Abdominal Obesity, Visceral Fat and Type 2 Diabetes—"Asian Indian Phenotype"

INTRODUCTION

Obesity was identified as a nutritional disorder, thirty years ago, and still continues to be one of the most important yet preventable, health hazards. The prevalence of obesity has reached epidemic proportions in the past two decades with over 25% of the population now being obese in the US and 15% in Europe and the epidemic is now rapidly spreading to developing countries as well. The pace of increase in the prevalence of obesity is in keeping with rapid economic growth leading to surplus of food combined with marked decreasing physical activity.

EPIDEMIOLOGY OF OBESITY IN INDIA

India is currently experiencing a rapid epidemiological transition which has resulted in increased life expectancy and decreased mortality due to communicable diseases. As a consequence of industrialisation and urbanisation, there has also been an increase in the standard of living, leading to a nutritional transition with consumption of diets that are energy dense and high in fat and content. Moreover, with changes in occupation from predominantly agriculture-based manual labour jobs to sedentary office type jobs; there is a perceptible decrease in physical activity. This is the basis for the rapid weight gain and obesity seen in several parts of the sub-continent.

There is paucity on nationwide data on the prevalence of obesity. However, studies in different states of India provide some clues regarding the magnitude of the health threat due to this problem. Table 9.1 provides the published data on obesity from different studies which shows that the prevalence of obesity ranges from 10 to 50%. However, the only nationwide study is the national health survey on women and this revealed a low prevalence rate. According to the Nutrition Foundation of India, the prevalence of obesity is 1% for males and 4% for females in the slums
while the corresponding figures for the middle socioeconomic class was 32.2% and 50%, respectively.\textsuperscript{6}

THE CHENNAI URBAN POPULATION STUDY (CUPS)

A recent population-based study conducted by us; the Chennai Urban Population Study (CUPS) assessed the prevalence of various non-communicable diseases in urban Indians studied at Chennai. This was conducted in two residential areas (representing middle and low-income group) in Chennai and had a response rate of 90.2%.\textsuperscript{9-12}

Over 35% of the males in the middle-income group were obese compared to 13% in the low-income group. The corresponding figures for females were 33% and 24% respectively.\textsuperscript{9} Abdominal obesity among the middle income was 47.4% compared to 19.2% in the low-income group.

The rising prevalence of obesity has several health consequences as obesity is a predecessor for many related conditions like diabetes, dyslipidaemia, hypertension and coronary heart disease.
Asian Indian (South Asian) Phenotype

For several years it has been recognised that south Asians (subjects originating in India, Pakistan, Sri Lanka, Bangladesh and Nepal) have certain unique clinical and biochemical characteristics that are collectively referred to as the "Asian Indian phenotype" (Figure 9.1). Despite relatively lower prevalence rates of obesity as defined by body mass index (weight in kg/height in square metres), they tend to have larger waist measurements and waist:hip ratios, and thus have a greater degree of central body obesity. This is associated with a characteristic metabolic profile with higher plasma insulin levels, a greater degree of insulin resistance as measured by glucose clamp studies and a higher prevalence of diabetes.

Further, Indians also tend to have excess body fat and particularly abdominal and truncal adiposity. For any given waist circumference they also have increased body fat and moreover for any given body fat, they still have increased insulin resistance.

Pattern of Body Fat Distribution

It is now becoming increasingly clear that the regional distribution of fat plays a major contributory role for metabolic abnormalities. Research during the last two decades has suggested that the distribution of adiposity is important in understanding the association of obesity with disturbances in metabolism, particularly those of glucose and lipids. Abdominal adiposity assessed using waist circumference is considered to be more appropriate than generalised adiposity assessed by BMI.
Abdominal Obesity, Visceral Fat and Type 2 Diabetes—"Asian Indian Phenotype" 141

However, while the waist circumference gives us an overall indication of accumulation of total body fat in the abdomen, it does not distinguish between the different fat depots and this is discussed in some detail below:

Over 65% of the body fat is subcutaneous, nearly 20% is abdominal and the rest is intramuscular, hepatic fat, etc. Abdominal fat plays a major role in metabolic abnormalities. Abdominal fat includes intra-abdominal fat (visceral) which constitutes approximately 80% and the rest as subcutaneous fat. However, the proportion may vary greatly in different individuals.

OBESITY AND DIABETES

Several cross-sectional epidemiological studies suggest that obesity and abdominal obesity are strongly linked to diabetes. Indeed, obesity is considered to be the link between insulin resistance and metabolic abnormalities which includes diabetes, hypertension and dyslipidaemia, all of which are risk factors for coronary artery disease (Figure 9.2). Evidence for the link between obesity and diabetes, comes from the epidemiological and intervention studies with weight reduction as the main target. The Diabetes Prevention Programme demonstrated that a 7% reduction in body weight by exercise and diet could prevent diabetes in subjects with impaired glucose tolerance by as much as 58%. The Finnish Diabetes Prevention study also showed similar findings. A study on Japanese women suggested that reducing the intra-abdominal fat to 60 cm² was beneficial in reducing cardiovascular risk factors.

![FIGURE 9.2 : Adipose tissue – adverse effects](image-url)
OBESITY AND DIABETES—INDIAN SCENARIO

In the Chennai Urban Population Study (CUPS), the prevalence of diabetes increased with increase in quartiles of body mass index (BMI), the prevalence being 2.9%, 8.1%, 17.6% and 19.5% in the first, second, third and fourth quartiles of BMI respectively (Figure 9.3). Prevalence of diabetes in subjects with abdominal obesity was significantly higher compared to those without abdominal obesity (27.8% vs 9.0%). The prevalence of impaired glucose tolerance (IGT) also increased with increase in quartiles of body mass index being 2.2%, 3.2%, 5.9% and 12.1% in the first, second, third and fourth quartiles of BMI respectively and the increase was statistically significant (Trend chi square: 29.9, p<0.001) (Figure 9.3). Prevalence of IGT in subjects with abdominal obesity (15.0%) was also significantly higher compared to subjects without abdominal obesity (2.6%). Body mass index showed a strong association with glucose intolerance both in univariate and multiple logistic regression analysis. Moreover, even at lower BMI, categorised as low-risk according to WHO guidelines, the prevalence of diabetes was high among urban Indians.12

ADIPOSITY AND DIABETES

Fat storages in adipose tissue have been shown to be linked to insulin resistance and diabetes (Figure 9.2). Though studies have shown both total fat and visceral fat to be associated with diabetes, visceral fat is considered to be more important as it has been shown to have a strong correlation with glucose intolerance and insulin resistance.30-32 The visceral fat stored beneath the muscles and wrapped around the internal organs is considered to be the most ‘atherogenic’, ‘diabetogenic’ and ‘hypertensiogenic’ fat depot of the human body.30-32 However, this is still a debated issue with some authors suggesting that subcutaneous fat is more strongly associated with diabetes while others reported that visceral fat is a stronger risk factor for diabetes.33-35
OBESITY AND DIABETES—INDIAN SCENARIO

In the Chennai Urban Population Study (CUPS), the prevalence of diabetes increased with increase in quartiles of body mass index (BMI), the prevalence being 2.9%, 8.1%, 17.6% and 19.5% in the first, second, third and fourth quartiles of BMI respectively (Figure 9.3). Prevalence of diabetes in subjects with abdominal obesity was significantly higher compared to those without abdominal obesity (27.8% vs 9.0%). The prevalence of impaired glucose tolerance (IGT) also increased with increase in quartiles of body mass index being 2.2%, 3.2%, 5.9% and 12.1% in the first, second, third and fourth quartiles of BMI respectively and the increase was statistically significant (Trend chi square: 29.9, p<0.001) (Figure 9.3). Prevalence of IGT in subjects with abdominal obesity (15.0%) was also significantly higher compared to subjects without abdominal obesity (2.6%). Body mass index showed a strong association with glucose intolerance both in univariate and multiple logistic regression analysis. Moreover, even at lower BMI, categorised as low-risk according to WHO guidelines, the prevalence of diabetes was high among urban Indians.12

![Graph showing prevalence of diabetes and impaired glucose tolerance across BMI quartiles](image)

FIGURE 9.3: Prevalence of diabetes in quartiles of body mass index—CUPS12

ADIPOSY AND DIABETES

Fat storages in adipose tissue have been shown to be linked to insulin resistance and diabetes (Figure 9.2). Though studies have shown both total fat and visceral fat to be associated with diabetes, visceral fat is considered to be more important as it has been shown to have a strong correlation with glucose intolerance and insulin resistance.30,32 The visceral fat stored beneath the muscles and wrapped around the internal organs is considered to be the most ‘atherogenic’, ‘diabetogenic’ and ‘hypertensiogenic’ fat depot of the human body.30,32 However, this is still a debated issue with some authors suggesting that subcutaneous fat is more strongly associated with diabetes while others reported that visceral fat is a stronger risk factor for diabetes.33-35
VISCERAL FAT AND DIABETES

Three pathological mechanisms have been proposed to explain the association of visceral fat with diabetes. The first is based on the common soil hypothesis according to which visceral fat is simply a marker for some underlying genetic/environmental factors that lead to diabetes. The second mechanism suggests that visceral fat is uniquely deleterious because of its anatomical site with its direct venous drainage to the liver. Increased supply of FFAs to liver increases hepatic insulin resistance. Finally visceral fat depot may produce metabolic markers and factors, which are directly involved in the pathological sequelae of diabetes.

Cnop et al.\textsuperscript{35} in a cross-sectional study done on 174 individuals suggested that visceral fat was the best variable predicting insulin resistance which explained 54\% of the variance in insulin sensitivity. Park et al.\textsuperscript{36} in a euglycaemic clamp study on nine young men suggested that insulin sensitivity correlated with both subcutaneous and visceral fat. Among Japanese, visceral fat was identified as a predictor of impaired glucose intolerance even after adjusting for total fat and subcutaneous fat.\textsuperscript{35, 36}

Metabolically, visceral fat is considered to be more active in producing free fatty acids (FFAs). Further pharmacological interventions support that visceral fat could be more active as interventions with insulin sensitizers like glitazones reduce visceral fat, but increase subcutaneous fat.\textsuperscript{37-40}

ASSOCIATION OF VISCERAL FAT WITH DIABETES—INDIAN SCENARIO

Very few studies in Indians have looked at visceral fat.\textsuperscript{41, 42} A study in southern part of India suggested that visceral fat correlated with insulin secretion.\textsuperscript{41} Misra et al.\textsuperscript{43} showed a strong relation between subcutaneous fat with glucose disposal but this which was done using MRI which focused more on subcutaneous fat than on visceral fat.

VISCERAL FAT AND DIABETES—THE CHENNAI URBAN RURAL EPIDEMIOLOGY STUDY

The Chennai Urban Rural Epidemiology Study (CURES) is an ongoing epidemiological study, conducted on a representative population of Chennai and the methodological details and several aspects of CURES have been published elsewhere.\textsuperscript{44} Anjana et al.\textsuperscript{45} studied visceral and subcutaneous fat in 82 type 2 diabetic and 82 age and sex matched non-diabetic subjects in the CURES study. Computed tomography (CT) was widely used to assess visceral fat and dual energy X-ray absorptiometry (DEXA) was used to assess the total and central abdominal fat.\textsuperscript{42}

It was found that diabetic subjects had significantly higher visceral fat (measured by CT) and central abdominal fat (measured by DEXA) compared to non-diabetic subjects\textsuperscript{42} (Table 9.2). However, subcutaneous abdominal fat, visceral to subcutaneous abdominal fat and visceral to total fat ratio measured by CT showed no significant difference. Similarly with DEXA, total body fat and non-abdominal fat did not differ significantly between diabetic and non-diabetic subjects but abdominal fat was significantly greater in the diabetic group.
Abdominal obesity indices such as waist and sagittal abdominal diameter showed a strong correlation with visceral fat and central abdominal fat both in diabetic and non-diabetic subjects. Logistic regression analysis revealed visceral fat (Odds ratio (OR): 1.011, p=0.004) and central abdominal fat (OR: 1.001, p=0.013) to be associated with diabetes even after adjusting for age and gender. However, subcutaneous abdominal fat did not show a significant association with diabetes.

**ADIPOCYTOKINES AND DIABETES**

Adipocytokines are bioactive substances secreted by adipose tissue (Figure 9.2). These include adiponectin, leptin and resistin and visfatin. Studies have suggested that these cytokines are linked to metabolic abnormalities inclusive of diabetes, dyslipidaemia and coronary artery disease.45, 46 Adiponectin has been considered to have many beneficial metabolic functions such as regulation of energy homeostasis, decreased plasma glucose, increased clearance of glucose load, and decreased insulin resistance.45 Adiponectin also decreases muscle and liver triglyceride content, increases NEFA uptake and enhances hepatic insulin-mediated suppression of glucose production.47-50 It has been suggested that the suppression of adiponectin production in obesity may be mediated through an autocrine negative feedback on its metabolic pathway in adipose tissue.51

Adiponectin has been shown to be inversely related to both obesity and insulin resistance.52 Hypoadiponectinaemia has also been observed in subjects with type 2 diabetes and coronary artery disease.46 Studies on experimental models suggest that adiponectin ameliorates hyperglycaemia and hyperinsulinaemia in both insulin resistant lipoatrophic mice and obese mice.49 Administration of adiponectin also results in weight loss in mice without altering food intake.53
Leptin, the product of the \textit{ob} gene, plays a key role in the regulation of body weight\cite{31}. It is considered to be the hormonal signal bridging the adipose tissue to the central nervous system (CNS) for the control of appetite and energy expenditure\cite{32,33}. Leptin is produced mainly from differentiated adipocytes and serum leptin levels are strongly correlated with adiposity\cite{34,35}. Increasing evidence suggests that leptin promotes fatty acid oxidation and reduces ectopic fat accumulation, thereby increasing insulin sensitivity\cite{36,37}. However, the literature is inconsistent on the association of leptin with type 2 diabetes in humans.

Resistin belongs to a family of cysteine rich secretory proteins named FIZZ (found in inflammatory zone). Resistin, also known as FIZZ3, is an adipocyte specific secretory factor\cite{38}. Steppan et al.\cite{39} demonstrated that in mice, administration of recombinant resistin leads to impaired glucose tolerance and insulin action. They also showed that anti-diabetic agent rosiglitazone decreased circulating resistin levels and administration of anti-resistin antibody improved blood sugar and insulin action in mice with diet induced obesity. The incomplete homology between rodent and human resistin and the differences in the expression suggest that resistin in humans may have a different physiologic role than that in mice.\cite{40} Resistin was found not to be associated with insulin resistance or type 2 diabetes in humans.\cite{41,42} Youn et al.\cite{43} demonstrated that serum resistin levels were associated with type 2 diabetes, but not with insulin resistance or obesity. Thus in humans, the role of resistin in the development of insulin resistance and type 2 diabetes remains unclear.

Visfatin is a recently identified adipokine which is found to be highly enriched in visceral adipose tissue (and hence its name) and plasma levels of visfatin increase during the development of obesity.\cite{44} Visfatin also has insulin-mimetic properties and lowers plasma glucose levels in mice. It was also found that visfatin binds to, and activates, insulin receptor. Hence visfatin is considered to be a missing link between intra-abdominal obesity and type 2 diabetes.\cite{45} Recent studies, however, have shown contrasting results. While some studies have shown that increased visfatin levels were associated with type 2 diabetes,\cite{46} others have shown that visfatin was not associated with insulin sensitivity.\cite{47} Even though mechanism of action is currently unclear, visfatin could play an important role in the development of obesity and/or type 2 diabetes.

### ADIPONECTIN AND DIABETES IN INDIANS

Migrant Indian studies have documented that Indians have low levels of adiponectin, which is considered to play a major role in contributing to metabolic abnormalities.\cite{48} In CURES, we estimated adiponectin in 200 individuals with and without diabetes. Adiponectin values were significantly lower in diabetic subjects (males: 5.2 \(\mu\)g/ml vs 8.3 \(\mu\)g/ml, \(p=0.001\), females: 7.6 \(\mu\)g/ml vs 11.1 \(\mu\)g/ml, \(p<0.001\)) compared to non-diabetic subjects (Figure 9.4). Adiponectin clustered with metabolic abnormalities and showed a strong positive association with HDL cholesterol.\cite{49} A prospective study done in India also showed that lower adiponectin levels predicted future development of type 2 diabetes.\cite{50} It seems likely that lower adiponectin may at least in part explain the high risk for insulin resistance, diabetes, and dyslipidaemia (particularly low HDL levels) among Indians.
GENETICS OF OBESITY AND BODY FAT DISTRIBUTION

Some of the genes implicated in common forms (apart from the rare genetic syndromes) of obesity are peroxisome proliferator-activated receptor gamma 2 gene (PPAR gamma 2), peroxisome proliferator-activated receptor gamma co-activator-1 alpha (PPARGC1A), leptin, leptin receptor, resistin, uncoupling protein-1 (UCP-1) and UCP-2. The Pro12Ala variant of the PPAR gamma 2 is inconsistently associated with obesity in different ethnic groups. The Pro12Ala was also associated with increased subcutaneous and intra-abdominal fat in overweight Korean females. The Q223R polymorphism of the leptin receptor gene was found to be associated with obesity and body fat percentage. A study from Korea showed that the minor allele G of the UCP-1 A-1766G polymorphism was associated with significantly higher abdominal obesity and body fat percentage. Esterbaur et al found association between obesity and a common polymorphism in the UCP2 promoter region at position -866. A recent study from our group which looked at the Thr394Thr, Gly482Ser and +A2962G polymorphisms of the PPARGC1A gene showed that the A allele of the Thr394Thr (G→A) polymorphism was associated with increased total, visceral and subcutaneous body fat as measured by computed tomography (CT) and dual energy X-ray absorptiometry (DEXA) in Asian Indians.

OBESITY, ADIPOCYTOKINES AND INFLAMMATION

Adipose tissue are sources for inflammatory factors like tumour necrosis factor-α (TNF-α) and interleukin-6, and thus contribute to a proinflammatory milieu (Figure 9.2). Following a high fat diet, the TNF-α production from adipose tissue increased in experimental models indicating the direct link between diet and inflammatory markers. It has been suggested that the effect of TNF-α on insulin resistance is mediated through NEFA as TNF-α knock out mice had significantly reduced production of NEFA and increased insulin sensitivity. Studies have demonstrated that
about 35% of the production of interleukin-6 (IL-6) is from adipose tissue. IL-6 has been shown to be increased in subjects with diabetes, coronary artery disease and in those who take a high fat meal. IL-6 decreases glucose uptake by insulin sensitive tissues increases hepatic glucose production, production of NEFA and triglycerides.

Studies on these markers have suggested a strong association with obesity indices and visceral fat. Serum CRP measured by a highly sensitive assay (hs-CRP), has become an important marker of vascular inflammation. High levels of hs-CRP are a predictor for diabetes. Recent studies have suggested a strong association of adiponectin levels with hs-CRP.

**BODY FAT AND INFLAMMATORY MARKERS IN INDIANS**

Studies on migrant Indians have reported that Indians have higher plasma levels of hs-CRP compared to Europeans. In CURES, we looked at hs-CRP levels in subjects with and without diabetes. Hs-CRP levels were significantly higher among diabetic subjects (2.89 mg/L) compared to non-diabetic subjects (0.99 mg/L). Hs-CRP levels significantly increased with increase in tertiles of body fat (Tertile I: 0.98 mg/L, Tertile II: 1.56 mg/L, Tertile III: 3.86 mg/L, ANOVA p<0.001) (Figure 9.5). Linear regression analysis using hs-CRP as dependent variable revealed that body fat had a strong association with hs-CRP (β = 0.105, p < 0.001). It is of interest that when diabetes was used as the dependent variable in logistic regression analysis, hs-CRP showed a positive association with diabetes (p < 0.001). In this study, body fat also showed a very strong association with diabetes, which was independent of age and gender. However, the latter association was influenced by hs-CRP. This suggests that the association of body fat with diabetes is mediated through hs-CRP.

**FIGURE 9.5** : Mean hs-CRP values in relation to tertiles of body fat - CURES
CONCLUSIONS

Asian Indians have a unique body phenotype with relatively lower body mass index (generalised obesity) but increased truncal adiposity and body fat. Body fat, particularly visceral fat seems to play a major role in increased susceptibility to diabetes although more studies are needed. Adiponectin clusters with insulin resistance and has an inverse relation with diabetes. Further, adipose tissue also secretes inflammatory markers, which have an important role in the development of diabetes. Asian Indians have increased Adiponectin and hs-CRP levels compared to Europeans and these factors seem to be closely related to both body fat and diabetes.

REFERENCES


68. Youn BS, Yu KY, Park HJ, et al. Plasma resistin concentrations measured by enzyme-linked immunosorbent assay using a newly developed monoclonal antibody are elevated in individuals with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2004;89:150.


