-Obese (36)			
51**	20.16	0.88	18.83*	150	192
± 1.77	± 0.55	± 0.008	± 1.01	± 10.26	± 10.61

* P< 0.001 **P< 0.001

BMI, body mass index
W/H, waist to hip ratio
% BF, body fat
FGL, fasting glucose level
PPGL, postprandial glucose level

Higher age group of non obese patients could be due to longer standing of diabetes with weight decrease due to either dietary measures or longer period of uncontrolled diabetes in this research work. Steven *et al.*, (1994) had also reported that % BF being a more consistent index of obesity and showed diabetic risk than BMI and as W/H ratio.

Mean fasting and 2 hrs. FGL and PPGL in obese and non obese patients were 147 ± 9.39mg dl^{-1}, 194 ± 8.94mg dl^{-1} and 150 ± 10.26mg dl^{-1}, 192± 10.6mg dl^{-1}, respectively,

Table 2: Age, BMI, W/H % BF, PGL and PPGL of obese and non-obese male and female diabetic patients were recorded. Figures in parenthesis indicated the number of patients (upto to 40 and above 40 years).

Age Yrs.	BMI Kg m^{-2}	W/H Ratio	%BF	FGL mg dl^{-1}	PPGL mg dl^{-1}
	Obese patients up to 40 years (5)				
37 ± 1.53	22.1 ± 1.22	0.85 ± 0.013	25.88 ± 2.66	126 ± 17.71	167 ± 16.67
	Now-Obese patients up to 40 years (8)				
38 ± 1.035	21.1 ± 1.001	0.83 ± 0.021	20.26 ± 2.51	139 ± 16.91	157 ± 18.44
	Obese patients above 40 years (29)				
55 ± 1.44	21.9 ± 0.59	0.85 ± 1.037	28.67 ± 1.037	151 ± 10.52	197 ± 9.92
	Now-Obese patients above 40 years (29)				
53 ± 1.15	19.78** ± 0.72	18.42* ± 1.082	18.42* ± 1.082	127 ± 6.67	183 ± 11.07

* P< 0.001 **P< 0.05

Table 3: FGL and PPGL of obese and non-obese and non-obese diabetic patients taking oral hyperglycemic drugs and their good, bad and borderline control. Figures in parenthesis indicated number of patients.

Control	Group	FGL mg dl^{-1}	PPGL mg dl^{-1}
Good 44	Obese (21)	123 ± 4.32	167 ± 5.10
	Non-obese (23)	103* ± 4.81	147** ± 7.20
Bad 17	Obese (10)	198** ± 24.23	255**** ± 16.20
	Non-Obese (7)	162*** ± 15.10	253*** ± 25.46
Borderline 9	Obese (3)	150**** ± 3.17	179 ± 6.64
	Non-Obese (6)	151 ± 5.19	180***** ± 11.87

* P< 0.05, ** P< 0.01, *** P< 0.0001, **** P< 0.001, ***** P< 0.05

Table 4: Percentage and number of obese and non-obese diabetic patients with their w/h ratio and body mass index with respect to their good, bad and borderline control.

	Obese 34 (49 %)			
Group	Low 11 (32 %)	High 23 (68 %)	Low 11 (32 %)	High 23 (68 %)
Good control 21	5	16	5	16
Bad control 10	5	5	5	5
Borderline control 3	1	2	1	2
	Non-Obese 36 (51 %)			
Good control 23	16*	7	23	---
Bad control 7	4	3	5	2
Borderline control 6	3	3	4	2

*P< 0.01

Table 5: The number and percentage of diabetic parents with percentage body fat with their respective dose level and control.

	Obese 34 (49 %) Level of dose of oral hypoglycemic drugs	
Group	Low (4)	High (30)
Good control 21	4	17
Bad control 7	----	10
Borderline control 3	----	3
	Non-obese 36 (51 %)	
Group	Low (10)	High (26)
Good control 23	7	16
Bad control 7	3	4
Borderline control 6	----	6

and no significant difference was noted between two groups (Table 1). Neither there was any significant difference in glucose levels in older (> 40 years) and younger subjects (< 40 years) (Table 2). BMI & % BF of obese subjects > 40 years age was significantly ($P < 0.001$ and $P < 0.05$ respectively) higher (Table 2). Bulpitt *et al*., 1998 worked on diabetes and reported that severity of diabetes increases with increasing BMI and % BF. Patients were divided into good, bad and borderline control groups of diabetes. Mean and ± SD of fasting and postpandid glucose levels (FGL and PPGL) are given. Statistical comparison were made with the good control group only. It was in general obesity could not be related to the control states of diabetes (Table 3). Obese good control patients (n= 21) showed significantly ($P < 0.05$) higher fasting and postprandial glucose levels when compared with non-obese good control patients (n= 23) (Table 3). It has been earlier reported by Borkan *et al.* (1986) that obese diabetes have significantly higher fasting and postprandial glucose levels. Also Jacobs *et al*. (1997) worked and proved that obesity is positively associated with high concentration of blood glucose showing that obesity is a risk factor for poor glycemic control. Among good control patients, non-obese patients showed significantly ($P < 0.001$) lower incident of both increased waist hip ratio and higher BMI (Table 4), while bad control and borderline patients showed non-significant distribution when compared according to low and high W/H ratio and BMI thus it appears that bad control is not related to obesity but may be due to inadequate dosage of hypoglycemic drugs and this study has already been reported by Bruno *et al.* (1998) (Table 4).

Obesity does not appeared to be related to increased insulin resistance as almost equal number of obese (17) and non-obese (16) subjects required high dosage for good control (Table 5). However, it has been earlier reported by Defronzo (1988); Lea and Morely (1998); Ten (2000) that type 2 obese patients respond to high dosage of oral hypoglycemic drugs due to insulin resistance. Table 6 showed that 7 out of 8 good control non-obese diabetics were on low dosage of sulfonylurea while 4 out of 6 obese patients with good control

Group	Low dose 4	High dose 4	Group	Low dose 4	High dose 4
Good control 6	4	2	Good control 8	7	1
Bad control 1	----	1	Bad control 4	3	1
Borderline control 1	----	1	Borderline control 1	----	3

Metformin 18 (26 %)

	Obese 11			Non-Obese 7	
Group	Low dose	High dose 11	Group	Low dose	High dose 7
Good control 7	----	7	Good control 6	----	6
Bad control 4	----	4	Bad control 1	----	----
Borderline control 4	----	----	Borderline control 1	----	1

Sulfonylurea + Metrofmin 29 (41 %)

	Obese 15			Non-Obese 14	
Group	Low dose	High dose 15	Group	Low dose	High dose 14
Good control 6	----	8	Good control 9	----	9
Bad control 1	----	5	Bad control 3	----	3
Borderline control 1	----	2	Borderline control 2	----	2

were on low dosage of sulfonylurea. While all 7 obese diabetic patients and 6 non obese diabetics showed a good control on high dosage of metformin and 4 obese diabetic subjects showed a bad control even on high dosage metformin. All 29 patients on combination therapy in this study were on high dose of sulfonylurea and metformin with 8 obese and 9 non-obese showing a good control. It appeared that all combination therapy patients originally belong to insulin resistance, thus needing high dosages of oral hypoglycemic drugs. Smith and Aronson (1984) have reported a better control of hyperglycemic by combination therapy in patients who do not response to even high dosage of sulfonylurea.

Thus it can be concluded that bad control of the patient could not be related to obesity, rather it reflects under dosage or non-compliance of oral hypoglycemic drugs. For achieving good control proper dosage must be determined and this should be determined only by response of the patient. Many diabetes might become non-obese due to poor control by utilizing the body fat instead of glucose.

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