ABDOMINAL ADIPOSITY AND METABOLIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

The incidence of type 2 diabetes mellitus as well as its related morbidity and mortality has been well correlated with generalised obesity, measured by body mass index (BMI). However, recent research emphasizes the role of central/abdominal adiposity measured by waist circumference (WC) or waist: hip ratio (WHR) as a risk factor. Our aim was to investigate the association of overall overweight/obesity as indexed by BMI and abdominal adiposity as indexed by WHR with the metabolic control of 50 type 2 diabetes mellitus subjects. We evaluated the metabolic control in 50 type 2 diabetes mellitus subjects, ages 45 to 65 years, by estimating the blood glucose levels, glycated haemoglobin levels (HbA_{1C}), lipid and lipoprotein levels. Students 't' test was used to determine the associations between BMI, WHR and the metabolic status of diabetic subjects. Hyperglycemia and dyslipidemia were apparent in all the subjects. No distinct changes in blood glucose levels and lipids (except HDL-cholesterol) levels of the male subjects were noted with high BMI. Appreciable lowering of the HDL-cholesterol levels was however observed with an increase in BMI. In contrast, higher blood glucose values and highly significant increases in total cholesterol ($p<0.01$), LDL-cholesterol ($p<0.01$) with prominent decrease in HDL-cholesterol ($p<0.05$) levels was observed in overweight/obese female subjects. Also, the overweight/obese female subjects had significantly lower ($p<0.05$) apo A1 levels and a distinctly lower ($p<0.05$) A1:B ratio. Analyses based on WHR revealed highly significant increases ($p<0.05$) in the 2 hour post prandial blood glucose (PP_2BG) and HbA_{1C} levels of male subjects while slightly higher PP_2BG values were obtained for female subjects with high WHR. For both, male and female subjects, moderate deterioration of the lipid and lipoprotein profile was noted in relation to high WHR. The influence of generalized overweight/obesity versus abdominal obesity was also evaluated. Blood glucose levels were appreciably elevated in the abdominally obese male subjects. Unfavourable alteration in the lipid profile of the male subjects with high WHR was also noted. No such distinct differences of the effect of BMI and WHR on the glycemic and lipemic status of female subjects was observed. These results indicate that metabolic de-control in the diabetic state is observed with increases in both, BMI and WHR. However, the effect is more pronounced in type 2 diabetic subjects with high WHR.

KEYWORDS: Type 2 diabetes mellitus, BMI, WHR, Glycemic control, Lipemic status

INTRODUCTION

Obesity is the most powerful environmental risk factor for type 2 diabetes mellitus [1,2] and body mass index (BMI) is a standard predictor of diabetic status, plasma glucose and glycated haemoglobin (HbA_{1C}) concentrations in populations at risk for type 2 diabetes mellitus [3]. The prevalence of diabetes is 2.9 times higher in overweight (BMI $\geq$ 27.8 in men and $\geq$ 27.3 in women) than in normal weight subjects 20 to 75 years of age [2,4]. However BMI, one of the most commonly used indicator of obesity, is not a perfect one since it does not take into account the body fat pattern [5]. Recently, an understanding of the importance of regional fat distribution, particularly abdominal obesity, as a risk factor for metabolic diseases has become a matter of extensive investigations.

Abdominal obesity, measured by an elevated waist to hip ratio (WHR), is shown to be a strong risk factor for type 2 diabetes mellitus [6]. Prospective studies also support the association of various anthropometric indices of abdominal adiposity and the future development of diabetes [7,8]. It has been suggested that abdominal adiposity is an independent predictor of alterations in the plasma lipid, lipoprotein and plasma glucose concentrations [7,9-11].

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There appears to be a biologically plausible metabolic basis for the detrimental influence of abdominal adiposity. High proportion of upper-body fat or abdominal fat, independent of overall obesity, is recognised as an important component in the insulin resistance linked to obesity and type 2 diabetes mellitus [8,12,13]. Insulin resistance and hyperinsulinemia are associated with lipoprotein lipase (LPL) deficiency, which causes elevation in the levels of free fatty acids and a reduction in high-density lipoprotein cholesterol (HDL-C) levels. These elevated levels of free fatty acids may induce insulin resistance in the peripheral tissues and liver (8,14). Insulin resistance eventually produces sufficient glucose intolerance to result in frank diabetes (14).

The association of fat distribution with insulin resistance and the resultant metabolic de-control may however, differ with ethnicity. A few studies have suggested less influence of fat distribution on the carbohydrate and lipid metabolism for African-Americans compared to non-Hispanic white individuals, while other studies indicate a difference in the association [8]. Asian Indians (living in the United States) are more susceptible to developing abdominal adiposity and insulin resistance, which might account for the excessive morbidity and mortality from diabetes in this population [15]. However, the data in this area is scant and very less information on the influence of fat pattern on the metabolic status of Indian population is available.

This study was therefore planned to evaluate the association of both, overweight/ obesity and abdominal obesity on the metabolic control viz., glycemic and lipemic profile of type 2 diabetic subjects.

METHODS AND MATERIALS

Subjects: A total of 50 type 2 diabetes mellitus subjects (28 males and 22 females) were enrolled for the study. The subjects were recruited from the Diabetic Clinic of Vadodara. The mean age of the male and female subjects was 55.9 ± 6.5 and 52.1 ± 9.2 years respectively. The duration of the disease was 15.4 ± 5.4 years for the male subjects and 11.2 ± 7.8 years for the female subjects. Information regarding the general habits of the subjects was obtained using a pre-tested, structured questionnaire.

Anthropometric Measurements: Height was measured without shoes to the nearest 0.5cm and weight of the subjects (without shoes) was measured on a pre-standardized weighing scale to the nearest 100g. Body mass index (BMI) was calculated using the formula weight (in kg) divided by height (in m^2). Waist and hip circumferences were measured to the nearest cm with a dressmaker's tape and the waist to hip ratio (WHR) was calculated.

Assay Methods: Venous blood sample of all the subjects was collected after an overnight fast. The blood sample collected with fluoride and EDTA preservatives was used for blood glucose and glycated haemoglobin (HbA_{1c}) analysis. The serum was used for the estimation of lipid profile. Diagnostic kits procured from Bayer Diagnostics, India were used for blood glucose estimations. The HbA_{1c} levels were determined by the Variant Hemoglobin A_{1C} Programme using the High Performance Liquid Chromatography Technique [16]. Randox Diagnostic kits procured from United Kingdom were used to estimate triglyceride (TG), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) (Direct method). Low-density lipoprotein cholesterol s(LDL-C) levels were obtained by calculation. Apolipoproteins (apo) A1 and B were measured on the Array Protein Systems [Beckman Instruments, USA] following the principle of antigen-antibody reaction by rate nephelometry.

Statistical Analysis: Results are expressed as means ± SD. Analysis of differences between the means was performed using students "t" test. All tests were considered significant at $p < 0.05$ level.

RESULTS

Table 1 shows the main characteristics of the study subjects. No difference between the sexes was observed with respect to physical activity. Smoking, alcohol and tobacco intake was more in male subjects than in the female subjects. The prevalence of overweight was more pronounced in both the sexes as compared to obesity, whereas the prevalence of abdominal obesity was higher in female subjects (72.7%) as compared to the male subjects (42.9%).

Table 1: Characteristics of the Study Subjects (Mean ± S.D)

Variables	Males	Females
n	28	22
Age (years)	55.9 ± 6.5	52.1 ± 9.2
Duration of diabetes (years)	15.4 ± 5.4	11.2 ± 7.8
Anthropometric Characteristics		
Weight (kg)	72.8 ± 7.0	61.0±12.5
Body Mass Index (BMI)*, kg/m^2	25.6 ± 2.4	25.9 ± 6.1
Waist Circumference (WC), cm	102.3 ± 15.6	92.6±15.5
Waist to Hip Ratio (WHR)$^+$	1.0 ± 0.1	0.9 ± 0.1
General Habits		
Non-Sedentary (No.(%) of subjects)	16 (57.1)	15 (68.2)
Smokers (No.(%) of subjects)	9 (32.1)	2 (9.1)
Alcohol users (No.(%) of subjects)	12 (42.9)	1 (4.5)
Tobacco users (No.(%) of subjects)	3 (10.7)	0 (0.0)
Prevalence, n (%)		
Overweight/Obesity, BMI>25 kg/m^2	14 (50.0)	11 (50.0)
Overweight, BMI = 25 to 29.9 kg/m^2	13 (46.4)	7 (31.8)
Obesity, BMI $\geq$ 30 kg/m^2	1 (3.6)	4 (18.2)
Abdominal Obesity $	12 (42.9)	16 (72.7)

** BMI = Weight (kg)/ Height (m)^2*
$^+$ WHR = Waist measurement (cm)/ Hip measurement (cm)
$ Abdominal Obesity was defined as waist/hip ratio $\geq$ 0.85 for women and $\geq$ 1.0 for men

Table 2: Influence of BMI and WHR on the Blood Glucose levels of Type 2 Diabetic Subjects (Mean ± SD, mg/dl)

Variables	FBG	PP_2BG	HbA_{1C} (%)		MBG
Males (n=28)					
Based on BMI					
BMI<25 kg/m^2(n=14)	158.9±47.3	243.6±53.3	8.5±0.8		198.3±27.7
Overweight/Obesity, BMI>25 kg/m^2 (n=14)	159.1±50.8	262.6±74.6	8.7±1.2		202.0±40.3
Overweight, BMI = 25 to 29.9 kg/m^2 (n=13)	158.2±52.8	260.0±77.0	8.6±1.2		199.8±41.1
Based on WHR					
WHR < 1.0 (n=16)	146.9±48.3	229.3±64.4	8.2±1.1		188.3±35.8
Abdominal Obesity, WHR $\geq$ 1.0 (n=12)	175.1±44.9	284.9±50.7#	9.1±0.7#		215.9±24.8#
Females (n=22)					
Based on BMI					
BMI<25 kg/m^2(n=11)	154.3±49.6	225.1±52.7	8.6±1.0		201.6±33.7
Overweight/Obesity, BMI>25 kg/m^2(n=11)	173.5±44.6	253.5±89.0	9.0±2.4		215.1±78.6
Overweight, BMI = 25 to 29.9 kg/m^2(n=7)	166.7±48.3	250.4±100.8	8.7±1.9		202.5±64.9
Based on WHR					
WHR < 0.85 (n=6)	160.2±59.9	224.2±32.0	8.6±2.1		199.5±59.0
Abdominal Obesity (WHR$\geq$0.85 cm) (n=16)	165.6±39.9	245.2±83.4	8.9±0.4		208.7±14.0

** MBG — Mean blood glucose*
 # Significantly different from subjects with normal WHR at $p < 0.05$

Based on the BMI, no changes in the fasting blood glucose (FBG) and HbA_{1C} levels of the male subjects was noted with respect to the degree of overweight/obesity. Moderate elevation in the PP_2BG levels was observed in the group of subjects with BMI > 25.0 kg/m^2 and BMI = 25.0 to 29.9 kg/m^2. In female subjects, FBG, PP_2BG and HbA_{1C} levels were higher in overweight/ obese subjects as compared to the normal weight subjects (Table 2). Between the sexes, no significant differences were noted in the blood glucose levels of the subjects.

Analyses on the basis of WHR (Table 2) revealed worsening of the glycemic control with abdominal obesity in male subjects. Highly significant increases in the PP_2BG levels (55.6 mg%, $p < 0.05$) and HbA_{1C} levels (0.9%, $p < 0.05$) were noted for subjects with WHR $\geq$ 1.0. The FBG and HbA_{1C} levels of the female subjects in the two groups based on WHR did not show much difference. A slightly higher value for PP_2BG levels was, however, noted in subjects with WHR $\geq$ 0.85. Comparison between the sexes revealed that abdominally obese male subjects had marginally higher (39.7 mg%) PP_2BG levels than the female subjects.

The influence of generalised overweight/obesity versus abdominal obesity was also evaluated. Higher values for FBG (16.0 mg%), PP_2BG (22.3 mg%) and HbA_{1C} (0.4 %) were obtained for male subjects with WHR $\geq$ 1.0 as compared to the subjects with BMI > 25.0 kg/m^2. No such differences in the effect of BMI and WHR on the blood glucose values of the female subjects were observed.

Dyslipidemia was apparent in all the subjects of both the sexes. As shown in Table 3, except for HDL-C levels, the lipid levels did not differ with BMI. Lower HDL-C values were obtained for male subjects with BMI > 25.0 kg/m^2 (1.1 mg%) and BMI > 25.0 to 29.9 kg/m^2 (4.3 mg%). In contrast, very highly significant increases in total cholesterol (TC) (47.6 mg%, $p < 0.01$ and 61.8 mg%, $p < 0.001$) and LDL-C (28.4 mg%, $p < 0.01$ and 31.6 mg%, $p < 0.01$) levels were observed in female subjects with BMI > 25.0 kg/m^2 and BMI > 25.0 to 29.9 kg/m^2 respectively. The TC and LDL-C levels of female subjects with BMI > 25.0 kg/m^2 were also significantly higher (33.8 mg%, $p < 0.05$ and 21.7 mg%, $p < 0.05$) than the male subjects of the same group. The HDL-C levels of the overweight/obese group of female subjects exhibited a significant decrease (16.3 mg%, $p < 0.05$) but were still significantly higher (4.0 mg%, $p< 0.05$) than the HDL-C levels of the male subjects.

Moderate deterioration of the lipid profile was observed in relation to the increase in WHR (Table 3). For both, male and female subjects, the triglyceride (TG) levels were elevated (27.0 mg% and 16.6 mg%) in subjects with high WHR ($\geq$ 1.0 and $\geq$ 0.85 respectively). Marginal reduction in the HDL-C levels was also noted for subjects with abdominal obesity. The male subjects had significantly lower (10.7 mg%, $p < 0.05$) HDL-C levels than the corresponding female subjects. As a result, in both the sexes, there was a small rise in the atherogenic indices of TC: HDL-C and LDL-C: HDL-C. Compared to the female subjects, the male subjects had significantly higher ($p < 0.05$) TC: HDL-C ratio.

Table 3 : Influence of BMI and WHR on the Lipid Profile of Type 2 Diabetic subjects (Mean ± SD, mg/dl)

Variables	TG	TC	HDL-C	LDL-C	T C:HDL-C	LDL-C:HDL-C
Males (n=28)						
Based on BMI						
BMI < 25 kg/m^2 (n=14)	178.4 ± 79.2	200.0 ± 38.7	43.4 ± 5.7	121.6 ± 28.8	4.8 ± 0.9	3.0 ± 0.8
Overweight/Obesity, BMI > 25 kg/m^2 (n=14)	185.1 ± 72.4	204.1 ± 29.5^a	42.3 ± 6.9 ^{a}	127.5 ± 30.5 ^{a}	4.8 ± 0.8	3.0 ± 0.8
Overweight, BMI = 25 to 29.9 kg/m^2 (n=13)	181.8 ± 81.3	206.3 ± 32.0	39.1 ± 6.6	126.2 ± 24.3	5.3 ± 1.1	3.3 ± 0.9
Based on WHR						
WHR < 1.0 (n=16)	170.2 ± 81.4	197.4 ± 33.5	42.3 ± 7.2	120.5 ± 28.9	4.8 ± 1.0	2.9 ± 0.8
Abdominal Obesity, WHR $\geq$ 1.0 (n=12)	197.2 ± 64.4	208.2 ± 34.8	38.6 ± 5.7^b	130.0 ± 30.1	5.4 ± 0.9 ^{b}	3.4 ± 0.9
Females (n=22)						
Based on BMI						
BMI < 25 kg/m^2 (n=11)	144.1 ± 55.9	190.3 ± 27.1	62.6 ± 15.1	120.8 ± 24.2	4.2 ± 0.8	2.6 ± 0.7
Overweight/Obesity, BMI > 25 kg/m^2 (n=11)	148.7 ± 83.9	237.9 ± 36.4**	46.3 ± 11.6*	149.2 ± 22.4**	4.5 ± 1.3	2.9 ± 1.1
Overweight, BMI = 25 to 29.9 kg/m^2 (n=7)	166.0 ± 91.8	252.1 ± 32.8***	56.5 ± 18.0	152.4 ± 15.5**	4.3 ± 0.8	2.7 ± 0.5
Based on WHR						
WHR < 0.85 (n=6)	134.3 ± 49.3	210.5 ± 38.8	57.2 ± 19.7	136.8 ± 24.9	3.9 ± 0.8	2.6 ± 0.7
Abdominal Obesity (WHR $\geq$ 0.85 cm) (n=16)	150.9 ± 76.8	215.4 ± 41.2	49.3 ± 14.7	134.3 ± 28.5	4.6 ± 1.1	2.9 ± 0.9

* *Significantly different from subjects with BMI < 25 kg/m^2 at p < 0.05*

** *Significantly different from subjects with BMI < 25 kg/m^2 at p < 0.01*

*** *Significantly different from subjects with BMI < 25 kg/m^2 at p < 0.001*

a *Significantly different from female subjects with BMI > 25 kg/m^2 at p < 0.05*

b *Significantly different from female subjects with abdominal obesity at p < 0.05*

The TG, TC, LDL-C (particularly in male subjects) and HDL-C (particularly in female subjects) levels of the groups with high BMI and high WHR did not show significant differences. However, in case of female subjects, marginally higher LDL-C values were seen in the group with high BMI (14.9 mg%) while in male subjects, noticeably lower HDL-C values (3.7 mg%) and higher TC: HDL-C ratio was obtained for subjects with WHR $\geq$ 1.0 as compared to overweight/obese subjects.

Table 4 shows the effect of BMI and WHR on the apolipoprotein status of type 2 diabetic subjects. The values of apo A1and B were not noticeably influenced by BMI in case of male subjects. However, apo A1 levels in male subjects was significantly lower (19.2 mg%, $p < 0.05$) when compared to the female subjects. Among the female subjects, overweight/obese subjects had significantly lower levels of apo A1 (29.8 mg%, $p < 0.05$) and as a consequence, significantly lower ($p < 0.05$) A1: B ratio than subjects with BMI < 25.0 kg/m^2.

Table 4: Influence of BMI and WHR on the Apolipoprotein Status of Type 2 Diabetic Subjects (Mean ± SD, mg/dl)

Variables	Apo A1	Apo B	A1: B
Males (n=28)			
Based on BMI			
BMI < 25 kg/m^2 (n=14)	128.1±21.6	118.9±28.7	1.2±0.6
Overweight/Obesity, BMI > 25 kg/m^2 (n=14)	121.4±15.7 [a]	114.3 ± 25.5	1.1±0.2
Overweight, BMI = 25 to 29.9 kg/m^2 (n=13)	124.8±9.0	117.9±22.6	1.1±0.2
Based on WHR			
WHR < 1.0 (n=16)	128.7±20.1	111.1±27.4	1.3±0.5
Abdominal Obesity, WHR $\geq$ 1.0 (n=12)	119.4±16.3 [bb]	124.1±25.0	1.0±0.2 [b]
Females (n=22)			
Based on BMI			
BMI < 25 kg/m^2 (n=11)	170.4±35.1	109.2±20.3	1.6±0.5
Overweight/Obesity, BMI > 25 kg/m^2 (n=11)	140.6±28.3[*]	123.9±24.0	1.1±0.6[*]
Overweight, BMI = 25 to 29.9 kg/m^2 (n=7)	162.0±32.1	119.9±27.8	1.3±0.3
Based on WHR			
WHR < 0.85 (n=6)	164.5 ± 37.2	113.0±23.2	1.5±0.4
Abdominal Obesity (WHR $\geq$ 0.85 cm) (n=16)	146.4 ± 28.8	115.2±25.5	1.3±0.5

[*] *Significantly different from subjects with BMI < 25 kg/m^2 at $p < 0.05$*

[a] *Significantly different from female subjects with BMI > 25 kg/m^2 at $p < 0.05$*

[b] *Significantly different from female subjects with abdominal obesity at $p < 0.05$*

[bb] *Significantly different from female subjects with abdominal obesity at $p < 0.01$*

Appreciable lowering in apo A1 levels and the favourable A1: B ratio was observed for both, male and female subjects with abdominal obesity. In case of male subjects, marginal increment (13.0 mg%) in the apo B levels was also noticed. Between the sexes, male subjects had very significantly lower apo A1 values (27.0 mg%, $p < 0.01$) and significantly lower A1: B ratio ($p < 0.05$) as compared to the female subjects with high WHR.

In both male and female subjects, the apo A1 levels did not exhibit significant differences on comparison between groups with high BMI versus high WHR. However, apo B levels in the male and female subjects followed contrary trends. In male subjects with high WHR, marginally higher apo B values (9.8 mg%) were noticed whereas in case of female subjects, elevated apo B levels (8.7 mg%) were obtained for the group with BMI > 25.0 kg/m^2.

DISCUSSION

Adiposity carries a penalty in that it leads to a worsening of all the elements of the metabolic syndrome viz., insulin resistance, hyperinsulinemia, dyslipidemia and hypertension [2,14,17-19]. The metabolic consequences of obesity are varied depending on the aetiology, distribution and character of the excess adipose tissue. In the late 1940s, Vague [20] suggested that the relative proportion of body fat in the upper body versus lower body was an important factor to consider while investigating obesity-related health problems. However, it was only since the 1980s that more attention has been focussed on abdominal obesity, rather than obesity *per se* as an important correlate for various metabolic disturbances [7,11,21-24].

In the present study we attempted to establish the influence of overweight/obesity (measured by BMI) and abdominal obesity (indexed by WHR) with the metabolic status of type 2 diabetic subjects. The results clearly demonstrated the unfavourable interaction of obesity with the metabolic profile of diabetic subjects. Insulin resistance and the resultant hyperglycemia, affect each and every lipid and lipoprotein fraction. Therefore, the poor glycemic and lipemic control as observed in this study is witnessed in most of the type 2 diabetic subjects [25,26]. However, the effect of body fat distribution in relation to glycemic and lipemic control varied

between the sexes. These male-female differences regarding the impact of overweight/obesity on disorder might be explained by the differences in the operation of the risk factors or the causal pathways leading to the disorder [27].

The blood glucose levels and lipid profile did not greatly alter with the degree of overweight/obesity as indexed by BMI in male subjects. The alterations in the serum lipids, lipoproteins and blood glucose levels of the male subjects were more pronounced with high WHR. In contrast, female subjects demonstrated higher blood glucose values and lipid and lipoprotein abnormalities in relation to both high BMI and high WHR. Between the sexes, metabolic de-control due to high WHR was more apparent in male type 2 diabetic subjects.

High BMI is associated with elevated abdominal and peripheral adiposity [28]. It is now recognised that excess abdominal distribution of fat is more closely associated with the development of metabolic abnormalities. It can therefore, be speculated that the unfavourable changes observed with high BMI may in fact be attributed to the detrimental influence of abdominal adiposity on the metabolic processes. While the cause of this association is not fully established, the possible mechanism is hypothesised to be mediated by the intra-abdominal fat depot. A preponderance of enlarged fat cells in this type of adipose tissue increases the risk of glucose intolerance, hyperinsulinemia and hypertriglyceridemia [8,14,24]. These hypertrophied adipocytes are more responsive to lipolytic hormones than smaller fat cells leading to increased delivery of free fatty acids into the portal circulation. Elevated levels of free fatty acids may induce insulin resistance in peripheral tissues and liver as well as leading to increased rates of hepatic glucose production [8,24]. Therefore, poor glycemic status may be observed with abdominal adiposity.

The most striking endocrine alteration in most forms of obesity and particularly in the abdominal obesity is the combination of hyperinsulinemia, insulin resistance and potential atherogenic abnormalities. Multiple modifications of serum lipids and lipoproteins as evidenced in this study are frequently noted in overweight/obese individuals. The most common modifications are hypertriglyceridemia and decreased HDL-C levels [29,30,31]. Since apo A1 and B are the major protein components of HDL-C and LDL-C respectively, changes in the levels of these lipoproteins are reflected in the serum levels of apolipoproteins. Alterations in plasma lipids and lipoproteins concentrations have also been cross-sectionally associated with increased abdominal adiposity [7-11].

These results clearly indicate deterioration of metabolic profile with increases in both, BMI and WHR. However, abdominal obesity indexed by WHR has a more hazardous and detrimental influence on the metabolic status of type 2 diabetic subjects.

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