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ABDOMINAL FAT DISTRIBUTION AND CARDIOVASCULAR RISK FACTORS IN HYPERTENSIVE FEMALES

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ABSTRACT

The link between abdominal fat distribution and insulin related cardiovascular risk factors in black and white female hypertensives who were on drug treatment for hypertension was investigated with computed tomography scan, sonar, anthropometric measurements and blood testing. Fasting blood samples were tested for: insulin, glucose, triglyceride, apoprotein B, apoprotein A1, total cholesterol, HDL cholesterol, lipoprotein a, uric acid, fibrinogen and plasminogen activity. Albumin and creatinine were measured in urine samples. Black subjects were slightly more obese than their white counterparts as judged from their body mass indexes (34.39±6.60 vs. 32.08±6.77 kg/m ^{2}, p<0.187) and they had similar waist to hip ratios (0.80±5.70 vs. 0.79±5.61, p=0.540). Despite this, white subjects had more intra-abdominal fat than black subjects (162. 76±63.97 vs. 131.17±63.89 cm ^{2} , p=0.207) and this difference became more pronounced after excluding the values of six black diabetic subjects (162.76 vs. 107.53±9.10 cm^2, p=0.000) who all had visceral fat areas larger than 177 cm^2. Visceral fat areas correlated with fasting glucose (r=0.79), triglyceride (r=0.60) and insulin resistance (r=0.70) in black subjects and with LDL particle size (r=-0.60) triglyceride (r=0.60) and insulin resistance (r=0.60) in white subjects. Hypertriglyceridaemia seems to be the mediator of dyslipidaemia in particular a decrease in HDL cholesterol levels and an increase in the number of small atherogenic LDL particles. This may happen at triglyceride levels considerably lower than 2.3 mmol/l, which is generally accepted as the high-risk cut-off point. Waist to hip ratio did not seem to be a good indicator of visceral fat or cardiovascular risk in the present study and it was concluded that waist circumference or intra-abdominal sonar may be more reliable in this regard. The present study also showed that cardiovascular risk assessment of white females with apparently normal LDL cholesterol levels might be inconclusive without the measurement of apo B. High lipoprotein (a) levels in black females may not be so innocuous as previously thought, especially if it occurs in conjunction with high fibrinogen and high LDL cholesterol levels as seen in some subjects in the present study.

Keywords: Visceral fat; Free fatty acids; Insulin resistance syndrome; Cardiovascular risk.

INTRODUCTION

Although obesity has been linked to hypertension (Meisler & St Jeor, 1996), diabetes (Levitt *et al.*, 1993) and cardiovascular disease (Kaplan, 1989), there are conflicting reports about the risks of obesity in different ethnic groups in South Africa. Du Plessis *et al.* (1997), for example, found that waist circumference (android obesity) correlated strongly with low HDL cholesterol levels (r=-0.79) in white hypertensive females. Walker *et al.* (1989), on the other hand, reported that rural black females had a low frequency of adverse metabolic sequelae associated with obesity, while Greer *et al.* (2000) stated that obesity was not a risk factor for cardiovascular disease in an apparently healthy population of black females in the North West Province. However, it should be noted that none of these researchers measured the size of the deep intra-abdominal fat deposits which may be the true mediator in the clustering of metabolic risk factors (see Figure 1) variously described as "Syndrome X" (Reaven, 1988), the "deadly quartet" (Kaplan, 1989), or the insulin resistance syndrome (Reaven & Chen, 1996). Hypertension and severe obesity have increased to epidemic proportions amongst black females in South Africa and there is some concern that this combination may also increase their risk of type 2 diabetes through down regulation of the insulin receptors (Joffe & Seftel, 1994). Once this happens, their risk for coronary heart disease (CHD) may increase dramatically judging from the Atherosclerosis Risk in Communities study (ARIC) where 27% of CHD cases in black American females could be attributed to diabetes compared to 8% of the cases in black men (Nabulsi *et al.*, 1995).

STATEMENT OF THE PROBLEM

The purpose of this study was to establish the relationship between body fat distribution and insulin related cardiovascular risk factors in black and white hypertensive females on anti-hypertensive drugs.

METHOD AND PROCEDURE

Subjects and procedures

Approval for this study was obtained from the Ethics Committee at the University of the North and the Soutpansberg Branch of the South African Medical and Dental Association. Sixty hypertensive female volunteers (30 black and 30 white) with uncomplicated essential hypertension were recruited through letters to 70 general practitioners as well as an interview on the local radio station and articles in the local newspapers. Only subjects who could supply proof of anti-hypertensive drug prescription (n=10) by general practitioners or subjects who were directly referred (n=50) by 12 doctors who responded to a letter of request, were included in the study. All the subjects had been on anti-hypertensive treatment for at least three months at the time of the study. After blood testing had been done six black females were found to be diabetic, but they were not excluded as the study would then no longer be a true reflection of hypertensive females who were on treatment for "uncomplicated essential hypertension".

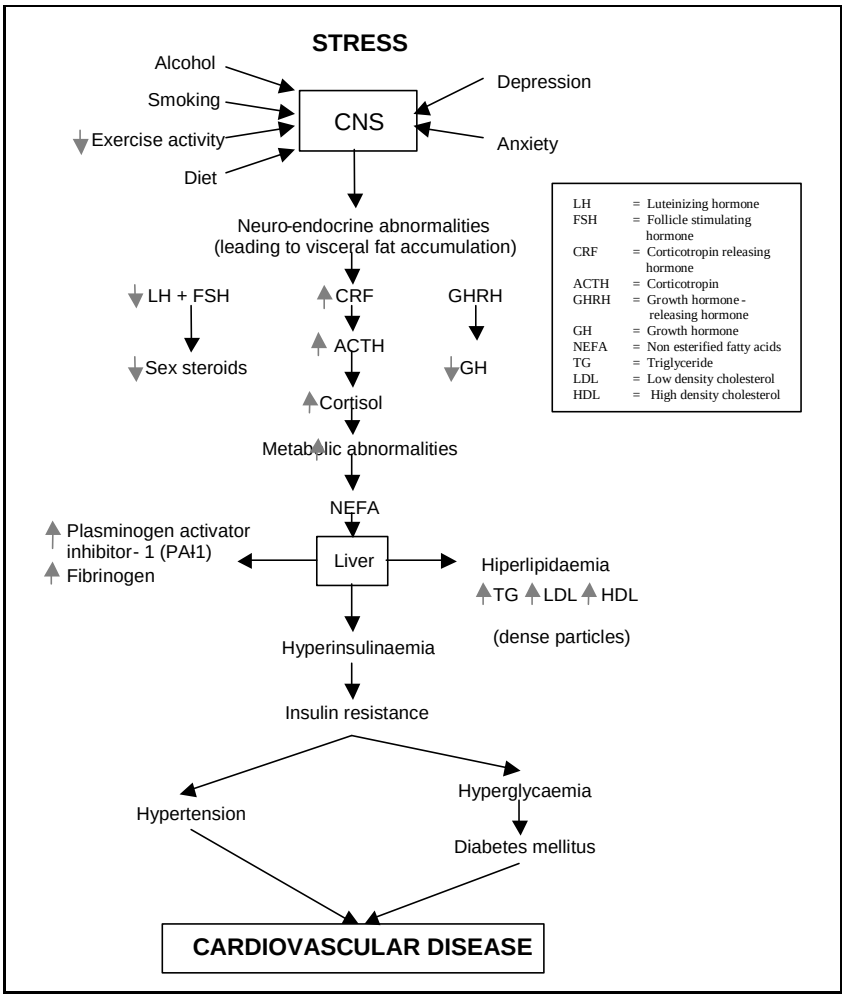

Figure 1. **CASCADE OF CENTRAL OBESITY AND ITS COMPLICATIONS**
(adapted with permission from Van der Merwe, 1997)

Body Mass Index

Subjects were weighed in their underclothes on an electronic scale to nearest 0.5 of a kilogram. Body height was measured with a Holtain anthropometer to the nearest 0.1centimeter. Body mass Index (BMI) was calculated as kilogram weight per height in meters squared (Heyward & Stolarczyk, 1996).

Waist to Hip ratio (WHR)

Waist and hip circumferences were measured with a steel tape according to the descriptions of Heyward and Stolarczyk (1996). Waist to hip ratio was calculated from the waist circumference measured in centimeters at the narrowest part of the torso, divided by the hip circumference

measured in centimeters at the level of the maximum extension of the buttocks.

Ultrasound measurements

B-mode ultrasound measurements of subcutaneous and intra-abdominal fat layer thickness were taken with a Siemens sonar machine (Sonoline Prima Model). The site of measurement was 5 cm from the umbilicus on the xipho-umbilical line with the subject in a recumbent position with her heels, buttocks and shoulders in contact with the table (Armellini *et al.*, 1993). A 5 MHz transducer was used for the measurement of subcutaneous fat thickness and a 3.5 MHz transducer for visceral thickness. Thickness of subcutaneous fat layers was measured directly from frozen images on the screen by electronic calipers which were placed at the skin-fat and fat-muscle interfaces. Visceral fat layers were measured from the internal face of the abdominal muscle to the anterior wall of the aorta as described by (Armellini *et al.*, 1993). All the measurements were done by a practicing gynaecologist at the Pietersburg Medical Centre.

Computed tomography scan measurements

Computed tomography scans were done at the level of the umbilicus with a General Electric CT pace. The following radiographic parameters were used: thickness of the slice 10 mm, 120 kV, 180 mA and 2 seconds scanning time. Subjects were in the supine position and photographic images were taken in resting expiration. The region of interest was outlined with a light pen cursor and the number of pixels within the fat density range (-130 and -30 Hounfield Units) were assessed (Van der Merwe, *et al.*, 1996). The cross sectional area of intra-abdominal (including retroperitoneal, mesenteric and omental adipose tissue) fat was calculated according to the anatomical boundaries as described by Kvist *et al.* (1986) and Kvist *et al.* (1988).

Blood pressure

Subjects were sitting in a comfortable chair, which provided back support during measurement, which was done according to the 1993 guidelines of the World Health Organisation/International Society of Hypertension (WHO/ISH, 1993). Blood pressure was measured after the subjects had been seated for several minutes in a quiet room and the measurement was done with a Dyna Pulse 200M computer based blood pressure monitoring and tracking system. Great care was taken to avoid tension in the arm muscles and the forearm was supported with the cubital fossa at heart level. Cuff sizes were varied according to the circumferences of the mid upper arms of the subjects. Cuffs were rapidly inflated manually where after deflation took place automatically according to a pre-programmed speed of air release. After the first measurement, two more measurements were taken at five-minute intervals. The average of the three measurements was calculated.

Blood Tests

The majority of the blood tests were done to identify subjects with metabolic risk factors associated with the insulin resistance syndrome such as high fasting insulin, glucose, triglyceride, apoprotein B, fibrinogen and uric acid levels, as well as low apoprotein A and HDL cholesterol levels. Lipoprotein (a) may not be associated with the insulin resistance syndrome, but it was done because it may be a potent predictor of CHD, especially in black subjects (Morris, 1990). Venous samples were taken at Du Buisson Pathologists in Pietersburg after an overnight fast of 10 hours. The samples were analysed at their clinical trials division in Lynnwood, Pretoria. The following methods were used: Glucose - Beckman

CX7 glucose oxygen depletion method; Insulin- Radioimmunoassay with the Coat-A-Count kit from Diagnostic Products Corporation; Total cholesterol - Beckman CX7 Enzymatic method; HDL cholesterol - Beckman CX7 Spectrophotometric method; LDL cholesterol- Calculated with the Friedewald *et al.* (1972) formula: LDL cholesterol = total cholesterol - [HDL cholesterol + triglyceride / 2.18]; Uric acid - Beckman CX7 Enzymatic Trinder method; Apolipoproteins (a) A1 and B - Quantitative determination by immunoprecipitin analysis (Incstar); Fibrinogen - ACL_{TM} (automated coagulation laboratory) fibrinogen nephelometric method; Plasminogen - ACL_{TM} Chromogenic method. Insulin resistance was calculated from fasting glucose and insulin concentrations according to the computed-solved homeostasis model of Matthews *et al.* (1985). According to this model, the plasma glucose: insulin response of normal subjects with 100% ˙-cell function and C-peptide response will be: insulin = 5 (glucose - 3.5) and the amount of deviation of basal plasma glucose and insulin levels from these values will be indicative of the degree of ˙-cell disfunction and insulin resistance. If it is assumed that normal-weight subjects younger than 35 years have 100% ˙-cell function and an insulin resistance value of 1, the following formulas can be used to calculate ˙-cell function and insulin resistance:

˙-cell function (%) = 20 x insulin / (glucose -3.5)
Insulin resistance = insulin / ($22.5e^{linglucose}$) (Matthews *et al.*, 1985).

Statistical analysis

Statistical analysis was done on a personal computer with a Statistical Package for Social Sciences (SPSS for Windows version 8). In this package the statistical methods used for analysing continuous data are based on the assumption that the data comes from a population with normally distributed values. In those cases where the data was not normally distributed logarythmic transformation of the data was used. The statistics that were done included; descriptive statistics (means and standard deviations), comparison between groups (Independent-samples T-test), relation between two variables (Bruvis Pearson product moment correlation co-efficients, regressions and scatterplots), relation between more than two variables (multiple linear regression). This latter method was not only used to build models, but it was also used to remove the effect of "nuisance variables" on the relation between two variables of interest.

RESULTS

Physical characteristics

TABLE 1. **MEANS, STANDARD DEVIATIONS AND SIGNIFICANCE OF DIFFERENCES IN *ANTHROPOMETRIC* MEASUREMENTS AND ABDOMINAL FAT DISTRIBUTIONS IN BLACK AND WHITE HYPERTENSIVE FEMALES**

Measures	Black (n = 30)	White (n = 30)	P value
Age (years)	46.93 ± 11.10	52.23 ± 9.81	0.055
Body mass (kg)	87.42 ± 17.46	88.22 ± 22.65	0.878
Height (m)	159.35 ± 5.08	165.36 ± 6.64	0.000*
BMI (kg/m^2)	34.39 ± 6.60	32.08 ± 6.77	0.187
Waist (cm)	96.94 ± 13.39	95.48 ± 15.03	0.693
Hip (cm)	120.02 ± 13.33	118.84 ± 16.58	0.762
WHR	0.80 ± 5.70	0.79 ± 5.61	0.540
Sonar 1 (mm)	56.22 ± 22.25	53.60 ± 21.91	0.651
Sonar 2 (mm)	25.44 ± 8.68	23.36 ± 7.13	0.317
CT (1) (cm^2)	131.17 ± 63.89	162.76 ± 63.97	0.061
CT (2) (cm^2)	437.58 ± 164.50	342.79 ± 145.89	0.020*
CT1/CT2	0.31 ± 0.147	0.52 ± 0.247	0.000*

* = Statistically significant
Sonar 1 = intra-abdominal sonar
Sonar 2 = subcutaneous abdominal sonar
CT (1) = visceral fat area
CT (2) = subcutaneous abdominal fat area
CT1/CT2 = ratio of visceral to subcutaneous abdominal fat areas

The anthropometric results as well as sonar and computed tomography scan measurements are given in Table 1. It is clear from the BMI values in Table 1 that black subjects were slightly but not significantly ($p<0.187$) more obese than the white subjects (34.39±6.60 vs. 32.08±6.77 kg/m^2) and that they had similar ($p<0.540$) waist to hip ratios (0.80±5.70 vs. 0.79±5.61). Black subjects had insignificantly ($p<0.061$) smaller visceral fat areas than white subjects (131.17±63.89 vs. 162.76±63.97 $cm^{2)}$ but they had significantly ($p<0.020$) larger subcutaneous abdominal fat areas (437.58±164.50 vs. 342.79±145.89 $cm^{2)}$ despite the similarity of their WHR's. Although the difference in visceral fat area was not statistically significant, it should be noted that six black subjects were diabetic and they all had large visceral fat areas with values ranging between 177 and 265 cm^2. When the values of the six diabetic subjects were excluded from the calculations there was a highly significant ($p<0.000$) difference in the visceral fat areas of black and white females (107.53±9.10 vs. 162.76±63.97 cm^2), as can also be seen in Figure 2.

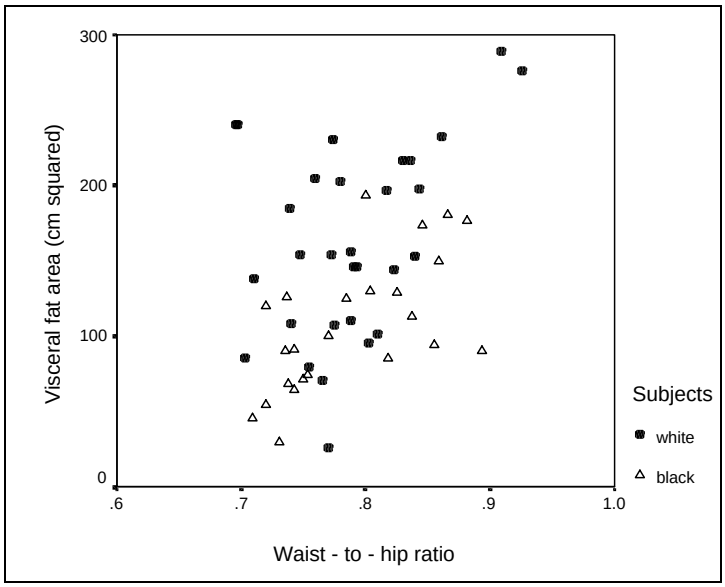

FIGURE 2. **RELATION BETWEEN WAIST-TO-HIP RATIO AND VISCERAL FAT AREAS IN NON-DIABETIC BLACK AND WHITE HYPERTENSIVE FEMALES**

The visceral fat of the six diabetic females were significantly ($p<0.008$) more than that of their non-diabetic peers with fasting glucose levels lower than 5.5 mmol/l (n=20) irrespective of whether visceral area was measured by CT scan (225.70±33.65 vs. 104.38±44.44 $cm^{2)}$ or visceral thickness was measured by sonar (80.90±21.24 vs. 50.76±17.30 mm). The two black diabetic subjects whose sonars can be seen in Figure 3, for example, had visceral fat layers (74.7 and 99.1 mm) that were four times thicker than their subcutaneous abdominal fat layers (18.6 and 23.1 mm), whereas visceral fat layers were on average slightly more than two times thicker than subcutaneous fat layers in the whole group of black subjects (56.22±22.25 vs. 25.44±8.68 mm). Visceral fat thus seems to be a good predictor of fasting glucose levels in black subjects as can be seen in Figure 4, where 62% of the variance in their fasting glucose levels could be explained by the size of their visceral fat areas. This relationship was independent of possible confounders such as BMI, WHR, % body fat, waist circumference and age. Even after the omission of the data from the diabetic subjects, the relationship persisted and although it was weaker $R^2=0.24$, it was still significant (Figure 5). Visceral fat areas, as measured by computed tomography, not only correlated significantly with fasting glucose levels in black subjects (Figure 4), but it was also the best correlate of most other insulin related metabolic disturbances in black and white subjects (Table 2). Waist to hip ratio was not a good predictor of insulin related metabolic disturbances. In fact, it was not even better than overall obesity (BMI) in this regard. This latter result seems to be an indication that WHR may not be such a good surrogate of visceral fat as is generally accepted. As can be seen in Figure 6B, WHR could explain only 16% of the variation in the size of visceral fat areas in white subjects, compared to the 82% that could be explained by the thickness of visceral fat layers as measured by sonar (Figure 6A). Sonar did not seem to be such a good predictor of visceral fat area in black subjects but it was also better than WHR (R^2 of 0.61 vs. 0.36).

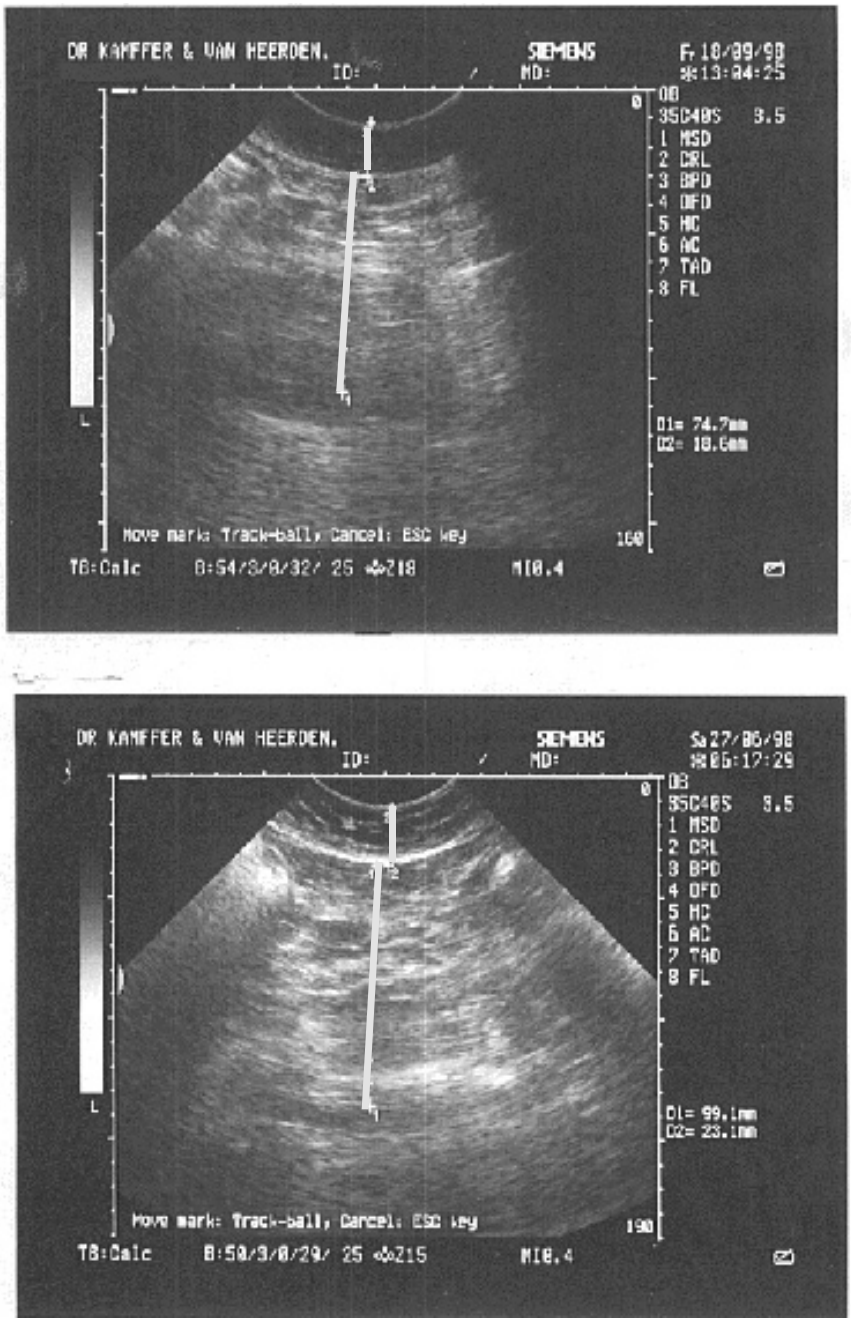

FIGURE 3. **ULTRASOUND MEASUREMENT OF SUBCUTANEOUS ABDOMINAL AND VISCERAL FAT IN TWO BLACK DIABETIC SUBJECTS**

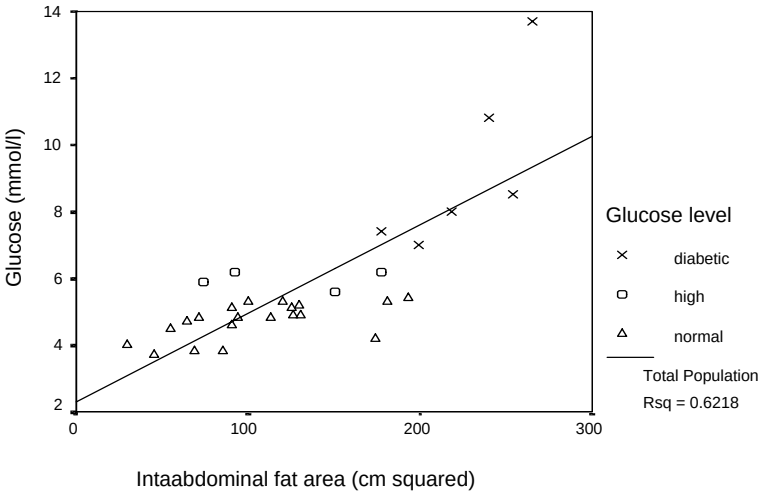

FIGURE 4. **RELATION BETWEEN VISCERAL FAT AREAS AND FASTING GLUCOSE LEVELS IN BLACK AND WHITE FEMALE HYPERTENSIVES (R^2=0.62)**

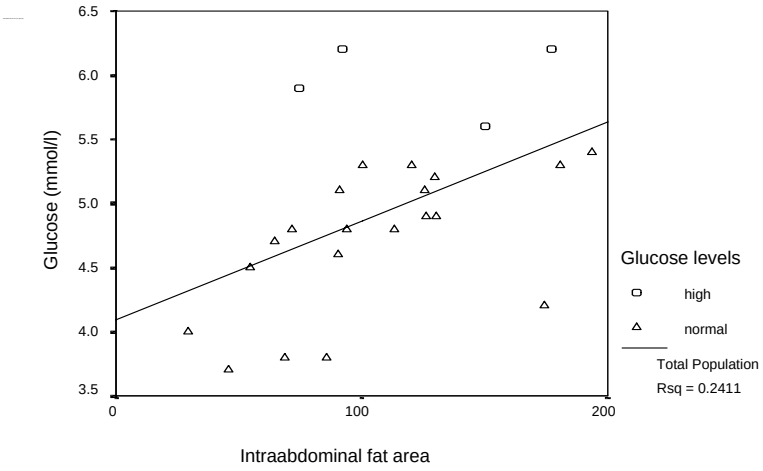

FIGURE 5. **RELATION BETWEEN VISCERAL FAT AREAS AND FASTING GLUCOSE LEVELS IN NON-DIABETIC BLACK AND WHITE FEMALE HYPERTENSIVES (R^2=0.24)**

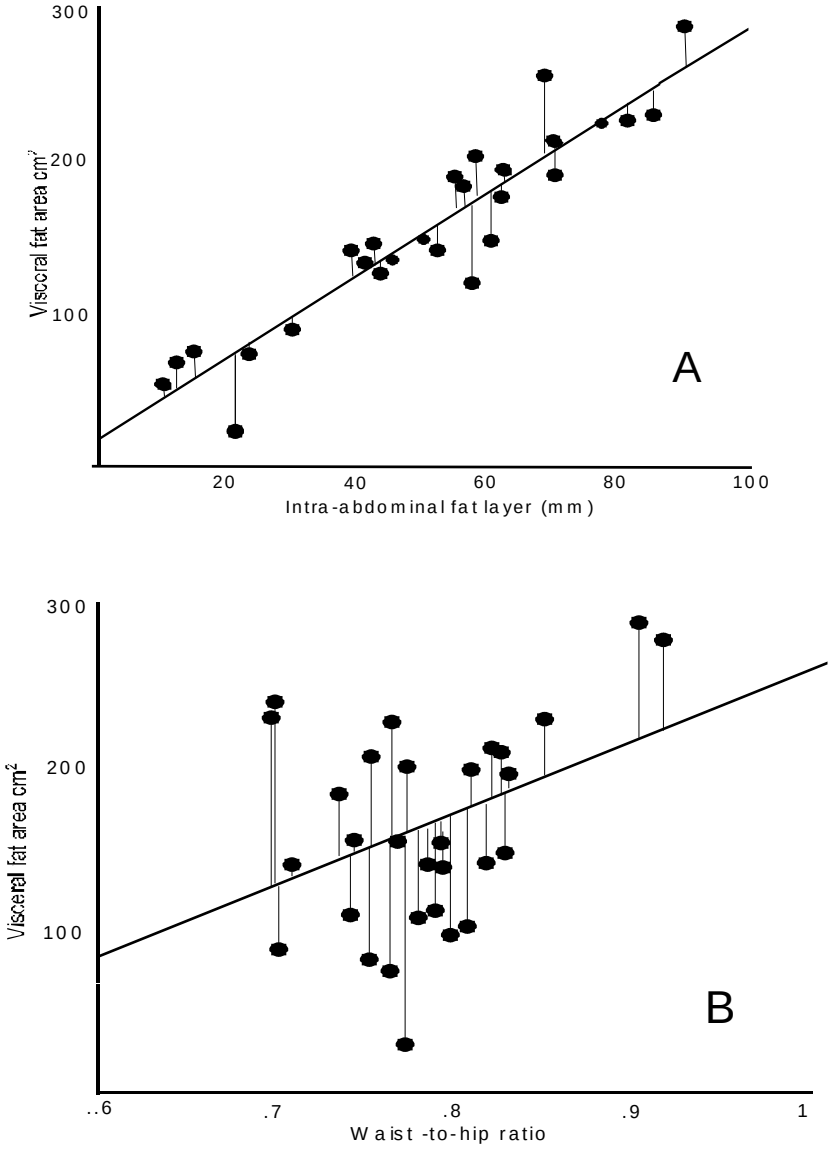

FIGURE 6. **REGRESSION LINES SHOWING DIFFERENCES BETWEEN MEASURED VISCERAL FAT AREAS (DOTS) AND VISCERAL FAT AREAS AS PREDICTED FROM INTRA-ABDOMINAL FAT LAYER THICKNESS (R^2=0.82) AND WHRS (R^2=0.16) IN WHITE FEMALES**

TABLE 2. **CORRELATION MATRIX OF FAT MEASUREMENTS AND METABOLIC PARAMETERS IN BLACK AND WHITE HYPERTENSIVE FEMALES**

	Insulin	Insulin Resistance	Triglyceride	HDL-C	LDL-C to LDL apo B	Albumin/Creatinine Ratio	Glucose	Fibrinogen	UricAcid
Visceral fat area in black subjects	0.3	0.7	0.6	-0.2	-0.4	0.37	0.79	0.2	0.5
Visceral fat area in white subjects	0.5	0.6	0.6	-0.4	-0.6	0.24	0.29	0.18	0.4
Thickness of intra-abdominal fat layer in white subjects	0.4	0.42	0.28	-0.4	-0.4	0.2	0.23	0.2	0.32
Waist circumference in black subjects	0.29	0.33	0.37	-0.3	-0.3	0.15	0.56	0.38	0.49
Waist-to-hip ratio in white subjects	0.1	0.1	0.38	-0.4	-0.2	-0.1	0.6	-0.1	0.14
Waist-to-hip ratio in black subjects	0.13	0.15	0.41	-0.49	-0.17	0.51	0.31	0.13	0.51
BMI in black subjects	0.15	0.35	0.26	-0.27	-0.25	0.39	0.45	0.34	0.39
BMI in white subjects	0.54	0.55	0.11	-0.37	-0.18	0.34	0.23	0.03	0.34

= $p<0.05$

The blood serum and urine values of black and white subjects are compared in Table 3.

Various South African studies reported higher total cholesterol levels in white females (values ranging from 5.4 to 7.26 mmol/l) compared to black females (values ranging from 4.73 to 5.23 mmol/l) (Oelofse *et al.*, 1996; Seedat *et al., 1992*; Seedat *et al.*, 1993; Mollentze *et al.*, 1995; Steenkamp *et al.*, 1990). It, therefore, was not surprising that black subjects in the present study had significantly ($p<0.000$) lower total cholesterol values than their white counterparts (5.01±1.02 vs. 6.05±1.03 mmol/l).

TABLE 3. **MEANS, STANDARD DEVIATIONS AND SIGNIFICANCE OF DIFFERENCES BETWEEN METABOLIC RISK FACTORS IN BLACK AND WHITE HYPERTENSIVE FEMALES**

	Black (n =30)	White(n =30)	P value
Total cholesterol (mmol/l)	5.01 ± 1.02	6.05 ± 1.03	0.000*
LDL cholesterol (mmol/l)	3.12 ± 0.90	3.78 ± 0.99	0.01*
HDLcholesterol (mmol/l)	1.34 ± 0.32	1.46 ± 0.42	0.238
HDL/Total cholesterol	27.90 ± 8.21	24.37 ± 6.20	0.065
Triglyceride (mmol/l)	1.20 ± 0.66	1.80 ± 0.81	0.000*
apo B (g/L)	1.01 ± 0.31	1.19 ± 0.21	0.012*
apo A1(g/L)	1.48 ± 0.23	1.56 ± 0.32	0.254
Lp (a) (mg/dl)	30.79 ± 25.68	11.75 ±13.31	0.000*
LDL chol/ LDL apo B	1.30 ± 0.17	1.31 ± 0.21	0.884
Uric acid (mmol/l)	0.34 ± 0.095	0.38 ± 0.072	0.045*
Fibrinogen (g/L)	4.06 ± 0.82	3.49 ± 0.94	0.016*
Albumin/creatine ratio	1.68 ± 2.13	1.62 ± 2.07	0.906
Plasminogen activity (%)	112.43 ± 15.26	112.63 ±18.56	0.964
Insulin (µU/ml)	12.89 ± 6.02	13.04 ± 9.03	0.118
Glucose (mmol/l)	5.78 ± 2.14	5.11± 0.65	0.111
Beta-cell function (%)	143.97 ± 95.93	194.59 ± 110.81	0.035*
Insulin resistance (HOMA units)	3.4 ± 2.24	3.74 ± 2.24	0.539

- = Statistically significant

Given the fact that about 67% of total cholesterol is carried by LDL particles, it is to be expected that black subjects would have significantly lower ($p<0.01$) LDL cholesterol levels than white subjects (3.12±0.90 vs. 3.78±0.99 mmol/l). About 93% of apo B is carried on the LDL particles and it is therefore no surprise that black subjects also had significantly lower ($p<0.012$) apo B levels (1.01±0.31 vs. 1.19±0.21 g/L). If these lipid values are seen in conjunction with the fact that black subjects also had significantly ($p<0.000$) lower triglyceride levels (1.20±0.66 vs. 1.80±0.81 mmol/l) but not significantly higher HDL-C to total cholesterol ratios ($p<0.065$) than their white counterparts (27.90±8.21 vs. 24.37±6.20), black female subjects seem to be at lower risk of CHD in this study. This may however not apply to black diabetic subjects as indicated later in the text. A combination of HDL - C lower than 1.03mmol/l and triglyceride higher than 1.69 mmol/l, proved to be a particularly potent atherogenic factor for females in the Framingham study (Oberman *et al.*, 1992) and five white and two black subjects in the present study had such a combination. It should also be noted in Table 4, that the two black subjects with this combination (subjects numbers 16 and 21) also had high apo B levels (1.5 and 1.8 g/L), small dense LDL - C particles as evident from their LDL - C to LDL apo B ratios (1.15 and 1.08), high uric acid levels (0.38 and 0.61 mmol/l) and high insulin levels (28 and 12.1 µU/ml). If this is seen in conjunction with their

particularly low HDL -C levels (0.94 and 0.95 mmol/l) and HDL to total cholesterol ratios (15 and 14) but high triglyceride levels (2.18 and 2.31 mmol/l), it is evident that they may be at high risk of CHD in the future. As can be seen in Table 4 the five white subjects all had very high triglyceride levels (values ranging from 2.49 to 3.65 mmol/l) and low HDL -C to Total cholesterol ratios (values ranging from 13 to 20). Four of them had high insulin levels (values ranging from 15.2 to 44.3 µU/ml) and small dense LDL-C particles (LDL - C to LDL apo B ratios ranging from 0.93 to 1.14).

TABLE 4. **CLUSTERING OF METABOLIC RISK FACTORS IN SUBJECTS WITH HIGH TRIGLYCERIDE BUT LOW HDL CHOLESTEROL LEVELS**

Sub	Tri-glyceride mmol/l	HDL-C mmol/l	HDL-C to total-C ratio	apo B g/l	LDL-C to LDL apoB ratio	Insulin µU/ml	Insulin resistance HOMA units	Uric acid mmol/l	A/C ratio	glucose mmol/l	SBP mm Hg
16	2.18	0.94	15	1.5	1.15	28	6.46	0.38	1.9	5.2	160
21	2.31	0.95	14	1.8	1.08	12.1	3.02	0.61	1.2	5.6	132
36	2.63	0.85	20	1	0.93	44.3	10.47	0.36	7.6	5.3	158
39	2.64	0.9	13	1.5	1.38	15.2	3.89	0.42	1.2	5.7	171
49	3.65	0.99	15	1.4	1.14	19.4	5.13	0.46	0.8	5.9	162
58	2.49	0.87	18	1.1	1.09	6.8	1.41	0.37	5.4	4.7	173
59	2.58	0.99	18	1.3	1.1	39.2	8.51	0.44	4.9	4.9	235

sub = subject; A/C ratio = urinary albumin to creatinine ratio; SBP = systolic blood pressure

Small dense LDL-C particles may easily penetrate the vascular wall especially with transendothelial leakiness as evident from micro-albuminuria (Yudkin *et al.*, 1988) or an increase in the albumin to creatinine ratio (A/C>3). It is therefore particularly alarming that three of the five white subjects (36, 58 and 59) had urinary albumin creatinine ratios ranging from 4.87 to 7.56, especially given the fact that all of them had poorly controlled blood pressure with systolic blood pressure values ranging from 158 to 235 mmHg. Both the black (16 and 21) and three of the five white subjects (36, 39 and 49), had fasting glucose values equal to or higher than 5.2 mmol/l, which may be indicative of an increased risk of future diabetes, especially given the fact that they were all insulin resistant and hyperinsulinaemic as well. Besides the subjects indicated in Table 4 there were six more black women and 12 more white women who had three or more of the metabolic risk factors as listed in Table 4. It was disconcerting that four of these six black women

were diabetic and the fact that three of the four had triglyceride levels higher than 1.82 mmol/l did not augur well for their future risk of CHD. This should be seen in conjunction with the fact that three of the four subjects with elevated triglyceride levels also had a combination of small dense LDL particles (LDL-C to LDL apo B ratios ranging from 0.95 to 1.09) and micro-albuminuria (urinary albumin to creatinine ratios ranging from 3.23 to 9.55). Hypertriglyceridaemia was the most common metabolic disorder amongst the 12 white subjects as eight of them had triglyceride levels ranging from 1.69 to 3.14 mmol/l. As was the case with the black subjects, high triglyceride levels tended to cluster with hyperapo B and small dense LDL particles. This is evident from the fact that five of the eight subjects had apo B levels ranging from 1.3 to 1,7 g/L and four of the eight had small dense particles (LDL cholesterol to LDL apo B ratios ranging from 0.83 to 1.17). It should be noted that high triglyceride levels were related to small LDL particles even in white subjects with low LDL cholesterol levels who would normally be regarded as a low CHD risk group. In fact, as can be seen in Figure 7, 75% of the variance in LDL particle size in this group could be explained by triglyceride levels and six of the 11 subjects had small dense LDL particles (LDL cholesterol to LDL apo B ratio <1.17) which may be particularly atherogenic (Sniderman & Cianflone, 1995).

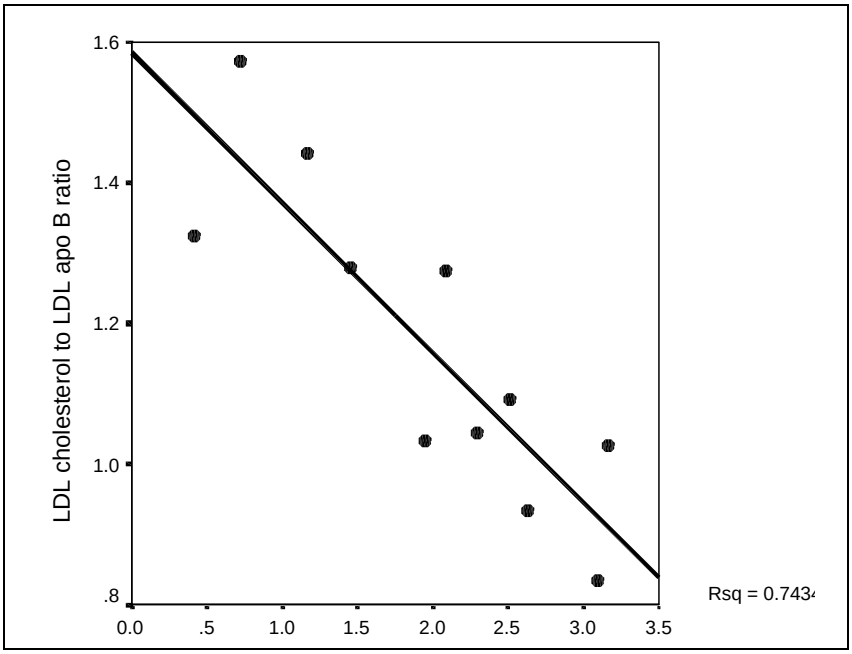

FIGURE 7. **RELATION BETWEEN SERUM TRIGLYCERIDE LEVELS AND LDL PARTICLE SIZE IN WHITE FEMALES WITH LOW LDL CHOLESTEROL LEVELS (R^2=0.74)**

Reaven (1994) described hypertriglyceridaemia as the best established downstream consequence of insulin resistance, and the present study not only seems to confirm this, but it also shows that triglyceride may be the mediator in the lipid abnormalities associated with the

insulin resistance syndrome. White subjects with triglyceride levels higher than 2.3 mmol/l (n=9), for example, had significantly ($p<0.000$) smaller LDL particles than their peers with triglyceride levels lower than 1.6 mmol/l (n=14) as evident from their LDL-C to LDL apo B ratios (1.08±0.16 vs. 1.44±0.13). White subjects with such high triglyceride levels also had significantly ($p<0.04$) lower HDL -C levels (1.15±0.4 vs. 1.61±0.38, $p=0.04$) but significantly ($p<0.003$) higher urinary Albumin Creatinine ratios than those with low triglyceride levels (3.80±2.99 vs. 0.68±0.45). Black subjects with triglyceride levels higher than 1.6 mmol/l (n=6) had significantly ($p<0.036$) higher fasting glucose (7.31±2.86 vs. 4.83±0.93 mmol/l), insignificantly higher ($p<0.073$) insulin resistance (5.37±2.98 vs. 2.54±1.11 HOMA units) and lower ($p<0.002$) HDL -C to Total cholesterol ratios (20±7.09 vs. 32.75±6.71) than their peers (n=16) with triglyceride levels lower than 1 mmol/l. This result seems to be an indication that the current triglyceride cut off point (2.3 mmol/l) may be too high to identify black patients who may be at risk of CHD.

Black subjects had significantly ($p<0.016$) higher fibrinogen levels than their white counterparts (4.06±0.82 vs. 3.49±0.94 g/L) (Table 3), which may be an indication of a higher blood clotting potential, especially if it is seen in conjunction with their significantly ($p<0.000$) higher Lp (a) levels (30.79±25.68 vs. 11.75±13.31 mg/dl). Particularly disconcerting was the fact that 10 black subjects had a combination of fibrinogen levels higher than 4 g/L and Lp (a) higher than 30 mg/dl. Fortunately most of the black subjects with high Lp (a) levels did not have concomitantly high LDL cholesterol levels, but there was one subject with an Lp (a) level of 83.4 (mg/dl), an apo B level of 1.8 g/L, a LDL cholesterol level of 4.69 mmol/l and a fibrinogen level of 5.1 g/L, who should have been seriously considered for lipid lowering drug treatment. Theoretically the black subjects could be protected against blood clotting due to a higher plasminogen activity but, as indicated in Table 3, there was not a significant ($p<0.964$) difference in the plasminogen activity of black and white subjects (112.43±15.26 vs. 112.63±18.56 %). Blood pressure control was equally poor ($p<0.153$) in black and white females as evident from their average systolic (144.73±16.01 vs. 151.83±21.59 mm Hg) and diastolic blood pressures (81.3±11.36 vs. 85.10±9.82 mm Hg). There were eight black (27%) and 13 white (43%) subjects with isolated systolic hypertension (systolic blood pressure higher than 140 mm Hg and diastolic pressure lower than 90 mm Hg). Particularly striking was the high variability of systolic blood pressure in four white subjects, with values ranging between 150 and 190 mm Hg. It was also disconcerting that all the white subjects with large metabolic risk clusters, as indicated in Table 4, had uncontrolled blood pressure. The rest of the white subjects with large metabolic risk clusters were not much better off in this respect and in total 13 of the 17 white subjects with large metabolic risk clusters had uncontrolled blood pressure. This seems to be an indication that blood pressure control may not be achieved in white hypertensive females unless there is a concomitant improvement in their metabolic profiles. Although there is a fervent hope that this may be possible merely by prescribing metabolically neutral drugs like angiotensin converting enzyme inhibitors and calcium channel blockers, it may be more realistic to use these drugs in conjunction with lifestyle modification.

DISCUSSION

Black females may have smaller visceral fat areas than white females as evident from abdominal CT scans done on urban (Van der Merwe *et al.*, 1996) and rural females (Phoshoko, 2000). Van der Merwe *et al.* (1996), for example, found that healthy obese black females had smaller visceral fat areas than their white counterparts (115.5 vs. 148.5 cm^2) despite the fact that they were carefully matched for WHR (0.81 vs. 0.79), percentage body fat (41 vs. 40.2%) and age (37 years). It was interesting to note that the average visceral fat area (116.5 cm^2) of obese, but non-diabetic rural black females under the age of 50 (Phoshoko, 2000) was equal to that (115.5 cm^2) of similarly aged healthy Johannesburg black females (Van der Merwe *et al.*, 1996) and slightly larger than that of their non-diabetic peers in the the present study (100.42 cm^2). The average visceral fat area of these rural black females (116.5 cm^2) was however considerably lower than that of white females (149.87cm^2) in the present study or that (148.5 cm^2) of Van der Merwe *et al.* (1996). Non-diabetic rural black females older than 50 had significantly ($p<0.006$) larger visceral fat areas (139.5±46.7 vs. 116.5±36.4 cm^2) than their younger counterparts as could have been expected (Phoshoko, 2000), but once again it was considerably smaller than that of their white peers (173.81 cm^2) in the present study. If the relatively large numbers of females that were scanned in the present study (n=60) and in the rural study of Phoshoko (2000) (n=85) are taken into consideration, as well as the fact that they were all scanned by the same radiologist in Pietersburg, it seems likely that black females may carry less visceral fat than white females. This may be despite the higher general obesity levels of black females, in fact, it should be noted that rural black females scanned by Phoshoko (2000) had a higher average BMI than white subjects (35.4 vs. 32,08 kg/m^2) in the present study. It seems possible that the smaller visceral fat areas of black subjects in the present study may be one of the reasons why fewer of them had large insulin related metabolic risk clusters compared to white subjects (8 vs. 17).

There are various confounders that may explain the smaller visceral fat areas in black females, in particular lifestyle related factors such as higher levels of physical activity and lower levels of stress, smoking, alcohol consumption and fat intake, but it does not seem to be the case in this study. Although it is not indicated in the results, it should be noted that very few black (n=3) or white (n=4) females were smokers, their alcohol consumption was universally ($p<0.10$) low (0.25 vs. 1.45 g/day), they were equally ($p<0.312$) inactive (daily energy expenditures of 28.9 vs. 29.88 kcal/kg) and they had similar ($p<0.58$) aerobic capacities (23.12 vs. 21.90 ml O_2 /kg/min). It should also be noted that black females scored significantly ($p<0.05$) higher than their white counterparts on the Tension-Anxiety (12.30 vs. 8.97) and Depression-Dejection (17.63 vs. 12.03, $p<0.045$) scales of the POMS test developed by McNair *et al.*, 1971). Black and white females consumed equal ($p<0.437$) amounts of fat per day (84.02 vs. 91.14 g/day but black females consumed insignificantly higher ($p<0.159$) amounts of total energy (2791.17 vs. 2485.93 kcal/day). Overall this seems to indicate that black and white females are equally exposed to coronary deathstyles, unlike the past where only white subjects could afford these lifestyles (Seftel, 1994). Urbanization and alienation from traditional cultures and lifestyles may have particularly detrimental effects on the blood pressure and insulin functioning of black migrants. Increases in the blood pressure of black people who migrated from a rural to an urban environment were well documented in Kenya (Sever & Poulter, 1989), Zimbabwe (Mufunda *et al.*, 1993) and Malawi (Simmons *et al.*, 1986) and a poignant example of what may happen to insulin functioning is the Australian aborigines who became insulin resistant within weeks after migration (O'Dea, 1992). The

real challenge of future researchers would therefore be to identify high-risk subjects at an early stage and judging from the present study a central or intra-abdominal fat distribution may be a potent CHD risk indicator. Visceral fat area not only correlated significantly with fasting glucose levels (r=0.79) and insulin resistance (r=0.70) in black females but also with most of the other CHD risk factors associated with the insulin resistance syndrome. As can be seen in Table 2 this applied equally to black and white subjects. It is unfortunate that WHR is so widely used as a surrogate for visceral fat distribution and CHD risk in epidemiological surveys in South Africa is as quite a large number of high-risk subjects may slip through the net by virtue of their low WHRs. In the present study for example, 17 white and eight black subjects had three or more insulin related metabolic disturbances despite the fact that their WHRs were quite similar to that of subjects without clustering of metabolic risk factors. It should also be noted in Figure 3 that some of the white subjects had visceral fat areas larger than 200 cm^2 despite WHRs of only 0.7. Black diabetic females showed even larger discrepancies as they all had large visceral fat areas but WHRs ranging from 0.78 to 0.88. Sonars seemed to be a good substitute for CT scans in identifying white females with large intra-abdominal fat areas and high CHD risk, while even waist circumference may be better than WHR in this regard. Després *et al.* (1995) suggested that a waist circumference of 1 m should be used as a cut-off point for identifying subjects at risk of CHD and it was striking to note that black diabetic subjects all had waist circumferences larger than 105 cm. Although smaller numbers of black females may be susceptable to visceral fat accumulation, it may effect them just as adversely as white females, if not more so. It was particularly disconcerting that six of the eight black females with visceral fat areas larger than 177 cm^2 were diabetic of whom four had three or more insulin related metabolic risk factors. It can be envisaged that large increases in the visceral fat stores of some black (diabetic) and most white subjects in the present study would have increased the direct supply of free fatty acids to their livers via the portal vein (Figure 1). In fact, Björntorp (1996) estimated that 50 % or more of the FFA in circulation could come from enlarged visceral adipocytes, which are highly sensitive to lipolytic stimuli. Once the liver is exposed to excessive amounts of FFA, it may reduce insulin binding to the hepatocytes which in turn may have a large impact on peripheral insulin concentrations as the liver normally removes about 40% of the insulin secreted by the pancreas (Osei & Schuster, 1994). In this way elevated FFA of visceral origin may not only lead to acute hyperinsulinaemia, but also to longer term peripheral insulin resistance through down- regulation of the receptors (Groop *et al.*, 1991). Insulin normally co-ordinates lipid metabolism very precisely but once insulin resistance develops, insulin may lose its antilipolytic ability with a consequent increase in lipolysis and the amount of FFA in circulation (Frayn *et al.*, 1996). This makes it extremely difficult to disentangle cause and effect in the relationship between FFA and insulin sensitivity. However, it is clear (Figure 8) that there may be a self-perpetuating cycle between insulin resistance and elevated plasma FFA concentrations.

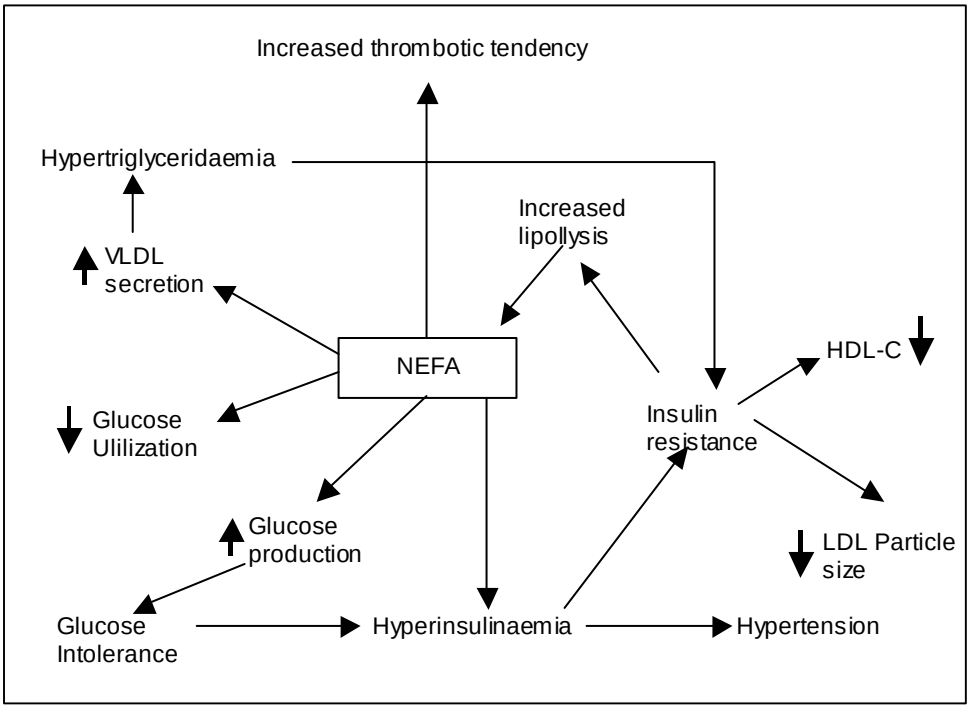

FIGURE 8. **NON-ESTERIFIED FATTY ACIDS AS THE CENTRAL FEATURE OF THE INSULIN RESISTANCE SYNDROME**

It can be envisaged that increased oxidation of FFA in the portal vein system of viscerally obese subjects may lead to a build-up of acetyl-CoA which in turn may stimulate the enzyme pyruvate carboxylase as the first step towards hepatic gluconeogenesis (Van der Merwe, 1997). Once the hepatic output of glucose increases in viscerally obese subjects, the extra glucose will be competing with FFA for the same oxidation pathway in the skeletal muscle where any increase in FFA supply and oxidation will cause a build-up of long chain acyl-CoA and acetyl-CoA, which will inhibit the pyruvate dehydrogenase enzyme, and consequently also glucose oxidation (Randle *et al.*, 1963). The net result of an increase in FFA in the circulation may thus not only be an increase in glucose production, but also a decrease in glucose utilization (Figure 8). Such a sequence of events may result in chronic hyperglycaemia and glucose toxicity with downregulation of the insulin receptors and ultimately a reduction in insulin sensitivity (Rossetti *et al.*, 1990; Van der Merwe, 1997). This chain of events may not only initiate hyperglycaemia, but it may also sustain it in the long run, especially in viscerally obese subjects with a constant large supply of FFA to the liver.

Joffe and Seftel (1994) warned that obesity and hypertension in combination with decreased physical activity, repeated pregnancies and diabetogenic drugs, like the thiazides, may considerably increase the risk of diabetes in black females. The results of the present study seem to indicate that their concern may not be unfounded. The 20% of black subjects that were diabetic in the present study may seem very high at first glance, but it was in accordance with the results of Levitt and Mollentze (1995). They found three times more diabetics amongst rural black hypertensives on anti-hypertensive drug treatment, compared to

hypertensives who did not receive drug treatment (16.8% vs. 5%). The trend was the same amongst urban black hypertensives (19 vs. 9.4%). Phosoko (2000) reported that nine out of 94 (9.5%) obese black rural females subjected to glucose tolerance testing were diagnosed with type 2 diabetes. Greer *et al.* (2000) reported a diabetic incidence of only 1.6% amongst black females in the North Western Province, but it should be noted that they excluded all subjects receiving any form of chronic medication. It seems likely that a substantial number of these excluded subjects could not only have been hypertensive, but obese and diabetic as well, judging from the results of the present study. A striking feature of earlier reports on NIDDM amongst black South Africans was the low incidence of diabetic macrovascular disease, as well as the less pronounced elevations of serum lipoproteins and hemostatic factors (Adelstein *et al.*, 1979; Seftel *et al.*, 1978). Black diabetic females in the present study, however, were not only viscerally obese and insulin resistant, but they generally had high triglyceride, apo B, uric acid and fibrinogen levels as well as high albumin to creatinine ratios. These metabolic profiles were strikingly different from that of their non-diabetic peers and similar to that of white females with large metabolic risk clusters as indicated in Table 4. Given their adverse metabolic profiles, black diabetic subjects in the present study seem to be particularly at risk of CHD in the future, especially if it is taken into consideration that 27% of all CHD cases amongst black American females participating in the Atherosclerosis Risk in Communities study could be attributed to diabetes (Nabulsi *et al.*,1995).

The high triglyceride levels of diabetic subjects is a particular cause of concern, especially given the fact that high triglyceride levels was shown to be a more potent predictor of CHD amongst a large group of diabetics than total cholesterol levels (West *et al.*, 1983). Triglyceride rich lipoproteins may be the driving force behind lesion progression in small plaques (<50%) and the Monitored Atherosclerosis Progression Study (MARS) (Blankenhorn *et al.*, 1993), for example, reported atherosclerotic progression in 40-50% of the MARS patients despite the fact that their LDL cholesterol levels were aggressively lowered to levels below 2.59 mmol/L (Blankenhorn *et al.*, 1993). If it is taken into consideration that the small lesions may be particularly dangerous, because their thin fibrous caps are more likely to rupture and release their necrotic cores into the lumen, it is obvious that lowering of plasma triglyceride levels should be an important therapeutic target. Apart from its possible involvement in atherogenesis, hypertriglyceridaemia may also represent a procoagulent state involving derangements of both coagulation and fibrinolysis (Hamsten *et al.*, 1994). It may be dangerous to conclude that obesity is not a risk factor for cardiovascular disease in black females (Greer *et al.*, 2000) when 32% of the subjects are obese, and approximately 16% have triglyceride levels higher than 2.08 mmol/l and fibrinogen levels higher than 4.65g/L. It should also be noted that of all the cardiovascular risk factors measured by Greer *et al.* (2000) triglyceride was the strongest correlate of WHR ($r=0.424$, $p<0.001$). Most other epidemiological studies that have also downplayed triglyceride as an independent CHD risk factor were applicable to males whereas elevated plasma triglyceride levels may be particularly associated with increased risk for coronary heart disease in females, normal cholesterolaemic and diabetic individuals (Bradley & Gianturco, 1994). An increased influx of FFA to the liver may not only be involved in the development of insulin resistance as indicated in Figure 1, but it may also contribute to an increase in the number of apo B containing lipoproteins in the plasma. It is known for example, that newly synthesized hepatic apo B may be destined for either intra-cellular degradation or secretion as part of VLDL particles and excessive availability of lipid or fatty acids may enable the nascent apo B polypeptide chain to adopt a certain conformation which directs the protein away from the

degradative pathway (Frayn *et al.*, 1996; Gibbons, 1990; Sniderman & Cianflone, 1995). Microsomal transfer protein, which is the protein involved in the combining of lipids to apo B and the assembly of VLDL particles prior to secretion, is normally negatively controlled by insulin, but that may not be the case in insulin resistant subjects (Maritz, 1997). In addition to this, the normal acute suppressive effect of insulin on hepatic VLDL secretion may be impaired in insulin resistant subjects (Eckel *et al.*, 1995). Insulin may also be unable to stimulate LPL activity in the adipose tissue of insulin resistant subjects with a consequent reduction in the hydrolysis of triglyceride rich VLDL or chylomicron particles (Eckel *et al.*, 1995). The cumulative effect of this would be an increase in intermediate density lipoproteins (IDL) and chylomicron remnants (Maritz, 1997). Since IDL is the precursor to LDL-C, an increased production of LDL-C can be expected, although it may not be reflected in increased LDL cholesterol concentrations, as the LDL particles that are formed, may be lipid depleted and more dense (Frayn *et al.*, 1996). In this scenario hyperapo B or elevated blood levels of apo B may be associated with premature CHD, despite normal or only slightly elevated levels of LDL-C as was the case in some white and black diabetic subjects in the present study (Table 3). This latter result is also an indication that lipograms may not be complete without measurement of apo B that may identify subjects with a preponderance of small dense LDL-C particles which may be prone to oxidation, especially in insulin resistant subjects like those in the present study. Normally the poly-unsaturated fatty acids carried on the LDL -C particles are protected against oxidation by vitamin E, but it should be noted that insulin resistant subjects were reported to have lower plasma vitamin E levels (Galvan *et al.*, 1996). Apparently there is a net loss of vitamin E to the body tissues to buffer insulin-induced production of hydrogen peroxide. Lipograms of black females may also not be complete without Lp (a) which may be indicative of an increased risk for blood clotting, especially if it is seen in conjunction with their high fibrinogen levels, as reported in the present study and the study of Greer *et al.* (2000). Although the link between insulin and blood pressure levels is very controversial due to the conflicting results from epidemiological studies in different populations (Hall *et al.*, 1994; Tsuruta *et al.*, 1996), almost all the subjects in the present study were insulin resistant, while the majority of the black (17) and white (21) subjects had uncontrolled blood pressure. Hyperinsulinaemia and insulin resistance may thus not only be more common amongst hypertensive females (especially black females) than commonly thought (Joffe *et al.*, 1992), but it may it may also make it more difficult to achieve blood pressure control (especially amongst white females). The therapeutic goal of anti-hypertensive treatment should therefore be not only the lowering of blood pressure, but also the improvement of insulin functioning. It is doubtful if this can be achieved with anti-hypertensive drug treatment without adjunctive lifestyle changes which are widely recommended, but seldom implemented.

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