

## OBESITY: IMPACT ON MORBIDITY AND MORTALITY

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**Abstract:** As per WHO, (World Health Organisation), BMI ( $\text{Kg/m}^2$ ) is categorised as **Normal** - 18-25, **Over weight** - 25-30, **Grade I obesity** - 30-35, **Grade II obesity** - 35-40, and **Morbid obesity** - greater than 40. However, in Indian context obesity in adults is defined as  $\text{BMI} > 27.0 \text{ kg/m}^2$ . The subjects having BMI levels of 23-26.9 are in the overweight group. Traditionally, obesity was believed to be associated with affluent life style in the west. Obesity is taking epidemic shape in recent time and is affecting the newly rich population due to changing lifestyle and underlying genetic factors. It is a systemic metabolic disorder and affects whole body but more so the body metabolism. Main impact is on the insulin resistance and its ill effects on different systems. In this article the impact of obesity on morbidity and mortality is discussed with special relevance to insulin resistance, diabetes mellitus and cardiovascular effects.

### INTRODUCTION

The change in body weight follows the laws of physics and dictates that if caloric intake is greater than caloric output weight gain will occur. However, regulation of body homeostasis is a complex integration of genetic, social behavioral and physiologic factors, many of which have yet to be fully understood. There is definitive role of genetic factors in the pathophysiology of obesity. The genetic and social adaptations that have been passed through the millennia have resulted in the populations with ever increasing waistlines and risk for serious morbidity and mortality. It is noteworthy that obesity in middle aged humans is a risk factor for many age related diseases and decreases life expectancy by about 7 years which is roughly comparable to the combined effects of cardiovascular diseases and cancer on the lifespan.

As per WHO, (World Health Organisation), BMI is categorised as 18-25 - Normal 25-30 - Over weight 30-35 - Grade I obesity 35-40 - Grade II obesity greater than 40 - Morbid obesity. However, in Indian context obesity in adults is defined as  $\text{BMI} > 27.0 \text{ kg/m}^2$ . The subjects having BMI levels of 23-26.9 are in the overweight group. Traditionally, obesity was believed to be associated with affluent life style in the west. However, obesity is a fast growing problem in developing countries. Several studies in India have shown that changes in dietary pattern, physical activity levels, lifestyles associated with affluence and migration to urban areas are related to increased frequencies of obesity and the risk of diseases, such as coronary heart disease and diabetes mellitus. In the last two decades India is in the midst of epidemic of metabolic syndrome, obesity, diabetes mellitus and cardiovascular diseases. The phenomenon is present across population including persons in the lower and mid income group. But there is definite difference in urban and rural population and rich and poor. As per study undertaken by Nutrition Foundation of India (NFI), 32.3 per cent of middle class men, and 50 per cent of

women are obese. From the most recent nationally representative estimates for the prevalence of overweight and obesity in 14 countries of the region, it is apparent that overweight and obesity is endemic in much of the region, prevalence ranging from less than 5% in India to 60% in Australia. Moreover, although the prevalence in China is a third of that in Australia, the increase in prevalence in China over the last 20 years was 400% compared with 20% in Australia<sup>1</sup>. The prevalence of abdominal obesity was higher than the prevalence of overweight/obesity. US data shows that 30% of the US population is obese and 64% is overweight. Obesity is second to smoking as a preventable cause of death and is expected to be first by the end of this decade. Now obesity is recognized as an illness and even the insurance companies have started paying for the treatment of obesity.

### IMPACT OF OBESITY ON METABOLISM AND DIFFERENT SYSTEMS

#### *Ectopic lipids and the metabolic syndrome*

The metabolic syndrome reflects a failure of a system designed to promote intracellular lipohomeostasis, preventing lipotoxicity in the organs of over nourished individuals. When normal, healthy individuals consume surplus calories, the excess fuel is stored as triglycerides in white adipocytes. These cells also appear to protect lean tissues against the harm of lipotoxic damage by secreting leptin, a hormone with an antisteatotic role. Early in obesity, adipocytes increase their secretion of leptin in an attempt to enhance oxidation of the surplus lipids in lean tissues by activating AMPK-activated kinase and reducing activity of lipogenic enzymes. However, deficiency or unresponsiveness of leptin prevents these protective attempts, resulting in ectopic accumulation of lipids. Among cells that are harmed by ectopic accumulation of lipids are pancreatic  $\beta$ -cells and myocardiocytes. This can lead to type 2 diabetes mellitus and/or lipotoxic cardiomyopathy. Unresponsiveness to leptin is probably the most common cause of liporegulatory failure and the metabolic syndrome<sup>2</sup>.

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## BMI-ASSOCIATED DISEASE RISK

The use of body mass index (BMI) has been proposed by the National Institutes of Health<sup>3</sup> and the World Health Organization<sup>4</sup> as a method for defining overweight and obesity. This classification system is based on epidemiologic data indicating that the risk of premature mortality usually begins to increase at a BMI of 25 to 29.9 kg/m<sup>2</sup>, and increases further at a BMI of 30 kg/m<sup>2</sup>. Other factors, such as waist circumference, weight gain since young adulthood, fitness level, and ethnic or racial background, also influence the relationship between BMI and overall disease risk. The underweight subjects (BMI<18.5) are also at risk for increased disease risk. Other factors which increase the risk in obese patients are:

- Large waist circumference (men>40 in; women >35 in)
- 5 kg or more weight gain since age 18-20 y
- Poor aerobic fitness
- Specific races and ethnic groups

## DISEASES ASSOCIATED WITH OBESITY

Obesity leads to many complications. Some of these are:

1. Hypertension
2. Diabetes
3. Dyslipidemia
4. Gall stones
5. Arthritis
6. Coronary heart disease
7. Certain type of cancers
8. Infertility
9. Low self esteem
10. Snoring and sleep apnoea etc

## METABOLIC SYNDROME

### *Impact on Mortality*

Isomaa and colleagues have evaluated differences in mortality between subjects with and without the metabolic syndrome (as defined by WHO).

The all-cause mortality rate was significantly higher in subjects with the metabolic syndrome (18.0% vs 4.6%,  $P < 0.001$ ), as was cardiovascular mortality (12.0% vs 2.2%,  $P < 0.001$ ) (5). Obesity decreases life expectancy by about 7 years which is roughly comparable to the combined effects of cardiovascular diseases and cancer on the lifespan.

### *Impact on Cardiovascular Health*

Although it has been widely assumed that the metabolic syndrome is associated with an increased risk of cardiovascular disease, relatively little research has been done on the prevalence of cardiovascular morbidity and mortality in patients with the syndrome.

Following the introduction of the WHO definition, Isomaa and colleagues<sup>5</sup> assessed cardiovascular morbidity and mortality in a cohort of subjects (N = 3,928; age, 35 to 70 years) being followed in a longitudinal study in Finland and Sweden (the Botnia study). Median follow-up was 6.9 years.

Subjects meeting the WHO definition of metabolic syndrome were significantly more likely to have a history of coronary heart disease, myocardial infarction, and stroke than those without the syndrome. The presence of metabolic syndrome was associated with significantly increased risk of coronary heart disease (relative risk, 2.96,  $P < 0.001$ ), myocardial

infarction (RR 2.63,  $P < 0.001$ ), and stroke (RR 2.27,  $P < 0.001$ ). Overall, the prevalence of coronary heart disease, MI, and stroke were approximately 3-fold higher in the group with metabolic syndrome.

### *Elevated risk of CVD prior to clinical diagnosis of Type 2 diabetes*

In an epidemiologic study of female nurses (The Nurses Health Study; age, 35-55 y) after 2.2 million person-years of follow-up, the relative risk of cardiovascular disease was significantly elevated prior to diagnosis of diabetes. During 20 years of follow-up, 110,227 women remained free of diabetes and 5894 were diagnosed with type 2 diabetes. 1556 new cases of myocardial infarction, 1405 strokes, 815 cases of fatal coronary heart disease, and 300 fatal strokes were documented. Among the nurses who developed diabetes, the age-adjusted relative risk of myocardial infarctions or stroke was 2.82 for the period before diagnosis and 3.71 for the period after diagnosis compared with women who did not develop diabetes during the same period. The relative risk of a myocardial infarction in subjects with a diagnosis of diabetes at baseline was 5.02. These results suggest that aggressive management of cardiovascular risk is warranted in individuals at increased risk for type 2 diabetes.

This study provides strong evidence for adopting a strategy for diabetes prevention rather than just a policy screening frequently for type 2 diabetes in high-risk subjects. The latter strategy could not prevent cases of CVD that develop prior to the onset of clinical diabetes(6).

### *Characteristics of metabolically normal obese and metabolically abnormal obese subjects*

Although obesity is associated with insulin resistance and a cluster of other metabolic disorders, there is a distinct population of obese yet 'metabolically normal' (ie, insulin sensitive) individuals based on accepted cut-point for insulin sensitivity (8 mg/min x kg LBM [lean body mass] by hyperinsulinemic/euglycemic clamp). (43) forty-three obese, sedentary, postmenopausal women were examined. 17 seventeen were identified as metabolically normal, obese; 26 were metabolically abnormal (insulin resistant); and the two groups were compared using a number of physical, physiologic, and metabolic parameters. Only lean mass, glucose disposal, and visceral adipose tissue were found to be statistically different between the two groups. In fact, the glucose disposal values for the metabolically normal obese women were comparable to those found in healthy, young nonobese women and this group had on average 49.6% less visceral adipose tissue than their metabolically abnormal counterparts<sup>7</sup>.

In terms of lipid levels and blood pressure differences between insulin-sensitive and insulin-resistant, obese, post-menopausal women, significant between-group differences were observed in triglyceride and HDL levels; the metabolically normal obese women had significantly lower triglyceride and higher HDL levels (both  $P < 0.01$ )<sup>7</sup>.

### *Oral glucose tolerance in insulin-sensitive and insulin-resistant obese subjects*

In terms of glycemic control between insulin-sensitive and

insulin-resistant, obese, post-menopausal women, significant between-group differences were observed in fasting glucose and insulin levels, 2 h insulin levels, and insulin area as might be expected as insulin sensitivity was used as a point of differentiation.

This study in identifying phenotypic characteristics that are protective against metabolic factors associated with the insulin resistance syndrome found that lower amounts of visceral adipose fat, which accounted for 22% of the between-group variance, despite large quantities of total body fat, probably contributed to a favorable metabolic profile. Consistent with this, lower triglyceride and higher HDL levels were also seen in the insulin-sensitive group. Combined with the lower levels of visceral fat, this is in accordance with the idea that insulin-resistance is associated with an unfavorable body fat distribution and disturbances in lipid-lipoprotein profile, independent of the level of obesity<sup>6</sup>.

#### ***Waist size vs BMI and the metabolic syndrome***

The San Antonio Heart Study is a population-based, 8-year longitudinal study that evaluated the incidence of diabetes and cardiovascular disease among Mexican Americans and non-Hispanic whites in San Antonio, Texas<sup>8</sup>. The study cited here looked at the development of metabolic syndrome in 1968 subjects who did *not* meet the World Health Organization criteria for the metabolic syndrome at baseline.

After 8 years of follow-up, both BMI and waist circumference proved to be highly predictive of eventual development of the metabolic syndrome. Subjects with baseline BMI >30 or waist circumference  $\geq 40$  inches in men or  $\geq 35$  inches in women were 3 and 8 times more likely to develop metabolic syndrome than those with BMI <25 or with smaller waist circumference. Up to one third of those with high BMI and increased waist circumference developed the metabolic syndrome, versus one tenth of those in the lighter, thinner group.

#### ***Both insulin resistance and decreased insulin secretion predict the risk of developing type 2 diabetes: 7-year incidence***

In the *San Antonio Heart Study*, the risk of converting to type 2 diabetes was significantly associated with insulin resistance (high HOMA-IR) and impaired insulin secretion (low ratio of early insulin increment to early glucose increment,  $\Delta I30-0/\Delta G30-0$ ). Also among converters to diabetes, the only subjects with adverse cardiovascular risk factors (high systolic blood pressure and triglyceride levels and low HDL) were converters to diabetes with high HOMA-IR and  $\Delta I30-0/\Delta G30-0$  (insulin-resistant subjects). This led the authors to suggest that treatment options to reduce the risk of developing diabetes should focus on insulin-sensitizing interventions rather than therapies that increase insulin secretion, because of the latter's potential increase of cardiovascular risk<sup>8</sup>.

#### ***Intra-abdominal fat mass and CHD risk in type 2 diabetes***

In a prospective cohort study among female registered nurses in the U.S., 44,702 women (age, 40-65 y) who were free of prior coronary heart disease, stroke, or cancer, provided waist and hip circumferences<sup>9</sup>. After an 8-year follow-up, after adjusting for

BMI, age (continuous), age<sup>2</sup>, smoking, parental history of myocardial infarction, alcohol consumption, physical activity, menopausal status, hormone replacement therapy, aspirin intake, saturated fat, and antioxidant score, waist circumference significantly correlated to an increased risk in coronary heart disease ( $P < 0.001$  for trend). Waist circumference and waist-to-hip ratio (WHR) were independently strongly associated with increased risk also among women with a BMI  $\geq 25$ . After adjusting for reported hypertension, diabetes, and high cholesterol, a waist circumference of  $\geq 30$  or a WHR of  $\geq 0.76$  was associated with a 2-fold higher risk of coronary heart disease.

#### ***Abdominal fat distribution increases the risk of coronary heart disease***

Abdominal fat distribution increases the risk for coronary heart disease (CHD) among lean, overweight, and obese persons. The risk of CHD begins to increase at a normal BMI, which is 23 kg/m<sup>2</sup> for men and 22 kg/m<sup>2</sup> for women<sup>10</sup>. Data from both the Iowa Women's Health Study<sup>11</sup> and the Nurses' Health Study<sup>9</sup> found that women in the lowest BMI but highest waist-to-hip circumference ratio tertiles (a measure of abdominal adiposity) had a greater risk of fatal and nonfatal myocardial infarctions than women in the highest BMI but lowest waist-to-hip circumference ratio tertiles.

#### ***Relationship between weight gain in adulthood and risk of type 2 diabetes mellitus***

An increase in weight since young adulthood (18-20 years of age) in men and women is associated with increased risk of developing type 2 diabetes. A weight gain of 10 kg, which is the average amount of weight gained by US adults from 20 to 50 years of age, is associated with a two- to threefold increase in the risk of diabetes<sup>9</sup>. Weight gain during adulthood is also associated with an increased risk of coronary heart disease, hypertension, and cholelithiasis compared with those who maintain their weight after 18 to 20 years of age.

## **HYPERTENSION AND OBESITY**

There is linear relationship between HT and BMI<sup>12</sup>. With increasing BMI the prevalence of hypertension increases. As per NHANES III age adjusted prevalence of HT (>140/90) was 42% males and 38 % females as compared to 15% in lean body weight subjects. With every 10% increase in body weight the BP increases by 6.5 mmHg.

## **CEREBROVASCULAR AND THROMBOTIC COMPLICATIONS**

Fatal and non fatal stroke incidence is twice in obese as compared with lean body weight subjects<sup>1</sup>. Risk of stroke increases with increasing BMI in both males and females. There is increase in other thrombotic events as well like DVT, venous stasis and pulmonary embolization. Prevalence of DVT increases due to increased intra abdominal pressure, impaired fibrinolysis and increased inflammatory mediators.

## **PULMONARY DISEASES<sup>13</sup>**

Obesity is associated with restrictive lung disease due to

pressure placed over chest wall and thoracic cage. There is restrictive lung function i.e., reduced respiratory compliance, increased work of breathing and reduced total lung capacity. Obesity is also associated with limited ventilation of lung bases. The major reasons of restrictive lung functions are due to following factors:

- Reduced ventilatory response to hypercapnia and hypoxemia or both
- Mechanical factors: respiratory muscles fail to meet increased ventilatory demand
- Other factors like elevated diaphragm and inadequate inspiratory muscle strength

*Pickwickval* is severe form of obesity hypoventilation syndrome characterized by extreme obesity, irregular breathing, somnolence, cyanosis and secondary polycythemia and RV dysfunction.

Obstructive sleep apnoea (OSA) is common in obese subjects. In this condition there are episodes of apnea/hypopnoea during sleep, partial/complete upper airway obstruction despite persistent respiratory effort, larger neck girth >17 and 16 in men and women. BMI >30 and abdominal fat distribution is associated with OSA.

## MUSCULOSKELETAL DISEASES

Hyperuricemia and gout both are associated with obesity. Male sex, diabetes, obesity and insulin resistance syndromes are associated with hyperuricemia. Osteoarthritis in weight bearing joints specially knee joint is common in obese patients<sup>14</sup>.

## CANCER RISK

Several studies have shown a strong association between adiposity and increased risk of cancers of breast in postmenopausal women; of the endometrium, kidney, and gall bladder in women; and of colon in men. However, it is only recently that in a prospectively studied population, it was clearly demonstrated that increased body weight was associated with increased death rates for all cancers combined and from cancers at multiple specific sites<sup>15,16</sup>. More than 900,000 US adults who were free of cancer at enrollment in 1987 were followed for 16 years, at which time 57,145 died from cancer. Overweight and obesity contributed significantly to mortality from cancer. On the basis of the association observed in this study, it was estimated that obesity could account for 14% of all deaths from cancer in men and 20% of those in women. Obesity correlates with ingestion of high fat, high calorie diet which itself is risk factor for cancer.

Other problems associated with obesity are being discussed in other chapters of this special issue. Some of these are listed below:

## GENITOURINARY TRACT DISORDERS

Obesity is associated with following disorders in women of childbearing age.

- PCOD
- Irregular menses

- Pregnant overweight women are at risk for HT and GDM
- Urinary incontinence

Obesity is also associated with increased congenital malformations in babies born to obese mothers<sup>17</sup>.

## NEUROLOGICAL DISORDERS

As discussed above there is increased prevalence of stroke in subjects with obesity<sup>12</sup>. Other specific problem in obesity is idiopathic intracranial hypertension (pseudotumour cerebri) which is characterized by headache, vision abnormalities, tinnitus and sixth nerve palsy.

Risk of IHH increases with 10% weight gain and weight loss improves IHH.

## GASTROINTESTINAL DISORDERS

There is strong association between obesity and gastroesophageal reflux disease. Subjects who are obese have increased prevalence of hiatus hernia as well.

There is linear relationship between obesity and gallstones. As per NHS study the prevalence of gallstones is 1% with a BMI of 30 and 2% with a BMI of 45%. Gallstone risk also increases with rapid weight loss during treatment of obesity. Weight loss >1.5 kg per week is associated with increase bile saturation and enhanced cholesterol crystal nucleation and reduced gallbladder contractility. Obesity is also a strong risk factor for pancreatitis<sup>18</sup>. Obesity associated pancreatitis is severe and there is increased risk of death. The mechanisms of pancreatitis are:

- Increased peripancreatic and retroperitoneal fat deposition
- Peripancreatic fat necrosis and subsequent local and systemic complications

## HEPATIC DYSFUNCTION

**Non-alcoholic** fatty liver disease is very common in obese patients<sup>19</sup>. This condition is associated with hepatomegaly, abnormal LFT, steatosis, statohepatitis and rarely fibrosis and cirrhosis. The prevalence of steatosis in obesity is 75%, statohepatitis is 20% and cirrhosis occurs in 2% cases.

**Mechanisms of NAFLD are** as follows:

- **Steatosis**
  - Increased lipolysis of adipose tissue so increased TG
  - Increased delivery of FFA to liver
  - Inadequate hepatic FA oxidation
- **Peroxidation of hepatic lipids**
- **Cytokines**
  - Direct cellular injury
  - Inflammation and
  - fibrosis

## RENAL DYSFUNCTION

Central obesity is independently associated with risk of albuminuria in normoglycemic subjects. This may explain high diabetic renal disease in South Indians<sup>20</sup>. Possible mechanisms are increased metabolic demand, increased glomerular pressure and glom hypertrophy, secondary focal segmental

glomerulosclerosis. Insulin resistance (IR) accelerates structural changes and thr' Angiotensin II so increased collagen production and deposition.

## DIRECT COST OF CHRONIC DISEASES IN THE UNITED STATES

It is estimated that obesity accounts for 6% of the nation's total healthcare expenses, with \$51.6 billion/year in direct costs and over \$100 billion/year in both direct and indirect costs<sup>21-22</sup>. Direct costs include the costs of personal health care, hospital care, physician services, allied health services, and medications. Indirect costs include the value of lost productivity from illness or premature mortality. The estimated direct cost of obesity is comparable to that of other prevalent, chronic diseases, such as type 2 diabetes and coronary heart disease, and is more costly than both hypertension and stroke. Moreover, obesity contributes to the development of other chronic diseases; it is estimated that 61% of the direct cost of type 2 diabetes, 17% of the direct cost of coronary heart disease, and 17% of the direct cost of hypertension are attributable to obesity.

## CONCLUSION

Overweight/obesity is a disease process but needs to be publicized and effort needs to be made by policy makers. Main mortality comes from associated metabolic syndrome leading on to DM, CHD, Stroke, cancer etc. It is a systemic disease affects most of systems. Recent studies have shown that obesity is emerging as a risk factor for renal dysfunction. The silver line in the obesity related complications is that by reducing weight most of the complications can be reversed.

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## DRUG PROFILE

### SITAGLIPTIN PHOSPHATE

**Mechanism of Action:** Sitagliptin phosphate is orally-active selective inhibitor of the dipeptidyl (DPP-4) enzyme for the treatment of type 2 diabetes. (DPP-4) inhibitors are a class of agents that act as incretin enhancers. By inhibiting the (DPP-4) enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagons-like peptide-I (GLP-1) and glucose – dependent insulinotropic polypeptide (GIP). The incretins are part of endogenous system involved in the physiologic regulation of glucose homeostasis, increase insulin synthesis and release it from pancreatic beta cells, GLP-1 also reducing glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. **Indications:** The drug is indicated as an adjunct to diet and exercise to improve glycemic control in combination with metformin, sulfonylurea, thiazolidendiones. **Dosage and Administration:** The recommended dose is 100 mg once daily as monotherapy, as combination therapy with metformin sulfonylurea and can be taken with or without food. For patients with mild renal insufficiency (creatinine clearance (CrCl) > 50ml/min, no dosage adjustment is required; Moderate renal insufficiency CrCl>30 to <50ml/min. the dose is 50 mg once daily in severe renal insufficiency (CrCl<30mL/min, is 25 mg once daily hence, an assessment of renal function is recommended prior to initiation and periodically thereafter. The drug is not recommended for use in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. **Hypersensitivity reactions:** include anaphylaxis angioedema, exfoliative Stevens Johnson. The drug is generally well tolerated; gastrointestinal side effects noticed are abdominal pain (2-3%), nausea (1.4%), vomiting, diarrhea(3.0%). **Pregnancy:** There are no adequate and well controlled studies in pregnant women, therefore safety in pregnant women is not known Sitagliptin is secreted in the milk of lactating rats, should not be used in nursing mother. **Pediatric:** safety and effectiveness in children under 18 years have not been established. No dosage adjustment is required and is generally well tolerated in the elderly.