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Effect of Pioglitazone on Body Composition in Asian Indian Diabetics Suggest Role of Limb Fat in their High Insulin Resistance

Prashant Mathur[1], Sandeep Kumar Mathur[2*], Poonam Punjabi[3], Radhika Vaishnav[4] and Mukul Mathur[5]

[1]Department of Clinical Pharmacy, Division of Pharmaceutical Sciences, SGRRITS, Patel Nagar, Dehradun-248001, India.
[2]Department of Endocrinology, SMS Medical College, Jaipur, India.
[3]Department of Physiology, SMS Medical College, Jaipur, Rajasthan, India.
[4]Vadodara Stroke Center, Vadodara, India.
[5]Department of Pharmacology, SMS Medical College, Jaipur, Rajasthan, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author SKM designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors SKM, PM and MM managed the clinical process and data collection. Author PM managed the literature searches. Author RV performed the data analyses of the study and prepared tables and figures. All authors read and approved the final manuscript.

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Short Communication

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ABSTRACT

Aim: To study (1) effect of pioglitazone mono-therapy on body composition in treatment naive type-2 diabetes mellitus patients and (2) relationship between changes in body composition and insulin resistance induced by pioglitazone.
Methods: *Subjects:* 49 newly diagnosed non-obese T2DM patients were recruited. *Design:* Open label observational study. *Drug and Dose:* pioglitazone 30 mg orally once daily for at least 6

**Corresponding author: Email: drsandeepmathur@rediffmail.com;*

months. *Exclusion:* Primary un-responsiveness at 3 months (10 subjects) and adverse effect (2 subjects). Final analysis done on 37 subjects (Mean age 47.9 years, male:female ratio 20:10) *Controls:* 37 healthy control subjects (Mean age 47 years M:F ratio 27:10) with normal glucose as per American Diabetes Association criteria. Study parameters were: Plasma glucose, Lipid profile, body mass index, HOMA-R, HOMA-B and body composition measured by dual-energy X-ray absorptiometry (DEXA) at start and after at least 6 months of follow up.

Results: Treatment with pioglitazone was associated with significantly decreased glycated hemoglobin (HbA1c), fasting and post-prandial plasma glucose, insulin resistance and triglycerides HDL ratio.Significant increase in total body, limb and head fat mass was observed. The trunk composition did not show significant change. The DEXA Parameters of body composition of diabetics became comparable with controls. Significant correlation was seen between decrease in FPG, PPG, insulin resistance and increase in limb fat mass.

Conclusions: Pioglitazone alters body composition by increasing limb and head fat content, without altering trunk fat. Decrease in insulin resistance by it is related to increase in limb fat mass.

Keywords: Diabetes mellitus; body composition; pioglitazone; insulin resistance.

1. INTRODUCTION

Asian Indians have a typical “lean-fat” phenotype [1]. Diabetics belonging to this population show relatively normal body mass index and whole body fat content, but excess visceral fat and high insulin resistance [2]. Mathur et al. [3] also observed that diabetics when compared to controls had comparable body fat mass but more lean mass in trunk. Whether this phenotype is a reflection of poor adipogenesis in diabetics remains unexplored.

Pioglitazone is widely used in the treatment of type-2 diabetes mellitus (T2DM). It acts predominantly in adipose tissue through activation of the nuclear receptor peroxisome proliferator–activated receptor γ (PPAR-γ) [4]. It results in a decrease in free fatty acid and insulin resistance while improving glycaemic control, but also causes weight gain and redistribution of body fat in individuals with T2DM [5–7]. Its paradoxical effect on body fat content and insulin resistance is thought to occur via enhancing the process of adipogenesis i.e. proliferation and differentiation of pre-adipocytes into metabolically favorably functioning mature adipocytes [8-10]. Our hypothesis is that the effect of pioglitazone on body composition and insulin resistance could provide indirect evidence of the role of poor adipogenesis in Asian Indian diabetic phenotype.

2. METHODS

2.1 Subjects

Individuals in this study belonged to two groups classified based on their diabetic status: Diabetic patients and non-diabetic controls. Diabetic patients received Pioglitazone treatment, and study parameters were measured in these patients at the initiation of the treatment (baseline) and after 6 months of treatment (follow-up). Initially, 49 diabetic subjects were treated with Pioglitazone 30 mg PO once daily for at least 6 months. Inclusion criteria were BMI<30 and no contraindication to the drug. The institutional ethics committee approved the experimental protocol and patients gave their informed written consent prior to participation. Ten of the diabetic subjects did not show significant glycaemic response to pioglitazone upto 3 months of treatment and were consequently switched to another anti diabetic drug. Two subjects exhibited adverse effects to pioglitazone therapy, and were also excluded from the study, leaving 37 subjects.

2.2 Methods

The following parameters were assessed in diabetic and non-diabetic groups at baseline: Body Mass Index (BMI), Plasma glucose, Homeostasis Model Assessment for insulin resistance (HOMA-R), and beta-cell function (HOMA-B), lipid profile and body composition (by dual-energy X-ray absorptiometry, DEXA). In the diabetic patient group, plasma glucose, BMI, HOMA-R, HOMA-B levels were reassessed after 6 months of therapy.

2.3 Laboratory Measures

Blood samples were obtained at 8:00 am after an overnight fasting of at least 8 hours. Following biochemical parameters were measured on Kopran AU/400 fully automated analyzer: serum

glucose, lipid profile, (Total cholesterol, Phospholipids Triglycerides, LDL, HDL, and VLDL), SGOT, SGPT. Serum insulin was measured by chemiluminescent immunometric assay using Immulite 2000 machine. HbA1c was measured by turbimetry method using BioSystems kits (Non-diabetic reference range 4.0 - 6.5). Insulin Resistance and beta cell function were assessed by Homeostasis Model Assessment (HOMA-R and HOMA-B, respectively) [11].

Body fat distribution (total body fat and regional fat distribution) was measured by Dual X-Ray Absorptiometry (DEXA) Hologic Explorer model (S/N91395). The body regions were defined as per the software of the system (i.e. Left and right upper and lower limbs, trunk, head and total). The android region delineated by an upper horizontal border below the chin, vertical borders lateral of ribs and lower border passing through the hip joints. The gynoid region was defined by the region below the oblique lines passing through the the hip joints.

2.4 Statistical Analysis

All parameters are presented as mean ± SD. Statistics were performed using AnalystSoft Inc., StatPlus:mac LE - free statistical analysis program for Mac OS, Version 2009 in conjunction with Microsoft Excel. Differences in means of baseline parameters and 6-month follow-up diabetic patients were assessed using paired t-tests. Comparisons between levels of control group and diabetics before treatment and control group and diabetics after 6-month follow-up were performed using unpaired 2-sample t-tests. P values less than 0.05 were considered significant. Linear correlation was performed and Pearson correlation coefficient was used to determine the relationship between change in parameters of body fat composition with change in parameter of adiposity i.e. BMI, changes in sugar, change in insulin resistance and change in beta cell function after six months of therapy. To assess the linearity of the relationship between HOMA-R and gynoid or android fat parameters, we performed linear regression analysis and plotted the associated scatter plots.

3. RESULTS

Out of 49 patients initially enrolled in this study, a total of 37 remained that were followed for 6 months without change in treatment or any adverse effects. The mean age for the diabetic patient group was 49.7 years, with a mean age for females (n=10) of 44.8 years and a mean age for males (n=27) of 51.5 years. Treatment-naïve age and gender matched non-diabetic controls were also studied here. The mean age for the control group (n=37) was 47 years, with a mean age for females (n=10) of 43.7 and males (n=27) of 48.1. These results are summarized in Table 1, along with the means of the parameters in this study that were measured in non-diabetic controls, diabetic baseline (1^{st} month) and diabetic follow-up (6^{th} month) subjects. The body composition parameters that for the three groups are summarized in Table 2.

The baseline diabetic group was initially compared to the age and gender matched non-diabetic control group using unpaired t-tests. The results are shown in Table 3. A significant ($p < 0.05$) difference was observed between the two groups for BMI, total lipids, phospholipids, triglycerides, total cholesterol, HDL, LDL, VLDL, serum creatinine, HOMA- B, HOMA-R, fasting and post-prandial blood glucose and Hb1Ac. However, body composition parameters did not show any statistically significant difference in these two groups in regions other than the head. Though diabetics had less fat in all regions of the body, it was significantly ($p < 0.05$) less in head region. For the patient group, most parameters showed a significant difference after 6 months of treatment with Pioglitazone. The parameters showing a significant ($p < 0.05$) decrease following treatment were: phospholipids, triglyceride, total cholestrol, LDL cholestrol, VLDL cholestrol, HOMA-R, fasting and postprandial plasma glucose and HbA1c. All limbs and head & neck showed significant increase in fat mass and percentage fat, but there was no significant change in trunk fat mass and percentage. This regional change in fat mass and percentage was reflected in increase in total body fat content. The lean and bone mass did not show any significant change. There was a significant ($p < 0.05$) correlaton between increase in limb fat mass and decrease in HOMA-R.

Remarkably, no significant differences were observed for nearly all parameters when comparing non-diabetic controls with patients treated with Pioglitazone for 6 months. These results are all summarized in Table 4. We also did gender wise comparison of android and gynoid region in controls, diabetics before treatment and after treatment (Table 5). Their significance level is shown in Table 6. There was significant ($p < 0.05$) increase in gynoid fat mass

as well as percentage in both genders after treatment with pioglitazone. In male there was no increase in android fat mass or percentage. In female though there was increase in android region mass, but there was no incease in fat percenage.

To study the association between insulin resistance measured as HOMA-R and body composition, we performed linear correlation between them. In controls there was a significant ($p<0.05$) positive correlation (R greater than zero) between BMI and HOMA-R. In diabetics before treatment there was significant positive correlation between trunk fat and HOMA-R; but in the same patients, after 6 months of treatment, no correlation was observed between trunk fat and HOMA-R. On correlation analysis of change in HOMA-R and change in body composition parameters, a statistically significant ($p<0.05$) negative (R value below zero) relationship was observed between increase in limb fat and decrease in HOMA-R, fasting blood glucose and post prandial glucose following 6 months of treatment.

On linear regression analysis of change in regional body composition versus change in HOMA-R, we observed a significant negative correlation between the increase in gynoid fat and decrease in HOMA-R. However, there was no association between the change in android region (trunk), head and neck composition and change in HOMA-R before and after treatment.

4. DISCUSSION

Here we have described results of six months of treatment of T2DM patients with pioglitazone, where we observed a statistically significant ($p < 0.05$) increase in limb, gynoid, and head fat, but no significant change in trunk (android) fat. These findings are important in light of three other observations made in this study: firstly, diabetics before starting the treatment had high insulin resistance, but marginally less (although not statistically significant), gynoid and limb fat mass. Secondly, their body composition and insulin resistance became comparable to control after treatment with pioglitazone. Thirdly, there was significant ($p < 0.05$) association between increase in limb and gynoid fat mass and decrease in insulin resistance. Therefore these results show that high insulin resistance in Asian Indian diabetics is reversible by expansion of gynoid and limb fat mass induced by pioglitazone. As pioglitazone enhances adipogenesis, hence our results provide indirect evidence of a role for poor adipogenesis of gynoid and limb fat in the pathogenesis of "lean high insulin resistant" phenotype of Asian Indian diabetics.

Table 1. General characterstics and biochemical parameters (Mean ± SD) of controls, diabetics before and after 6 months of treatment

	Non-DM controls	DM before treatment	DM 6 month after treatment
Age	47.07	49.7	
Sex	27 male, 10 female	27 male, 10 female	
Height (cm)	162.27±8.28	164.5±9.18	164.5±9.18
Weight (Kg.)	67±13.23	64±9.3	67.6±9.7
Body mass Index	25.6±4.2	23.8±2.8	25±3.1
Total lipids (mg/dl)	571.3±127.2	674.5±141.7	626.4±133.6
Phholipids (mg/dl)	183.6±31	217.7±39.5	204.8±38.9
Triglyceride (mg/dl)	133±76.71	181.4±84.6	160.1±74.5
Total cholestrol (mg/dl)	180.8±43.9	203.8±39.5	185.6±40.5
HDL cholestrol (mg/dl)	49.2±6.9	45.4±6.03	49±5.9
LDL cholestrol (mg/dl)	103.6±33.4	119.9±33.9	103.2±32.6
VLDL cholestrol (mg/dl)	26.6±15.3	37.1±17.5	31.97±14.9
Serum creatinine (mg/dl)	1.11±0.15	0.89±0.19	1.09±0.21
HOMA-B	86.4±80.4	14.07±11.7	29.8±22.9
HOMA-R	1.24±0.79	2.6±1.96	1.27±1.0
Insulin	5.54±3.46	5.01±3.6	4.17±3.1
Fasting glucose (mg/dl)	90.68±10.24	214.7±56.6	122.7±31.2
HbA1c (gm/dl)	1.08±0.25	1.78±0.26	1.27±0.25
HbA1c%	6.17±0.93	10.4±2.02	7.4±1.29

Table 2. Body composition parameters (Mean ± SD) of controls, diabetics before and after 6 months of treatment

	Non-DM Controls	DM before treatment	DM 6 month after treatment
Left arm			
BMC (g)	134.2±31.7	143.47±53.9	129.3±31.3
Fat (g)	1089.4±463.8	951.6±403.1	1065.4±451.2
Lean (g)	2295.7±624.2	2092±567.67	2064.9±587
Lean +BMC (g)	2433.4±661.1	2234.14±597.1	2194.8±613.3
Total mass (g)	3517.6±803.08	3186.6±661.4	3260.2±722.2
% Fat	31.2±10.98	30.03±11.2	32.6±11.7
Right arm			
BMC (g)	142.6±35.98	141.8±31.6	171.9±201.1
Fat (g)	1116.5±522.4	999.5±418.7	1095.9±441.7
Lean (g)	2414.4±590.7	2240.2±586.7	2193.8±558.3
Lean +BMC (g)	2549.6±620.14	2382±612.2	2334.8±586.6
Total mass (g)	3713.8±811.7	3381.5±724.8	3429±647.5
% Fat	30.9±10.5	29.6±10.7	32±11.3
Trunk			
BMC (g)	398.4±84.12	434.95±95.9	421.3±86.9
Fat (g)	10469.4±7438.1	9326.1±2939.7	9799.9±3192.1
Lean (g)	22059.3±4100.1	21468.6±3706.7	21749.5±3203.6
Lean +BMC (g)	22458.9±4157.4	21903.6±3575.7	22170.8±3243.8
Total Mass (g)	42877.5±69328.7	31229.7±5161.8	31970.7±4664.7
% Fat	29.1±7.5	29.5±7.4	30.3±7.44
Left leg			
BMC (g)	327.1±63.6	329.78±64.6	336.2±65.4
Fat (g)	3164.8±1270.7	2868.9±1087.7	3340.7±1339.5
Lean (g)	6698.1±1837.7	6395.5±1226.4	6618.2±1307.4
Lean +BMC (g)	6991±1909.6	6725.3±1278.5	6954.3±1359.4
Total mass (g)	10303.3±2050.4	9583.8±1443	10295.1±1633.2
% Fat	30.6±9.8	29.7±10.02	32.1±10.29
Right leg			
BMC (g)	334.6±64	342.8±68.5	343.09±64.97
Fat (g)	3252.4±1255.8	2906.1±1125.1	3426.2±1368.3
Lean (g)	6932.1±1523.6	6528.4±1285.7	6648.9±1300.8
Lean +BMC (g)	7266.72±1579.7	6871.2±1342	6991.95±1349.8
Total Mass (g)	10519.2±2045	9777.3±1526.9	10418.2±1709.5
% Fat	30.7±9.4	29.5±10.04	32.47±10.02
Head			
BMC (g)	576.1±98.3	562.89±140.5	589.06±102.85
Fat (g)	1038.97±231.6	932.5±189.4	1034.3±132.9
Lean (g)	3518.4±750.1	3183.1±641.7	3518.3±448.96
Lean +BMC (g)	4094.5±804.3	3745.25±732.18	4107.4±481.21
Total mass (g)	7609.7±10590	4679.5±919.3	5141.7±610.4
% Fat	20.1±0.71	19.38±3.3	20.1±0.56
Total			
BMC (g)	1915.1±321.5	1955.73±342.9	1977.6±339.09
Fat (g)	19220.7±7082.6	17984.7±5639.17	19762.5±6484.7
Lean (g)	43947.7±8459.1	41907.8±7192.8	42794.2±6923.5
Lean +BMC (g)	45862.9±8713.3	43863±7413.1	44752.4±7126.4
Total mass (g)	64615.8±13508.2	61848.3±9182.4	62974.3±13221.7
% Fat	28.5±7.25	28.89±7.8	30.4±7.95

Table 3. Shows significance level of difference between the general characterstics and biochemical parameters in the controls and diabetics before and after 6 months of treatment (p value)

Parameters	Controls vs. DM before treatment	DM before vs. after treatment	Controls vs. DM after 6 months of treatment
Height (cm)	0.286414136	n/a	0.286414136
Weight (Kg)	0.246762108	**4.11458E-05**	0.984065956
BMI	**0.037254332**	**4.09064E-05**	0.516105573
Total lipids (mg/dl)	**0.001509747**	**0.018429254**	0.073404701
Phospholipids(mg/dl)	**9.93989E-05**	0.084934397	**0.011621667**
Triglycerides (mg/dl)	**0.012017568**	**0.027246503**	0.128324661
Total Cholesterol (mg/dl)	**0.020783906**	**0.004760943**	0.632434741
HDL Cholesterol (mg/dl)	**0.015168471**	**0.008277423**	0.904230765
LDL Cholesterol (mg/dl)	**0.040980772**	**0.007136855**	0.960564233
VLDL Cholesterol (mg/dl)	**0.007658369**	**0.010304113**	0.130393209
Sr. Creatinine(mg/dl)	**4.12804E-06**	**5.04076E-06**	0.750310842
HOMA- B	**7.68268E-07**	**0.000210229**	**0.000101238**
HOMA-R	**0.000207925**	**0.000106707**	0.881825775
Insulin	0.521932786	0.172099813	0.077814356
Blood glucose (mg/dl)			
Fasting	**9.3618E-21**	**8.02697E-11**	**9.48937E-08**
Post .Meal	**6.71128E-10**	**1.93209E-09**	**0.000534498**
SGOT	0.509835378	0.131084317	0.441254733
SGPT	0.260359607	0.085288509	0.293332019
Hb1Ac (gm %)	**3.325E-16**	**2.90683E-10**	**0.004419195**
Hb1Ac (%)	**4.40583E-15**	**4.35681E-10**	**5.87038E-05**

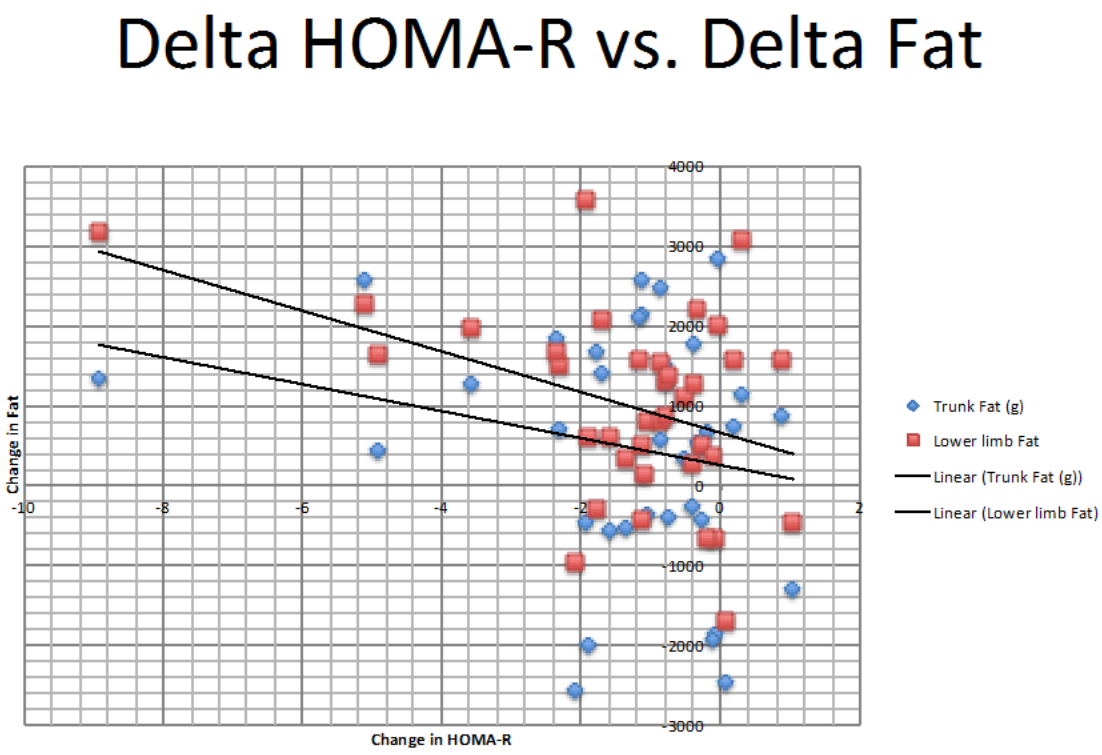

Fig. 1. Shows relation between change in HOMA-R and change in lower limb and trunk fat

Table 4. Shows significance level of difference between the DEXA parameters of body composition in the controls and diabetics before and after 6 months of treatment (p value)

Parameters		Controls vs. DM before treatment	DM before vs. after treatment	Controls vs. DM after 6 months of treatment
L Arm	BMC (g)	0.368792424	0.113945232	0.512808554
	Fat (g)	0.176947242	**0.010514302**	0.822669133
	Lean (g)	0.14616109	0.520286851	0.105657904
	Lean +BMC (g)	0.180581259	0.388419365	0.114163471
	Total mass (g)	0.0568661	0.352170026	0.151535428
	% Fat	0.652847321	**0.000605917**	0.60562548
R Arm	BMC (g)	0.926209485	0.362861906	0.38582668
	Fat (g)	0.291345005	**0.018578018**	0.855275292
	Lean (g)	0.207101752	0.236399558	0.103240423
	Lean +BMC (g)	0.245878253	0.232305602	0.130165665
	Total mass (g)	0.06736166	0.499517423	0.099578009
	% Fat	0.607337002	**0.000249653**	0.661855866
Trunk	BMC (g)	0.087698752	0.084161454	0.255826936
	Fat (g)	0.387446757	0.056649912	0.616383107
	Lean (g)	0.517769986	0.307713529	0.718318346
	Lean +BMC (g)	0.548542505	0.334591002	0.740571051
	Total mass (g)	0.311552339	0.091711898	0.342882075
	% Fat	0.798022461	0.164119017	0.492409271
L Leg	BMC (g)	0.859217626	0.081095195	0.551232692
	Fat (g)	0.285596897	**4.12931E-05**	0.563876812
	Lean (g)	0.407566055	**0.016794746**	0.830063395
	Lean +BMC (g)	0.484136466	**0.014915863**	0.924531807
	Total mass (g)	0.085120169	**7.58374E-05**	0.984822092
	% Fat	0.685593125	**0.000247657**	0.531892632
R Leg	BMC (g)	0.597462181	0.957893	0.574388
	Fat (g)	0.215614	**3.5E-06**	0.570846
	Lean (g)	0.222044	0.186041	0.392685
	Lean +BMC (g)	0.2496	0.196064	0.42384
	Total mass (g)	0.081288	**0.000263**	0.818359
	% Fat	0.584446	**3.47E-06**	0.440098
Head	BMC (g)	0.640442059	0.097982096	0.581795593
	Fat (g)	**0.033736573**	**0.001478624**	0.915715346
	Lean (g)	**0.04243508**	**0.001989403**	0.999745802
	Lean +BMC (g)=	0.054688214	**0.003032919**	0.933560226
	Total mass (g)	0.097904149	**0.00265767**	0.161288506
	% Fat	0.170049433	0.190155432	0.716821953
Total	BMC (g)	0.600830458	0.461941644	0.418920086
	Fat (g)	0.40905105	**0.000101127**	0.732445808
	Lean (g)	0.267499836	**0.016546025**	0.522994174
	Lean +BMC (g)	0.291309787	**0.016384232**	0.550317667
	Total mass (g)	0.306167613	0.485166325	0.598970144
	% Fat	0.841552314	**0.000637083**	0.300205651

Asian Indian people irrespective of diabetes have typical thin-fat phenotype and it is commonly called as “Asian Indian phenotype” [1]. Studies report that non-diabetic Asian Indians, on comparison with other ethnic backgrounds, show higher body fat content and insulin resistance but comparable BMI [12-16]. It is generally believed that their higher diabetes risk is because of excess fat, particularly the visceral fat [1]. Our results expand on these reports by showing that DEXA body composition of diabetic Asian Indians and non-diabetic controls is comparable. Thus, we describe an “Asian Indian diabetic phenotype” which is not associated with excess fat including trunk (android) fat. In fact diabetics have marginally lower fat mass, though the difference was statistically insignificant. The majority of previous studies on body composition

Table 5. Body composition parameters of android and Gynoid region of male and female controls, diabetics before and after 6 months of treatment (Mean ± SD)

	Non DM controls	Diabetic before treatment	Diabetic after treatment
Android region-females			
BMC (g)	345.27±68.32	364.16 ±78.82	375.90±74.69
Fat (g)	10577.2±4753.76	10282.9±1934.95	11350.5±1657.95
Lean (g)	18430.52±3031.96	17233.9±1979.85	18301.1±2093.58
Lean +BMC (g)	18755.84±3075.2	17598.1±2014.8	18677±2107.4
Total mass (g)	69984.4±134133.2	27880.9±3333.6	30027.4±3482.43
% Fat	34.55±765	36.73±3.9	37.73±2.36
Android region-males			
BMC (g)	418.8±81.64	461.2±89.1	438.1±86.3
Fat (g)	10429.6±8293.1	8971.8±3191.7	9225.6±3448.1
Lean (g)	23403.3±3626.9	23037.1±2866.3	23026.7±2534.86
Lean +BMC (g)	23823.04±3675.3	23498.2±2894.01	23464.8±2568.7
Total mass (g)	32837.92±6319	32470±5209.1	33690.4±4892.9
% Fat	27.1±6.5	26.9±6.7	27.5±6.8
Gynoid region- females			
BMC (g)	547.4±108.05	531.48±81.41	557.52±68.87
Fat (g)	8234.95±2405.89	7376.42±1275.66	8800.71±2265.12
Lean (g)	10035.8±2613.98	9917.17±1255.15	10299.66±1379.2
Lean +BMC (g)	10453.8±2557.2	10448.66±1275.66	10857.2±1406.9
Total mass (g)	19234.42±4149.3	17786.38±1842.62	19657.9±3242.3
% Fat	85.01±10.3	82.6±9.7	88.5±10.5
Gynoid region- males			
BMC (g)	705.3±104.5	724.8±107.04	724.3±115.99
Fat (g)	5743.9±2248.4	5181.9±2194.9	6013.7±2481.2
Lean (g)	14961.4±2383.9	14037.5±1818.6	14366.1±1999.62
Lean +BMC (g)	15666.6±2471.6	14762.34±1896.7	15090.4±2079.02
Total mass (g)	21410.7±3967.4	19944.3±3082.8	21104.2±3325.6
% Fat	52.6±13.14	50.5±15.2	55.7±15.12

in Asian Indians either compared their non-diabetics with those of other racial background or focused on abdominal subcutaneous or visceral fat [12-16]. To the best of our knowledge, there are few studies in which body composition of Asian Indian diabetics has been compared with that of non-diabetics by DEXA method. Anjana Mohan et al found South Indian diabetics when compared with non-diabetics had comparable BMI and overall adiposity but higher visceral fat content [2]. However they did not measure limb or gynoid fat in that study. Our findings are consistent with previous study done in other populations in which lower amount of adiposity in the lower extremities was associated with higher insulin resistance and unfavourable glucose levels in obese and overweight individuals [17].

We have observed in our study that pioglitazone appears to reverse the diabetic phenotype by increase in limb and gynoid fat mass. This finding is consistent with those of other studies on effect of pioglitazone on body composition. Bray et al. [18] observed that pioglitazone increased peripheral fat more than trunk fat. Smith et al. [19] also find that in the pioglitazone-treated patients subcutaneous fat was increased at all the sites but the visceral fat did not change significantly.

We observed that insulin resistance in non-diabetic controls is related to BMI (overall adiposity), while in diabetics it is related to trunk fat, and pioglitazone-induced decrease in it is related to expansion in limb and Gynoid fat. In other words, different depots of body fat play an important role in insulin resistance in these three different situations. One explanation for these finding is the adipose tissue overflow hypothesis. It is possible that poor fat storage capacity of Gynoid and limb fat depots under condition of positive calorie balance lead to ectopic fat deposition in trunk region (visceral organs), hence causing high insulin resistance at a relatively lower BMI. In other words, the primary defect underlying high insulin resistant Asian

Indian diabetic phenotype is in the limb and Gynoid fat and that the role of trunk fat in insulin resistance is secondary to it. Some of the recent studies find that insulin resistance is due to ectopic fat in liver and muscle and not due to omentum fat further support our findings [20,21].

An important limitation of present study is that we did not measure visceral or subcutaneous adipose tissue directly. Gowri Thilagam T et al. [22] find that pioglitazone decreases visceral fat and increases subcutaneous abdominal fat in Asian Indian diabetics, hence providing indirect evidence that excess visceral fat in diabetics is also possibly caused by poor adipogenesis of limb and gynoid region. As DEXA measure fat content in limb instead of subcutaneous or intramuscular fat, hence it cannot be predicted mass of which adipose tissue is increased by pioglitazone. However, from the point of view of understanding the cellular and molecular basis of Asian Indian diabetic phenotype there is a need for further investigations into the adipogenesis of gynoid and limb fat in this population.

Table 6. Shows significance level of difference in Android and Gynoid fat in male and female controls subjects and diabetics subjects before and after 6 months of treatment (p value)

Parameters	Gender	Controls vs. DM before treatment	DM before vs. after treatment	Controls vs. DM after 6 months
Android region				
BMC (g)	All	0.087698752	0.084161454	0.255826936
	Females	0.57407501	0.470064363	0.351399861
	Males	0.077118068	**0.00983887**	0.406143179
Fat (g)	All	0.387446757	0.056649912	0.616383107
	Females	0.85814155	**0.003678586**	0.633031339
	Males	0.397888527	0.413467243	0.489200283
Lean (g)	All	0.517769986	0.307713529	0.718318346
	Females	0.309862972	**0.015476907**	0.912785732
	Males	0.682316206	0.975428504	0.660181656
Lean +BMC (g)	All	0.548542505	0.334591002	0.740571051
	Females	0.324461341	**0.01474911**	0.934102907
	Males	0.719720401	0.921277261	0.679748349
Total Mass (g)	All	0.311552339	0.091711898	0.342882075
	Females	0.334199286	**0.001172215**	0.358817202
	Males	0.816339243	0.681156078	0.923967817
% fat	All	0.798022461	0.164119017	0.492409271
	Females	0.429981694	0.24530965	0.222262197
	Males	0.91300912	0.333079992	0.79814951
Gynoid region				
BMC (g)	All	0.740633	0.413502807	0.575809
	Females	0.714126838	0.060306477	0.805710805
	Males	0.499676884	0.956162618	0.528918487
Fat (g)	All	0.247408	**0.043965928**	0.566566
	Females	0.33199365	**0.008829018**	0.594852252
	Males	0.35701612	**0.000504553**	0.677099283
Lean (g)	All	0.300268	0.281743752	0.598597
	Females	0.898464056	0.227861427	0.780952208
	Males	0.115408757	0.116910763	0.324789423
Lean +BMC (g)	All	0.35066	0.281744	0.663554
	Females	0.995487815	0.194020522	0.667285602
	Males	0.137583345	0.126471971	0.358257655
Total mass (g)	All	0.081452	**0.033961**	0.89987
	Females	0.327481263	**0.02296098**	0.802419873
	Males	0.135417042	**0.002077769**	0.759545316
% fat	All	0.633557	0.126619	0.484415
	Females	0.595994974	**0.012129249**	0.461822815
	Males	0.591955033	**0.000661635**	0.423100693

The another limitation of this study was that we did not have any comparator drug and observed body compostion change could also be attributed to caloric restriction and increased physical activity. However these life-style changes are well known to decrease body fat content instead of the increase in limb fat that is observed here.

5. CONCLUSION

Asian Indian diabetics have comparable body composition to non-diabetic controls. Pioglitazone-induced normalization of their high insulin resistance is related to increase in limb fat content. Therefore we provide indirect evidence of a role of poor adipogenesis of their gynoid and limb fat in their “lean high insulin resistant” phenotype.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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