



# IMSA

INTERNATIONAL MEDICAL SCIENCES ACADEMY

July- September 2008  
VOL. 21 NO. 3

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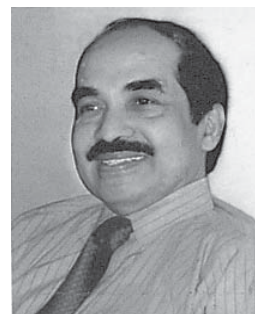
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## PRESIDENT'S WRITES

Dear Fellows and Members,

JIMSA has chosen 'Obesity' as the topic for this issue and very relevantly so. Obesity can lead to diabetes, cardiovascular disease and other health problems. Obesity is increasing in proportion the world over and various causative factors can be attributed. However, the age-old advice of good sense in the intake of food and doing regular exercise is all that is often needed to curb the onslaught of the obesity epidemic. This is better said than done in the present age of greed and ill sustaining life styles. Obesity has medical and surgical interests and is so apt for a discussion in the multidisciplinary forum of IMSA. Once again may I urge all of our fellows & members to make to Dubai for the IMSACON 2008.



*K. Jagadeesan*

**Dr. K. Jagadeesan**  
President, IMSA

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All fellows and members of IMSA can have access to the site and get information about its objectives, benefits to the fellows/members, chapters and their activities including seminars, refresher courses, rural CME;s etc. and also IMSACON - a regular annual event of international standard; application form for enrollment as fellow/member can also be downloaded. Fellows - members and even not fellows - members can have access to full text in the quarterly journal - jimsa from July - Sept. 2003 onwards by putting their E-mail address under 'user name' and using the password 'UserJimsa'.

## Dr. Pinnamaneni Narasimha Rao International Award

### Appeal by Vice-President IMSA



Dr. P. Narasimha Rao  
Ex. President, IMSA World H.Q.



Dr. R.R. Thukral  
Vice President IMSA World H.Q.

Dear Fellows and Members

You are aware late Dr. P. Narasimha Rao, an international figure both in academic and teaching had been the President of this prestigious organization for more than a decade from 1990 to 2002. He was President of Medical Council of India and Vice Chancellor of various Universities. He had to his credit several outstanding contributions to the medical fraternity till his death. He had been in close association with IMSA since its very inception in 1981. The Academy has flourished tremendously during his tenure as President. Keeping in view his status, services rendered to the mankind and on the insistence of senior Fellows, the Academy has established an International Award in his honour named 'Dr. Pinnamaneni Narasimha Rao International Award', on the lines of Dr. B.C. Roy National Award. Substantial funds are needed for this prestigious award. Initially, the family of Dr. P. Narasimha Rao has contributed a fair amount of money and has also assured to contribute more.

I appeal to all our Fellows and Members to contribute generously for this noble cause in the memory of this dedicated acadamecian - Dr. P. Narasimha Rao. A separate account has been opened for this Award.

### IMSA Chapter Activities

#### CME Tamil Nadu Chapter

13-07-2008	Dr.D.Muthukumar :	" Stem Cell Therapy"
10-08-2008	Dr. J. Jagan Mohan :	" Management Of Hand Injuries"
14-09-2008	Dr. S.Jayachandran:	" Oral Ulcers And Management"

### Election of Fellows and Members (July - September 2008)

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### IMSA Fellows/Members Directory 2007

Dear Fellows and Members

International Medical Sciences Academy has published Directory of IMSA Fellows and Members containing information about their mailing addresses, telephone Nos. email addresses, wherever available. The Directory was released at the inaugural function of IMSACON 2007 held at Manipal, Karnataka in November, 2007. I shall request you to send a demand draft of Rs. 250 soon to enable us to send to you a copy of the Directory by post. You can also collect in person from IMSA office if you so wish.

Secretary General, IMSA

### Suggestions to Enhance Image of Medical Profession and Improve Doctor-Patient Relationship

President, Vice President and Trustees of IMSA have stressed that IMSA must engage itself in enhancing the image of Medical Profession by organizing seminars/conferences on various issues relating to medical profession, medico legal, patient — doctor relationship protocol of drug trials and research etc. It was also desired that suggestions be invited from all fellows and members, for improving relationship among doctors and patients.

The Fellows and Members are, therefore, requested to send their suggestions & ways and means to IMSA World Headquarter at New Delhi, for enhancing image of medical profession and improving doctor — patient relationship.

Secretary General, IMSA



# JIMSA

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## FROM EDITOR'S DESK

This issue on '*Obesity : New Challenges*' focuses on a number of important subjects related to this topic. I sincerely thank **Prof. Richa Dewan**, Head of Department of Medicine, Maulana Azad Medical College, for offering her services as a Guest Editor of this valuable publication. Her keen interest and pains taking efforts in bringing out this very informative issue, deserves all the appreciation. No doubt, it has been a commendable task achieved by her. This issue includes wide ranging subjects, contributed by a galaxy of eminent experts. I am confident, readers of JIMSA will find this publication of immense benefit and will most certainly like to preserve a copy in their personnel reference libraries. Dr. Richa Dewan has really worked hard in the compilation of this exhaustive collection of scientific material; I extend my grateful thanks to her once again and also to all the contributors of this special issue.

I take this opportunity to thank all the members of Editorial and Advisory Boards for their assistance and also the various pharmaceutical firms, without whose help this publication would not have been possible.

**P. D. Gulati**

## JIMSA BEST PUBLISHED ARTICLE AWARDS

Journal of International Medical Sciences Academy has instituted award for **three (3)** best original articles published during the previous 3 years; **guidelines** are as below:

- (1) **Original articles** belonging to any discipline of medicine published in JIMSA during the previous three years.
- (2) Age Limit for the principal author/main researcher should be 45 years and below.
- (3) Number of awards: Three (3) annually, carrying a gold plated medal, citation and cash prize (1st Rs. 3000/-, 2nd Rs. 2000/-, 3rd Rs. 1000/-)
- (4) Awardee should preferably be a fellow/member of IMSA; non-fellows/ non members can also be considered for the award if the original work is outstanding; and if selected for the award will be required to apply for fellowship/membership of IMSA.
- (5) Awardees should preferably plan to receive the award at the annual IMSA conference - IMSACON.

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### OUR GUEST EDITOR



*Dr Richa Dewan*

Dr. Richa Dewan, joined Maulana Azad Medical College as Assistant Professor of Medicine in 1984, after a brilliant under graduate and post graduate career at the same institute. She was appointed professor in 1992 and became Head of the Department in 2005. She got promoted to the rank of Director Professor in 2007. During all these year she has established herself as an excellent undergraduate and postgraduate teacher and a research worker.

Her main area of interest has been 'Gastroenterology' she gained expertise in endoscopic procedures. The other important field in which Dr. Dewan got interested has been HIV Management: she has developed a '*National Centre of Excellence for HIV Management*' and for the training of health professionals.

During the last 2 decades of her clinical practice, she has actively participated in the academic programmes organized by API, Indian Society of Gastroenterology, Indian Medical Association and several others. Besides being an astute clinician and an eminent internist, she is an excellent orator. During her short tenure as Head of the Department she has promoted the growth of various specialties and has encouraged her colleagues to achieve excellence in their respective specialities. She has published over 100 papers in the National and International Journals. She has also initiated several public awareness programmes with the help of her departmental colleagues.

### EDITORIAL

This special issue on **Obesity: New Challenges** has been brought out to highlight the increasing problem of obesity and related morbidity afflicting people of all age groups in India and southeast Asia region. 21<sup>st</sup> century has seen India in the middle of epidemic of obesity among young and adolescents. Indians are genetically susceptible to weight accumulation especially around the waist. Studies on 22 different SNPs (single nucleotide polymorphism) near to MC4R gene, have identified a SNP named rs12970134 to be mostly associated with waist circumference. Of all the states in India Punjab has the highest prevalence of obesity among men and women (30 and 37%). Urbanization has been recognized as its strongest risk factor, prevalence being three times commoner in urban areas. In clinical practice, obesity is commonly measured by body mass index (measures generalized obesity) and waist hip ratio (measures central obesity). Other methods are primarily research tools. Excessive fat accumulation in body is primarily due to imbalance between energy intake and expenditure. Multiple environmental and genetic factors are responsible for obesity. Origin of obesity may begin in utero when the fetus is exposed to over nutrition (diabetic mother) or during childhood when the adipocytes are still proliferating. Only two percent are attributed to pathological causes mainly endocrine. Adipose tissue plays an important role in body metabolism, energy reservoir and as an endocrine organ. Molecules produced by adipocytes like leptins, adiponectin, adipocins etc play a major role in body's energy management. Leptin is an important protein hormone, which helps to regulate body weight, metabolism and reproduction. Adiponectin acts as anti-inflammatory and antiatherogenic by preventing insulin resistance. Abdominal obesity, more prevalent among Indians, is a risk factor for premature coronary artery disease, dyslipidemia, hypertension, stroke and diabetes. Recent studies have shown obesity to be an independent risk factor for chronic kidney disease and renal malignancy. The respiratory complications of hypoventilation due to obesity have been recognized for a long time. Charles Dickens in his first novel nearly two centuries ago described the character Mr. Samuel Pickwick so precisely that it gave rise to the term "Pickwickian Syndrome", for extreme obesity associated hypoventilation. Obstructive sleep apnea is 30 times more common in morbidly obese and a 12-fold reduction in overall life expectancy. Children may suffer emotional and physical setback. Obese women are more prone to polycystic ovarian syndrome; pregnancy and fertility related complications stress incontinence, cholecystitis and malignancy of endometrium and breast. The management of obesity has been a major challenge faced by clinicians and researchers in last few decades. Most treatment options use a combination of dietary plus life style modifications and drugs. Objectives of weight loss have to be well defined with realistic goals and should not compromise patients' physical and emotional health. 10 % weight reduction in first six months followed by maintenance of that weight is recommended. Before starting the therapy every patient must undergo a thorough clinical examination and baseline laboratory tests. While on treatment a very close supervision by a health professional is necessary as patient may require dose adjustment of any drugs for associated co morbidities. The treating physician must also address the emotional health of the patient in order to have better treatment outcomes. A number of drugs have evolved so far but none is free of side effects, thereby limiting their use. Currently three drugs are being used in the management of obesity, Sibutramine, Orlistat and Rimonabant. Intake of cannabis has been seen to be associated with an increase in appetite. Rimonabant is the first of the new class of agents that act by selectively blocking cannabinoid -1 receptors with resultant central and peripheral metabolic effects. It has a higher affinity for central receptors as compared to peripheral receptors. The drug has a long duration of action and good oral bioavailability. It reduces food intake and increases energy expenditure. Bariatric surgery has a definite place in the treatment of morbid obese not overlooking the risks and complications. A multidisciplinary approach is recommended for managing obesity.

*Richa Dewan*

*Department of Medicine*

*Maulana Azad Medical College, New Delhi, India*



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## OBESITY EPIDEMIC IN INDIA

Richa Dewan, Praveen Gupta

Department of Medicine, Maulana Azad Medical College,  
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**Abstract :** Urbanization and economic growth in India has brought in its wake, the problem of obesity among the young and children. Indians are prone to central obesity which is a risk factor for metabolic and vascular complications even at a lower Body Mass Index. A BMI of  $>23$  kg/m<sup>2</sup> has been shown to be associated with increased risk of diabetes. Indians have a higher visceral fat mass than white Caucasians and African Americans. Fat cells form a metabolically and hormonally active organ which function as both endocrine and paracrine organ in the body. Adipocyte secretes a range of molecules that affect metabolism, vascular function, appetite and the immune and haemostatic systems. The prevalence of obesity correlates directly with socioeconomic class and is higher among women. Though excess intake of calories is related to obesity but repeated episodes of malnutrition, followed by nutritional rehabilitation, alter the body composition and increase the risk of obesity during childhood. Malnutrition causes impaired linear growth and favors adiposity. National Nutrition Monitoring Bureau has reported that pattern of food consumption in India, shows increased intake of animal products, sugars and fat since 1971. Increased caloric intake coupled with reduced physical activity have contributed significantly to the obesity epidemic. The demographic and epidemiological transition, the forces of internal migration and urbanization, have led to changes in food consumption patterns and physical activity patterns. Genetic influences though not proven probably do play an important role in concert with environmental factors. Globalization of trade has encouraged people to grow cash crops for export thereby reducing the availability of these nutrients for the local population. The movement of population into urban area has significantly altered the work related physical activity and the inculcation of westernized type dietary habits have compounded the epidemic of obesity in India.

### INTRODUCTION

Over last few years, India has undergone rapid economic development. But this development has brought the increasing burden of non communicable diseases. Obesity is one of the preventable risk factor for non communicable diseases which has emerged as a major health problem both in developed and underdeveloped countries<sup>1,2</sup>. Obesity can be defined on the basis of body mass index BMI, weight (kg)/height (m<sup>2</sup>)<sup>3</sup> and can be used to assess individual and community nutritional status<sup>4</sup>. Today whole world is facing epidemic of obesity.<sup>5</sup> Developed countries had paid attention to the epidemic, but developing countries were not able to give attention to such extent. One reason is the presence of communicable diseases and other being financial problems. India has controlled under nutrition to a large extent, but is now facing an epidemic of obesity. This epidemic is assuming serious proportions in cities and is particularly affecting young adults and children.

Previously nutrition research in India had focused on under-nutrition related to nutrient deficit and high rates of infection. Data from the National Family Health Survey 1998/99 (NFHS 2), however shown that the 12% of the women can be classified as overweight (BMI  $> 25$  kg/m<sup>2</sup>) and 2% are obese (BMI  $> 30$  kg/m<sup>2</sup>). Furthermore, in the large cities where 4% of the samples live, 37% of women are overweight or obese, while in the rural areas where 74% reside, 43% have a low BMI. Socioeconomic status is an important predictor of both over and underweight.

As rates of overweight and obesity rise, India is beginning to experience the burden of associated chronic diseases, particularly cardiovascular disease and adult onset diabetes<sup>5,6</sup>. WHO estimate that diabetes in India will increase from 19.4 million in 1995 to 57.2 million in 2025<sup>5</sup>.

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e-mail: rdewan3@gmail.com

### DEFINITION OF OBESITY AND APPLICABILITY OF INTERNATIONAL CRITERIA TO INDIAN

World Health Organization (2000) recommended BMI as cut-offs for the diagnosis of obesity in developed countries (kg/m<sup>2</sup>): preobese 25.00–29.99, obese class I 30.00–34.99, obese class II 35.00–39.99, obese class III 40.00<sup>7</sup>.

Over last few years it has been observed that the distribution of fat is also an important determinant of morbidity and mortality, and that 'central' obesity may be more pathological than generalized obesity (measured as BMI).

Recommendations have come for the diagnosis of central obesity for **men and women** respectively:

WORLD HEALTH ORGANIZATION (2000):

Waist: hip ratio

$>1.0$ ;  $>0.85$ ; Waist circumference (mm) ; Moderate risk 940, 800 ; Severe risk 1020, 880

Research over the last few years has recognized fat cells as metabolically and hormonally active organ which function as both endocrine and paracrine organ in the body. Adipocyte secretes a range of molecules that affect metabolism, vascular function, appetite and the immune and haemostatic systems<sup>8,9</sup>. Research so far have suggested that deranged adipocyte function may be involved in the pathogenesis of insulin resistance syndrome, type 2 diabetes and atherosclerosis<sup>9</sup>.

In developing countries, metabolic and vascular risks for 'obesity' manifest at a lower BMI compared with those in developed countries. Thus, the BMI classification of obesity based on large-framed European populations may be inappropriate for Indians (and other Asians) having a small body frame<sup>10</sup>. For a given BMI Indians have a higher percentage body fat than white Caucasians and African Americans<sup>11,12,13</sup>. Indians have a higher visceral fat mass than white Caucasians and African Americans as shown by various studies in India

<sup>14, 15, 16, 17, 19</sup>, UK<sup>18, 20</sup> and the USA.<sup>11, 13, 21</sup> Magnetic resonance imaging has shown that the visceral adiposity in Indians is accompanied by higher central subcutaneous adiposity i.e. higher sub scapular, triceps skin fold thickness as well as higher posterior subcutaneous fat thickness.<sup>11</sup> Visceral fat is primarily responsible for the various metabolic consequences of central obesity. The metabolic effects of subcutaneous adiposity need to be studied further. Higher risk of diabetes and impairment of glucose tolerance at lower BMI in Indians has been highlighted in a small prospective study. The 10-year risk of developing impairment of glucose tolerance or diabetes in normal glucose-tolerant middle-aged men and women (n=191) is 2.4 times higher in subjects with a BMI of >23 kg/m<sup>2</sup> compared with those with a lower BMI.<sup>22</sup> In a large cross-sectional study of glucose tolerance in six cities in India (National Urban Diabetes Survey), a BMI of >23 kg/m<sup>2</sup> has been shown to be associated with increased risk of diabetes.<sup>17</sup> Preliminary analysis of bioimpedance measurements has shown that BMI substantially underestimates adiposity in Indian men.<sup>23, 24</sup> Thus, in rural men with a mean BMI of 21 kg/m<sup>2</sup>, one-third are adipose (body fat >25%), while 80% of the urban middle-class men are adipose at a mean BMI of 24.1 kg/m<sup>2</sup>. Only 7% of these urban men would be classified as obese by the World Health Organization (2000) criteria (BMI >30 kg/m<sup>2</sup>). Thus Indians are considerably adipose at a relatively lower BMI. On the basis of these data World Health Organization Expert Consultation (2004) has reduced the 'obesity-related action point' in the Asians to 23 kg/m<sup>2</sup>.<sup>25</sup>

## CAUSES OF THE EPIDEMIC

Urbanization is strongest risk factor for obesity.<sup>26</sup> Obesity is three times more common in urban areas comparing to rural areas, although it is increasing rapidly even in villages because traditional villages are also becoming urbanized in their habits. Another related risk factor is higher socio-economic status. Weight gain occurs when energy intake by an individual exceeds energy expenditure over a period of time. Changing patterns of food intake and physical activity contribute to the positive energy balance. Genetic as well as non-genetic determinants affect an individual's response to energy intake as well as physical activity, and therefore influence the balance between the two factors.<sup>27</sup>

It is possible that a '**thrifty genotype**' may have helped man survive famine conditions by successfully depositing fat. However, in the current situation of excess food and reduced activity, this genotype may lead to obesity.

Presently the contribution of genetic factors to obesity is not clear at the population level. However, a number of rare syndromes of extreme obesity have been related to specific mutations in genes.<sup>28</sup> Studies in twins also favor a role for genetic factors in the etiology of obesity.<sup>29, 30</sup> It is possible that like other chronic polygenic disorders (diabetes and hypertension); the expression of obesity is influenced by environmental condition.

## ORIGIN OF ADIPOSITY IN INDIA

Obesity is now increasingly reported in young Indian adults

and even in children. According to the World Health Organization<sup>31</sup>, India has a preschool childhood obesity prevalence of about 1%. Repeated episodes of malnutrition, followed by nutritional rehabilitation, are known to alter body composition and increase the risk of obesity.<sup>32</sup> The discordance between linear growth and adipocyte development will enhance adipocyte development when linear growth is affected by malnutrition. It is likely that these factors will contribute to increasing problem of obesity in India, given the enormous number of stunted children which is estimated at between 52.0% and 63.0%.<sup>33</sup>

**Childhood obesity** increases the risk of obesity in adulthood and parental obesity interacts quite strongly to alter this risk, and there are several interactive factors contributing to the increased prevalence of obesity in childhood.

India, which is rapidly urbanizing, demonstrates increases in calorie intake, increases in fat intake, and increased levels of sedentary habits. Lifestyle changes resulting in physical inactivity and sedentary behaviors are important in contributing to obesity in children. This is exemplified by more time in a day spent by children in physically passive behaviors such as TV viewing, working or playing games on a computer, talking on the telephone etc.

There are reports from urban parts of India, which provide some insight into the problem. A study in Bombay revealed that the prevalence of obesity among young adult males varied from **10.7% to 53.1%**<sup>34</sup>, while another from Delhi, showed an overall prevalence of **27.8%**.<sup>35</sup> and it is higher in females than males (**33.4% vs. 21.3%**). A study conducted in Kashmir showed the obesity prevalence to be **15.0%**; females having a prevalence of **23.7%** compared with **7.0%** among males.<sup>36</sup> Prevalence of obesity varies with socio-economic status in urban India as shown by data from the **Nutrition Foundation of India**.<sup>37</sup> Upper strata is having higher prevalence rates (32.2% among males, 50% among females) than the middle classes (16.2% males, 30.3% females), followed by the lower socio-economic groups (7.0% males, 27.8% females) and the poor in urban slums with the lowest (1.0% males, 4.0% females). But these **reports are not truly representative of the problem** in the country as they used a body mass index (BMI) cut-off of 25.0 kg per m<sup>2</sup> which include both overweight and obesity beginning at a BMI of 30.0 kg per m<sup>2</sup> and above<sup>31</sup>. Surveys conducted by the **Food and Nutrition Board** (i.e. District Nutrition Profiles survey)<sup>33</sup>, is the only representative survey which have reported prevalence of 0.3% and 0.7% in rural and 0.4% and 0.7% in urban men and women, respectively, using a BMI cut-off of 30.0 kg per m<sup>2</sup>. **National Family Health Survey** showed a prevalence rate of 2.2% for women aged 15–49 years using BMI. 30.0 kg/m<sup>2</sup>.<sup>38</sup> It varied depending on residence (urban. 5.8% vs. rural. 0.9%), increasing with educational achievement from 0.9% for illiterate to 6.5% for those with secondary education. However, it is increasingly evident that, in populations from the Indian sub-continent, BMI does not provide a good indicator of body fat (i.e. that body fat content is higher) for any given BMI among Indians<sup>39</sup>. Increasing BMI is associated with central

adiposity and higher waist/hip ratios along with risk of NCDs appearing at much lower BMI (25.0 kg/m<sup>2</sup>) than among other population groups<sup>40</sup>.

### **DIETARY CONSUMPTION AND LIFESTYLE CHANGES DURING THE NUTRITION TRANSITION IN INDIA**

Rapid quantitative changes in dietary intake in developing countries indicate an increase in per capita availability of food and are also accompanied by qualitative changes in the diet. Food balance data from the Food and Agriculture Organization (FAO) show that the change in energy intake in Asian countries has been small, but there have been large changes in consumption of **animal products, sugars and fats**<sup>41</sup>. The net effect has been a marked shift in the diet with **energy from fat (both animal and vegetable) increasing each year**. Data from India show that higher-income groups consumed a diet with 32% of the energy from fat while the lower-income groups consumed only 17% energy from fat. More recent dietary surveys in Delhi also confirm that the upper income groups in urban India currently consume higher levels of energy from fat as compared with the urban poor or rural populations.

### **TRENDS AND PATTERNS IN FOOD CONSUMPTION IN INDIA**

There have been many nationally representative surveys on diet, nutrition and food consumption patterns in India since the 1970s. They include:

1. National Nutrition Monitoring Bureau (NNMB) surveys of diet and nutrition on a continuous basis in 10 states in India since 1971. On some occasions, these NNMB surveys have been linked with the National Sample Survey Organization (NSSO) and the National Council of Applied Economic Research (NCAER);
2. National Family Health Survey (NFHS) conducted by the Ministry of Health and Family Welfare and coordinated by the International Institute for Population Sciences, Bombay. The NFHS surveys cover 24 states and provide anthropometric data on women aged 15 to 49 years;
3. District Nutrition Profiles survey organized by the Food and Nutrition Board, Department of Women and Child Development, Government of India.

The data from several of these surveys have been collected and are summarized below.

NNMB survey in India has shown adequacy in calorie intake during the 1970s and up to the early 1980s. There is gradual improvement in caloric intake per head, typified by an increase in consumption of cereal grains, while the intake of most other food items such as milk, oil, sugar, etc. remained largely unchanged. Many of these surveys revealed disparities in the intakes of most foods between rural and urban populations and between different socio-economic groups. There is gradual reduction in cereal grain consumption between 1975 and 1995 that has not affected the average energy intake. This is largely the result of a progressive increase in the intake of protein,

and probably fats. The latter is due to a phenomenal increase in the consumption of milk and milk products and an increase in the intake of animal products (designated flesh foods) and fats and oils. The production of pulses and legumes is a concern and consequently their cost and consumption have fallen dramatically. This is a cause for much concern since pulses and legumes are a very important source of vegetable proteins in the habitual Indian diet. Trends in the changes in consumption of urban populations are not readily available, although the surveys conducted between the late 1970s and the 1990s show wide differences between the socio-economic strata in an urban environment. Recent data from the District Nutrition Profiles survey<sup>33</sup>, have shown differences in the intakes of vegetables and fruits and fats and oils between urban and rural populations. The National Family Health Survey<sup>38</sup> provides information on the consumption of specific and selected foods once a week at least and demonstrates, for instance, that the percentage of women consuming meat/chicken/fish once a week is higher in urban than rural locations

### **INTAKE OF FAT IN THE DIET**

There is progressive increase in the intake of fat over last few years as shown by analyses carried out by the FAO. When the dietary energy supply increases, the fat calorie ratio (i.e. the contribution of fat to energy) increases mainly due to the increase in consumption of animal products. Food balance data from the FAO show India at the bottom of the group of countries with a fat calorie ratio over 15% (15.3%) with a total fat intake at 37.8 g per day and a 27.5% animal fat to total fat ratio.<sup>41</sup> Trends based on food balance sheet data show that the per capita supply of animal products has increased from 7.0 g in 1965 to 12.9 g in 1999, thus contributing almost twice the energy content (increased from 104 to 192 kcal per capita per day).

Estimates from the NNMB helped to assess the fat intake from Indian dietary components. It has now been recognized that components of the Indian diet such as cereals, pulses, tubers and vegetables have 'invisible fat', in addition to the obviously visible fats consumed in the daily diet. It has been computed that 10–15% of the daily energy in the diet can come from this invisible component and this level is adequate to meet the essential fatty acid requirements for both linoleic acid and alpha linolenic acid. Dietary fat intake, based on household surveys, suggests that the visible fat in poor rural diets is largely vegetable-based with negligible animal fats. The differences in the dietary fat intake between rural and urban and lower and higher socio-economic groups are largely due to large differences in the intakes of visible fats, except in the highest income group where much of it is from animal sources, with the invisible fat intake being similar among these groups.<sup>42</sup>

### **CONSUMPTION OF FRUITS AND VEGETABLES AND DIETARY FIBER**

Horticultural products are good sources of vitamins, minerals and fiber as well as bioactive compounds like phytochemicals. Horticulture has shown dramatic improvement over last few

years in India, as the area under cultivation and the horticultural outputs have increased. India has a prominent share in the global production of fruits and vegetables.<sup>43</sup>

But much of this does not seem to be reflected in increases in the consumption of fruits and vegetables – perhaps largely the result of their production as cash crops for export and sale. This can lead to a considerable loss of soil and micronutrients that are not beneficial to the local population. However, economic development seems to lead to improvements in intakes of legumes and vegetables (as well as animal products) and these changes may be beneficial. But these changes with socio-economic status are also often associated with reduced intakes of coarse cereal grains and increased reliance on highly polished varieties that may reduce the intakes of dietary fiber.

## CHANGES IN PHYSICAL ACTIVITY PATTERNS

Physical activity has declined in the world as a result of increasing mechanization<sup>43</sup>. Time in a day or week dedicated to paid work has declined in several countries as a result of shorter work shifts, shorter weeks and longer vacations. Concurrent to this, increased urbanization, universal use of motor cars, mechanization of most manual jobs outside the occupational sphere and increasing leisure time have aggravated this trend. Increased leisure time is most often dedicated to sedentary activities like television viewing, thus altering the structure of leisure time and encroaching on time normally allocated to other activities including weekday sleep.

## CONCLUSION

The important determinants that characterize the epidemic of obesity in India are: the demographic and epidemiological transition, the forces of internal migration and urbanization, the changes in food consumption patterns and physical activity patterns that in turn are contributing to increasing sedentary life style, and of other non communicable diseases. Globalization of trade encourages cash crops for export and the resultant movement of important micronutrients, which are now not available to the local population. This results in the inculcation of imbalanced and excessive calorie Western-type diet, together with the widening of economic inequalities in the society. Changes in lifestyles will further fuel this.

## REFERENCES

1. WHO. *Diet, nutrition and prevention of chronic diseases*. WHO Tech Report Series No 797. Geneva: World Health Organization, 1990.
2. WHO. *Obesity: preventing and managing the global epidemic*. Report of WHO consultation on Obesity. Geneva June 5–7 1997. Geneva: World Health Organization, 1998
3. Garrow JS *Obesity and related diseases*. Edinburgh: Churchill Livingstone, 1988.
4. Bailey KV, Ferro-Luzzi A. Use of body mass index of adults in assessing individual and community nutritional status. *Bull World Health Organ* 1995; 73:673–80
5. King, H., Aubert, R. E. & Herman, W. H. Global burden of diabetes. *Diabetes Care* (1998) 21: 1414–1431.
6. Reddy, K. S. & Yusuf, S. (1998) *The emerging epidemic of cardiovascular disease in developing countries*. *Circulation* 97: 596–601.
7. World Health Organization *The problem of overweight and obesity*. In *Obesity: Preventing and Managing the Global Epidemic*. WHO Technical Report Series no. 894, pp. 5–15. WHO: Geneva(2000) .
8. Mohamed-Ali V, Pinkney JH & Coppack SW Adipose tissue as an endocrine and paracrine organ. *Journal of Obesity and Related Metabolic Disorders* (1998) 22, 1145–1158.
9. Gema F, Javier G, Francisco J & Mary'a A *The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation*. *American Journal of Physiology* (2001) 280, E827–E847.
10. James WPT, Chunming C & Inoue S *Appropriate Asian body mass indices? Obesity Reviews* (2002) 3, 139.
11. Chandalia M, Abate N, Garg A, Stray-Gundersen J & Grundy SM *Relationship between generalized and upper body obesity to insulin resistance in Asian Indian men*. *Journal of Clinical Endocrinology and Metabolism*(1999) 84, 2329–2335.
12. Chowdhury B, Lantz H & Sjoström L *Computed tomography determined body composition in relation to cardiovascular risk factors in Indian and matched Swedish males*. *Metabolism* (1996) 45, 634–644.
13. Banerji MA, Faridi N, Atluri R, Rochelle L & Lebovitz HE *Body composition, visceral fat, leptin, and insulin resistance in Asian Indian men*. *Journal of Clinical Endocrinology and Metabolism* (1999) 84, 137–144.
14. Ramachandran A, Snehalatha C, Dharmaraj D & Vishwanathan M *Prevalence of glucose intolerance in Asian Indians: urban-rural difference and significance of upper body adiposity*. *Diabetes Care* (1992) 15, 1348–1355.
15. Shelgikar KM, Hockaday TDR & Yajnik CS *Central rather than generalised obesity is associated with hyperglycaemia in Indians*. *Diabetic Medicine* (1991) 8, 712–717.
16. Misra A, Pandey RM, Devi R, Sharma R, Vikram NK & Khanna N *High prevalence of diabetes, obesity and dyslipidaemia in urban slum population in northern India*. *International Journal of Obesity* (2001) 25, 1722–1729.
17. Snehalatha C, Viswanathan V & Ramachandran A *Cutoff values for normal anthropometric variables in Asian Indian adults*. *Diabetes Care* (2003) 26, 1380–1384.
18. McKeigue PM, Shah B & Marmot MG *Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians*. *Lancet* (1991) 337, 971–973.
19. Snehalatha C, Ramachandran A, Vallabi K, et.al. *Computed axial tomographic scan measurement of abdominal fat distribution and its correlation with anthropometry and insulin secretion in healthy Asian Indians*. *Metabolism* (1997) 46, 1220–1224.
20. Forouhi NG, Jenkinson G, Thomas EL, Mullick S, et.al. *Relation of triglyceride stores in skeletal muscle cells to central obesity and insulin sensitivity in European and South Asian men*. *Diabetologia* (1999) 42, 932–935.
21. Raji A, Seely EW, Arky RA & Simonson DC *Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians*. *Journal of Clinical Endocrinology and Metabolism* (2001) 86, 5366–5371.
22. Yajnik CS, Shelgikar KM, Naik SS, et.al. *Impairment of glucose tolerance over 10 yr in normal glucose tolerant Indians*. *Diabetes Care* (2003c) 26, 2212–2213.
23. Lubree HG, Rege SS, Bhat DS, et.al. *Body fat and cardiovascular risk factors in Indian men in three geographical locations*. *Food and Nutrition Bulletin* (2002) 23, 146–149.
24. Joglekar AA, Yajnik CS, Lubree HG, et.al. *Body fat and metabolic syndrome in men from rural and urban India*. In *Proceedings of the 18th Congress of the International Diabetes Federation*, Abstr. no. 1395; available at <http://www.idfparis2003.org> (2003)
25. World Health Organization Expert Consultation *Appropriate Body Mass Index (BMI) for Asian Populations and its Implication for Policy and Intervention Strategies*. *Lancet* (2004) 363, 157–163.
26. Fall CHD *Non-industrialized countries and affluence. In type 2 diabetes: the thrifty phenotype*. *British Medical Bulletin* (2001) 60, 33–50.
27. Prentice A *Obesity and its potential mechanistic basis. In type 2 diabetes: the thrifty phenotype*. *British Medical Bulletin* (2001) 60, 51–67.
28. Barsh GS, Farooqi IS & O'Rahilly S *Genetics of bodyweight regulation*. *Nature* (2000) 404, 644–651.
29. Bouchard A, Tremblay J, Deapres A, et.al. *The response to long-term overfeeding in identical twins*. *New England Journal of Medicine*(1990) 322, 1477–1482.
30. Sims EAH *Destiny rides again as twins overeat*. *New England Journal of Medicine* (1990) 322, 1522–1523.
31. World Health Organizations (WHO). *Obesity: Preventing and Managing the Global Epidemic*. Report of a WHO consultation. WHO Technical Report Series No. 894. Geneva: WHO, 2000.
32. Shetty PS. *Diet and life-style and chronic non-communicable diseases: what determines the epidemic in developing societies?* In: Krishnaswami K, ed. *Nutrition Research: Current Scenario and Future Trends*. New Delhi: Oxford & IBH Publishing Co., 2000: 153–67.
33. Government of India. *India Nutrition Profile*. New Delhi: Department of Women and Child Development, Ministry of Human Resources, Government of India, 1998.
34. Dhurandhar NV, Kulkarni PR. *Prevalence of obesity in Bombay*. *Int. J. Obes. Relat. Metab. Disord.* 1992; 16: 367–75.
35. Gopinath N, Chadha SL, Jain P, Shekawat S, Tandon R. *An epidemiological study of obesity in adults in the urban population of Delhi*. *J. Assoc. Physicians India* 1994; 42:212–5.
36. Zargar AM, Masoodi SR, Laway BA, Khan AK, Wani AI, Bashir MI, Akhtar S. *Prevalence of obesity in adults – an epidemiological study from Kashmir valley of Indian Subcontinent*. *J. Assoc. Physicians India* 2000; 48: 1170–4
37. Gopalan C. *Obesity in the urban middle class*. *NFI Bull.* 1998; 19: 1–4.
38. National Family Health Survey. *India Main Report*, 1991. Chapter 7: *Nutrition and the prevalence of anaemia* [Online]. Accessed 31 August 2001.
39. Dudeja V, Misra A, Pandey RM, Devina G, Kumar G, Vikram NK. *BMI does not accurately predict overweight in Asians in northern India*. *Br. J. Nutr.* 2001; 86: 105–12.
40. Yajnik CS. *The insulin resistance epidemic in India: fetal origins, later lifestyle, or both?* *Nutr. Rev.* 2001; 59: 1–9.
41. Food and Agriculture Organization (FAO)/World Health Organization (WHO). *Fats and Oils in Human Nutrition*. Report of a joint expert consultation. *FAO Food & Nutrition Papers*, Vol. 57. Rome: FAO, 1994; 1–147.
42. Ghafourounisa. *Fats in Indian diets*. *NFI Bull.* 1989; 10: 1–5.
43. Kaul GL. *Fruit and vegetable production in India*. *NFI Bull.* 1998; 19: 5–8.
43. Ferro-Luzzi A, Martino L. *Obesity and physical activity*. In: *The Origins and Consequences of Obesity*. Ciba Foundation Symposium, Vol. 201. Chichester: John Wiley & Sons, 1996; 228–46.

## AETIOPATHOGENESIS OF OBESITY

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**Abstract :** Obesity is a problem of energy balance, which develops when energy intake is more than the total energy expenditure (BMR, Thermogenic Physical Activity & Non Exercise Activity Thermo genesis). Adipose tissue consists of adipocytes which store the lipids, and also produce various molecules which affect the body's energy management like leptin, adiponectin, adipisin, resistin etc. Leptin has been proven to be the principal afferent signal in the negative feedback loop regulating the size of the adipose tissue mass, thereby regulating obesity. Leptin receptors are found in hypothalamus, where an increase in leptin level, leads to decreased appetite and increased energy expenditure, via Melanocyte Stimulating Hormone (MSH). Low leptin levels stimulate Neuropeptide Y, causing an increase in food intake and decreased energy expenditure. Obesity results from either impaired secretion of leptin, or due to resistance to the action of leptin. Ghrelin, which is an endogenous ligand for the growth hormone secretagogue receptor, when secreted into the plasma by neuroendocrine cells of stomach, acts on hypothalamus via Neuropeptide Y & Agouti Related Peptide (AgRP), which are potent orexigenic peptides. Stomach has an important role in energy homeostasis, apart from ghrelin release, gastric distension and emptying play an important role in regulating food intake. Various molecules like cholecystokinin and enterostatin act on stomach and inhibit gastric emptying, thereby reducing food intake. Hypothalamus is the central agency for integration of all signals for maintenance of energy balance of body. Orexin, Melanin Concentrating Hormone, NP-Y and AgRP stimulate appetite, while MSH and GLP-1 suppress appetite. Knowledge of molecular basis of the signalling will help modulate therapeutic measures for obesity.

### INTRODUCTION

Obesity has gone from being a merely medical diagnosis to a morbid state with widespread physical, mental and social ramifications. No disorder can be effectively managed if its cause is not known and blaming obesity on the gluttonous habits of the person is not tenable any longer<sup>1</sup>. We are still unravelling the interlinking and intertwined threads of metabolism that make up the complex tapestry of obesity. This review is an overview of the latest research available in medical literature on the aetiopathogenesis of obesity.

### ADIPOSE TISSUE

At the basic level obesity occurs whenever the energy expenditure falls behind the energy intake leading to the body storing the excess energy as adipose tissue. As with all human physiology there is a homeostatic loop involving energy intake and disposal; with the adipose tissue itself playing a vital part. Adipose tissue consists of the much maligned adipocyte which stores the lipids in its cytoplasm and the stromal and vascular framework from which the preadipocytes are derived. However the adipocyte is not content just to act as a lipid store but also moonlights as a prolific endocrine cell producing various molecules which affect the body's energy management<sup>2</sup>. Leptin is the major molecule secreted that has been extensively studied and is discussed in detail below. Other molecules include Adiponectin which enhances insulin sensitivity and lipid oxidation; adipisin or Factor D a complement molecule; resistin which contributes to insulin resistance. A less understood part is the role of Brown Adipose Tissue (BAT). In

essence BAT contains an enzyme which decouples the oxidative respiratory chain from ATP generation leading to dissipation of the energy as heat. In mice BAT activity is increased by the sympathetic stimulation mediated by leptin leading to thermogenic dissipation of energy<sup>3</sup>. Mice deficient in BAT become obese and might become diabetic. Stimulation of the BAT by  $\beta$ 3 agonists on the other hand would protect the mice from obesity<sup>4</sup>

### LEPTIN

Leptin (leptos – greek: thin) circulates as a protein of relative molecular mass 16,000 in mouse and human plasma<sup>5</sup>. It was initially conceptualised during experiments on mice in which recessive mutations in the obese (ob) and diabetes (db) genes lead to obesity and diabetes resembling human morbid obesity<sup>6</sup>. It was postulated on the basis of further cross circulation experiments that the ob gene encoded for a circulating factor that regulated energy balance and that the db gene encoded the receptor for this factor<sup>6</sup>. This was confirmed when leptin RNA was found to be expressed in adipocytes and the plasma levels of leptin were highly correlated with adipose tissue mass<sup>7</sup>. Leptin levels underwent a sharp fall in both humans and mice after weight loss<sup>7</sup>. Obese humans tend to have high levels of leptin thus making leptin the principal afferent signal in the negative feedback loop regulating the size of the adipose tissue mass. As would be expected administration of leptin by injection results in a dose dependent decrease in body weight and this weight loss is restricted to the adipose tissue mass with sparing of lean body mass<sup>8</sup>. The leptin receptor (Ob – R) is encoded by the db gene. It is a member of the cytokine family of receptors first isolated in the choroid plexus of mice<sup>9</sup>. Mutations in the Ob – R result in an obese phenotype identical to ob mice indicating Ob – R essentiality in leptin action. The leptin

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receptor is expressed in high levels in the hypothalamic neurons. Low leptin levels lead to stimulation of neuropeptide Y or its receptors; Neuropeptide Y being the most potent orexigenic stimulus when administered intrathecally<sup>10</sup>. This then leads to the starvation response including an increased food intake, decreased energy expenditure,  $\bar{GHRH}$  and  $\bar{GnRH}$ . Weight gain and a consequent increased leptin acts through the Melanocyte Stimulating Hormone (MSH) and its precursor Proopiomelanocortin (POMC) in the hypothalamus resulting in a decreased food intake and increased energy expenditure<sup>11</sup>. Leptin appears to act within a largely long term system of controlling feeding behaviour and energy balance and influences the quantity of food consumed relative to the amount of energy expended.

This nearly perfect Leptin system of long term energy balance can go wrong at three sites<sup>12</sup>

1. Failure to produce leptin: as occurs in ob/ob mice; analogous to type 1 diabetes mellitus. Several families with early onset morbid obesity caused by inactivating mutations in leptin have been described<sup>13</sup>.
2. Inappropriately low leptin secretion for a given fat mass. In such patients the adipose tissue would expand until normal leptin levels are reached thus resulting in obesity.
3. Relative or absolute insensitivity to leptin at its site of action: as occurs in db/db mice; analogous to type 2 diabetes mellitus. Such patients will usually have high circulating leptin levels. The resistance might be at the receptor level in form of mutations of the db gene. Mechanisms of resistance could also involve POMC mutations preventing synthesis of MSH & mutations involving the melanocortin 4 receptor<sup>14</sup>. Involvement of peptide processing enzymes Carboxypeptidase E (product of the *fat* gene) and PC-1 leads to obesity and hyperleptinaemia in mice; as does mutation of the *tub* gene. Additionally the entry of leptin into the cerebrospinal fluid may be limiting in some patients and morbid obesity could result when the plasma leptin levels exceed the capacity of the transport system<sup>15</sup>.

The above mentioned mutations are a rare cause of human obesity. The exact aetiology of common obesity is still unknown there being no evidence of polymorphisms of leptin or leptin receptor gene among the common forms of obesity<sup>16</sup>.

## GHRELIN

Ghrelin is an endogenous ligand for the growth hormone secretagogue receptor (GHS receptor)<sup>17</sup>. GHSs were a non natural synthetic group of molecules developed as a research tool<sup>18</sup>. GHSs act on a G protein coupled receptor (GHS Receptor type Ia – GHS-RIa) distinct from that of GHRH. Tomassetto et al isolated ghrelin as the 'motilin related peptide' with structural and effect related similarities to the duodenal hormone motilin and Kojima et al correctly identified it as the endogenous ligand for the GHS-RIa receptor which is predominantly expressed in the pituitary and the hypothalamus<sup>17,19</sup>.

Ghrelin itself is expressed mainly in the stomach by neuroendocrine cells (P/D1 cells in humans) in the fundus and is secreted into the circulation. Ghrelin concentrations in the plasma rise progressively during fasting and fall to a nadir within an hour of refeeding. Both open and closed gastric ghrelin cells exist in the stomach suggesting

they receive both luminal and neuroendocrine information. Gastric ghrelin production is regulated by nutritional and hormonal factors. Inhibitory signals include somatostatin, interleukin 1 $\beta$ , growth hormone, high fat diet and vagal tone. Fasting and low protein diet leads to increased expression and plasma concentrations of ghrelin. This is in contrast to majority of gut hormones whose secretion increases with food intake and decreases with fasting. Ghrelin administered into the periphery or cerebral ventricles potently stimulates food intake leading to weight gain in rodents<sup>20</sup>. The premeal increase of ghrelin may trigger the desire to eat in animals and humans. Ghrelin secreted into the plasma acts on the hypothalamus through Neuropeptide Y (NPY) and Agouti related Peptide (AgRP), two potent orexigenic peptides<sup>21</sup>. NPY promotes net energy gain by increasing food intake, decreasing energy expenditure and exerting effects in peripheral tissues, including stimulation of glucocorticoid and insulin secretion that favour deposition of triglycerides in white adipose tissue. AgRP is a 132 amino acid peptide, synthesized in the brain exclusively in the arcuate nucleus by neurons that project to the paraventricular nucleus and lateral hypothalamic area. AgRP's antagonism of the melanocortin 4 receptor stimulates food intake and decreases energy expenditure. A 17% diet induced weight loss leads to a 24% increase in plasma ghrelin levels indicating that ghrelin is at least partially responsible for the poor adherence to weight reducing diets<sup>22</sup>. The success of gastric bypass in maintaining weight reduction is consequently due in part to the very low ghrelin levels found in these patients<sup>22</sup>.

## HYPOTHALAMUS

From the above discussion it is clear that the hypothalamus is the central agency for integration of all the signals both neuronal and endocrine and maintaining the energy balance in the body. Neural impulses mostly vagal and hormonal signals in form of leptin, ghrelin, insulin, cholecystokinin all act on the hypothalamus along with metabolites like glucose. These diverse signals cause the release of the various peptides in the hypothalamus which modify both food seeking and energy expending behaviour. Orexin, melanin concentrating hormone (MCH), NPY and AgRP stimulate appetite whereas MSH and GLP-1 (Glucagon like peptide 1) would suppress appetite. This might be partially routed through the autonomic nervous system. In mice sympathetic activation of BAT is one of the methods of increased energy expenditure.

Another method of thermogenesis is the NonExercise Activity Thermogenesis (NEAT)<sup>23</sup>. NEAT is the thermogenesis that accompanies all the routine activities of daily life like walking, standing, fidgeting, posture maintenance etc., in short all activities apart from volitional exercise. If energy balance is ideal almost 70 percent of the extra energy expenditure on overfeeding is attributed to NEAT. The relative strength of induction of NEAT would determine to some extent the amount of extra energy leftover which would be stored as fat.

Lesions of the hypothalamus like tumours or inflammation can cause hypothalamic dysregulation resulting in obesity.

## HYPOTHALAMO-PITUITARY-ADRENAL AXIS

Central obesity is one of the hallmarks of Cushing's syndrome. Even though serum cortisol might be higher in obese patients, an overnight dexamethasone suppression test will be positive in an overwhelming 90% of patients thereby preventing confusion. The remaining 10% can be excluded on the basis of a 2 day low dose dexamethasone suppression test.

However more ominous is the permissive role of glucocorticoids in the development of central obesity in 'common' obesity (as opposed to those associated with specific disorders/mutations). The thrifty phenotype hypothesis suggests that in response to undernutrition, a foetus will selectively distribute nutrients to preserve brain growth at the expense of other organs such as liver, pancreas, and muscle<sup>24</sup>. The stress response to foetal undernutrition will lead to an increased ACTH secretion and a probable resetting of the HPA axis. As these individuals experience improved postnatal nutrition, the compensatory catch up growth is associated, as early 5yrs of age, with increased visceral adipose tissue and later with insulin resistance<sup>25</sup>. This might in part explain the explosion of obesity and diabetes in India and also the relatively higher incidence of diabetes in poor migrants from developing countries settling in urban centres/developed countries.

## STOMACH

The stomach plays an extremely important role in energy homeostasis, ghrelin release being only one of the mechanisms. Gastric distension and emptying play important roles in regulating food intake. Gastric distension with food relays a satiety signal to the hypothalamus through vagal afferents inhibiting further food intake<sup>26</sup>. Anorexigenic molecules like cholecystokinin not only suppress feeding on a hypothalamic level but also decrease gastric transit, thereby further inhibiting food intake<sup>27</sup>. On the other hand rapid gastric emptying is associated with overeating and obesity. Lesions of the ventromedial nucleus (VMH) of the hypothalamus result in disruption of autonomic control of the stomach causing an accelerated transit of food from the stomach<sup>28</sup>. As the stomach does not appropriately distend with food satiety signalling is defective resulting in overeating and obesity. This is thought to be the major cause of the obese VMH syndrome.

Leptin and its receptor have been identified in the gastric mucosa in humans<sup>29</sup>. Gastric leptin can be released into the blood and gastric juice after feeding, insulin-induced hypoglycemia, or infusion of CCK-8, pentagastrin, and secretin. Gastric leptin may have a role in appetite regulation by acting directly in the hypothalamus or in synergy with CCK via the vagal pathway or by modifying absorption of dietary protein and fats<sup>30</sup>.

Enterostatin, a derivative of procolipase (protein necessary for intestinal fat digestion) is also produced by the gastric chief cells. Enterostatin increases during fat feeding, where it is found in circulating blood as well as in intestinal lumen and the lymph<sup>31</sup>. Enterostatin inhibits gastric emptying and signals the hypothalamus as a satiety factor thereby reducing food intake.

## CONCLUSION

Multiple signals converge on the hypothalamus to regulate energy balance in the body. Knowledge of the molecular basis of the signalling will help modulate therapeutic measures to induce and maintain weight loss and prevent weight gain in the first place. However research into obesity has still a long way to go before translating into therapeutic measures.

## REFERENCES

1. *Stunkard AJ, Harris JR, Pedersen NL, McClearn GE. The body-mass index of twins who have been reared apart. N Engl J Med. 1990 24;322(21):1483-7*
2. *Calabro P, Yeh ET. Obesity, inflammation, and vascular disease: the role of the adipose tissue as an endocrine organ. Subcell Biochem. 2007;42:63-91.*
3. *Inokuma K, Okamatsu-Ogura Y, Omachi A, Matsushita Y, Kimura K, Yamashita H, Saito M. Indispensable role of mitochondrial UCP1 for antiobesity effect of beta3-adrenergic stimulation. Am J Physiol Endocrinol Metab. 2006;290(5):E1014-21*
4. *Nakamura K, Morrison SF. Central efferent pathways mediating skin cooling-evoked sympathetic thermogenesis in brown adipose tissue. Am J Physiol Regul Integr Comp Physiol. 2007;292(1):R127-36*
5. *Halaas, J.L. et al. Weight reducing effect of the plasma protein encoded by the obese gene. Science. 1995. 269, 543 - 546.*
6. *Coleman DL. Obese and diabetes: two mutant genes causing diabetes-obesity syndromes in mice. Diabetologia. 1978;14(3):141-8*
7. *Maffei, M. et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nature Med. 1995 1, 1155-1161*
8. *Halaas, J. L. et al. Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. Proc. Natl Acad. Sci. 1997 94, 8878-8883*
9. *Tartaglia, L. A. et al. Identification and expression cloning of a leptin receptor, OB-R. Cell 1995 83, 1263-1271*
10. *Stephens, T.W. et al. The role of neuropeptide Y in the antiobesity action of the obese gene product. Nature. 1995; 377, 530-534*
11. *Satoh, N. et al. Satiety effect and sympathetic activation of leptin are mediated by hypothalamic melanocortin system. Neurosci. Lett. 1998; 249, 107-110*
12. *Jeffrey M. Friedman & Jeffrey L. Halaas. Leptin and the regulation of body weight in mammals. Nature. 1998; 395; 763 - 770*
13. *Montague, C. T. et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997; 387, 903-908*
14. *Rovere, C., Viale, A., Nahon, J. L. & Kibiagi, P. Impaired processing of brain proneurotensin and promelanin-concentrating hormone in obese fat/fat mice. Endocrinology 1996;137, 2954-2958.*
15. *Caro JF, Kolaczynski JW, Nyce MR, et al. Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. Lancet. 1996; 348, 159-161*
16. *Maffei M, Stoffel M, Barone M, et al. Absence of mutations in the human ob gene in obese/diabetic subjects. Diabetes 1996; 45, 679-682*
17. *Kojima, M., Hosoda, H., Date, Y., et al. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature (London) (1999) 402, 656-660*
18. *Bowers, C. Y., Momany, F. A., Reynolds, G. A., and Hong, A. On the in vitro and in vivo activity of a new synthetic hexapeptide that acts on the pituitary to specifically release growth hormone. Endocrinology (1984) 114, 1537-1545*
19. *Tomasetto, C., Karam, S. M., Ribieras, S., et al. Identification and characterization of a novel gastric peptide hormone: the motilin-related peptide. Gastroenterology (2000) 119, 395-405*
20. *Nakazato, M., Murakami, N., Date, Y., et al. A role for ghrelin in the central regulation of feeding. Nature 2001; 409, 194-198*
21. *Shintani, M., Ogawa, Y., Ebihara, K., et al. Ghrelin, an endogenous growth hormone secretagogue, is a novel orexigenic peptide that antagonizes leptin action through the activation of hypothalamic neuropeptide Y/Y1 receptor pathway. Diabetes 2001; 50, 227-232*
22. *Cummings DE, Weigle DS, Frayo RS, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med. 2002 23;346(21):1623-30*
23. *Levine JA. Nonexercise activity thermogenesis (NEAT): environment and biology. Am J Physiol Endocrinol Metab. 2004 ;286(5):E675-85*
24. *Hales CN and Barker DJP. The thrifty phenotype hypothesis. Br Med Bull 2001; 60: 5-20*
25. *Ong KKL, Ahmed ML, Emmet PM, et al., and the Avon Longitudinal Study of Pregnancy and Childhood Study Team. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. Br Med J. 2000; 320: 967-971*
26. *Schwartz, G. J. The role of gastrointestinal vagal afferents in the control of food intake: current prospects. Nutrition 2000; 16, 866-873*
27. *Forster, E. R., Green, T., Elliot, M., Gastric emptying in rats: role of afferent neurons and cholecystokinin. Am. J. Physiol. (1990) 258, G552-G556*
28. *Duggan, J. P., and Booth, D. A. Obesity, overeating, and rapid gastric emptying in rats with ventromedial hypothalamic lesions. Science (1986) 231, 609-611*
29. *Bado, A., Levasseur, S., Attoub, S., et al. (1998) The stomach is a source of leptin. Nature (London) 394, 790-793*
30. *Wang, L., Barachina, M. D., Martínez, V., et al. Synergistic interaction between CCK and leptin to regulate food intake. Regul. Pept. (2000) 92, 79-85*
31. *Lindqvist, A., and Erlanson-Albertsson, C. Fat Digestion- its role in appetite regulation and energy balance-The importance of enterostatin and tetrahydrolipstatin. Curr. Med. Chem.-Central Nervous System Agents (2003)3, 157-175*

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## ADIPOCYTE- AN ENDOCRINE ORGAN

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**Abstract :** The adipose tissue primarily consists of two functionally distinct types- brown and white adipose tissue. Brown adipose tissue is specialized for heat production by non-shivering thermo genesis and metabolism of this fat doesn't produce ATP. Whereas the white adipose tissue serves as a major energy reservoir and stores triacylglycerols in periods of energy excess and mobilizes the same during energy deprived states. White adipocytes are the major secretory cells of adipose tissue, making it a key endocrine organ. Adipocytes secrete a number of hormones and diverse range of protein factors termed as 'adipokines', which are collectively involved in metabolic regulation and are linked to pathogenesis of obesity. Adiponectin is the most abundant protein produced by adipose tissue, and it plays a negative feedback role in fat storage. Adiponectin is an endogenous anti-inflammatory and anti-atherogenic factor that is protective against insulin resistance and macroangiopathy. It has been seen that low circulating serum adiponectin levels correlate strongly with increasing BMI, obesity and insulin resistance. Leptin was one of the earliest adipokines to be identified as the product of ob gene in mice. Primary target of leptin is the hypothalamic arcuate nucleus and its systemic response is inhibition of food intake and an increase in overall energy expenditure. Apart from these hormones, adipocytes also secrete a number of cytokines and acute phase proteins, thus leading to increase in the circulating levels of inflammation related factors. This lead to emergence of the concept that obesity is a state of chronic mild inflammation and this inflammatory state plays a causal role in development of Type-2 Diabetes and metabolic syndrome in obese individuals.

### INTRODUCTION

Obesity is a prevalent health hazard particularly in industrialized countries and is closely associated with a number of pathological disorders, including non-insulin-dependent diabetes, hypertension, cancer, gallbladder disease, and atherosclerosis.<sup>1, 2</sup> Obesity is fundamentally a problem of energy balance; it develops when energy (food) intake is in excess of total energy expenditure (Basal Metabolic Rate, 'thermogenesis', physical activity, 'non-exercise activity thermogenesis'). Differences between intake and expenditure are primarily buffered by changes in the amount of lipid (triacylglycerols) deposited in the specialized fuel storage organ, white adipose tissue (or white fat).

The adipose tissue primarily consists of two functionally distinct types – brown and white adipose tissue. Brown adipose tissue is specialized for heat production by non-shivering thermogenesis, and in this tissue the stored lipid droplets serve primarily as a fuel for the production of heat. The mitochondria in these cells are unique; their membranes contain an uncoupler of oxidative phosphorylation (UCP -1 protein) and metabolism of this fat does not produce ATP. Whereas the white adipose tissue serves as a major energy reservoir and stores triacylglycerols in periods of energy excess and mobilizes the same during energy deprived states. In addition to fuel storage, white adipose tissue can act as a thermal insulator to heat loss and as a cushion to protect other organs.

### ADIPOSE TISSUE AS AN ENDOCRINE ORGAN

The adipose tissue is made up of mature adipocytes, which store lipid; in addition it has a variety of other cells (e.g. fibroblasts, endothelial cells, macrophages) which constitute around 50% of the total cellular content. White adipocytes are

major secretory cells, making adipose tissue a key endocrine organ. Adipose tissue is now considered as the largest endocrine organ in most humans – and more so in the overweight and obese individuals.

Quantitatively, the most important secretion from adipocytes is fatty acids, which is released during the periods of negative energy balance (particularly fasting). In addition to fatty acids, several other lipid moieties are also released; these include prostanooids (which are synthesized by the tissue itself), and cholesterol and retinol, which are not synthesized but are rather stored and subsequently released.

Adipose tissue is now recognized as the source of key hormones which play an important role in the regulation of energy balance and adipocytes are also known to secrete a diverse range of protein factors and signals termed 'adipokines', which are involved in metabolic regulation and are increasingly considered to be directly linked to the pathogenesis of common obesity. These adipokines act both locally and distally through autocrine, paracrine and endocrine effects to regulate fat cell differentiation, and sense and adjust systemic energy balance.<sup>3</sup> As energy surplus develops, adipocyte differentiation and lipid accumulation are inhibited through feedback loops of adipocyte-derived factors such as TNF- $\alpha$ , angiotensinogen (AGT), and resistin (for resistance to insulin). In states of energy deficit or excess, there is a corresponding change in the levels of adipocyte secreted proteins, (such as adiponectin, leptin), and trophic substances such as acylation stimulating protein (ASP) and angiotensin II (AngII). In states of energy excess, these signal a drive to adipocyte formation and renewed triglyceride accumulation. Insulin is central to this process, promoting lipogenesis and energy storage.

Increased activity of three of these adipokines namely tumor necrosis factor, interleukin 6, and resistin, play a role in the development of the insulin resistance present in obesity. In contrast, other adipokines, like adiponectin and leptin, are

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insulin sparing through stimulatory effects on the beta oxidation of fatty acids in skeletal muscle.

## SECRETORY FUNCTIONS OF ADIPOSE TISSUE<sup>4</sup>

The following is a list of key substances known to be secreted by adipose tissue – table.

**Table: Substances secreted by the adipose tissue:**

<b>Hormones</b>	
·	Leptin
·	Adiponectin
·	Resistin
·	Glucocorticoids
·	Estrogens
<b>Cytokines</b>	
·	IL-6
·	TNF- $\alpha$
·	VEGF
·	TGF $\beta$
·	HGF
<b>Enzymes</b>	
·	Aromatase
·	11- $\beta$ HSD - 1
·	Complement factors
·	adipsin
<b>Others</b>	
·	PAI-1
·	Acylation-stimulating protein (ASP)
·	Angiotensinogen

### **Adipokines**

The adipokines are highly diverse in terms of protein structure and physiological function. They include classical cytokines, growth factors and proteins of the alternative complement system; proteins involved in the regulation of blood pressure, vascular haemostasis, lipid metabolism, glucose homeostasis and angiogenesis.

#### **Adiponectin**

Adiponectin [Adipocyte complement-related protein (ACRP)], is expressed abundantly and exclusively in white adipose tissue.<sup>5</sup> It is the most abundant protein produced by adipose tissue. Serum adiponectin is found to circulate as oligomers of four to six trimers each.<sup>6</sup> Its serum concentrations are reduced in obese mice and humans and rise following weight loss. This suggests that adiponectin plays a negative feedback role in fat storage.<sup>7</sup> It has also been observed in studies on human subjects that low circulating serum adiponectin levels correlates strongly with increasing BMI, obesity and insulin resistance.<sup>8, 9</sup>

Adiponectin appears to be an endogenous anti-inflammatory and anti-atherogenic factor that is protective against insulin resistance and macroangiopathy.<sup>10</sup> Its concentrations correlate with the insulin sensitivity state and rise in response to insulin. Further, evidence has emerged from studies which suggest that the insulin sensitizing action of thiazolidinediones (acting via

PPAR) may be mediated through increased adiponectin.<sup>11</sup>

Adiponectin has a tendency to retard atherosclerosis. This effect is either mediated through a direct action of adiponectin on the endothelium or indirectly through reduction in the expression of leukocyte adhesion molecules and inflammatory cytokines (e.g. TNF  $\alpha$ ).<sup>8, 14, 15</sup>

In view of such extensive favorable actions of adiponectin and the initial encouraging results seen in animal studies, this molecule and its associated receptors could be the target of future successful preventive strategies or therapies in obesity, atherosclerosis and type 2 diabetes mellitus.<sup>8, 15, 16</sup>

#### **Leptin**

Leptin was one of the earliest adipokines to be identified as the product of the *ob* gene in mice. Non production of leptin by a mutant strain of mice (*ob/ob*) produced a state of obesity, elevated cortisol levels, insulin resistance, and reproductive dysfunction.<sup>17</sup>

Leptin's primary physiologic function is the defense of body fat. Declining levels in adipose tissue and serum signal the presence of energy deficit to the brain. It is an essential signal from adipocytes to the hypothalamus in the control of appetite and energy balance and is believed to keep the CNS informed about the body's energy reserves. Leptin acts through cell surface receptor, OB-R and signal transduction involves Janus kinases.<sup>18</sup>

The primary target of leptin is believed to be the neurons of the hypothalamic arcuate nucleus neurons. The systemic response is inhibition of food intake and an increase in overall energy expenditure by the organism.<sup>19</sup> Leptin reduces the levels of intracellular lipid in skeletal muscle, liver and pancreatic beta cells, thereby improving insulin sensitivity. In muscle this insulin sensitizing effect is achieved through inhibition of malonyl CoA, permitting increased transport of fatty acids into mitochondria for beta oxidation. These changes are partially mediated by central sympathetic activation of adrenergic receptors.<sup>20</sup> Peripheral effects of leptin include modulation of reproduction, angiogenesis, immunity and regulation of triacylglycerol metabolism.<sup>18</sup>

Though studies have described a positive correlation between BMI and circulating leptin levels in humans<sup>21</sup>, the role of leptin in the pathogenesis of common obesity is still not well elucidated. Except in rare instances of genetic leptin deficiency syndromes, exogenous leptin has not proved to be effective in regulating appetite or raising body metabolism.<sup>22,23</sup>

#### **Resistin**

This name for this hormone was coined after an association was observed between "resistin" and insulin resistance.<sup>24</sup> However, later work suggested that the likely effect of resistin was on hepatic glucose output rather than insulin sensitivity of peripheral tissues.<sup>25</sup> The hormone is believed to be expressed at much higher levels in visceral fat as compared to subcutaneous fat. Inflammatory cytokines and steroids are believed to increase expression of resistin while

thiazolidinediones inhibit it.

The physiological role of resistin is still unclear and under evaluation

## INFLAMMATION AND OBESITY

A number of inflammation-related proteins are released by white adipocytes. One of the most important recent developments in obesity research is the emergence of the concept that obesity is characterized by chronic mild inflammation. The basis for this view is that the circulating level of several cytokines and acute phase proteins associated with inflammation is increased in obese individuals. As adipocytes secrete a number of cytokines and acute phase proteins, it is considered that the expanded adipose tissue mass contributes, either directly or indirectly, to the increased production and circulating levels of inflammation-related factors in obesity. In other words, the state of inflammation in adipose tissue in obesity leads to an increased production and release of inflammation-related factors.

## ADIPOSE TISSUE AND THE DISEASES OF OBESITY

The central change to the body in obesity is the increase in the amount of adipose tissue – which may constitute more than half of total body mass in those with a BMI that is in excess of the threshold of obesity. It is not, however, only the total amount of fat that is important, but also its distribution. Thus, a more central fat deposition ('android' or 'apple' type, as compared to 'gynoid' or 'pear' shaped) is associated with a greater risk of the metabolic syndrome and several of the other diseases linked to obesity. The current view is that the inflammatory state of obesity plays a key causal role in the development of type 2 diabetes and the metabolic syndrome (which includes atherosclerosis, hypertension and dyslipidemia). A central hypothesis is that the increase in inflammation-related adipokine production that occurs in obesity lead to the associated diseases. In this context, the reduction in adiponectin in the obese is thought to be of particular significance in view of the anti-inflammatory effect of this adipokine.

## CONCLUSION

The mechanisms by which obesity contributes to insulin resistance, hypertension, and endothelial disease are among the most important questions facing medical investigators today. Research into the function and regulation of adipocyte signaling proteins, adipocytes differentiation, and the control

of fat partitioning will likely result in further insight into these mechanisms and the discovery of therapies for treatment of obesity and obesity related diseases.

## REFERENCES

1. *Kuczmarski R. J., K.M. Flegal, S. M. Campbell, and C. L. Johnson.* Increasing prevalence of overweight among US adults. *The National Health and Nutrition Examination Surveys, 1960 to 1991.* JAMA, 1994; 272: 205–211.
2. *Wolf, A. M., and G. A. Colditz.* Social and economic effects of body weight in the United States. *Am. J. Clin. Nutr.* 1996; 63, Suppl.:466S–469S
3. *Ahima RS, Flier JS.* Trends in Endocrinology and Metabolism 2000; 11: 327–332.
4. *Ahima RS.* Adipose Tissue as an Endocrine Organ. *Obesity* 2006; 14: 242S–249S.
5. *Kahn BB, Flier JS.* Obesity and insulin resistance. *J Clin Invest* 2000; 106:473–481.
6. *Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, Engel J, Brownlee M, Scherer PE.* Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin: implications for metabolic regulation and bioactivity. *J Biol Chem* 2002; 278:9073–9085.
7. *Yang WS, Lee WJ, Funahashi T, et al.* Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. *J Clin Endocrinol Metab* 2001; 86:3815–3819.
8. *Hotta K, Funahashi T, Arita Y, et al.* Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000; 20:1595–1599.
9. *Weyer C, Funahashi T, Tanaka S, et al.* Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 2001; 86:1930–1935.
10. *Ouchi N, Kihara S, Arita Y, et al.* Novel modulator for endothelial adhesion molecules: adipocytes-derived plasma protein adiponectin. *Circulation* 1999; 100:2473–2476.
11. *Combs TP, Wagner JA, Berger J, et al.* Induction of adipocyte complement-related protein of 30 kilodaltons by PPAR agonists: a potential mechanism of insulin sensitization. *Endocrinology* 2002; 143:998–1007.
12. *Yamauchi T, Kamon J, Waki H, et al.* Globular adiponectin protected ob/ob mice from diabetes and apoE deficient mice from atherosclerosis. *J Biol Chem* 2002; 278:2461–2468.
13. *Berg AH, Combs T, Du X, Brownlee M, Scherer PE.* The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 2001; 7:947–953.
14. *Maeda N, Shimomura I, Kishida K, et al.* Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat Med* 2002; 8:731–737.
15. *Kubota N, Terauchi Y, Yamauchi T, et al.* Disruption of adiponectin causes insulin resistance and neointimal formation. *J Biol Chem* 2002; 277:25863–25866.
16. *Spranger J, Kroke A, Mohlig M, et al.* Adiponectin and protection against type 2 diabetes mellitus. *Lancet* 2003; 361:226–228.
17. *Zhang Y, Proenca R, Maffei M, et al.* Positional cloning of the mouse obese gene and its human homologue. *Nature.* 1994; 372:425–32.
18. *Fruhbeck G, Gómez-Ambrosi J, Muruzabal J, Burrel MA.* The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation. *Am J Physiol Endocrinol Metab.* 2001; 280:E827–47.
19. *Schwartz MW, Woods SC, Porter D Jr, Seeley RJ, Baskin DG.* Central nervous system control of food intake. *Nature.* 2000; 404:661–71.
20. *Friedman J.* Fat in all the wrong places. *Nature* 2002; 415:268–269.
21. *Friedman JM.* The function of leptin in nutrition, weight, and physiology. *Nutr Rev* 2002; 60:S1–S14.
22. *O'Rahilly S, Sadaf Farooqi I, Yeo GSH, Challis BG.* Minireview: human obesity—lessons from monogenic disorders. *Endocrinology* 2003; 144:3757–3764.
23. *Michael W, Rajala and Philipp E. Scherer.* Minireview: The Adipocyte—At the Crossroads of Energy Homeostasis, Inflammation, and Atherosclerosis. *Endocrinology* Vol. 144, No. 9 2003; 3765–3773.
24. *Steppan CM, Bailey ST, Bhat S, Brown EJ, et al.* The hormone resistin links obesity to diabetes. *Nature.* 2001; 409:307–12.
25. *Rajala MW, Obici S, Scherer PE, Rosselli L.* Adipose-derived resistin and gut-derived resistin-like molecule- $\beta$  selectively impair insulin action on glucose production. *J Clin Invest* 2003; 111:225–230.

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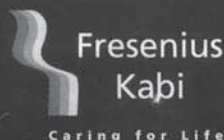


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## OBESITY: IMPACT ON MORBIDITY AND MORTALITY

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**Abstract:** As per WHO, (World Health Organisation), BMI (Kg/m<sup>2</sup>) 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 BMI > 27.0 kg/m. 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 BMI > 27.0 kg/m<sup>2</sup>. 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%, steatohepatitis 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.

## REFERENCES

1. *Asia pacific cohort studies collaboration. The burden of overweight and obesity in the Asia-*

- Pacific region. Obes Rev. 2007;8(3):191-6. Review.*
2. **Unger RH.** Weapons of lean body mass destruction: the role of ectopic lipids in the metabolic syndrome. *Endocrinology. 2003.*
3. **National Institutes of Health and National Heart, Lung, and Blood Institute.** Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. *Obes Res. 1998;6(suppl 2):1S-209S.*
4. **World Health Organization.** *Obesity: preventing and managing the global epidemic. Report of a WHO Consultation on Obesity.* Geneva: World Health Organization, 1998.
5. **Isomaa B et al.** Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care. 2001;24:683-689.*
6. **Hu FB et al.** Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. *Diabetes Care. 2002; 25:1129-1134.*
7. **Brochu M et al.** What are the physical characteristics associated with a normal metabolic profile despite a high level of obesity in postmenopausal women? *J Clin Endocrinol Metab. 2001;86:1020-1025.*
8. **Han TS et al.** Analysis of obesity and hyperinsulinemia in the development of metabolic syndrome: San Antonio Heart Study. *Obes Res. 2002;10:923-931.*
9. **Rexrode KM et al.** Abdominal adiposity and coronary heart disease in women. *JAMA. 1998;280:1843-1848.*
10. **Stamler J, Wentworth D, Neaton JD.** Is relationship between serum cholesterol and risk of premature death from coronary disease continuous or graded? Findings in 356,222 primary screenings of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA 1986;256:2823-2828.*
11. **Folsom AR, Kushi LH, Anderson KE, et al.** Associations of general and abdominal obesity with multiple health outcomes in older women. *Arch Intern Med 2000;160:2117-2128.*
12. **Hathial M.** Blood pressure control among Indians with hypertension: the I-Target survey. *J Indian Med Assoc. 2007 Jul;105(7):401-2, 404, 410.*
13. **Sharma SK, Vasudev C, Sinha S et al.** Validation of the modified Berlin questionnaire to identify patients at risk for the obstructive sleep apnoea syndrome. *Indian J Med Res. 2006 Sep;124(3):281-90.*
14. **Allman-Ferinelli MA, Aitken RJ, King LA.** Osteoarthritis - the forgotten obesity-related epidemic with worse to come. *Med J Aust. 2008 Mar 3;188(5):317.*
15. **Calle EE et al:** Overweight, obesity and mortality from cancer in a prospectively studied cohort of US adults. *N Eng J Med 348:1625-1638,2003.*
16. **Adami HO et al:** Obesity and cancer mortality from cancer. *N Eng J Med 348:1623-24,2003.*
17. **Prentice et al:** Maternal obesity increases congenital malformations. *Nutr Rev 54: 146-150,1996.*
18. **Abuhtal M, Armstrong T.** The impact of obesity on the course and outcome of acute pancreatitis. *Obes Surg. 2008 Mar;18(3):326-8. Epub 2008 Jan 18*
19. **Huang HL, Lin WY, Lee LT.** Metabolic syndrome is related to nonalcoholic steatohepatitis in severely obese subjects. *Obes Surg. 2007 Nov;17(11):1457-63.*
20. **Unnikrishnan RI, Rema M, Pradeepa R.** Prevalence and risk factors of diabetic nephropathy in an urban South Indian population: the Chennai Urban Rural Epidemiology Study (CURES 45). *Diabetes Care. 2007 Aug;30(8):2019-24. Epub 2007 May 8.*
21. **Thompson D, Edelberg J, Colditz GA, et al.** Lifetime health and economic consequences of obesity. *Arch Intern Med 1999;159:2177-2183.*
22. **Wolf AM, Colditz GA.** Current estimates of the economic cost of obesity in the United States. *Obes Res. 1998;6:97-106.*

## 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.

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## OBESITY AND CARDIOVASCULAR RISK: METABOLIC SYNDROME

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**Abstract:** Increased abdominal fat distribution is a risk factor for coronary artery disease, dyslipidemia, hypertension, stroke and type 2 diabetes. Multiple environmental and genetic factors are thought to influence the manifestation of abdominal obesity. Intraabdominal fat increases with age in both overweight and normal weight individuals. Men have twice as much abdominal fat as women, due to hormonal effect. Two groups of patients with abdominal obesity are at high risk for premature CAD, one with Type 2 diabetes and second, familial combined hyperlipidemia. Familial combined hyperlipidemia is characterized by metabolic syndrome in addition to disproportionate elevation of apolipoprotein B. Individuals with metabolic syndrome may have normal LDL levels but their LDL particles are small and dense, so current lipid lowering guidelines may underestimate their risk. Studies have shown prevalence of metabolic syndrome to be in the range of 20-30% in developed countries. The presence of metabolic syndrome is estimated to increase the risk of CAD by 1.6 to 3.0 fold. Individuals with combination of metabolic syndrome and diabetes have a higher prevalence of CAD (19.2%) as compared to diabetics without metabolic syndrome (13.2%). Metabolic syndrome patients with elevated Apo B levels (> 90<sup>th</sup> percentile for age) have Familial combined hyperlipidemia and should be targeted for aggressive lipid lowering therapy. Apo B levels increase with age therefore age appropriate apo B levels must be used in diagnosis. Apo B level is a better predictor for future cardiovascular events than LDL cholesterol. Apo B is better predictor for CAD risk in individuals with low LDL level. In addition of Apo B measurement of non HDL cholesterol is recommended as it quantifies the atherogenic Apo B containing lipoproteins. So there is increasing requirement of aggressive lipid lowering in patterns of metabolic syndrome. Therapy targeting LDL and Apo B are recommended. But rising of HDL is also an important target to be achieved. So the combination of lipid lowering therapy in form of statins and fibrates or niacin is recommended, only if lifestyle modifications are not sufficient. A word of caution is needed in administering niacin therapy in diabetes, though recent studies have found it to be safe.

### INTRODUCTION

Regional body fat distribution has an important influence on metabolic and cardiovascular risk factors. Increased abdominal (visceral) fat accumulation is a risk factor for coronary artery disease (CAD), dyslipidemia, hypertension, stroke, and type 2 diabetes. The recent emphasis on treatment of the dyslipidemia of the metabolic syndrome has compelled practitioners to consider lipid-lowering therapy in a greater number of their patients, as one in two individuals over age 50 has the metabolic syndrome. Individuals with the metabolic syndrome typically have normal low-density lipoprotein cholesterol levels, and current lipid-lowering guidelines may underestimate their cardiovascular risk. Multiple environmental and genetic factors are thought to influence the manifestation of abdominal obesity. Intraabdominal fat increases with age in both overweight and normal weight individuals independently of changes in total body fat<sup>1</sup>. Sex steroid hormones appear to contribute to body fat distribution, as men have twice as much abdominal fat as women<sup>2,3</sup>, and estrogen deficiency (at menopause) is associated with a preferential increase in intraabdominal fat, which is blunted by estrogen replacement therapy<sup>4,5</sup>. There is also evidence that increased abdominal adipose tissue is associated with physical inactivity, increased plasma cortisol, and intrauterine environment<sup>6</sup>. Inheritance clearly plays a role in body fat distribution, as family studies have shown that genetic factors account for about 50% of the variance in intraabdominal fat

after adjusting for age, sex, and total body fat<sup>7</sup>. Genetic factors that predispose individuals to gain weight centrally may explain the susceptibility of certain ethnic groups to DM<sup>2,8,9</sup>.

### LINK BETWEEN OBESITY AND METABOLIC ABNORMALITIES

Two subgroups of patients with the abdominal obesity are at particularly high risk for premature CAD. One, individuals with type 2 diabetes, accounts for 20–30% of early cardiovascular disease. The second, familial combined hyperlipidemia, accounts for an additional 10–20% of premature CAD. Familial combined hyperlipidemia is characterized by the metabolic syndrome in addition to a disproportionate elevation of apolipoprotein B levels. The measurement of fasting glucose and apolipoprotein B, in addition to the fasting lipid profile, can help to estimate CAD risk in patients with the metabolic syndrome. Distinct Metabolic Features are seen in individuals with increased amounts of abdominal (visceral) adipose tissue: Hypertriglyceridemia, Reduced high density lipoprotein (HDL), and Small, dense low density lipoprotein (LDL) particles characterize the dyslipidemia associated with increased abdominal fat. Individuals with the metabolic syndrome typically have normal LDL cholesterol levels, but their LDL particles are small and dense, and current lipid-lowering guidelines may underestimate their coronary artery disease (CAD) risk. Further evaluation of apolipoprotein B (apo B) in patients with the metabolic syndrome can help detect patients with familial combined hyperlipidemia (FCHL) and identify them as candidates for aggressive lipid lowering.<sup>(11)</sup>

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As the prevalence of the metabolic syndrome rises with increasing obesity and sedentary lifestyle, so does the disease burden of increased type 2 diabetes mellitus and cardiovascular disease.

## METABOLIC SYNDROME

Many prospective studies have shown that increased abdominal (visceral) fat accumulation is an independent risk factor for CAD, hypertension, stroke, and type 2 diabetes (DM2)<sup>12,13</sup>. The strong link between increased abdominal (visceral) fat and hyperinsulinism, insulin resistance, elevated plasma free fatty acid (FFA) levels, hypertension, predisposition to thrombosis, hypertriglyceridemia, small, dense LDL particles, and reduced HDL has been recognized for decades. This has been given many names such as syndrome X or metabolic syndrome; criteria proposed to diagnose are: *National Cholesterol Education Programme/Adult Treatment Panel III (NCEP/ATP III) diagnostic criteria for the metabolic syndrome* — *Diagnosis is made when 3 or more of the following are present:*

- Waist circumference : Men > 102 cm , women > 88 cm.  
( For Indians – Men - 90 cm, women - 80 cm)
- Fasting triglycerides > 150 mg/dl
- Blood pressure > 130/85 mmHg
- HDL cholesterol < 50 mg/dl for women; < 40 mg/dl for men
- Fasting glucose > 110 mg/dl

*WHO criteria for the metabolic syndrome, as identified by one of the following:*

- Type 2 diabetes
- Impaired fasting glucose (101-125 mg/dl)
- Impaired glucose tolerance (140-199 mg/dl 2 hours after 75g of glucose)
- If normal fasting glucose, glucose uptake below the lowest quartile for background population under hyperinsulinaemic, euglycaemic conditions Plus 2 of the following :
- Antihypertensive medication and/or blood pressure > 140 mmHg systolic or > 90mmHg diastolic
- Triglycerides > 150 mg/dl
- HDL < 35 mg/dl for men or < 39 mg/dl for women
- BMI > 30 kg/m<sup>2</sup> and/or waist-hip ratio > 0.9 men, > 0.85 women
- Urinary albumin excretion > 20 µg/minute or albumin-creatinine ratio > 30 µg/mg

*AACE clinical criteria for diagnosis— Risk factors are as follows :*

- Overweight/obesity : BMI > 25 kg/m<sup>2</sup>
- Elevated triglycerides : > 150 mg/dl
- HDL cholesterol : Men < 40 mg/dl, women < 50 mg/dl
- Blood pressure : > 130/85 mmHg
- 2-hour post 75 g glucose challenge : > 140 mg/dl
- Fasting glucose : Between 110 and 126 mg/dl
- Additional risk factors :

- Family history of type 2 diabetes
- Hypertension
- Coronary heart disease (CHD)
- Polycystic ovary syndrome
- Sedentary lifestyle
- Advanced age
- Ethnic groups at high risk for type 2 diabetes or CHD

Of all these criteria, ATP III criteria to diagnose IRS seems to be more practical during an office visit. This also has some shortcomings such as inadequate measure of glucose tolerance, and inability to detect prothrombotic (PAI), pro-inflammatory C-reactive protein (CRP) and adipocytokines (adiponectins).

## PREVALENCE AND RISK OF METABOLIC SYNDROME

Many studies have shown significantly increased CAD risk with the features of the metabolic syndrome, described under different names, but until recently limited information was available about the prevalence of the syndrome in the general population<sup>14,15</sup>. It is now clear that the metabolic syndrome is very common in westernized countries and varies with age, ethnicity, and body mass index<sup>16,17</sup>. Ford et al.<sup>18</sup> studied 8814 men and women (>20 yr old) and found a 24% prevalence of the NCEP-defined metabolic syndrome (in individuals with and without diabetes) using National Health and Nutrition Examination Survey III (NHANES III) data. The prevalence increased with age, and 33–45% of subjects over 50 yr met the criteria for the metabolic syndrome. Alexander et al.<sup>19</sup> studied a subset of NHANES III participants (>50 yr old) and confirmed a 43.5% prevalence of the metabolic syndrome (in subjects with and without diabetes) using NCEP criteria. As expected, the concordance of the metabolic syndrome with diabetes was high, as the majority of individuals with diabetes (86%) or impaired fasting glucose [6.1 mmol/liter (110 mg/dl); 71%] met the criteria for the metabolic syndrome. In contrast, diabetes without the metabolic syndrome was uncommon (13% of individuals with diabetes), and the prevalence of the metabolic syndrome in normoglycemic individuals was 26%.

The presence of the metabolic syndrome is estimated to increase the risk of coronary heart disease by 1.6- to 3.0-fold. Although individuals with the combination of the metabolic syndrome and diabetes have a high overall age-adjusted prevalence of CAD (19.2%), the presence of the metabolic syndrome in subjects without diabetes appears to convey a moderate risk of CAD (13.9%) compared with those with neither (8.7%). Several groups have recently shown that individuals with the metabolic syndrome (without diabetes) had a 12–14% risk of CAD compared with a 6–9% risk in individuals without the metabolic syndrome<sup>20</sup>. Recently published American Heart Association guidelines describe the presence of the metabolic syndrome, without diabetes, as a moderate CAD risk factor<sup>21</sup>. No study to date has established the contribution of familial combined hyperlipidemia to CAD

risk in nondiabetic individuals with the metabolic syndrome

## SCREENING OF METABOLIC SYNDROME PATIENTS

The metabolic syndrome is a common population trait comprised of a heterogeneous group of oligogenic disorders, such as DM2 and familial combined hyperlipidemia. The identification of these metabolic syndrome subtypes by measuring fasting glucose and apo B can help target these high risk patients for lipid-lowering therapy. Patients with the metabolic syndrome should be screened for DM2, as individuals with DM2 and the metabolic syndrome are at high risk for CAD. Current guidelines recommend that patients with DM2 should be aggressively treated for dyslipidemia with the goal to maintain LDL below 2.6 mmol/liter (100 mg/dl), triglyceride below 1.7 mmol/liter (150 mg/dl), and HDL above 1.02 mmol/liter (40 mg/dl)<sup>22</sup>.

Metabolic syndrome patients with elevated apo B levels (>90th percentile for age) have FCHL and should be targeted for aggressive lipid-lowering therapy. Apo B levels increase with age; therefore, age-appropriate apo B levels must be used in diagnosis. Several large prospective studies have shown that the apo B level is a better predictor of future cardiovascular events than the LDL cholesterol level<sup>23</sup>. Recently, the Apolipoprotein-Related Mortality Risk Study published prospective data in 175,553 men and women and found that the total apo B level was a better predictor of future CAD risk than LDL cholesterol. Importantly, they also found that apo B was a better predictor of CAD risk in individuals with low LDL levels, supporting the idea that patients with low LDL cholesterol levels and increased quantities of small, dense atherogenic particles (VLDL, IDL, and LDL) are at risk for CAD.

The presence of the metabolic syndrome is estimated to increase the risk of coronary heart disease by 1.6- to 3.0-fold. Although individuals with the combination of the metabolic syndrome and diabetes have a high overall age-adjusted prevalence of CAD (19.2%), the presence of the metabolic syndrome in subjects without diabetes appears to convey a moderate risk of CAD (13.9%) compared with those with neither (8.7%). Several groups have recently shown that individuals with the metabolic syndrome (without diabetes) had a 12–14% risk of CAD compared with a 6–9% risk in individuals without the metabolic syndrome<sup>19,20</sup>. Recently published American Heart Association guidelines describe the presence of the metabolic syndrome, without diabetes, as a moderate CAD risk factor. No study to date has established the contribution of familial combined hyperlipidemia to CAD risk in nondiabetic individuals with the metabolic syndrome.

## METABOLIC SYNDROME: TARGETING HIGH RISK PATIENTS

The recent emphasis on treatment of the dyslipidemia of the metabolic syndrome has compelled practitioners to consider

lipid-lowering therapy in a greater number of their patients, as epidemiological studies have shown that one in two individuals over 50 yr of age has the metabolic syndrome. It is not yet clear whether all of these patients should be treated with lipid-lowering medications, and the economic impact of such a decision is enormous.

Although the primary focus on CAD prevention remains on LDL lowering, LDL cholesterol levels may underestimate CAD risk in the metabolic syndrome. Studies investigating the lipid profiles of men with premature CAD have shown that approximately 50% had normal LDL cholesterol levels, but these men had low HDL and elevated triglyceride levels and may have had the metabolic syndrome<sup>24</sup>. Recent *post hoc* analyses of the placebo-treated groups in the 4S and AFCAPS/TexCAPS trials showed that nondiabetic individuals with the metabolic syndrome (21% of 4S and 46% of AFCAPS/TexCAPS) had an increased risk of major coronary events during follow-up compared with those without the metabolic syndrome. Importantly, the increased event rate with the metabolic syndrome remained significant after adjustment for the Framingham 10-yr risk score, implying independent contributions of the metabolic syndrome and the Framingham score in predicting future CAD risk<sup>25</sup>.

The metabolic syndrome is a common population trait comprised of a heterogeneous group of oligogenic disorders, such as DM2 and familial combined. The identification of these metabolic syndrome subtypes by measuring fasting glucose and apo B can help target these high risk patients for lipid-lowering therapy. Patients with the metabolic syndrome should be screened for DM2, as individuals with DM2 and the metabolic syndrome are at high risk for CAD.

Current *guidelines* recommend that patients with DM2 should be aggressively treated for dyslipidemia with the goal to maintain (i) LDL < 2.6 mmol/liter (100 mg/dl); (ii) triglyceride < 1.7 mmol/liter (150 mg/dl); and (iii) HDL > 1.02 mmol/liter (40 mg/dl) (50).

Metabolic syndrome patients with *elevated apo B levels* (>90th percentile for age) have FCHL and should be targeted for aggressive lipid-lowering therapy. Apo B levels increase with age; therefore, age-appropriate apo B levels must be used in diagnosis<sup>(26)</sup>. Several large prospective studies have shown that the apo B level is a better predictor of future cardiovascular events than the LDL cholesterol level. Recently, the Apolipoprotein-Related Mortality Risk Study published prospective data in 175,553 men and women and found that the total apo B level was a better predictor of future CAD risk than LDL cholesterol<sup>27</sup>. Importantly, they also found that apo B was a better predictor of CAD risk in individuals with low LDL levels, supporting the idea that patients with low LDL cholesterol levels and increased quantities of small, dense atherogenic particles (VLDL, IDL, and LDL) are at risk for CAD. In addition to apo B, the measurement of non-HDL cholesterol (total cholesterol minus HDL cholesterol) can be used to assess the quantity of atherogenic apo B-containing lipoproteins (VLDL, IDL, and LDL). Some investigators have proposed that non-HDL cholesterol could replace the LDL measure in patients with hypertriglyceridemia (dyslipidemia with DM2 or FCHL), because these patients have more cholesterol in VLDL particles, and LDL cholesterol alone can underestimate their CAD risk.

The current *NCEP guidelines* recommend a non-HDL cholesterol goal of less than 3.4 mmol/liter (<130 mg/dl) in hypertriglyceridemic patients >2.3 mmol/liter (>200 mg/dl) (5). Total apo B and non-HDL cholesterol levels are generally highly correlated, but less so at higher triglyceride levels.

## TREATMENT OF DYSLIPIDEMIA

Comprehensive treatment of patients with the metabolic syndrome has recently been described in detail (28). The treatment of the dyslipidemia of the metabolic syndrome should be focused on lowering LDL and apo B and increasing HDL. Statin treatment has been shown to reduce cardiovascular events in persons with low LDL cholesterol levels at baseline. The percent reduction in LDL cholesterol and apo B by statin medications is similar, but apo B may be a better marker of treatment efficacy in metabolic syndrome patients with normal LDL cholesterol (29).

Although LDL cholesterol has remained the primary target of lipid-lowering therapy, raising HDL levels is now an important secondary target to reduce CAD risk. Combination lipid-lowering therapy is frequently needed to treat the dyslipidemia of the metabolic syndrome (increased triglyceride, reduced HDL, and small, dense LDL particles), if lifestyle changes (weight loss and exercise) are inadequate.

Nicotinic acid and fibric acid derivatives both act to reduce triglyceride and increase HDL cholesterol. They are frequently used with statin medications. Although fibrate monotherapy lowers plasma triglyceride levels, it can lead to increases in LDL levels. Bile acid resin binders lower LDL cholesterol levels, but can increase triglyceride levels in individuals susceptible to hypertriglyceridemia. Although niacin is an inexpensive monotherapeutic agent that corrects the dyslipidemia of the metabolic syndrome, it may increase glucose levels in some patients (30). Several groups have recently shown that niacin use in diabetic individuals was safe and effective, resulting in only a transient worsening of glycemic control<sup>31,32</sup>.

## CONCLUSION

The decision to initiate lipid-lowering therapy in nondiabetic individuals with the metabolic syndrome can be difficult using current guidelines, as LDL levels may underestimate CAD risk in this population. The large population of individuals with the metabolic syndrome appears to be comprised of a heterogeneous group of disorders, and the identification of disease subtypes at high risk for CAD can help identify individuals as candidates for aggressive lipid-lowering interventions. Two subgroups of patients with the metabolic syndrome, those with DM2 or FCHL, are at particularly high risk for premature CAD. FCHL is characterized by the metabolic syndrome in addition to a disproportionate elevation of apo B levels. The measurement of fasting glucose and apo B in addition to the fasting lipid profile can help to estimate CAD risk and guide treatment decisions in patients with the metabolic syndrome.

## REFERENCES

1. Borkan GA, Hulst DE, Gerzof SG, Robbins AH, Silbert, CK Age changes in body composition revealed by computed tomography. *J Gerontol* 1983 38:673-677

2. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres JP Sex differences in the relation of visceral adipose tissue accumulation to total body fatness. *Am J Clin Nutr* 1993 58:463-467
3. Carr MC, Hokanson JE, Zambon A, et al. The contribution of intraabdominal fat to gender differences in hepatic lipase activity and low/high density lipoprotein heterogeneity. *J Clin Endocrinol Metab* 2001 86:2831-2837
4. Haarlo J, Marslew U, Goffredsen A, Christiansen C Postmenopausal hormone replacement therapy prevents central distribution of body fat after menopause. *Metabolism* 1991 40:1323-1326
5. Carr MC, Brunzell JD, Increased hepatic lipase activity and intraabdominal fat across the transition from pre- to postmenopause. Program of the 85th Annual Meeting of The Endocrine Society, Philadelphia, PA, 2003, p 374
6. Perusse L, Despres JP, Lemieux S, Rice T, Rao DC, Bouchard C Familial aggregation of abdominal visceral fat level: results from the Quebec family study. *Metabolism* 1996 45:378-382
7. Fujimoto WY The growing prevalence of non-insulin-dependent diabetes in migrant Asian populations and its implications for Asia. *Diabetes Res Clin Pract* 1992;15:167-183
8. Haffner SM, D'Agostino R, Saad MF, et al. Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared with non-Hispanic whites. The Insulin Resistance Atherosclerosis Study. *Diabetes* 1996 45:742-748
9. Marsh JB Lipoprotein metabolism in obesity and diabetes: insights from stable isotope kinetic studies in humans. *Nutr Rev* 2003 61:363-375
10. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults — Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001; 285: 2486-97.
11. Grundy SM, Cleeman JI, Baird MN — Implications of recent trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation* 2004; 110: 227-39.
12. Mazzone T — Strategies in ongoing clinical trials to reduce cardiovascular disease in patients with diabetes mellitus and insulin resistance. *Am J Cardiol* 2004; 93: 27C-31C.
13. Austin MA, King MC, Vranizan KM, Krauss RM Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. *Circulation* 1990 82:495-506
14. Lamarche B, Tchernof A, Moorjani S, et al. Small, dense low-density lipoprotein particles as a predictor of risk of ischemic heart disease in men: prospective results from the Quebec Cardiovascular Study. *Circulation* 1997 95:69-75
15. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001 24:683-689
16. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002 288:2709-2716
17. Ford ES, Giles WH, Dietz WH Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002 287:356-359
18. Alexander CM, Landsman PB, Teutsch SM, Haffner SM NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 2003 52:1210-1214
19. Meigs JB, Wilson PW, Nathan DM, et al. Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring Studies. *Diabetes* 2003 52:2160-2167
20. Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation* 2004 109:672-693
21. Haffner SM Dyslipidemia management in adults with diabetes. *Diabetes Care* 2004 27(Suppl 1):S68-S71
22. Lamarche B, Moorjani S, Lupien PJ, Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Quebec cardiovascular study. *Circulation* 1996 94:273-278
23. Genest JJ, McNamara JR, Salem DN, Schaefer EJ Prevalence of risk factors in men with premature coronary artery disease. *Am J Cardiol* 1991 67:1185-1189
24. Gorman CJ, Rhodes T, Mercuri M, The metabolic syndrome and risk of major coronary events in the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Am J Cardiol* 2004 93:136-141
25. Bachorik PS, Lovejoy KL, Carroll MD, Johnson CL Apolipoprotein B and AI distributions in the United States, 1988-1991: results of the National Health and Nutrition Examination Survey III (NHANES III). *Clin Chem* 1997 43:2364-2378
26. Walldius G, Jungner I, Holme I, et al. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet* 2001 358:2026-2033
27. Ginsberg HN Treatment for patients with the metabolic syndrome. *Am J Cardiol* 2003 91:29E-39E
28. Sniderman AD, Furberg CD, Keech A, et al. Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. *Lancet* 2003 361:777-780
29. Meyers CD, Carr MC, Park S, Brunzell JD Varying cost and free nicotinic acid content in over-the-counter niacin preparations for dyslipidemia. *Ann Intern Med* 2003 139:996-1002
30. Elam MB, Hunninghake DB, Davis KB, et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial. *Arterial Disease Multiple Intervention Trial. JAMA* 2000 284:1263-1270
31. Zhao XQ, Morse JS, Dowdy AA, Safety and tolerability of simvastatin plus niacin in patients with coronary artery disease and low high-density lipoprotein cholesterol (The HDL Atherosclerosis Treatment Study). *Am J Cardiol* 2004 93:307-312

## OBESITY AND RESPIRATORY COMPLICATIONS

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**Abstract:** Obesity has detrimental effect on almost all organ systems of the body. It involves respiratory system by altering respiratory mechanics; airflow resistance, breathing pattern, respiratory drive and causing impaired gas exchange. The obesity hyperventilation syndrome (OHS) was originally described in 1955 in subjects with obesity, chronic daytime hypercapnia, hypoxemia, polycythemia, hyper somnolence and right ventricular failure. Obesity causes various changes in respiratory mechanics. Reductions in lung chest wall and total respiratory system compliance is seen in especially OHS group. Respiratory system resistance is elevated in obese subjects i.e. around 30% increase in Simple Obesity and 100% increase in OHS. Respiratory resistance increases further in supine position as compared to upright body position. In OHS there is a decrease in respiratory drive even though there is extreme increase in respiratory work. The impairment in gas exchange depends on severity of the obesity. Impaired respiratory drive and increased work of breathing leading to hypoventilation contributes to hypercapnia and hypoxemia in OHS. Sleep related respiratory complications have been categorized under reading of obstructive sleep disorder breathing syndrome, which includes entire spectrum ranging from primary snoring to obstructive sleep apnea syndrome (OSA). In OSA syndrome, there is a complete cessation of airflow for at least 10 seconds and is associated with 4% fall in oxyhemoglobin saturation while in primary snoring there is no apnea, no sleep arousal and no reduction in oxygen saturation. Sleeplessness, fatigue, irritability and personality change has been observed in all forms. The diagnosis is made by focused history taking and physical examination of obese patients' who report of sleep difficulties and increased daytime sleepiness. The diagnosis can be confirmed by polysomnography. The therapeutic strategies for patients with sleep apnea involve conservative management, which includes avoidance of factors that increase severity of upper airway obstruction. Of the medical intervention that is done mainly includes the role of positive pressure ventilation in the form of CPAP, drugs like Protriptylene, Fluoxetine, Medroxyprogesterone, Acetazolamide have been tried with varying benefits. In resistant cases, tracheostomy and airway reconstruction in form of uvulopalatopharyngoplasty have been advised. Obese patients are also prone to other respiratory ailments such as pulmonary embolism, increased risk of gastric aspiration and difficulties during surgical and anesthetic procedures.

### INTRODUCTION

Obesity has detrimental effect on all most all the organ systems of the body<sup>1,2</sup>. It involves respiratory system by altering respiratory mechanics, airflow resistance, breathing pattern, respiratory drive and causing impaired gas exchange. Obesity can be divided into simple obesity (SO) & obesity hypoventilation syndrome (OHS) depending on the absence or presence of day time hypercapnoea. **The obesity-hypoventilation syndrome (OHS)** was originally described in 1955 in subjects with obesity, chronic daytime hypercapnia and hypoxemia, polycythemia, hypersomnolence, and right ventricular failure. In 1956, Burwell et al coined the term Pickwickian syndrome for these patients.<sup>3</sup> The majority of people with OHS have OSA.

The criteria of OHS include<sup>4</sup> : 1) BMI >30 kg/ m<sup>2</sup> ; 2) Daytime PaCO<sub>2</sub> > 45 mm Hg ; 3) Excessive daytime sleepiness; 4) Severe OSA (AHI >30) or sleep hypoventilation or both; 5) Absence of other known causes of hypoventilation

Various respiratory alterations and complications in an obese person can be broadly classified in to three main headings.

- 1) Alteration in respiratory system mechanics
- 2) Sleep related respiratory complications in obese
- 3) Respiratory complication in obese during critical illness
- 4) Other respiratory problems

Other diversified effects in each of the broad categories are shown in table 1.

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**Table 1 :** Effects of obesity on respiratory system

A	Alteration in respiratory system mechanics
	1) Decrease in respiratory system compliance 2) Increase respiratory system resistance 3) Alteration in respiratory drive 4) Impaired gas exchange 5) Altered respiratory muscle strength and endurance 6) Increase work of breathing 7) Abnormality in pulmonary function tests.
B	Sleep related respiratory complications
	1) Obstructive sleep disordered breathing syndrome (OSDB) - Primary snoring - Upper airway resistance syndrome - Sleep hypopnea syndrome - Obstructive sleep apnea syndrome (OSA)
C	Respiratory complication in obese during critical illness
	1) Risk of deep venous and pulmonary thrombosis 2) Risk of aspiration 3) Difficult endotracheal intubation and mechanical ventilation
D	Other respiratory problems
	1) Exacerbation of bronchial asthma 2) Anesthetic and perioperative difficulties.

### CHANGES IN RESPIRATORY MECHANICS IN OBESITY

Obesity causes various changes in the respiratory mechanics of a person leading to impaired respiratory compliance and increased respiratory resistance. Reductions in lung, chest wall and total respiratory system compliance is seen in especially in OHS.<sup>5-7</sup> group. Lung compliance is reduced due to increased pulmonary blood volume and closure of dependent airways<sup>8</sup>.

Chest wall compliance is reduced because of excess weight on the thorax and abdomen. Thus a more negative pleural pressure must be generated by the respiratory muscles to initiate airflow.<sup>5-8</sup>

Respiratory system resistance is elevated in obese subjects i.e. around 30% increase in SO and 100% increase in OHS. This increase is mainly due to increase in the chest wall resistance.<sup>6,7</sup> Respiratory resistance increases further in the supine position as compared to upright body position possibly due to compression of the supralaryngeal airway by fat and increased intrapulmonary blood flow leading to further airway narrowing.<sup>7,8</sup>

In OHS there is a decrease in respiratory drive even though there is extreme increase in respiratory work. Hypoventilation and tolerance of a higher  $P_{aCO_2}$  thus occurs & the set point of the CNS chemoreceptors is adjusted to a higher  $P_{aCO_2}$  with further decrease in respiratory drive. There is 25% greater respiratory rate and 25% lower  $V_T$ .<sup>9</sup> The impairment in the ventilatory responses to hypoxia<sup>10</sup> &  $CO_2$  is more as compare to those with SO.

The impairments in gas exchange depends on the severity of the obesity. Mildly reduced  $P_{aO_2}$  and widened alveolar-arterial oxygen difference ( $P_{aO_2}-P_{aO_2}$ )<sup>8,11</sup> is much more severe in people with OHS than with SO. Impaired respiratory drive and increased work of breathing leading to hypoventilation contributes to the hypercapnia & hypoxemia in OHS.

The abnormality in pulmonary function test depend on both the magnitude of the obesity, as well as the distribution of body fat (central/truncal vs peripheral predominance). People with central fat distribution have greater reductions in FVC, FEV<sub>1</sub>, and TLC<sup>13</sup>. It is because of the mechanical effect of the additional fat in the chest, abdominal wall and within the abdomen which compresses the thoracic cage and the diaphragm thus decreasing the lung volumes. In OHS FEV<sub>1</sub> / FVC ratio remains normal while in SO TLC remains normal.<sup>12</sup> Diffusing capacity also decreases slightly in proportion to the degree of obesity.<sup>13</sup> Reduction in the expiratory reserve volume (ERV) is the most common abnormality in PFT. ERV diminishes in proportion to the severity of obesity and is particularly abnormal in supine position.<sup>13</sup> with reductions found more in OHS patients.

## SLEEP RELATED RESPIRATORY COMPLICATIONS

The term **obstructive sleep disordered breathing syndrome (OSDB)** better describes this entire spectrum. With increasing order of severity they are:

- 1) Primary Snoring
- 2) Upper Airway Resistance Syndrome (UARS)
- 3) Sleep Hypopnea Syndrome
- 4) Obstructive Sleep Apnea Syndrome (OSA)

The basic pathogenic mechanism of OSDB is the upper airway narrowing. In obese patients, increased adipose tissue in the neck predispose the airway to narrowing which is confirmed

by MRI scans in patients with sleep apnea.<sup>14</sup> Also there is increased collapsibility of the pharynx due to impaired function of upper-airway dilator muscles. These events are generally most prominent during rapid-eye-movement (REM) sleep because of the hypotonia of the upper-airway muscles characteristic of this stage of sleep.

### **Obstructive sleep apnea**

- 1) Complete Cessation of airflow for atleast 10 seconds despite continuing ventilatory effort (apnea).
- 2) 5 or more episodes per hour of sleep.
- 3) Usually associated with a decrease of 4% in oxyhemoglobin saturation.

### **Obstructive sleep hypopnea**

- 1) Decrease of 30–50% in airflow for 10 seconds (hypopnea).
- 2) 15 or more episodes per hour of sleep.
- 3) May be associated with a decrease of 4% in oxyhemoglobin saturation.

### **Upper-airway resistance syndrome**

- 1) No significant decrease in airflow- i.e. no apnea / hypopnea.
- 2) 15 or more episodes of arousal per hour of sleep.
- 3) No significant decrease in oxyhemoglobin saturation.

### **Primary snoring**

- 1) No apnea / hypopnea.
- 2) No arousal during sleep.
- 3) No significant decrease in oxyhemoglobin saturation.

**Clinical features of OSDB** are attributed to arousal from sleep and/ or oxyhemoglobin desaturation and hypercarbia. Most commonly reported symptoms are loud habitual snoring, nocturnal choking episodes, morning headaches, and excessive daytime sleepiness (EDS). Sleepiness, fatigue, irritability, and personality change have been attributed to both nocturnal desaturation and the chronic sleep deprivation caused by sleep fragmentation

**Diagnosis** is made by a focused history taking and physical examination of every obese patients who report of symptoms of sleep disorders. This further helps in identifying the people at risk. The presence of certain physical characteristics like retrognathia and discrete upper-airway abnormalities, such as an enlarged soft palate or tonsillar hypertrophy, are clinical clues. An increased body-mass index, hypertension, and increased upper-body obesity, which is reflected by the neck circumference are good predictor of sleep apnea. The characteristics which are strongly associated with OSDB include, male sex, age > 40 years, BMI >25 kg/m<sup>2</sup>; or neck circumference >= 17 inches in men and >=16 inches in women, habitual snoring, nocturnal gasping, choking, or resuscitative snorting, observed apnea, history of systemic hypertension Sleep disordered breathing can be diagnosed in-laboratory by polysomnography (PSG). This involves recording of multiple variables during sleep, including the neurological variables like electroencephalogram (EEG), electro-oculogram (EOG) and electromyogram (EMG) and cardiorespiratory variables

like airflow, respiratory effort, oxygen saturation, snoring and ECG.

The **differential diagnosis** of increased day time sleepiness that need to be considered are insufficient sleep, circadian rhythm disorder(eg jet lag, shift work) insomnia, drugs(eg sedatives), depression, CNS abnormalities, post traumatic hypersomnia, sleep fragmentation, periodic limb movement disorder & narcolepsy.

**Therapeutic strategies** for patients with sleep apnea may be grouped into three general categories: conservative, medical, and surgical. The goals of treatment are to establish normal nocturnal oxygenation and ventilation, abolish snoring, and eliminate disruption of sleep due to upper-airway closure. Conservative treatment includes avoidance of factors that increase the severity of upper-airway obstruction — such as sleep deprivation<sup>15</sup> the use of alcohol, sedatives, and hypnotic agents; and increased weight. Positive airway pressure delivered through a mask is the initial medical treatment of choice in patients moderate to severe sleep apnea. *Continuous positive airway pressure* (CPAP) is applied to the upper airway with a nasal mask, nasal prongs, or a mask that covers both the nose and mouth. The level of positive pressure required to sustain patency of the upper airway during sleep is determined in a sleep laboratory. Patients treated with nasal CPAP have repeatedly demonstrated improvement in neuropsychiatric function and a lessening of daytime sleepiness. Nocturnal desaturation, ventilatory-related arousals, nocturnal dysrhythmias, pulmonary hypertension, and right-sided heart failure have also been effectively treated.

*Drugs* like protriptyline and fluoxetine decrease the amount of REM sleep and increase tone of upper airway muscles, and may be useful in mild OSA intolerant to CPAP.<sup>16</sup> Medroxyprogesterone in a dose of 60 mg /day may be useful for treatment of hypoventilation in patients with OHS by increasing the ventilatory response to hypercapnea. Acetazolamide in a dose of 250 mg/ day may be used to reduce the serum bicarbonate level and the resulting metabolic acidosis increases the minute ventilation and reduces the PaCO<sub>2</sub>.

*Tracheostomy* and *upper airway reconstruction* are also required in some patients. The most commonly performed procedure, uvulopalatopharyngoplasty, is curative in less than 50 percent of patients.<sup>17</sup>

## OTHER RESPIRATORY PROBLEMS

Obese adults are at increased risk for many chronic medical conditions, and this increases the likelihood of admission to an ICU & presents with many problems. They are:

- 1) Obesity is a major independent risk factor for pulmonary embolism and venous thromboembolism (VTE).<sup>18</sup> The risk of pulmonary embolism rises as BMI increases.
- 2) Risk of aspiration is higher among obese patients, as compared with non-obese patients.<sup>18</sup> Higher volumes, lower pH of gastric fluid, delayed gastric emptying, and increased intraabdominal pressure leading to a high incidence of gastroesophageal reflux account for the increased risk of aspiration.
- 3) Obesity poses an increased risk of complications and difficulties during anesthesia and perioperative period.

First, gas exchange disturbances such as hypoxia and hypercarbia, may be exaggerated during anesthesia<sup>18</sup> Second, the incidence of postoperative pulmonary complications such as VTE, aspiration pneumonia, atelectasis, worsened gas exchange and respiratory failure is greater among obese patients.

- 4) Endotracheal intubation and mechanical ventilation is also difficult in obese patient. Factors associated with difficult intubations include large neck circumference, limited neck mobility, small oropharyngeal opening and difficulty in mouth opening.

## CONCLUSION

Disturbances of respiratory function, including reduced respiratory system compliance, increased small airways resistance, impaired respiratory muscle function, increased work of breathing, impaired gas exchange, exercise intolerance, sleep-disordered breathing, and increased risks of venous thromboembolism and aspiration are common, particularly among severely obese patients. These changes are independent of any underlying parenchymal lung disease. Weight loss can significantly decrease the risk and severity of obesity-related respiratory disturbances & should be considered for inclusion in a structured rehabilitation program with dietary, behavioral, and exercise components in an effort to improve functional capacity and quality of life.

## REFERENCES

1. **Lean MEJ, Seidell JC.** Impairment of health and quality of life in people with large waist circumference. *Lancet* 1998; 351: 853-856.
2. **Mokdad AH, Ford ES, Bowman BA, et al.** Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003; 289:76-79
3. **Kessler R, Chaouat A, Schinkewitch P, et al.** The obesity-hypoventilation syndrome revisited. *Chest* 2001; 120:369-376
4. **Martin R. TJ, Sanders MH.** Chronic alveolar hypoventilation: a review for the clinician. *Sleep* 1995; 18:617-634
5. **Fontaine KR, Redden DT, Wang C, et al.** Years of life lost due to obesity. *JAMA* 2003; 289:187-193
6. **McCool FD, Rochester DF.** Nonmuscular diseases of the chest wall. In: Fishman AP, Elias JA, Fishman JA, et al, eds. Vol 2. 3ed ed. *Pulmonary diseases and disorders*. New York, NY: McGraw-Hill; 1998:1541-1560
7. **Rochester DF.** Obesity and pulmonary function. In: Alpert MA, Alexander JK, eds. *The heart and lung in obesity*. New York, NY: Futura Publishing Co; 1998:109-131
8. **Sharp JT, Henry JP, Sweany SK, et al.** The total work of breathing in normal and obese men. *J Clin Invest* 1964; 43:728-739
9. **Burki NK, Baker RW.** Ventilatory regulation in eucapnic morbid obesity. *Am Rev Respir Dis* 1984; 129:538-543
10. **Sampson MG, Grassino A.** Neuromechanical properties in obese patients during carbon dioxide rebreathing. *Am J Med* 1983; 75:81-90
11. **Zwillich CW, Sutton FD, Pierson DJ, et al.** Decreased hypoxic ventilatory drive in the obesity-hypoventilation syndrome. *Am J Med* 1975; 59:343-348
12. **Jenkins SC, Moxham J.** The effects of mild obesity on lung function. *Respir Med* 1991; 85:309-311
13. **Kress JP, Pohlman AS, Alverdy J, et al.** The impact of morbid obesity on oxygen cost of breathing (V o 2 resp) at rest. *Am J Respir Crit Care Med* 1999; 160:883-886
14. **Davies RJO, Stradling JR.** The relationship between neck circumference, radiographic pharyngeal anatomy, and the obstructive sleep apnoea syndrome. *Eur Respir J* 1990; 3:509-14.
15. **Neilly JB, Kribbs NB, Maislin G, Pack AI.** Effects of selective sleep deprivation on ventilation during recovery sleep in normal humans. *J Appl Physiol* 1992; 72:100-109.
16. **Hanzel DA, Proia NG, Hudgel DW.** Response of obstructive sleep apnea to fluoxetine and protriptyline. *Chest* 1991; 100:416-421
17. **Shepard JW Jr, Olsen KD.** Uvulopalatopharyngoplasty for treatment of obstructive sleep apnea. *Mayo Clin Proc* 1990; 65:1260-1267.
18. **Pietrantonio C, El Solh AA.** Weighty issues. *Advance for Managers of Respiratory Care* 2003; 12:33-36.

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## OBESITY AND RENAL DYSFUNCTION

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**Abstract:** Obesity is now major public health problems even in developing nations like India, with prevalence ranging from 10-50% been reported in various studies. Obese patients are well known to be at high risk of hypertension and diabetes, both are an independent risk factors for Chronic Kidney disease (CKD) Studies in recent years have highlighted that obesity has direct effect on renal functions. Morbid obesity causing FSGS leading to nephrotic syndrome has been described. Recently, obesity related Glomerulopathy have been described which presents with proteinuria mainly non-nephrotic range, it has a more benign course and slowly progresses to renal failure. It is a morphological distinct entity with subtle glomerular change unlike FSGS. It is still unclear whether increase in BMI has direct relationship with CKD or it causes development of renal failure due to increase prevalence of hypertension and diabetes in obese patients. Studies have shown that increasing BMI increases the risk of CKD especially in younger males. Also studies have highlighted that increasing components of metabolic syndromes makes a person more likely to develop CKD. Although several studies have shown glomerular changes in obese patients but its exact pathogenic link is still under investigation, various mechanisms have been highlighted foremost being hemodynamic factors. Obesity has been proposed to cause increased Glomerular filtration rate (GFR) by causing hypoalbuminemia, by effect of RAS on glomerular capillaries and arterioles, though some studies have shown that obese patients with predominantly central obesity have less GFR as opposed to obese patients with more uniform fat distribution. Various mechanisms have been described for this although more data support hyperfiltration. Cardiopulmonary dysfunction in obese patients leading to decreased renal blood flow and causing RAS activation have also been suggested to have a pathogenic role in causing renal dysfunction. Recently role of various hormones and cytokines have been described in obese and metabolic syndrome patients leading to renal dysfunction. Leptins has been shown to be responsible for causing endothelial cell proliferation and elaborating mesangial matrix. Role of other inflammatory mediator such as IL-6, TNF-alpha, adiponectin have been described in causing glomerular injury. Insulin resistance has also been shown to have a role in causing efferent arteriolar constriction and promoting glomerular hypertrophy. Direct effects of lipids in causing renal epithelial and mesangial cell injury have also been described. Paradoxically, obese patients have shown better outcome during dialysis and renal transplantations due to better nutritional status but morbid obesity makes the prognosis poor. So weight loss is the cornerstone of preventing renal dysfunction in obesity Though various medications in the form of thiazolidinediones and RAS inhibitors have been used, but treatment needs to be individualized. HMG COA reductase inhibitors have been shown to have reno-protective effect on some studies.

### INTRODUCTION

Obesity is now being recognised as a public health problem worldwide. More than two-thirds of American adults are overweight or obese<sup>1</sup>. Changes in diet coupled with an increasingly sedentary lifestyle have sparked off an epidemic of obesity in several Asian countries including India<sup>2</sup>. There is a paucity of nation wide data regarding the magnitude of this problem in India, however several published studies have reported a prevalence ranging from 10-50%<sup>3</sup>. Obesity is a link between insulin resistance and the other components of metabolic syndrome i.e. diabetes, hypertension and dyslipidemia. It is a well-recognized risk factor for diabetes and hypertension, the two most common etiologies of chronic kidney disease (CKD). Obesity was shown to strongly correlate with the prevalence of hypertension in both males and females in the Framingham study<sup>4</sup>. The landmark INTERSALT study also showed an association between body mass index (BMI) and blood pressure<sup>5</sup>. Prevalence rates of type 2 diabetes increase steeply across BMI categories, especially among women<sup>6</sup>.

Over the years, both experimental and clinical studies have brought forth evidence to suggest that obesity has a direct deleterious effect on renal function, increasing the risk of renal injury and CKD. Recognizing obesity as a risk factor for CKD

is important, as it would suggest a definite intervention to reduce the risk of development and progression of CKD.

### OBESITY RELATED GLOMERULOPATHY (ORG)

The renal effects of obesity in experimental animals and humans include both structural and functional adaptations, such as increased GFR, increased renal blood flow, and renal hypertrophy<sup>7,8</sup>. In 1974, an association between massive obesity and nephrotic-range proteinuria was first reported<sup>9</sup>. Since that time, the development of glomerulomegaly and focal segmental glomerulosclerosis (FSGS) has been linked to 'massive obesity'. Experimental studies on the obese Zucker rat has shown the development of nephrotic range proteinuria, glomerulosclerosis, and progressive renal failure<sup>10</sup>.

A review of 6818 native kidney biopsies<sup>11</sup> identified 103 cases of ORG and showed that it is distinct from idiopathic FSGS. ORG when compared to idiopathic FSGS, presents with proteinuria, but has a lower incidence of nephrotic range proteinuria and nephrotic syndrome and a more benign course with slower progression to renal failure. Morphologically it shows consistent presence of glomerulomegaly, milder foot process fusion, lower percentage of glomeruli affected by segmental sclerosis and a predilection for perihilar sclerosis. It was also reported to manifest with glomerulomegaly alone. 45% ORG biopsies showed focal glomerular basement membrane thickening and focal mesangial sclerosis as seen in

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early diabetic nephropathy.

The first line of therapy in ORG should be weight reduction, which alone can reduce proteinuria. Lipid lowering agents, especially HMG-CoA reductase inhibitors, are effective in reducing mesangial sclerosis and proteinuria in obese Zucker rats<sup>10</sup>, however their role in humans remains to be defined. ACE-I has been shown to be effective in reducing proteinuria in obese populations<sup>11</sup>. Longer follow-up will be required to determine the potential benefits of prolonged ACE inhibition in allaying progression to end-stage renal disease (ESRD) and preventing the possible evolution of ORG to FSGS.

## **OBESITY AND PROTEINURIA**

Proteinuria has been identified as a significant predictor of end-stage renal disease (ESRD)<sup>20</sup>. Microalbuminuria is a predictor of nephropathy in diabetic patients and is associated with renal functional abnormalities in non-diabetic subjects<sup>21,22</sup>. Signs of early endothelial dysfunction manifested as microalbuminuria was independently associated with central obesity<sup>23</sup>. In a study involving more than 5000 subjects in Okinawa<sup>24</sup>, hypertension and diabetes mellitus were superior to obesity in predicting the development of proteinuria in all subjects but when stratified with men and women, obesity was a significant risk factor for the development of proteinuria independent of both hypertension and diabetes mellitus in men.

## **OBESITY AND CKD**

It is still unclear whether increased BMI itself and renal failure actually have a cause-effect relationship or just the association as obesity leads to the two major causes of CKD, i.e. diabetes and hypertension.

## **EPIDEMIOLOGY OF OBESITY AND CKD**

Over the years, several epidemiological studies have reported an association between obesity and CKD. The Framingham study initially reported an increased risk of new onset CKD with the increase in BMI in both males and females<sup>4</sup>. Looking at metabolic syndrome as a whole, Chen et al, in a population based study<sup>25</sup> of more than 6000 adults in the Third National Health And Nutrition Examination Survey (NHANES III) showed that the risk of CKD and microalbuminuria progressively increased with increase in the number of components of the metabolic syndrome and it was an independent risk factor for CKD. In a Swedish study<sup>26</sup>, Ejerblad et al analysed the anthropometric data in a nationwide case-control study of incident moderate CKD. Overweight (BMI  $\geq 25$  kg/m<sup>2</sup>) at age 20 was associated with a significant three-fold excess risk for CKD, relative to BMI < 25. Obesity (BMI  $\geq 30$ ) among men and morbid obesity (BMI  $\geq 35$ ) among women anytime during lifetime was linked to three- to four-fold increases in risk. The strongest association was with diabetic nephropathy, but two- to three-fold risk elevations were observed for all major subtypes of CKD. A study<sup>27</sup> of a large cohort of 320252 adults who volunteered for health check up in Northern California also showed that a higher baseline BMI

was an independent predictor of ESRD even after adjusting for confounding factors including baseline blood pressure level and the presence or absence of diabetes mellitus. Thus, although hypertension and type-2 diabetes are important mediators, additional pathways also may exist. Iseki et al<sup>28</sup> examined the relationship between obesity (i.e., BMI) and CKD or ESRD using a community based screening registry in Okinawa, Japan and found that incidence of ESRD increased when BMI increased, particularly in men. In the hospital-based screening study<sup>28</sup>, the number of components of metabolic syndrome was significantly related with the prevalence of CKD. Thus the Asian experience also supports the obesity-CKD hypothesis.

## **PATHOPHYSIOLOGY OF RENAL FAILURE IN OBESITY**

Several studies have reported an association between obesity and CKD and experimental and clinical studies have delved on the glomerular changes in obese subjects. But the exact mechanistic link is complex, though we have gained some valuable insights from recent studies.

### **1. Hemodynamic Factors**

Haemodynamic factors play a significant role in obesity-induced renal dysfunction. This includes hypertension and other plausible phenomena, which need to be explored

#### **• Obesity, Hypertension and Renal Dysfunction:**

Epidemiological studies have demonstrated a direct relationship between obesity and hypertension<sup>4,5</sup>. Although the complex mechanisms causing obesity related hypertension have not been completely elucidated, hypertension and renal injury are mutually related in obesity. Several studies have shown a hypertensive shift in pressure natriuresis in obese subjects<sup>7,29,30</sup>. This is mainly due to increased tubular reabsorption of sodium, secondary to increased glomerular filtration rate (GFR) and renal plasma flow<sup>30,31</sup>. Increased sodium reabsorption associated with weight gain has also been attributed to: (1) increased renal sympathetic activity, (2) activation of the renin-angiotensin system, and (3) altered intrarenal physical forces (increased intra-renal pressure due to fat surrounding the kidney and obesity induced histologic changes within renal medulla)<sup>31</sup>. Although hyperinsulinemia was postulated to cause elevated arterial pressure in obese subjects, subsequent evidence have failed to link chronic hyperinsulinemia and hypertension<sup>33</sup>. Recent studies have also highlighted the importance of leptin and angiotensinogen in pathogenesis of obesity associated hypertension<sup>37</sup>. Ribstein et al also showed that obesity magnifies the effect of hypertension on albuminuria, with a steeper regression line between albumin excretion rate and arterial pressure in overweight compared to lean hypertensive subjects, suggesting that obese hypertensive patients are susceptible to the development of renal damage which further perpetuates and worsens the hypertension<sup>14</sup>.

- **Hyperfiltration:** Studies in animals and in humans have shown that obesity is associated with elevated GFR and increased renal blood flow<sup>7,13,30</sup> leading to increased filtration fraction. Elevation in GFR may be mediated in part by increased protein consumption. Afferent arteriolar dilation coupled with efferent renal arteriolar vasoconstriction as a result of elevated Angiotensin II causes increased transcapillary hydraulic pressure gradient. This leads to hyperfiltration, glomerulomegaly, and later focal glomerulosclerosis<sup>11</sup>. Obesity precipitates renal failure in those with reduced renal mass by hyperfiltration injury. In 54 patients with unilateral renal agenesis or remnant kidney, obesity was the only clinical variable statistically associated with the development of proteinuria and progression of renal failure<sup>12</sup>. Bagby et al<sup>16</sup> suggested that intrauterine growth restriction may lead to decreased nephron number and impaired kidney development, which if coupled with an excessive infant “catch-up” growth after birth may result in a mismatch between body size and nephron number. This would predispose to nephron hyperfiltration and hypertension later in life. A significant role of obesity in the progression of IgA nephropathy has been reported<sup>18</sup>. However, sub analysis of the MDRD study did not find any significant influence of baseline BMI on the progression of chronic renal insufficiency<sup>19</sup>.
- **Hypofiltration:** Paradoxically not all studies have shown an increase in GFR and renal blood flow in obese individuals. The pattern of obesity has been found to affect renal hemodynamics. An elevated BMI with central obesity results in reduced GFR, increased renal vascular resistance, and reduced effective renal blood flow as opposed to obesity with peripheral fat distribution<sup>37,38</sup>. So hyperfiltration may not be the norm in obese subjects, and values need to be interpreted in light of body fat distribution and method of GFR adjustment. Raised intra-abdominal pressure also causes increased intrathoracic pressure, impaired right ventricular filling, pulmonary hypertension, and diminished cardiac output, all of which may impair renal perfusion. Also, increased fat in the renal hilum may compress renal vessels and renal parenchyma, causing elevated renal interstitial fluid hydrostatic fluid and slower renal blood flow and renal tubular flow rates, as shown in obese dogs<sup>30</sup>. Though more data support hyperfiltration as the main contributor to renal dysfunction in obesity, hypofiltration is plausible, and more studies are needed to dwell on this hypothesis.

## 2. Cardiopulmonary factors:

Morbidly obese patients commonly have pulmonary hypertension, obstructive sleep apnoea, and cor-pulmonale<sup>39</sup>, which increase right ventricular overload and again cause increased venous pressures, including increased inferior vena caval and renal vein pressures. In addition, cardiac dysfunction, particularly impaired right ventricular function<sup>41</sup> and, to a lesser

extent, left ventricular function, has been described in patients with obesity. This has been attributed to impaired cardiac hemodynamics and direct myocardial lipotoxicity. Impaired cardiac output decreases renal perfusion. Together, these hemodynamic effects may contribute to activation of the RAS, renal sodium retention, and possibly hypertension and renal dysfunction

## 3. Obesity-metabolic syndrome-inflammation

Visceral adipose tissue is an endocrine organ and a site for elaboration and secretion of hormones and cytokines<sup>43</sup>. It is associated with a chronic, low-grade inflammatory state, suggesting that inflammation may be a potential mechanism whereby obesity leads to insulin resistance<sup>37,43</sup>. Since insulin is an anti-inflammatory hormone, insulin resistance per se promotes inflammation leading to a vicious cycle. In the NHANES III cohort<sup>44</sup>, the presence of metabolic syndrome was associated with greater odds for inflammation for various levels of creatinine clearance. In a gene expression study of 6 patients with obesity, proteinuria and biopsy proven ORG, Wu. et.al.<sup>45</sup> found increased expression of genes that are related to lipid metabolism, inflammatory cytokines, and insulin resistance in their glomeruli compared to the glomeruli of age and gender matched control donor kidneys. These findings strongly suggest that inflammatory cytokines and lipid by-products affect renal function in obese patients, but this is yet to be proven definitively. Here we briefly review the cytokines playing a role in obesity induced renal injury:

**Leptin:** It is derived from adipocytes and is structurally similar to IL-2. Increased adiposity results in increased leptin levels<sup>35,36,43</sup>. Leptin crosses the blood-brain barrier, where it decreases neuropeptide Y in the hypothalamus to suppress appetite and increase energy expenditure. In addition, it increases insulin sensitivity in various tissues. Patients with obesity and the metabolic syndrome are resistant to the hypothalamic effects of leptin and have elevated leptin levels. Leptin has direct as well as indirect effects on the kidney:

**Direct effect:** Because the short form of leptin receptor (Ob-Ra) is abundantly expressed in the kidney<sup>36</sup>, leptin is being postulated to be responsible for renal injury in obesity. Recombinant leptin stimulates the proliferation of cultured glomerular endothelial cells (but not mesangial cells) and increases TGF- $\beta$ 1 mRNA expression and production<sup>35,47</sup> and when infused in rats produces significantly increased type IV collagen protein, glomerulosclerosis, and proteinuria without increasing BP. *So leptin may play a role in the glomerulosclerosis that is observed in obese patients with proteinuria and/or CKD, independent of hypertension.*

**Indirect effects:** Leptin increases sympathetic nerve trafficking and renal sodium retention, which may cause hypertension<sup>36</sup>. Furthermore, it stimulates oxidative stress in endothelial cells and induces a proinflammatory state as a result of stimulation of Th1 cells<sup>36,49</sup>. Such effects may promote atherosclerosis.

- **IL-6 and CRP:** Plasma IL-6 levels positively correlate with obesity and insulin resistance and predict the development

of type 2 diabetes<sup>43</sup>. It mediates insulin resistance, increases platelet activity and atherogenicity, increases the expression of adhesion molecules on endothelial and vascular smooth muscle cells<sup>43</sup>, and activates the local renin-angiotensin system (RAS)<sup>48</sup>, thus promoting cellular injury. IL-6 also increases TGF- $\beta$ 1 signalling *via* modulation of TGF- $\beta$ 1 receptor trafficking, an effect that may enhance renal fibrosis<sup>49</sup>. It also increases CRP production and new data suggest that CRP may not be just a marker of inflammation and cardiovascular risk but also a contributor to vascular damage and cardiovascular events<sup>37</sup>.

**TNF- $\alpha$**  : TNF- $\alpha$  is produced by macrophages within adipose tissue, and its levels are elevated in the metabolic syndrome<sup>43</sup>. TNF- $\mu$  is one of the mediators of insulin resistance in adipose tissue: It has been shown to mediate inflammation<sup>51,53</sup> in several models of renal injury, including glomerulonephritis<sup>50</sup>, acute renal failure<sup>51</sup>, and tubulointerstitial injury<sup>52</sup>. These cytokines may be toxic to renal epithelial, mesangial, and endothelial cells. However, the specific role of TNF- $\alpha$  in metabolic syndrome-induced renal injury has not been studied.

**Adiponectin**: Adiponectin is an adipokine with insulin-sensitising, anti-inflammatory and anti-atherogenic properties<sup>54,55</sup>. Its levels correlate negatively with fat mass, body weight, BP, insulin resistance, inflammatory markers of the metabolic syndrome, and high triglyceride (TG) and LDL cholesterol levels and positively with HDL cholesterol and weight loss<sup>55</sup>. Hypoadiponectinemia is associated with vascular dysfunction and with cardiovascular events in patients without CKD<sup>56</sup>. It may thus protect various organs from the harmful effects of chronic inflammation. But studies have reported contradictory findings about the role of adiponectin in CKD. Becker et al.<sup>57</sup> found that low adiponectin levels in patients with mild or moderate renal failure were correlated with cardiovascular events, whereas Menon et al.<sup>58</sup> found that in patients with stage 3 or 4 CKD, all-cause and cardiovascular mortality were paradoxically higher in those with high adiponectin levels. The exact significance of adiponectin in the pathogenesis of CKD is still unclear.

#### 4. Insulin resistance

Obesity is characterised by an insulin resistance state which forms the basis of the metabolic syndrome. This has multifaceted direct and indirect effects on the kidney. As insulin reduces norepinephrine-induced efferent arteriolar constriction, insulin resistance may increase the transcapillary pressure gradient by increasing efferent arteriolar resistance. Hyperinsulinemia also stimulates the synthesis of growth factors such as insulin-like growth factor (IGF)-1 and IGF-2, which may promote glomerular hypertrophy<sup>33,34</sup>. Also, as we discussed earlier, insulin being an anti-inflammatory hormone, its resistance further promotes the milieu of inflammation thus promoting renal injury.

#### 5. RAS

Activation of the RAS and increased circulating levels of renin, angiotensinogen, angiotensin-converting enzyme, aldosterone, and, to some extent, angiotensin II (Ang-II) are common in obese individuals despite sodium retention and an apparently increased extra cellular fluid volume<sup>59</sup>. Several mechanisms have been implicated including sympathetic stimulation, hemodynamic alterations<sup>30,31</sup> as discussed earlier and synthesis of several proteins of the RAS by visceral fat<sup>60</sup>. Giacchetti et al.<sup>61</sup> recently found a significantly higher expression of angiotensinogen and Ang-II type 1 receptor mRNA in visceral adipose tissue than subcutaneous fat of both obese and lean individuals. Also 5% weight loss in obese individuals resulted in significant reductions of circulating levels and adipose tissue expression of RAS hormones<sup>59</sup>. The larger adipose tissue mass in obese individuals may be partly responsible for the increased circulating levels of RAS hormones. Ang-II is widely known to affect adversely progression of renal disease in several models of renal injury and in patients with CKD by causing hypertension, raised intraglomerular pressure, exacerbation of proteinuria, induction of intrarenal inflammatory cytokines and growth factors, and apoptosis<sup>62</sup>. It also increases insulin resistance and suppresses adiponectin levels in obesity<sup>60</sup>. So Ang-II has a dual effect of promoting the various components of metabolic syndrome and directly injuring the kidney. But most of these observations are from animal studies and need validation in humans.

#### 6. Renal Lipotoxicity

Studies suggest that lipids may cause renal mesangial and epithelial cell injury and may promote renal disease progression<sup>63,64</sup>. HMG-CoA reductase inhibitors have been found to improve proteinuria and preserve renal function<sup>65</sup>, suggesting a role for lipids per se in promoting renal injury. The mechanisms of renal lipotoxicity are not fully elucidated, but a number of experiments suggested a role for TG-rich lipoproteins, FFA and their metabolites, and albumin-loaded FFA in renal cell injury.

#### OBSESITY AND DIALYSIS

In contrast to the general population, a high BMI is associated with better outcome in dialysis patients<sup>66,67</sup>. This is known as a 'risk factor paradox' or 'reverse epidemiology' for cardiovascular disease in uremic patients<sup>68</sup>. However some studies have shown that high BMI dialysis patients with inferred high body fat actually had increased prevalence of atherosclerosis and increased mortality<sup>69</sup>. Thus there is conflicting data on effect of obesity on dialysis patients. It is hypothesized that nutrition exerts a much stronger influence on survival than atherosclerosis in CKD<sup>70</sup>. Malnutrition strongly increases the risk of death, while better nutrition gives survival benefit. So risk of death is highest in malnourished patients (low muscle and low fat mass) and lowest in well-nourished patients (high BMI, high muscle mass). Though obesity (high BMI, high fat mass) increases the risk of

atherosclerosis-related death, but the risk is not as high as malnutrition related death. So CKD patients with high body fat have intermediate survival.

## OBESITY AND RENAL TRANSPLANTATION

The impact of obesity on kidney transplant outcomes continues to be controversial. Some studies<sup>71</sup> suggest that extremes of very high and very low BMI before renal transplantation are important risk factors for patient and graft survival and in this particular study elevated BMI was significantly associated with worse graft survival independent of patient survival. While in other studies there are no significant adverse effect of obesity on renal transplant outcomes except an increase in wound complications, which were generally of minor consequence. Obesity seems to influence delayed graft failure, graft survival, and patient survival. A body mass index of 35 kg/m<sup>2</sup> or more is significant for greater post transplant complications, especially new-onset transplant diabetes mellitus, wound complications, and post transplant weight gain. It is suggested that any association of obesity with reduced patient survival in renal transplant recipients is mediated in part by its clustering with traditional cardiovascular risk factors such as hypertension, dyslipidemia, insulin resistance and post transplant diabetes mellitus, but what is not understood is what mediates the association of obesity with graft failure. Whether it is the higher incidence of cardiovascular co morbidities jeopardising the graft or factors specific to obesity, such as hyperfiltration and glomerulopathy, that might be implicated, currently remains unknown. It can be concluded, however, that pre- and post transplant obesity should be targeted as aggressively as the more well-established cardiovascular risk factors in order to optimise long-term renal transplant outcomes.

## POTENTIAL INTERVENTIONS TO PREVENT OBESITY INDUCED RENAL DYSFUNCTION

Weight loss and increased activity are the cornerstones of the treatment of obesity and the metabolic syndrome. Many other targeted interventions may be adopted. Bariatric surgery and surgical resection of abdominal adipose tissue improve the metabolic profile and reduce inflammatory cytokine levels both in the short term and up to 10 yr later<sup>37</sup>. However, the long-term safety of these procedures has not been established. PPAR- $\mu$  (the fibrates) and PPAR-I (the thiazolidinediones) agonists improve insulin sensitivity, but they are not without risks in the setting of renal disease and are known to cause myopathy and salt and fluid retention myopathy and sodium and fluid retention respectively. Blockade of the RAS is likely to be beneficial, but treatment will need to be individualized depending on the degree of renal dysfunction and the presence of other co morbidities. HMG-CoA reductase inhibitors have been renoprotective in some studies<sup>65</sup>. Large, randomised, controlled trials to examine the effects of each of these

interventions on renal function in patients with the metabolic syndrome are needed before any firm recommendations can be made.

## CONCLUSION

Obesity and metabolic syndrome are independent risk factors for CKD. Large-scale experimental and clinical trials are needed to understand the various mechanisms causing obesity induced renal dysfunction to propose definite targeted interventions for its prevention and treatment. As of now all obese patients should be advised weight reduction along with blood pressure and blood glucose control to prevent and treat all forms of kidney disease

## BIBLIOGRAPHY

1. **Ogden CL, Carroll MD, Curtin LR et al.** Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA* 2006; 295: 1549-1555
2. **Ganapati Mudur.** Asia grapples with obesity epidemics. *BMJ* 2003;326:515
3. **V Mohan and R Deepa.** Obesity and abdominal obesity in Asian Indians. *Indian J Med Res* 123, May 2006, p593-596
4. **Kannel WB, Garrison RJ, Dannenberg AL.** Secular blood pressure trends in normotensive persons: the Framingham Study. *Am Heart J* 1993; 125: 1154-8
5. **Stamler R, Shipley M, Elliot P, Dyer A, Sans S, Stamler J.** Higher blood pressure in adults with less education. Some explanations from INTERSALT. *Hypertension* 1992; 19: 237-41
6. **Must A, Spadano J, Coakley EH, et al.** The disease burden associated with overweight and obesity. *JAMA* 1999; 282: 1523-1529
7. **Chagnac A, Weinstein T, Korzets A et al.** Glomerular hemodynamics in severe obesity. *Am J Physiol Renal Physiol* 2000; 278: F817-F822
8. **Kasiske BL and Napier J.** Glomerular sclerosis in patients with massive obesity. *Am J Nephrol* 1985; 5: 45-50
9. **Weisinger JR, Kempson RL, Eldridge L & Swenson RS.** The nephrotic syndrome: A complication of massive obesity. *Ann Intern Med* 1974; 81: 440-447
10. **Kasiske BL, O'Donnell MP, Cleary MP, Keane WF.** Treatment of hyperlipidemia reduces glomerular injury in obese Zucker rat. *Kidney Int* 1998; 33: 667-72
11. **Neeraja Kambham, Glen S Markowitz, Anthony M Valeri, Julie Lin and Vivette D D'Agati.** Obesity-related glomerulopathy: An emerging epidemic. *Kidney Int* 2001; 59: 1498-1509
12. **Gonzalez E, Gutierrez E, Morales E et al.** Factors influencing the progression of renal damage in patients with unilateral renal agenesis and remnant kidney. *Kidney Int* 2005; 68: 263-270
13. **Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE.** Functional and structural changes in the kidney in the early stages of obesity. *J Am Soc Nephrol* 2001;12: 1211-1217
14. **Jean Ribstein, Guilhem du Cailar, Albert Mimran.** Combined renal effects of overweight and hypertension. *Hypertension*. 1995;26:610-615
15. **Manalich R, Reyes L, Herrera M, Melendi C, Fundora I.** Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. *Kidney Int* 2000; 58: 770-773
16. **Bagby SP.** Obesity-initiated metabolic syndrome and the kidney: A recipe for chronic kidney disease? *J Am Soc Nephrol* 2004;15: 2775-2791
17. **Vickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman PD.** Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. *Am J Physiol* 2000; 279: E83-E87
18. **Bonet F, Deprele C, Sassolas A et al.** Excessive body weight as a new independent risk factor for clinical and pathological progression in primary IgA nephritis. *Am J Kidney Dis* 2001; 37: 720-727
19. **Hunsicker LG, Adler S, Caggiula A et al.** Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. *Kidney Int* 1997; 51: 1908-1919
20. **Iseki K, Iseki C, Ikemiya Y & Fukiyama K.** Risk of developing end-stage renal disease in a cohort of mass screening. *Kidney Int* 1996; 49: 800-805
21. **Mogensen CE.** Microalbuminuria predicts clinical proteinuria and early mortality in maturity onset diabetes. *N Engl J Med* 1984; 310: 356-360
22. **Pinto-Sietsma SJ, Janssen WM and Hillege HL et al.** Urinary albumin excretion is associated with renal functional abnormalities in a nondiabetic population. *J Am Soc Nephrol* 2000; 11: 1882-1888
23. **Leise AD, Hense HW, Doring A et al.** Microalbuminuria, central adiposity and hypertension in non-diabetic urban population of MONIKA Augsburg survey 1994/95. *J Hum Hypertens* 2001; 15: 799-804
24. **Masahiko Tozawa, Kunitoshi Iseki, Chiho Iseki, Saori Oshiro, Yoshiharu Ikemiya and Shuichi Takishita.** Influence of smoking and obesity on the development of proteinuria. *Kidney Int* 2002; 62, 956-962
25. **Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, Whelton PK, He J.** The metabolic syndrome and chronic kidney disease in US adults. *Ann Intern Med* 2004;140: 167-174
26. **Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyren O.** Obesity and risk for chronic renal failure. *J Am Soc Nephrol* 2006;17: 1695-1702
27. **Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS.** Body mass index and risk for end-stage renal disease. *Ann Intern Med* 2006;144: 21-28
28. **Iseki K, Ikemiya Y, Kinjo K, Inoue T, Iseki C, Takishita S.** Body mass index and the risk of development of end-stage renal disease in a screened cohort. *Kidney Int* 2004; 65: 1870-1876

29. Rocchini AP. The influence of obesity in hypertension. *News Physiol Sci*. 1990; 5: 245–249
30. Hall JE. Mechanisms of abnormal renal sodium handling in obesity hypertension. *Am J Hypertens*. 1997; 10: S49–S55
31. Hall JE. The kidney, hypertension and obesity. *Hypertension* 2003; 41: 625–633
32. Hall JE. Hyperinsulinemia: a link between obesity and hypertension? *Kidney Int*. 1993; 43: 1402–1417
33. Fryxell J, Skjaerbaek C and Vestø E et al. Circulating levels of free insulin-like growth factors in obese subjects: the impact of type 2 diabetes. *Diabetes Metab Res Rev* 1999; 15: 314–322
34. Wolf G, Hamann A and Han DC et al. Leptin stimulates proliferation and TGF- $\beta$  expression in renal glomerular endothelial cells: potential role in glomerulosclerosis. *Kidney Int* 1999;56: 860–872
35. Wolf G, Chen S, Han DC, Ziyadeh FN. Leptin and renal disease. *Am J Kidney Dis* 2002; 39: 1–11.
36. Ihab M, Wahba and Robert H. Mak. Obesity and Obesity-Initiated Metabolic Syndrome: Mechanistic Links to Chronic Kidney Disease. *Clin J Am Soc Nephrol* 2007;2: 550–562
37. Scaglione R, Ganguzza A, Corrao S, Parrinello G, Merlino G, Diciara MA, Arnone S, D'Aubert MD, Licata G: Central obesity and hypertension: Pathophysiologic role of renal haemodynamics and function. *Int J Obes Relat Metab Disord* 1995;19 :403–409
38. Valencia-Flores M, Rebollar V, Santiago V, Orea A, Rodriguez C, Resendiz M, Castano A, Roblero J, Campos RM, Oseguera J, Garcia-Ramos G, Blwise DL: Prevalence of pulmonary hypertension and its association with respiratory disturbances in obese patients living at moderately high altitude. *Int J Obes Relat Metab Disord* 2004;28 :1174–1180
39. Wong CY, O'Moore-Sullivan T, Leano R, Hukins C, Jenkins C, Marwick TH: Association of subclinical right ventricular dysfunction with obesity. *J Am Coll Cardiol* 2006;47 :611–616
40. Wisse BE: The inflammatory syndrome: The role of adipose tissue cytokines in metabolic disorders linked to obesity. *J Am Soc Nephrol* 2004;15 :2792–2800
41. Beddhu S, Kimmel P, Nirupama R, Cheung A: Associations of metabolic syndrome with inflammation in CKD: Results from the third national health and nutrition examination survey (NHANES III). *Am J Kidney Dis* 2005;46 :577–586
42. Wu Y, Liu Z, Xiang Z, Zeng C, Chen Z, Ma X, Li L: Obesity-related glomerulopathy: Insights from gene expression profiles of the glomeruli derived from renal biopsy samples. *Endocrinology* 2006;147 :44–50
43. Sharma K, Considine RV: The ob protein (leptin) and the kidney. *Kidney Int* 1998;53 :1483–1487
44. Han DC, Isono M, Chen S, Casaretto A, Hong SW, Wolf G, Ziyadeh FN: Leptin stimulates type I collagen production in db/db mesangial cells: Glucose uptake and TGF-beta type II receptor expression. *Kidney Int* 2001;59 :1315–1323
45. Wassmann S, Stumpf M, Strehlow K, Schmid A, Schieffer B, Bohm M, Nickenig G: Interleukin-6 induces oxidative stress and endothelial dysfunction by overexpression of the angiotensin II type 1 receptor. *Circ Res* 2004;94 :534–541
46. Zhang XL, Topley N, Ito T, Phillips A: Interleukin-6 regulation of transforming growth factor (TGF)-beta receptor compartmentalization and turnover enhances TGF-beta1 signaling. *J Biol Chem* 2005;280 :12239–12245
47. Khan SB, Cook HT, Bhargava G, Smith J, Tam FW, Pusey CD: Antibody blockade of TNF-alpha reduces inflammation and scarring in experimental crescentic glomerulonephritis. *Kidney Int* 2005;67 :1812–1820
48. Cunningham PN, Dyanov HM, Park P, Wang J, Newell KA, Quigg RJ: Acute renal failure in endotoxemia is caused by TNF acting directly on TNF receptor-1 in kidney. *J Immunol* 2002;168 :5817–5823
49. Guo G, Morrissey J, McCracken R, Tolley T, Liapis H, Klahr S: Contributions of angiotensin II and tumor necrosis factor-alpha to the development of renal fibrosis. *Am J Physiol Renal Physiol* 2001;280 :F777–F785
50. Klahr S, Morrissey J: Progression of chronic renal disease. *Am J Kidney Dis* 2001;41[Suppl 1] :S3–S7
51. Kershaw E, Flier JS: Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab* 2004;89 :2548–2556
52. Diez JJ, Iglesias P: The role of the novel adipocyte-derived hormone adiponectin in human disease. *Eur J Endocrinol* 2003;148 :293–300
53. Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, Arita Y, Okamoto Y, Shimomura I, Hiraoka H, Nakamura T, Funahashi T, Matsuzawa Y; Osaka CAD Study Group: Coronary artery disease: Association of hypoadiponectinemia with coronary artery disease in men. *Arterioscler Thromb Vasc Biol* 2003;23 :85–89
54. Becker B, Kronenberg F, Kielstein JT, Haller H, Morath C, Ritz E, Fliser D; MMKD Study Group: Renal insulin resistance syndrome, adiponectin and cardiovascular events in patients with kidney disease: The Mild and Moderate Kidney Disease Study. *J Am Soc Nephrol* 2005;16 :1091–1098
55. Menon V, Li L, Wang X, Greene T, Balakrishnan V, Madero M, Pereira AA, Beck GJ, Kusek JW, Collins AJ, Levey AS, Sarnak MJ: Adiponectin and mortality in patients with chronic kidney disease. *J Am Soc Nephrol* 2006;17 :2599–2606
56. Engeli S, Bohnke J, Gorzelnik K, Janke J, Schlung P, Bader M, Luft FC, Sharma AM: Weight loss and the renin-angiotensin-aldosterone system. *Hypertension* 2005;45 :356–362
57. Engeli S, Schlung P, Gorzelnik K, Boschmann M, Janke J, Ailhaud G, Teboul M, Massiera F, Sharma AM: The adipose-tissue renin-angiotensin-aldosterone system: Role in the metabolic syndrome? *Int J Biochem Cell Biol* 2003;35 :807–825
58. Giacchetti G, Falola E, Mariniello B, Sardù C, Gatti C, Camilloni MA, Guerrieri M, Mantero F: Overexpression of the renin-angiotensin system in human visceral adipose tissue in normal and overweight subjects. *Am J Hypertens* 2002;15 :381–388
59. Ruster C, Wolf G: Renin-angiotensin-aldosterone system and progression of renal disease. *J Am Soc Nephrol* 2006;17 :2985–2991
60. Moorhead JF, Chan MK, El-Nahas M, Varghese Z: Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease. *Lancet* 1982;2 :1309–1311
61. Ruan XZ, Moorhead JF, Fernando R, Wheeler DC, Powis SH, Varghese Z: Regulation of lipoprotein trafficking in the kidney: Role of inflammatory mediators and transcription factors. *Biochem Soc Trans* 2004;32 :88–91
62. Tonelli M, Moya L, Sacks FM, Cole T, Curhan GC: Cholesterol and Recurrent Events Trial Investigators: Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. *J Am Soc Nephrol* 2003;14 :1605–1613
63. Arici M, Chana R, Lewington A, Brown J, Brunskill NJ: Stimulation of proximal tubular cell apoptosis by albumin-bound fatty acids mediated by peroxisome proliferator activated receptor-gamma. *J Am Soc Nephrol* 2003;14 :17–27
64. Leavay SF, McCullough K, Hecking D, Goodkin D, Port FK, Young EW. Body mass index and mortality in "healthier" as compared with "sicker" hemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2001; 16: 2386–2394
65. Kopple JD, Zhu X, Lew NL, Lowrie EG: Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. *Kidney Int* 1999; 56:1136–1148
66. Nishizawa Y, Shoji T, Ishimura T, Inaba M, Morii H. Paradox of risk factors for cardiovascular mortality in uraemia: is a higher cholesterol level better for atherosclerosis in uraemia? *Am J Kidney Dis* 2001; 38: S4–S7
67. Bedhu S, Pappas LM, Ramkumar N, Samore M. Effects of body size and body composition on survival in hemodialysis patients. *J Am Soc Nephrol* 2003;14: 2366–2372
68. Bedhu S. The body mass index paradox and an obesity, inflammation and atherosclerosis syndrome in chronic kidney disease. *Seminars in Dialysis* 2004;17: 229–232
69. Meier-Kriesche HU, Amdorfer JA, Kaplan B. The impact of body mass index on renal transplant outcomes: a significant independent risk factor for graft failure and patient death. *Transplantation* 2002;73(1):70–74
70. Johnson DW, Isbel NM, Brown AM, Kay TD, Franzen K, Hawley CM, Campbell SB, Wall D, Griffin A, Nicol DL. The impact of obesity on renal transplant outcomes. *Transplantation* 2002;74(5):675–681

## LITERATURE REVIEW

### ATTITUDE OF HEALTH CARE PROFESSIONALS TO BRAIN DEATH: INFLUENCE ON THE ORGAN DONATION PROCESS. Jonathan Cohen, Sharon Ben Ami, Tamar Ashkenazi and Pierre Singer *Clin Transplant* 2008; 22: 211–215.

The acceptance and application of the concept that brain death is a valid determination of death is the central issue in organ donation. However, whether attitude to brain death of health care professionals influences the organ procurement process has not been systematically studied. Questionnaires were distributed to health care professionals involved in the organ procurement process (intensive care, internal medicine, emergency room, anesthesia) in all hospitals in Israel. Attitude to brain death (defined as positive if the respondent accepted brain death as a valid determination of death, negative or do not know) and level of comfort in performing key donor-related tasks were analyzed. A total of 2366 completed questionnaires were returned (629 doctors and 1737 nurses; response rate 60.3%). Overall, 78.9% of respondents had a positive attitude to brain death. This was significantly associated with increasing age, higher professional status and was most prevalent amongst intensive care unit staff ( $p < 0.001$  for all variables). These respondents felt significantly more comfortable informing the transplant coordinator of a potential donor, explaining brain death to the family, raising the subject of organ donation, approaching the family about donation and providing support to the grieving family. In addition, they believed the transplant coordinator should be involved early in the donation process. The understanding and acceptance of brain death as a valid determination of death was associated with a positive effect on the level of comfort of health care professionals in performing key donor-related tasks. Reinforcing a positive attitude to brain death among health care professionals may facilitate the procurement process.

## CURRENT PERSPECTIVES OF POLYCYSTIC OVARY SYNDROME (PCOS)

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**Abstract:** PCOS is now recognized as a variant of metabolic syndrome, which may include hyperinsulinemia, hyperlipidemia, diabetes mellitus, and possibly cardiac disease along with its conventionally recognized gynecological and dermatological manifestations. Several studies have suggested a high prevalence of PCOS of about 5-10% in women of reproductive age and its significance is increased even more in present context of rising incidence of obesity and metabolic syndrome as a important contributory factor. So in this article we reviewed the current guidelines for diagnosis of PCOS, its metabolic complication and current practice of treatment, our experience with metformin comparing to aldosterone, with better understanding its pathogenesis and management.

It is diagnosed on the basis of peripubertal onset of menstrual problems with clinical or biochemical hyper androgenism with radiological inputs on the basis of AES 2006 criteria. Obesity tend to be central in its distribution, insulin resistance is independently present in patients of pcos, showing a high degree of hyperinsulinemia and impaired glucose tolerance, on conducting our study on 168 north Indian adolescent girls with PCOS having a mean age of 22.6 years and that concluded that impaired fasting glucose (IFG) was noted in 6/168(3.57%), IGT in 49/168(29.16%) and diabetes in 15/168(8.92%) making the total prevalence of glucose intolerance as 41.60%. ideally the management should be aimed at addressing the basic defect of the whole metabolic constellation. Current management comprises treatment of the presenting symptoms, as well as any other abnormality discovered on investigation. We compared spironolactone and metformin in the management of various components of PCOS and observed that spironolactone (50 mg/day) appears to be better than metformin in the treatment of hirsutism and hormonal derangements of PCOS and has better patient tolerance at lower doses. The fact that superior positive effects of metformin on insulin sensitivity did not translate into proportionate clinical benefits in these PCOS subjects raises doubts about insulin resistance as a sole pathogenetic mechanism. Although metformin is classed as category 'B' drug but has been used widely for induction of ovulation with good efficacy either as a sole agent or in combination with clomiphene citrate with no specific neonatal complications, but there is inadequate evidence at present to suggests it use to prevent gestational diabetes or recurrent miscarriage and more studies are required.

### INTRODUCTION

Initially called the Stein–Leventhal syndrome after its researchers in the 1930s, PCOS is now recognized to be a variant of metabolic syndrome which may include hyperinsulinemia, hyper-lipidemia, diabetes mellitus, and possibly cardiac disease, as well as the more conventionally recognized hirsutism, ovarian follicular atresia with anovulation, infertility, elevated androgen levels, endometrial cancer and obesity<sup>1</sup>. This clustering of metabolic characteristics is almost similar to earlier described metabolic malady referred to as “Syndrome X” or metabolic syndrome by Gerald Reaven. Thus PCOS now should be viewed not just as a gynecological or dermatological disorder, but a sex limited manifestation of metabolic syndrome that involves multiple body systems and probably stems from a key pathogenic element called hyperinsulinemia.

### PREVALENCE

PCOS is generally under diagnosed given the general concept about the condition among the practitioners. Clinicians should remember that menstrual abnormalities, such as cycles shorter than 21 days or longer than 35 days, are often associated with the condition. Many young women with these abnormalities are prescribed the oral contraceptive pill, which masks the condition until they try to achieve pregnancy. Several studies have suggested a prevalence of PCOS of 5%–10% in women

of reproductive age<sup>2,3</sup>. Polycystic ovaries alone were found in 20%–25% of women in surveys in the United Kingdom and New Zealand<sup>4</sup>. There are no systematic prevalence studies from our country however the condition seems to be very common than west and it seems to be on rise in our population.

### PATHOGENESIS

The pathogenesis of PCOS is poorly understood, but plethora of evidence is favoring the insulin resistance with consequent hyperinsulinemia as the primary defect<sup>5</sup>. The theca cells, which envelop the follicle and produce androgens for conversion in the ovary to estrogen, are over-responsive to stimulation by circulating concentrations of insulin and leutenising hormone (LH) which are generally raised. The rise in LH levels itself is thought to be caused by the relatively high and unchanging concentrations of estrogens that may alter the control of this hormone by the hypothalamic–pituitary axis. This combination of raised levels of androgens, estrogen, insulin and LH explains the classic PCOS presentation of hirsutism, anovulation or dysfunctional bleeding, and disorder of glucose metabolism. Paradoxically, although the insulin regulatory molecules on the theca cells are responsive to insulin, those in the muscle and liver are resistant<sup>6</sup>.

### DIAGNOSTIC CRITERIA

The diagnostic criteria for PCOS are generally based on peri-pubertal onset of menstrual problems with clinical or biochemical hyperandrogenism. The evolution of diagnostic criteria from NIH/NICHHD 1990<sup>7</sup> through Rotterdam 2003 conference<sup>8</sup> to current consensus by Androgen Excess Society

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2006 (AES)<sup>9</sup> has however continued to put major thrust on hyperandrogenemia and anovulation (Table 1). The polycystic ovaries characterized by peripheral cysts (10 or more), less than 10 mm in size in an enlarged ovary with significant increase in the central stroma on ultrasound examination is particularly controversial as a criterion<sup>4</sup>. Most of the available literature on PCOS does not include the presence of polycystic ovaries as a diagnostic criterion. Moreover polycystic ovaries are also found in women with no evidence of menstrual dysfunction or hyperandrogenism<sup>10</sup> and can also occur in early to mid-adolescence, in women with bulimia, recovery from anorexia nervosa, conditions of increased adrenal androgen production and hyperprolactinemia<sup>11</sup>. In view of the multitude of components the index of suspicion should be high.

**Table 1. Androgen Excess Society suggested criteria for the diagnosis of PCOS §.**

1. <b>Hyperandrogenism:</b> Hirsutism and/or Hyperandrogenemia and
2. <b>Ovarian Dysfunction:</b> Oligo- anovulation and/or polycystic Ovaries and
3. Exclusion of other androgen excess or related disorders

§ Possibly excluding 21-hydroxylase-deficient non-classic adrenal hyperplasia, androgen-secreting neoplasms, androgenic/anabolic drug use or abuse, Cushing's syndrome, the syndromes of severe insulin resistance, thyroid dysfunction, and hyperprolactinemia.

## PRESENTATIONS OF PCOS

PCOS is a life long condition which may have effects at all ages, not just in the reproductive years (Table 2). The condition may have its origins in fetal life as researchers have claimed that the children with either intrauterine growth retardation or post-term birth are more prone to hyperinsulinism, premature pubarche and signs of PCOS early in reproductive life<sup>12</sup>. **Teenagers** often have oligo- or amenorrhea, hirsutism, acne and weight disorders. **Women seeking to become pregnant** will have difficulties because of anovulation and menorrhagia is more common because of lack of ovulation and unopposed estrogen action. The absence of regular menstruation induced by progesterone withdrawal may lead to endometrial hyperplasia and uncontrolled bleeding. There is a theoretical risk of endometrial cancer and has been alleged to be four times more common and may even appear even in teenagers. However, recent studies have raised doubts about the validity of this dogma<sup>13</sup>. It is controversial whether miscarriage is increased in PCOS, or whether pregnancy loss is a result of excess body weight.

The incidence of obesity in women with PCOS varies between countries and ethnic groups. In the United States, about 50% of women with PCOS are overweight or obese, but this prevalence differs little from that in the general community. In our population with a cut-off of 25 Kg/m<sup>2</sup>, 33.92% were

non-obese and 66.08% in one study<sup>14</sup>. Obesity tends to be central (abdominal) in its distribution and even lean women with PCOS may have a fat distribution favouring central omental and visceral fat. **Insulin resistance** is independently related to PCOS, with women of normal weight with PCOS showing a degree of hyperinsulinaemia and impaired glucose disposal after meals and during glucose tolerance tests (oral or intravenous). It is uncertain whether this insulin resistance results from a specific genetic post-receptor defect, such as a defect in serine phosphorylation<sup>5</sup> or whether it is comparable to the problem seen in type 2 diabetes. We compared spironolactone and metformin in the management of various components of PCOS and observed that spironolactone appears to be better than metformin in the treatment of hirsutism and hormonal derangements of PCOS and has a better patient tolerance at lower doses. The fact that superior positive effects of metformin on insulin sensitivity did not translate into the proportionate clinical benefit in these PCOS subjects raises doubts about insulin resistance as the sole pathogenetic factor<sup>4</sup>. Certainly, hyperinsulinemia is common but is difficult to interpret clinically, given the fact that it also results from obesity. There is some data which may be suggesting hyperinsulinemia as an epiphenomenon as our earlier observation<sup>14, 15</sup>. **Glucose tolerance abnormalities and type 2 diabetes** are major complications in overweight women with PCOS. While fasting glucose level is usually normal postprandial glucose is abnormal as glucose disposal is impaired. We studied 168 north Indian adolescent girls with PCOS having a mean age of 22.6 years and concluded that impaired fasting plasma glucose (IFG) was noted in 6/168 (3.57%), IGT in 49/168 (29.16%) and diabetes in 15/168 (8.92%) making the total prevalence of glucose intolerance as 41.60%<sup>14</sup>. An excellent epidemiological study in the UK that followed up women with a histological diagnosis of PCOS

**Table 2. Common Symptoms, signs and metabolic abnormalities of PCOS**

Not all women with PCOS share the same symptoms:

1. Infrequent menstrual periods, no menstrual periods, and/or irregular bleeding
2. Hirsutism involving face, chest, stomach, back, thumbs, or toes
3. Acne vulgaris -moderate to severe
4. Male-pattern baldness or thinning hair
5. Acanthosis nigricans (patches of thickened and dark brown or black skin) on the neck, arms, breasts, or thighs
6. Skin tags in the armpits or neck area
7. Anxiety or depression
8. Sleep apnea syndrome
9. Overweight or obesity, usually central
10. Insulin resistance, glucose intolerance and type 2 diabetes
11. Hyperlipidemia
12. High blood pressure
13. Anovulation and infertility
14. High risk of coronary artery disease
15. Prothrombotic state
16. Elevated inflammatory markers like CRP, interleukins etc

after wedge resection of the ovaries found clear evidence of an increase in the rate of diabetes<sup>16</sup> and confirmed the results of many other studies from the US and Europe. Hypertriglyceridaemia, increased concentrations of LDL and decreased concentrations of HDL cholesterol are common in women with PCOS, particularly if obese. Levels of plasminogen activator inhibitor-1 may also be raised, suggesting a chronic underlying sub inflammatory process. The association of PCOS and cardiovascular dysfunction is still under investigation and data has been conflicting. A higher than expected prevalence of PCOS has been reported among young women with angiographically proven narrowing of the coronary vessels; women with PCOS were also more likely to have sonographic evidence of premature obstruction of other large vessels<sup>17,18</sup>. However, a UK study of medical records and death certificates of women with a histological diagnosis of PCOS revealed no evidence for an increase in myocardial infarction or other types of heart disease (Table 3).

	DIAGNOSTIC CRITERIA			
	FRANKS (USG) (N=300) (%)	CONWAY ET AL (USG) (N=556) (%)	GOLDZIEHER AND GREEN (HISTOLOGIC) (N=1079) (%)	GANIE M ASHRAF NICHHD# (N=168) (%)
Hirsutism	64	61	69	98
Acne	27	24	-	10.7
Obesity	35	35	41	60.2
Infertility	42	29	74	-
Amenorrhoea	28	26	51	10.7
Oligomenorrhoea	52	45	29	98.8
Regular menstrual cycle	20	25	158	0

# Adapted from Ganie M A et al (Ref 14)

## LABORATORY EVALUATION

**History and general examination:** These are required to elicit evidence of peripubertal menstrual dysfunction (age of menarche, duration of cycles, regularity, number of cycles in a year or cycle interval and flow ) and hirsutism severity ( as assessed qualitatively or semi quantitatively using the Ferriman–Gallwey score)<sup>19</sup>. Acne vulgaris, acanthosis nigricans, anthropometry especially waist circumference etc is to be noted. Mild clitoromegaly is not uncommon, but significant enlargement raises the possibility of virilisation. Gynecological examination is needed only to exclude other causes of bleeding and miscarriage.

**Pelvic ultrasound examination:** Transvaginal ultrasound is the best imaging mode. Transabdominal ultrasound examination requires more expertise to get a good view, particularly in obese women. Ovarian morphology (total volume, thecal hyperechogenicity and 2-10 peripheral follicles) should be assessed in addition to measuring endometrial thickness<sup>4</sup>. Also it gives a clue about possible adrenal or ovarian lesion.

**Hormone assays:** There is no uniform opinion regarding the endocrine and metabolic workup for the routine clinics. Since the universally employed criteria (NIH/NICHHD) demand the exclusion of late-onset congenital adrenal hyperplasia (measurement of 17-hydroxyprogesterone), thyroid

dysfunction (thyroid-stimulating hormone), hyperprolactinemia (prolactin), Cushing’s syndrome (basal cortisol or overnight dexamethasone suppression) and androgen secreting tumors (androgen levels), however these tests can be omitted if the clinical features are not suggestive. Measurement of testosterone (total or adjusted for sex-hormone-binding globulin) is helpful to show hyperandrogenemia and to rule out an androgen-secreting tumor<sup>15</sup>. The serum progesterone may actually demonstrate the anovulation which is one of the major criterion. It is essential to exclude glucose intolerance with GTT using fasting and 2 hour post 75 gram value. It is not clear if insulin measurement is indicated, as the measurement is cumbersome and interpretation is difficult. GTT primed insulin levels can be used for calculating indices of insulin resistance such as the homeostasis model assessment [HOMA], AUCi, CIGMA or quantitative insulin sensitivity check index [QUICKI]) but for research purposes most investigators still use clamp technique<sup>(20,21)</sup>.

**Other investigations:** Assessment of lipid status (total and HDL cholesterol and triglyceride levels), liver functions, uric acid etc to quantitate metabolic risk. Laparoscopy of the pelvis, computed tomography and magnetic resonance imaging for fat content estimation, ovarian and adrenal anatomy are needed as research tools and under special clinical circumstances. Endometrial biopsy and hysteroscopy may be used to investigate unexplained vaginal bleeding.

## MANAGEMENT OF PCOS

Ideally the management should be aimed at addressing the basic defect of the whole metabolic constellation. Current management comprises treatment of the presenting symptoms, as well as any other abnormalities discovered on investigation.

**Lifestyle modification:** Several studies have shown that weight loss can lead to resumption of ovulation within weeks<sup>22,23</sup>. Clark and colleagues demonstrated that even a 5% reduction in body mass restores ovulation and fertility<sup>24,25</sup> and devised a program of exercise and sensible eating that has become a model across the world for treating PCOS. Rapid changes in body composition and fat mass can be shown during lifestyle change. High-protein diets seem to be as effective as high-carbohydrate diets, provided that fat and total calories are comparable). While lifestyle changes are difficult to maintain, women seeking pregnancy are highly motivated, making this a first-line intervention in overweight women with PCOS<sup>22,25</sup>. Longer-term changes in weight are more difficult to maintain. Lifestyle changes are a first-line intervention in women with PCOS who are overweight, have glucose intolerance and are hyperlipidemic.

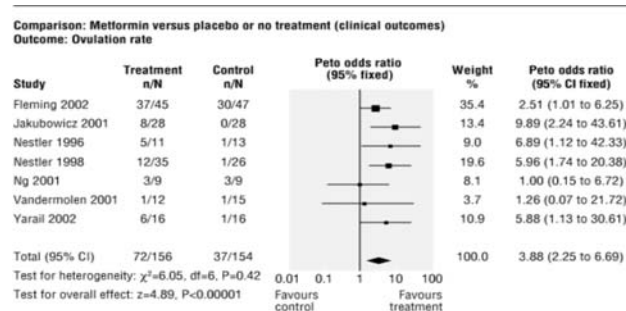
### Pharmacotherapy

This includes many agents which may be beneficial in addressing the individual components, however the most popular therapy nowadays is insulin sensitizers as this is supposed to break the root cause of syndrome, the insulin

resistance.

**Metformin:** Use of the insulin-sensitising drug metformin at doses of 500–2500 mg daily is controversial, but appears valuable in increasing menstrual cyclicity and pregnancy rate.<sup>26–29</sup> Recent systematic reviews suggest that the drug has efficacy for ovulation induction, either as a sole agent or in combination with clomiphene citrate<sup>28</sup>. It has been widely used for this purpose, and no specific neonatal complications have been described, despite it being classed as “category B” drug. There is inadequate evidence at present to suggest its use in pregnancy to prevent gestational diabetes or recurrent miscarriage, but there are some studies underway to address the issue (Fig 1).

**Fig 1. Metanalysis of studies investigating benefit of metformin in ovulation of induction in PCOS \***



Adopted from Lord J M (Ref 28)

The new insulin-sensitising agents, the “glitazones”- troglitazone (now discontinued), rosiglitazone and pioglitazone- have been shown to be very effective for ovulation induction. There is greater concern about the effects on the fetus of these drugs compared with metformin, and they should not be used by women trying to become pregnant<sup>29</sup>.

**Clomiphene citrate:** This is an oral oestrogen antagonist that raises circulating concentrations of FSH and induces follicular growth in most women with PCOS and anovulation. The initial regimen is 25–50 mg per day for 5 days. Therapy can be monitored by estrogen levels, follicular ultrasound examination and luteal progesterone level (> 20 nmol/L). Failure of response is associated with high body mass index and high androgen levels. Doses up to 200 mg per day can be used before failure of response is established. In the rare situation in which side effects limit treatment, tamoxifen can be used. Both treatments increase the risk of multiple pregnancies. Combination of clomiphene citrate and metformin has been used successfully in a subset for ovulation induction<sup>27</sup>.

**Gonadotrophin treatment:** Ovulation induction with gonadotrophins such as FSH has proved successful for at least three decades, but demands skill and experience to avoid multiple pregnancies and ovarian hyper stimulation syndrome. Patients start on low-dose recombinant FSH administered subcutaneously. Monitoring of ovarian response involves ultrasound examination, often with oestradiol measurement. Human chorionic gonadotrophin is given when one follicle

reaches 16–20 mm in size. Any more than two follicles of an appropriate size gives the risk of multiple pregnancies. Multiple gonadotrophin cycles may be required to achieve pregnancy, but this approach is preferable before more invasive procedures, such as in-vitro fertilization.

**In-vitro fertilization:** Provided there is no problem other than anovulation, this has little place in the management of infertility resulting from PCOS. Ovulation induction by a skilled reproductive endocrinologist is preferable to in-vitro fertilisation because of the risks of hyperstimulation and multiple pregnancy with the latter procedure.

### Surgical Treatment

Wedge resection of the ovaries has been abandoned because of concerns about pelvic adhesions, another cause of subfertility, and loss of valuable ovarian tissue. Ovarian diathermy or laser drilling has been used in recent years with apparently good results; a recent systematic review comparing drilling with clomiphene citrate and gonadotrophins proved equivalence in the studies examined. However, like wedge resection, this surgery may produce pelvic adhesions. Destructive surgery to the ovary should be used only after extensive discussion with the patient and not because the ovaries are found to be polycystic incidentally during routine laparoscopy.

**Reversing the basic defects in PCOS by metformin is currently considered to address the all components but some additional modalities are needed for the symptomatic treatment of the disturbing problems.** **Hirsutism** treatment classically has been by: the oral contraceptive pill (e.g., ethinylloestradiol 35 µg plus cyproterone acetate 2 mg daily for 21 of 28 days); cosmetic measures (e.g., laser electrolysis, bleaching, waxing or shaving); oral estrogen and cyproterone acetate (oestradiol valerate 2 mg daily and cyproterone acetate 50 mg for 14 days a month); spironolactone (75–200 mg daily); or other drugs, such as the antiandrogen flutamide or the antifungal agent ketoconazole. We found low dose spironolactone (50 mg /day) as better tolerated agent with excellent efficacy almost comparable to metformin by 6 months. These drugs either reduce androgen production or inhibit androgen-binding to the receptor. Response times for drugs can be from 3 -6 months. Obesity can be managed by drugs like sibutramin, orlistat or rimonabant. Menstrual dysfunction, including irregular periods, can be managed by administration of progestins (e.g., medroxyprogesterone acetate or norethisterone ) or the oral contraceptive pill. Endometrial hyperplasia should be assessed by ultrasound examination, endometrial biopsy or hysteroscopy, and can be treated by hormonal therapy, such as the oral contraceptive pill or progestins.

### LONG-TERM MANAGEMENT

Some investigators have suggested prophylactic use of metformin in young teenagers and older women to avoid the problems of the metabolic syndrome. This approach is

probably premature at present and may not be recommended. Advice about improved exercise and diet is more rational, given the abundant data on the role of lifestyle change in preventing and treating problems of glucose metabolism, hyperlipidemia, future fertility etc. Adult and young women with PCOS require ongoing surveillance to detect impaired glucose tolerance, hyperlipidemia, endometrial hyperplasia and consequent complications. Obese women, in particular, require regular (possibly annual) glucose tolerance testing because of the potential for rapid progression from normal to impaired glucose tolerance and diabetes. Thus key in reducing the mortality and morbidity because of many disorders stemming from this condition is to early recognition of the syndrome.

## REFERENCES

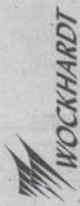
1. Lobo RA, Carmina E. The importance of diagnosing the polycystic ovary syndrome. *Ann Intern Med* 2000; 132: 989-993.
2. Knochenhauer ES, Key TJ, Kahsar-Miller M, et al. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab* 1998; 83: 3078-3082.
3. Diamanti-Kandaraki E, Kouli CR, Bergiele AT, et al. A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. *J Clin Endocrinol Metab* 1999; 84: 4006-4011.
4. Polson DW, Adams J, Wadsworth J, et al. Polycystic ovaries—a common finding in normal women. *Lancet* 1988; 1: 870-872.
5. Dunaif A, Segal KR, Futterweit W, et al. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 1989; 38: 1165-1174.
6. Stankiewicz M, Norman R. Diagnosis and management of polycystic ovary syndrome: a practical guide. *Drugs*. 2006;66:903-912.
7. Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine F, editors. *Polycystic ovary syndrome*. Boston: Blackwell, 1992: 377-384.
8. The Rotterdam ESHRE/ASRM sponsored PCOS Consensus WORKSHOP GROUP 2004. Revised 2003 consensus on diagnostic criteria and long term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;19: 41-47.
9. Azziz R, Carmina E, Dewailly D, Diamanti-Kandaraki E et al. Position statement: Criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: An Androgen Excess Society Guideline. *J Clin Endocrinol Metab* 2006;91:4237-4245.
10. Farquhar CM, Birdsall M, Manning P, et al. The prevalence of polycystic ovaries on ultrasound scanning in a population of randomly selected women. *Aust N Z J Obstet Gynaecol* 1994; 34: 67-72.
11. Adams J, Polson DW, Franks S. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. *Br Med J (Clin Res Ed)* 1986; 293: 355-359.
12. Ibanez L, Potau N, Ferrer A, et al. Anovulation in eumenorrheic, nonobese adolescent girls born small for gestational age: insulin sensitization induces ovulation, increases lean body mass, and reduces abdominal fat excess, dyslipidemia, and subclinical hyperandrogenism. *J Clin Endocrinol Metab* 2002; 87: 5702-5705.
13. Hardiman P, Pillay OS, Atiomo W. Polycystic ovary syndrome and endometrial carcinoma. *Lancet* 2003; 361: 1810-1812.
14. Ganje MA, Khurana M L, Eunice M, Gupta N, Dwivedi S N, Gulati M, and Ammini A.C. Prevalence of Glucose intolerance among adolescent and young women with polycystic ovary syndrome in India. *Indian J Endocrinol Metab* VI (1) 9-14:2004.
15. Ganje MA, Khurana M L, Eunice M, Gulati M, Dwivedi S N, Gupta N and Ammini A.C. Comparison of efficacy of metformin with spironolactone in the management of polycystic ovary syndrome: An open labeled study. *J Clin Endocrinol Metab* 89:2756-2762, 2004.
16. Norman RJ, Masters L, Milner CR, et al. Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. *Hum Reprod* 2001; 16: 1995-1998.
17. Wild S, Pierpoint T, McKeigue P, et al. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. *Clin Endocrinol (Oxf)* 2000; 52: 595-600.
18. Talbot EO, Guzick DS, Sutton-Tyrrell K, et al. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. *Arterioscler Thromb Vasc Biol* 2000; 20: 2414-2421.
19. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab* 1961; 21: 1440-1447.
20. Abassi F, Reaver GM. Evaluation of the quantitative insulin sensitivity index as an estimate of insulin sensitivity in humans. *Metabolism* 2002; 51: 235-237.
21. Legro RS, Finegood D, Dunaif A. A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 1998; 83: 2694-2698.
22. Pasquali R, Antenucci D, Casimirri F, et al. Clinical and hormonal characteristics of obese amenorrheic hyperandrogenic women before and after weight loss. *J Clin Endocrinol Metab* 1989; 68: 173-179.
23. Clark A M, Ledger W, Galletly C, et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum Reprod* 1995; 10: 2705-2712.
24. Clark A M, Thornley B, Tomlinson L, et al. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod* 1998; 13: 1502-1505.
25. Moran LJ, Noakes M, Clifton PM, et al. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003; 88: 812-819.
26. Norman RJ, Kidson WJ, Cuneo RC, et al. Metformin and intervention in polycystic ovary syndrome. *Endocrine Society of Australia, the Australian Diabetes Society and the Australian Paediatric Endocrine Group. Med J Aust* 2001; 174: 580-583.
27. Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. *Cochrane Database Syst Rev* 2003; (3): CD003053.
28. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ* 2003; 327: 951.

## LITERATURE REVIEW

### IMPACT OF OBESITY AS A MORTALITY PREDICTOR IN HIGH-RISK PATIENTS WITH MYOCARDIAL INFARCTION OR CHRONIC HEART FAILURE: A POOLED ANALYSIS OF FIVE REGISTRIES

Jawdat Abdulla, Lars Køber, Steen Z. Abildstrøm, et.al *European Heart Journal* 2008; 29: 594-601.

The objective of the study was to explore the influence of obesity on prognosis in high-risk patients with myocardial infarction (MI) or heart failure (HF). Individual data of 21 570 consecutively hospitalized patients from five Danish registries were pooled together. After a follow-up of 10.4 years, all-cause mortality using multivariate model and adjusted hazard ratios (HR) with 95% confidence intervals were calculated. Compared with normal weight [body mass index (BMI) 18.5–24.9 kg/m<sup>2</sup>], obesity class II (BMI ≥35 kg/m<sup>2</sup>) was associated with increased risk of death in patients with MI but not HF [HR = 1.23 (1.06–1.44), *P* = 0.006 and HR = 1.13 (0.95–1.36), *P* = 0.95] (*P*-value for interaction = 0.004). Obesity class I (BMI 30–34.9 kg/m<sup>2</sup>) was not associated with increased risk of death in MI or HF [HR = 0.99 (0.92–1.08) and 1.00 (0.90–1.11), *P* > 0.1]. Pre-obesity (BMI 25–29.9 kg/m<sup>2</sup>) was associated with decreased death risk in MI but not HF [HR = 0.91 (0.87–0.96), *P* = 0.0006 and 1.04 (0.97–1.12), *P* = 0.34] (*P*-value for interaction = 0.007). Underweight (BMI < 18.5 kg/m<sup>2</sup>) patients were in increased death risk regardless of MI or HF [HR = 1.54 (1.35–1.75) and 1.37 (1.18–1.59), *P* < 0.001]. In patients with MI but not HF, the relationship between BMI and mortality is U-shaped with highest mortality in underweight and obese class II, but lowest in the other BMI classes.



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## APPROACH TO A CASE OF CHILDHOOD OBESITY

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**Abstract:** Prevalence of obesity is rapidly increasing in children and adolescents all over the world, mainly due to life style factors. This is particularly crucial in South East Asia, as population here tends to have a higher percentage of body fat, greater tendency for hyperinsulinemia for same weight, abdominal obesity and complications related to it. An obese child is twice as likely to become an obese adolescent, who in turn is 6-7 times more likely to become an obese adult. Childhood obesity is defined in as more than 20% of ideal body weight, while in adolescents adult criteria are applicable. Over 98% of obese children presenting to a pediatrician are likely to have exogenous or simple obesity i.e. caused by imbalance of energy intake and expenditure, which are easily managed and future obesity is prevented by promoting healthy life style. Less than 2% of children will have a pathological or endogenous basis for the weight gain, the most frequent being endocrinal cause. An easy way to differentiate between pathological or endogenous obesity from exogenous obesity is the height of the child which tends to be short in case of pathological obesity. Clinicians need to develop awareness and treat childhood obesity in time to prevent future epidemic of obesity in adults. These patients can be managed by simple application of dietary measures, exercise, behavioral modification techniques and social support. Drug therapy and surgery are infrequently advised in childhood. Prevention of weight gain is of utmost importance as timely input from clinician can help prevent much morbidity and unhappiness.

### INTRODUCTION

Obesity is rapidly increasing in prevalence in childhood and adolescence in almost all parts of the world, mainly due to lifestyle factors. It is gaining more medical attention, because obesity and its consequent hypertension<sup>1</sup>, dyslipidemia, diabetes, polycystic ovarian syndrome (PCOS) and sleep apnea frequently persist into adulthood. The obese child is twice as likely to become an obese adolescent<sup>2</sup>, who in turn is 6-7 times as likely to become an obese adult. Obesity can impair mobility, interfere with daily living activities, reduce academic performance and self esteem. It also increases the risk in later life of osteoarthritis, coronary heart disease, gall bladder disease, gout, certain malignancies, and possible worsening of asthma and renal disease. Therefore the pediatrician must be alert not only to current but also future morbidity in the obese child. Because recurrence of weight gain is so common, the pediatrician needs to try strenuously to prevent obesity by identifying children at risk (small for dates, obese parent/s, urban, single or older parent families, poor lifestyle, predisposing condition e.g. steroid therapy, etc) and advocating a healthy lifestyle in them. This is especially crucial for us in South Asia, as we tend to have a higher percentage of body fat and greater tendency for hyperinsulinemia for the same weight, with more adverse body fat patterning including abdominal adiposity<sup>3</sup>. Children with low birth weight are most at risk for diabetes if they become obese later in life<sup>4</sup>. Fat children also tend to be teased and/ or dismissed as clumsy, lazy, stupid, or worthless. Fortunately, even a modest weight loss of 10-20% results in significant metabolic improvement.

### CLINICAL PRESENTATION

Ideally each child should have height and weight monitored regularly and the pediatrician should alert parents if the weight starts crossing percentile lines upwards. Parents may bring the child if they (or the school) are concerned about rapid weight gain, awkward appearance, lethargy and drop in school

performance, breathlessness on exertion, snoring or poor sleep, darkening of skin folds (acanthosis nigricans: AN), "small genital size" or prominent breasts (in boys) or "early breast development" (in girls), intertriginous infections or slipped capital femoral epiphyses.

### DEFINING OBESITY

Usually just a look at the child is enough to diagnose obesity! However, careful auxology is needed to decide how to proceed further. The child's height, weight, abdominal and hip circumferences are measured, and the weight-for-height, waist-hip ratio (WHR), and BMI [weight in kg/ (height in m)<sup>2</sup>] calculated<sup>5</sup>. If facilities are available, body fat and skinfold thickness can be measured<sup>6</sup>. Mid-parental height (MPH) is calculated and plotted on the growth curve. The child is overweight if she is up to 20% more than ideal body weight (IBW), and obese if > 20% above IBW. The Center for Disease Control (CDC) 2000 charts can be downloaded, and have age wise values and percentiles for BMI. In older adolescents, adult definitions apply: overweight if BMI > 25 kg/m<sup>2</sup>, obesity if BMI > 27 kg/m<sup>2</sup>, morbid obesity if BMI > 40, and super-obesity if BMI > 60. Care must be taken not to over-rely on simple weight measurements or BMI, as they do not distinguish muscle mass from fat mass. In case of doubt, actual measurement of fat mass using the impedance method may be needed. CT, MRI, ultrasound and DXA do quantitate fat tissue accurately, but are too cumbersome and expensive for routine clinical practice. WHR, an independent predictor of insulin resistance, is useful for follow-up.

### CAUSES

Body weight is controlled by the balance of energy intake and expenditure, which respond to several inter-linked signals from the gastrointestinal, endocrine, and nervous systems. The rapidly increasing incidence of obesity points to environmental causation. Several factors contribute. For example, TV watching correlates with weight gain, by promoting both inactivity and increased calorie intake (directly, and indirectly through advertisements of food products). Predominant breast feeding for the first 6 months of life and high levels of physical

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activity reduce obesity<sup>7</sup>. Even a small sustained excess in energy intake leads to significant weight gain, e.g. a single order of French fries (450 calories) daily would result in a weight gain of 1.5 kg per month! The fetus exposed to overnutrition in utero (e.g. the infant of the diabetic mother) and born large for date is predisposed to obesity later, while babies born small for date have the highest risk of obesity and metabolic syndrome if they become obese<sup>4</sup>. Over 98% of obese children presenting to a pediatrician are likely to have exogenous or "simple" obesity, i.e. that caused by an imbalance of energy intake and expenditure. The exact mechanisms are unclear, but both genetic influences (shown by several studies on adopted children and twins) and environmental factors (differences in food choices, levels of physical activity, attitudes to food, activity, body image, etc) are equally important. Therefore obesity runs in families, who share both genes and environment, and parental obesity is a strong risk factor. Health care personnel, by encouraging a healthy lifestyle, especially in those at high risk, can reduce the incidence and extent of obesity and its comorbidities.

Less than 2% children will have a pathologic basis for the weight gain, the most frequent being hypothyroidism and Cushing syndrome. Rare single gene disorders result in obesity and dysmorphia: Prader-Willi (15q11-q12), Lawrence Moon Beidl (16q21, 15q22-q23), Carpenter (unknown), Cohen (8q22-q23), Beckwith Weidmann (11p15.5), Alstrom (2p14-p13), nesidioblastosis (11p15.1), pseudohypoparathyroidism type IA (20q13.2), leptin deficiency (7p31.1) and leptin receptor abnormalities (1p31-p32). Other disorders include growth hormone deficiency (GHD), hypothalamic disorders (some syndromes mentioned, tumors like craniopharyngioma, infections; trauma), and actual hypogonadism (e.g. Turner or Klinefelter syndrome).

## ENDOCRINE CHANGES IN OBESITY

While endocrine causes of obesity are rare, it has several endocrine consequences. These include higher levels of growth hormone, with faster height gain; somewhat raised basal cortisol (which is easily suppressible); lower serum levels of T3 and T4 with normal levels of TSH; early onset of puberty or pubarche, especially in girls, and PCOS; and hyperinsulinemia with increasing incidence of type 2 diabetes (T2DM), more so in those with positive family history. The incidence of T2DM peaks around puberty, which is known to be an insulin resistant state. T2DM is particularly worrying because the chronic complications are the same as in adults, but appear earlier with pediatric onset<sup>8</sup>, this increasing societal disease burden many-fold.

## CLINICAL EVALUATION

The most important clinical feature which distinguishes pathological or endogenous from exogenous obesity is the height. Children with pathological states are short, while those with endogenous obesity tend to be taller than expected for age and genetic background. See what percentile the child's height falls on, vis-à-vis age and MPH: if the child is tall, the problem is likely to be exogenous. If the child is inappropriately short, pathological causes should be looked for.

History should include details of diet (including total fat intake in cooking, fat content in milk, frequency of snacks and of

eating out), activity patterns and duration of TV viewing, mental development and school performance. As mentioned above, examination includes accurate auxology (including parents' heights and weights), BP, fat distribution, skin changes (striae, acanthosis nigricans, hirsutism), dysmorphic features, pubertal staging, fundus exam and mental assessment. In boys, measure stretched penile length (SPL), since the penis is usually buried in abdominal fat. Psychologic assessment, including assessing self esteem, and attitude towards food, exercise, and relationships, of the child and significant family members, is important.

The hypothyroid child is always significantly short (with delayed bone age). Cushing syndrome is characterized by short height, moderate obesity (truncal in adults and older children, generalized in infants), severe hypertension, red striae, and occasional glucose intolerance. In contrast, exogenous obesity is characterized by tall stature, mild hypertension, acanthosis, and white striae (occasionally, with rapid weight gain, striae may be reddish initially). Micropenis may be seen in panhypopituitarism and some syndromes. Far commoner is the buried penis of exogenous obesity: parents are concerned about "small" genitalia, but the actual SPL is normal. In hypothalamic syndromes, obesity is variable, ranging from very marked and difficult to control, to mild; other clinical features would help with the diagnosis. In craniopharyngioma, obesity is multifactorial, and tends to worsen after surgery.

## INVESTIGATIONS

Investigations are guided by the clinical presentation, but the initial assessment could include bone age, serum T4, TSH, lipids, blood glucose and insulin (fasting and post-glucose). Children with exogenous obesity may have frank type 2 diabetes, impaired glucose tolerance, or just hyperinsulinemia with normal blood glucose levels. The levels of serum cortisol and urinary metabolites of cortisol may be somewhat raised, but are easily suppressible; urinary free cortisol levels are normal. Several authorities recommend the overnight dexamethasone suppression test straightaway rather than a basal serum cortisol: 1 mg dexamethasone is given orally at 11pm, cortisol is tested the next morning at 8 am. In hypopituitarism, low T4 would accompany normal/ low TSH; GH would not cross 10 ng/ ml on a stimulation test; gonadotrophins would be inappropriately low for age (e.g. low levels at age 8 are normal, but at age 16 are not). Androgen levels, karyotyping, or imaging studies (e.g. of the pituitary) will depend on the clinical picture.

## MANAGEMENT

Management of obesity depends on age, severity, underlying cause and level of motivation. In infants less than 2 years of age, urgent thyroid evaluation is needed, because of the devastating mental retardation which occurs if replacement is delayed. Severe calorie restriction at this age is avoided even in syndromal obesity, because of the risk of treatment-associated brain growth and reduced height gain. In pathologic obesity, e.g. due to Cushing/ hypothyroidism/ GHD, appropriate management/ replacement is needed.

Before planning control of exogenous obesity, the level of motivation of the family should be assessed. There is no quick

remedy, the only way to keep off excess weight being lifelong control of diet with exercise. If the family is not concerned, therapy is likely to be unsuccessful, and may impair the child's self-esteem and the success of future attempts at weight loss. In this situation, the gravity should be explained, and advice deferred to a later visit. On the other hand, clinicians should not ignore obesity altogether, because even modest weight loss, which is attainable, is enough to significantly improve the metabolic profile. Therefore the aim of therapy should be achieving and *maintaining* a 5-20% weight loss. Trying for ideal body weight is usually unrealistic, and therefore frustrating. Even small, long term changes may have greater health benefits rather than a drastic weight loss followed by regaining the weight. Rapid weight loss is necessary only if there is a life-threatening situation like extreme obesity, severe sleep apnea, or other severe cardiopulmonary manifestations, as in the Pickwickian syndrome.

Management consists of dietary measures and exercise, supported by behavioral modification techniques. Close supervision and family involvement are very important for success. Drug therapy and surgery are infrequently advised in childhood. However, once established, obesity management is very frustrating, as weight gain recurs rapidly. The challenge for pediatricians is to prevent obesity and reduce the health impact in those who are already obese.

### DIET THERAPY

Diet changes are critical, but drastic changes and a punitive attitude must be avoided. A balanced, healthy diet for the entire family is recommended (fat intake ~20-25% of total calories, protein 15%, remaining as carbohydrates, mostly complex carbohydrates, adequate fiber and micro-nutrients, and plenty of liquids). In most children, weight loss begins with just reduction of calorie-dense foods: chips, other fried foods, rich desserts, full fat milk and its products, and sweetened drinks. In their place the child is encouraged to take foods with low glycemic index (fruits, salads, whole wheat products, unsalted popcorn, roast gram or corn, whole daals etc.), low fat milk products and water<sup>9</sup>. The child should not remain hungry. Even in severe obesity, calorie restriction should be moderate. Very low calorie diets (400-800 calories per day) give rapid weight loss, with improvements in BP, blood glucose, insulin, leptin, and lipids, but losses are regained; long term losses are similar to those with low calorie diets. Moreover, they can be dangerous if not closely supervised, prolonged beyond 2-6 weeks, or not supplemented with adequate minerals and vitamins, and can also result in eating disorders, sagging breasts, and cholelithiasis. Unbalanced diets (very low fat/ very low carbohydrate, etc.) can cause cardiac arrhythmias, severe electrolyte disturbances, or other morbidities. Stringent dieting, a favorite technique of adolescents, must therefore be strongly discouraged, as it can slow height gain and pubertal development, cause weight loss plateau (due to slower metabolic rate), osteopenia, weakness, dizziness, poor academic performance, irritability, depression, and other behavioral problems.

### EXERCISE

All forms of physical activity increase energy expenditure (during and after the exercise), muscle mass, and insulin

sensitivity<sup>10</sup>. Regular exercise also helps regulate increased appetite. Though the quantum of loss with exercise is modest, it is essential for prevention of obesity, healthy weight loss, and maintenance of the loss. However, it cannot compensate for high calorie intakes, so it must accompany a careful diet. Exercise should be both aerobic and anaerobic. Compliance is better if activity is enjoyable and fun: walking with friends, swimming, dancing, sports. Initially low impact, moderate-intensity exercise (e.g. walking 30 min 4-5 days/ week) is started to avoid injuries. For those easily tired, even this can be broken up into multiple short bouts. As fitness improves, time and intensity are built up to 50-60 min 5-7 days/ week for long-term loss and maintenance. Gymnasiums and supervised programs may be useful for adolescents as they encounter other obese persons and see that weight loss is possible. Formal exercise should be supplemented with increased activity (e.g. stairs instead of lifts, walking for errands, etc.).

Clinicians must push strongly for facilities for increased activity in schools and the community.

### BEHAVIOR MODIFICATION AND SOCIAL SUPPORT

These are very important in all attempts to lose weight and sustain the loss, as long term changes in eating and activity patterns are necessary. Attempts are most successful if the entire family is convinced of the need for weight loss, and keen to participate whole-heartedly. To assess behavior patterns which need to change and track progress in changing them requires monitoring, usually by self report. Thus, the child and/ or parent maintain a food, activity and TV viewing diary daily for the first 6 months, one week per month later. A simple log can be downloaded from the website of the American Heart Association

[http://www.deliciousdecisions.org/ff/eee\\_habits\\_eat.html](http://www.deliciousdecisions.org/ff/eee_habits_eat.html). This helps track progress and identify problem areas. The second component is to avoid environmental cues which can trigger hunger, so parents are advised to keep undesirable foods out of the home, and reduce the frequency of eating out. The third component is reinforcement for better behaviors. Thus small low or zero calorie rewards (eg a hug/ praise/ sticker/ fancy pen/ red points...) and other motivational techniques ensure better compliance for a longer time. TV viewing and excessive tuitions should be discouraged in favor of healthier options like play. Occasional high calorie treats are a must to prevent frustration, which can lead to stealing food/ money and other dysfunctional behavior patterns. Group therapy, conducted by co-therapists (psychologist/ nutritionist/ exercise physiologist) with weekly treatment meetings over a 6 month period, and less intensive follow up contact, have been found to be successful. Recently, televised or internet based therapy has also been tried.

### MEDICATION

Pharmacotherapy is not recommended for use in children, though several anorectic agents (amphetamines, other appetite suppressants, antidepressants) are available. Insulin sensitizers (primarily metformin, also glitazones) have been shown to safely and effectively achieve weight loss, decrease body fat,

plasma leptin, insulin and lipids, in obese diabetic and non-diabetic adolescents, especially those with PCOS. The only two drugs approved for obesity in adults in Europe and the US are sibutramine and orlistat. Sibutramine, a selective serotonin and noradrenaline re-uptake inhibitor which suppresses appetite, can reduce weight by 5-15%<sup>11</sup>. Orlistat, an inhibitor of gastrointestinal lipases, decreases fat absorption by 30%, and causes significant weight loss, with improved lipid and glycemic profile. It may lead to flatulence, frequent stools, and deficiency of fat soluble vitamins like A and D<sup>12</sup>. Rimonabant is contraindicated below age 18 years, and can cause depression.

## SURGERY

Surgery is contraindicated in patients less than 18 years of age. Very rarely, e.g. in extreme obesity with severe sleep apnea or other complications, not responding to non-surgical treatment, gastroplasty may be considered<sup>13</sup>.

## MAINTAINING WEIGHT LOSS

A questionnaire based study of persons who lost and maintained significant loss found that the common features were consumption of a diet low in calories (1380/day) fat and low in fat (24% calories from fat); and daily consumption of breakfast. Less than 1% had low carbohydrate diets.<sup>14</sup> Continued self-monitoring of food intake and regular exercise of up to an hour daily were very strong predictors of weight maintenance. Decreased screen time (TV, computer, video games) has been shown to contribute significantly.

## PREVENTION

Given the difficulty in achieving and maintaining weight loss, all attempts should be made to prevent obesity (Table). Pediatricians must educate parents and significant others from the beginning to adopt healthy attitudes. Several schools serve/sell food which promotes obesity, and pay little attention to physical activity. Clinicians must also work with school authorities to alter these malpractices, at the same time identifying and paying attention to high risk children (obesity/diabetes/hypertension/dyslipidemia in parent(s)/sibling(s), maternal age over 35 years at birth, single child, single parent, rapid weight gain). All children should have growth charted through childhood, and rapid weight gain picked up early. Children with rapid weight gain and their parents should be helped make lifestyle changes. This is one area where a clinician's timely inputs can help prevent much morbidity and unhappiness.

### STRATEGIES FOR PREVENTION OF OBESITY

1. Physicians should recommend a healthy lifestyle rather than

thinness.

2. Physicians should encourage families to adopt sensible eating habits:
  - a. Avoid force feeding
  - b. Do not keep calorie dense foods and sweetened drinks at home
  - c. Do not use food as reward or punishment
  - d. Express affection and approval through ways other than food
  - e. Keep fat intake moderate
  - f. Encourage intake of unprocessed foods: fruits, salads, sprouts, etc.
3. Physicians and families should encourage physical activity, and minimize TV/ computer time.
4. Clinicians should identify high risk families and situations and emphasize prevention for the beginning.
5. Clinicians and families should emphasize that children need support not criticism, and that obesity is not only due to greed and sloth.
6. Clinicians and families must aim for gradual, permanent changes rather than drastic changes which are not sustainable.
7. Schools should influence attitudes by
  - a. Serving/ selling healthy food choices
  - b. Not allowing sweetened drinks and fried foods on campus
  - c. Increase time for physical activity
  - d. Allow premises to be used for sports after school hours
  - e. Identify high risk children and support weight loss attempts by them.
8. The community encourages physical activity, e.g. lobby for sports to be allowed in open spaces like parks (a major problem in cities).

## REFERENCES

1. Field A, Cook N, Gillman M. Weight status in childhood as a predictor of becoming overweight or hypertensive in early adulthood. *Obes Res* 2005;13:163-69.
2. Nader PR, O'Brien M, Houts R, Bradley R, Belsky J, Crosnoe R, Friedman S, Mei Z, Susman EJ. Identifying risk for obesity in early childhood. *Pediatrics* 2006 Sep; 118(3): e594-601.
3. Misra A, Vikram NK. Insulin resistance syndrome (metabolic syndrome) and obesity in Asian Indians: evidence and implications. *Nutrition*. 2004 May;20(5):482-91.
4. Bhargava SK, Sachdev HS, Fall CH, et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. *N Engl J Med* 2004 Feb; 350: 865-875.
5. Reilly JJ, Dorosty AR, Emmett PM. Identification of the obese child: adequacy of the body mass index for clinical practice and epidemiology. *2000 Int J Obes*;24:1623-27.
6. Must A, Dallal G, Dietz W. Reference data for obesity: 85th and 95th percentiles of body mass index (wt/ht<sup>2</sup>) and triceps skinfold thickness. *Am J Clin Nutr*;199153:839-46.
7. Krespo C, Smit E, Troiano R, Bartlett S, Macera C, Andersen R. Television watching, energy intake, and obesity in US children: results from the third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med*;2001 155:360-65.
8. Pinhal-Hamiel O, Zeitler P. Acute and chronic complications of type 2 diabetes mellitus in children and adolescents. *Lancet*;2007 368:1823-31.
9. Epstein L, Gordy C, Raynor H, Bedomme M, Kilanowski C, Paluch R. Increasing fruit and vegetable intake and decreasing fat and sugar intake in families at risk for childhood obesity. *Obes Res*;2001 9:171-78.
10. Jakicic JM. Exercise in the treatment of obesity. *Endocrinol Metab Clin North Am*. 2003 32(4):967-80.
11. Nisoli E, Carruba MO. Drug Saf. A benefit-risk assessment of sibutramine in the management of obesity. *2003;26(14):1027-48.*
12. O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G. A systematic review of the clinical effectiveness of orlistat used for the management of obesity. *Obes Rev* 2004 Feb;5(1):51-68.
13. *J Pediatr Surg*. Bariatric surgery in adolescence. Abu-Abeid S, Gavert N, Klausner JM, Szold A. 2003 Sep;38(9):1379-82.
14. Klem M, Wing R, McGuire M, Seagle H, Hill J. A descriptive study of individuals successful at long term maintenance of substantial weight loss. *Am J Clin Nutr*; 1998 66:239-46.

### ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

The need for uniform ethical guidelines for research on human subjects is universally recognised. It has acquired a new sense of urgency as the critical issues in the area of biogenetic research involving human subjects have become acute. Apart from the mandatory clinical trials on new drugs, a number of diagnostic procedures, therapeutic interventions and prevention measures including the use of vaccines, are being introduced which involve human subjects. Further the advent of new medical devices and radio-active materials and therapeutic benefits of recombinant DNA products have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

Any research using the human beings as subjects shall bear in

mind the following principles of : i) essentiality, (ii) voluntariness, informed consent, (iii) non exploitation, (iv) privacy and confidentially, (v) precaution and risk minimisation, (vi) professional competence, (vii) accountability & transparency, (viii) maximisation of public interest and distributive justice (ix) institutional arrangements (x) public domain (xi) totality of responsibility and (xii) compliance.

Recent advances in the field of Assisted Reproductive technologies, organ transplantation, Human genome analysis, and gene therapy promise unquestionable benefits to mankind. At the same time, they raise many questions of law and ethics, stimulating public interest and concern.

(Source : ICMR Publication 2000)

## OBESITY IN ELDERLY – IS IT HARMFUL?

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**Abstract:** Obesity has become a worldwide health problem even in elderly population. In India its prevalence is reported as 20.9% to 39.8% in this group of population. Changes in body composition occur during the ageing process. There is wasting of fat free mass, which is replaced by the fatty tissue. High prevalence of cardiovascular risk factors in this age group like hypertension and diabetes mellitus also play an important role in obesity. The physiological modifications of physical and motor skills that accompany the advancing age leads to restriction of physical activities. Limited physical activity, chronic inflammation and endocrine changes that occur with ageing contribute to obesity. Regular aerobic exercises along with caloric restriction remains the most successful method of weight reduction. Drug therapy should be individualized and must take into account of the other drugs that patient may be taking, to avoid any adverse drug interaction. Surgical treatment like bariatric surgery is hardly ever tried in this group because of the associated surgical risks. A clinical psychologist or a psychiatrist may also be involved to care for the emotional aspects of these patients.

### EPIDEMIOLOGY

Obesity has now become a world-wide health problem at all ages of the human lifespan. Obesity once considered a health problem of the West has also encroached upon the developing countries of the world.<sup>1</sup> India is also observing a gradual phenomenon of graying of her population. Elderly subjects comprise 6.7% of the Indian population. Elderly individuals particularly in high and middle income groups are vulnerable to over nutrition and obesity. A community based study conducted amongst elderly subjects in urban slums of Delhi reported a lower prevalence of overweight and obesity.<sup>2</sup> In an another study conducted in Chandigarh overweight was present in 60% of the elderly subjects whose daily caloric intake was more than 2000 Kcals.<sup>3</sup> In this study obesity and overweight were noticed to be maximum (39.8%) in 65 to 74 age group and comes down to nearly half (20.9%) as age increase beyond 85 years<sup>3</sup>. The prevalence of overweight and obesity was found to be higher (42.1%) in females as compared to the males (20.9%)

In children and adults, obesity is easily defined as an excess of body weight and adipose tissue, but there is no consensus on the definitions for obesity among the elderly for any race or ethnic group nor are there genetic determinants of these definitions. The World Health Organization has laid down values of BMI for the classification of overweight and obesity, as well as “at risk” values for waist circumference and waist-to-hip ratio., whether these values are appropriate targets for the elderly population are yet to be validated. Methods of assessing obesity among the elderly need to be reviewed so as to improve our understanding of the changes occurring at this stage of life and their relationships with concurrent metabolic changes and subsequent health problems.

Changes in body composition occur during the aging process. Obesity is accompanied by an increase in fat-free mass, but in the elderly, the wasting of fat-free mass can produce obesity characterized by a stable or low body weight but a high percentage of body fat.

The prevalence of this sarcopenic-obesity increases with age in each sex. Cross-sectional as well as longitudinal studies indicate that subjects classified as sarcopenic-obese show

significantly higher prevalence of physical impairment and disability, as well as higher prevalence of metabolic syndrome.

### PATHO-PHYSIOLOGY

Fat redistribution, absolute or relative sarcopenia, limited physical activity and fitness, chronic inflammation and endocrine changes that occur with aging are the factors that contributes to obesity.<sup>7,8</sup> These factors may be important in determining the onset, duration and consequences of obesity. The physiological modifications of physical and motor skills that inevitably accompany advancing age are even more emphasized by sedentary life style, which are cause and or effect of increased fat in the elderly individuals. The lack of sufficient exercise leads to loss of muscle tone and loss of mineral contents of the bone and as a result predisposes these individuals to fractures and immobilization. The mobility of the lower limbs is extremely reduced due to degenerative changes in knee and other joints of lower limbs.

Obese elderly patients often have impaired respiratory functions that involve the whole respiratory parameters. Incidence of sleep apnoea syndrome increases in elderly obese individuals that leads to hypoxia during sleep and leads to hallucinatory and cognitive disorders.

There is high prevalence of cardiovascular risk factors like high blood pressure and diabetes in these individuals. Prevalence of Type -2 Diabetes rises sharply among the elderly population which may be the end result of the interplay of genetic and environmental factors<sup>5</sup>. The most important environmental factor is the physical inactivity and obesity<sup>6</sup>. Current hypothesis suggest that type -2 diabetes is an inflammatory disease and the inflammation is the primary cause of obesity –linked insulin resistance and hyperglycemia. Obesity in insulin resistance individuals is associated with low grade chronic systemic inflammation as revealed by increased level of CRP,IL-6 and TNF. In addition to this, these people have low HDL and high fasting plasma sugars, which may be related to a high level of visceral fat accumulation during the aging process. This metabolic syndrome is associated with increased risk of cardiovascular disease independently of the traditional cardiovascular risk factors.

A large number of studies points that obesity in middle age increases the risk of future dementia independently of comorbid conditions. There is also a close association obesity

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and depression. Obese women negative emotional state seems to predict poor treatment outcome. Overweight and obese subjects have greater decrease in sexual desire as compared to normal weight subjects.

## MANGEMENT

There is overall deterioration in quality of life in elderly obese subjects, hence this subject needs to be seriously addressed by the health care providers. Weight maintenance along with leading a healthy life style in terms of diet and physical activity are the key component of preventive aspect. Measures to reduce weight should take into account the other obesity related co-morbid conditions. Sudden change in lifestyle may not be achievable so easily because of financial, social and other health constraints.

Medical nutritional therapy must take into account dietary habits, economic factors and patient preferences. Each elderly individual has unique need ,so diet should be prepared accordingly. A special care should be taken to provide enough fluids, fiber , calcium, iron , folic acid and vitamins A,D,B12 and C without adding extra calories. Initially aim should be for modest weight reduction and once a person is compliant more stricter goals can be given.

Exercise along with caloric restriction is by far the most successful method of weight reduction. Aerobic exercise and progressive resistance and endurance program not only will help in decreasing body weight but will also improve the functional ability of a person. The purpose of physical activity programmes should be aimed at improving the quality of life and functional capabilities.

Drug therapy for obesity may be useful in elderly, but while prescribing these drugs one must take into account the other drugs the patient may be taking to avoid any kind of adverse

drug interactions. Though literature is quite scarce in this field but bariatric surgery may prove useful in cases of morbid obesity which is not being controlled by other conventional methods. Along with weight reduction attention may also be given toward psychophysical health of the elderly people. It is necessary to give emotional support to the intense request for care, to the feeling of inadequacy, to the constant catastrophic thoughts that lead to anxiety and depression. Hence help of a psychologist or a psychiatrist may be required to deal with this problem.

As we are observing a world wide phenomenon of obesity even among our elderly population and obesity in elderly affects adversely their quality of life, hence this issue must be addressed adequately by the health care providers

## REFERENCES

1. **Flegal KM et al** Overweight and obesity in united states prevalence and trends,1960-94. *International Journal of Obesity*, 1998;22:39- 47.
2. **Obesity: prevention and managing the global epidemic.** WHO. TRS, 2000;894:20.
3. **Singh P,Kapil U,Dey AB.** Prevalence of overweight and obesity amongst elderly patients attending a geriatric clinic ina tertiary care hospital in Delhi.,India.*Indian J Med Sci*2004;58:162-3.
4. **Gopalan HS.**Nutritional status of the elderly in urban slums of Delhi.*NFI Bulletin* 2004;25:7.
5. **HM Swami,V Bhatia,AKGupta, SPS Bhatia:** An epidemiological study of obesity among elderly in Chandigarh.Vol.30.No.1(2005-03)
6. **Colditz: GA et al.** Weight as a risk factor for clinical diabetes in women. *American J of Epidemiology*, 1990;132:501-513.
7. **Lean MEJ et al.** Obesity, weight loss and prognosis in type 2 diabetes. *Diabetic Medicine*, 1990;7:228-233.
8. **Hodge AM; Dowse GK, Gareboo-H.** Incidence, increase of prevalence and prevalence and predictors of change in obesity and fat distribution over 5 years in rapidly developing population of mauritus. *International journal of obesity related metabolic disorders*, 1996 Feb: 20 (2):137-46.
9. **Yamashita S et al.** Insulin resistance and body fat distribution: Contribution of visceral fat accumulation to the development of insulin resistance and atherosclerosis diabetes care, 1996;19:287.

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## MEDICAL MANAGEMENT OF OBESITY

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**Abstract:** Medical management includes lifestyle modifications and pharmacotherapy. Methods of lifestyle modification alone, as a treatment for obesity are widely regarded as ineffective. Anti-obesity pharmacotherapy is an important adjunct to these measures. The ideal anti-obesity drug should cause significant reduction in body weight; it should have a favorable benefit-risk ratio; and it should be affordable. The accepted indications for drug therapy include a BMI of  $>$  or equal to  $30\text{kg/m}^2$  or  $>27\text{kg/m}^2$  with co morbidities. As a general guideline 10% weight loss is recommended. Three major drug options are currently approved. These include: Orlistat, Sibutramine and Rimonabant. Orlistat is a gastric and pancreatic lipase inhibitor and reduces dietary fat absorption by 30%. The major side effects are due to fat malabsorption. Sibutramine is a centrally acting mono-amine-reuptake inhibitor that mainly acts by increasing satiety. It also stimulates thermo genesis. Side effects include insomnia, nausea, dry mouth and constipation. It has potential cardiovascular side effects as well. Rimonabant is a CB-1 blocker and increases satiety. The most common side effects are nausea, dizziness, diarrhea and insomnia. There is no definitive data showing benefit of one anti-obesity drug over another and all three drugs are limited by modest efficacy and low rates of compliance. Therefore the choice of agent is based on patient preference, associated cardiovascular risk factors, adverse effects and affordability. There is a lack of head to head trials to guide their clinical use. Irrespective of which drug is initially selected, treatment should be discontinued if 5-10% weight loss does not occur in the first 3-6 months. Combination therapy has not been well researched. The optimum duration of therapy is unclear. The longest duration of therapy in clinical trials is 4 years for Orlistat and 2 years for Sibutramine and Rimonabant. It has been seen that drug discontinuation invariably leads to weight gain. In conclusion, treatment targeted at the individual is important but equally essential is to elicit changes in the society addressing all the factors considered to be obesogenic. The search for novel anti-obesity drugs is on.

### INTRODUCTION

The International Obesity Task Force estimates that more than 300 million individuals worldwide are obese and an additional 800 million are overweight. For the first time, the number of overweight individuals in the world is equivalent to the number underweight. Unless these trends are reversed, the health-related consequences will be serious. The current methods for lifestyle modification alone, as a treatment for obesity are widely regarded as ineffective.

Anti-obesity pharmaco-therapy is a important adjunctive treatment to lifestyle modification. The ideal anti-obesity drug has three important characteristics. First, it should cause sustained clinically significant reductions in bodyweight and reduce obesity-related morbidity and mortality. Second, the benefit-risk ratio of the drug must be favourable. The track record for safety of anti-obesity drugs has been particularly poor, whereas their potential for abuse by non-obese individuals striving to lose weight is high. Third, affordability.

The **indications for drug therapy** are:

- i) Patients with a body-mass index (BMI) of  $30\text{ kg/m}^2$  or greater or
- ii) A BMI of  $27.0-29.9\text{ kg/m}^2$  with a other comorbid conditions (eg. Diabetes, hypertension, obstructive sleep apnoea) are currently deemed eligible for antiobesity drug treatment.

Weight loss between 5-10% of initial bodyweight is associated with improvement in cardiovascular risk profile and reduced incidence of type 2 diabetes. Therefore, as a general guideline for weight reduction, i.e. 10% weight-loss is recommended.

Three **major drug options** for the long-term treatment of obesity are currently approved. These drugs are: **orlistat and sibutramine and rimonabant**.

### ORLISTAT

Orlistat, was approved in 1998. It is a gastric and pancreatic lipase inhibitor that reduces dietary fat absorption by around 30%. The compound is a partly hydrated derivative of an endogenous lipstatin produced by *Streptomyces toxytricini*. Typically, 120 mg three times daily is prescribed with meals; 60 mg orlistat is also currently available. Because of low systemic absorption and first-pass metabolism, the bioavailability of orlistat is less than 1%. Most of the drug is excreted unchanged in faeces.

**Efficacy:** In a 4-year double-blind placebo-controlled randomised study of 3305 obese patients, orlistat reduced weight by 2.7 kg on average and decreased the incidence of type 2 diabetes from 9.0% to 6.2%. Only 43% of patients completed this study and the beneficial effects were almost all in patients with impaired glucose tolerance at baseline. In a meta-analysis of 11 placebo-controlled trials of 1 year in 6021 overweight or obese patients, orlistat reduced weight by 2.9%. The number of patients reaching 5% and 10% placebo-subtracted weight-loss thresholds was 21% (19-24%) and 12% (8-16%) greater with orlistat than with placebo. Orlistat also reduced blood pressure by 1.8 mm Hg systolic (0.9-2.6 mm Hg) and 1.6 mm Hg diastolic (0.7-2.4 mm Hg), LDL cholesterol by 0.27 mmol/L (0.22-0.31 mmol/L), and fasting glucose in patients with diabetes by 0.8 mmol/L (0.3-1.3 mmol/L). No clinically significant effects on triglycerides or HDL cholesterol were seen. Drop out rates were high, averaging 33%. Other than diabetes incidence, there are no long-term outcome data showing that orlistat reduces major obesity-related morbidity and mortality.

**Adverse effects:** The major adverse effects with orlistat are gastrointestinal. Fatty and oily stool, faecal urgency, and oily spotting occurred in 15-30% of orlistat-treated patients (2-7% with placebo). Faecal incontinence was observed in 7% of orlistat-treated patients compared with 1% of those on placebo. To prevent possible deficiencies of fat-soluble vitamins, co-

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prescription of a daily multivitamin is recommended. Orlistat can reduce the absorption of amiodarone and ciclosporin and can potentiate the effect of warfarin. Systemic adverse effects are minimal because of the lack of systemic absorption.

## SIBUTRAMINE

Sibutramine is a centrally acting mono-amine-reuptake inhibitor that mainly acts to increase satiety. Sibutramine also stimulates thermogenesis; however, this secondary action plays a minor part in weight reduction. The drug was approved in USA in 1997 and in the European Union in 1999. Sibutramine undergoes extensive first-pass metabolism, mainly by hepatic cytochrome p450 3A4 enzymes, to active primary (M1) and secondary (M2) amine metabolites, which are more potent than the parent compound. Most of the drug and its active metabolites are renally excreted.

**Efficacy :** In three randomised double-blind, placebo-controlled weight-loss trials of 1 year, in 929 overweight or obese patients, sibutramine reduced weight by 4-6% (95% CI 3.8-5.4%). Drop out rates in these three trials averaged 48%. The number of patients reaching 5% and 10% placebo-subtracted weight-loss thresholds was 34% (28-40%) and 15% (4-27%) greater with sibutramine than with placebo. In long-term studies, sibutramine has had little effect on concentrations of LDL cholesterol and on glycaemic control, and has had conflicting effects (no change to mild improvement) on concentrations of triglyceride and HDL cholesterol.

Efficacy of sibutramine is greatly enhanced when used with intensive lifestyle modification and regular frequent follow-up visits. In a 1 year randomised trial, 224 obese adults received sibutramine alone, sibutramine plus brief individualised lifestyle modification, group lifestyle modification alone (30 sessions), or sibutramine plus 30 sessions of group lifestyle modification. Those in the lifestyle modification plus sibutramine group lost the most weight, an average 12.1 kg compared with 5.0 kg with sibutramine alone (mean difference 7.1 kg, estimated 95% CI 3.9-10.2 kg). As with orlistat, long-term data on the effect of sibutramine on major obesity-related morbidity and mortality are lacking. However, the ongoing Sibutramine Cardiovascular Outcomes (SCOUT) trial is assessing the efficacy of sibutramine in reducing myocardial infarction, stroke, and cardiovascular mortality in 9000 obese and overweight patients. This study should finish in 2008.

**Adverse effects :** Common side-effects include insomnia, nausea, dry mouth, and constipation. By contrast with fenfluramine and dexfenfluramine, sibutramine does not increase release of serotonin and has not been associated with valvular heart disease or pulmonary hypertension. Concomitant treatment with monamine-oxidase inhibitors or serotonergic drugs is also not recommended because of the potential risk of serotonin syndrome. Furthermore, sibutramine has been associated with small increases in blood pressure and pulse rate, leading to concerns about potential cardiovascular toxic effects. An independent review concluded that sibutramine had a favourable risk-benefit ratio. However, the drug is not recommended in patients with uncontrolled hypertension, pre-existing cardiovascular disease, or tachycardia.

## RIMONABANT

The ability of recreational marijuana to reliably stimulate appetite

generated interest in the use of endogenous cannabinoid agonists and antagonists for weight-related disorders. The endocannabinoid system includes two major receptors, the CB1 and CB2 receptors, and two major ligands, anandamide and 2-arachidonoyl-glycerol (2-AG). Endocannabinoids are polyunsaturated phospholipid-derived eicosanoids produced on demand from arachidonic acid that elicit many biological responses, including counteracting stressful stimuli such as food deprivation, aversive memories, and pain. In the brain, endocannabinoids act in a retrograde manner and are rapidly cleared. The CB1 receptor is a G-protein coupled receptor that is extensively expressed in the CNS, including in areas vital to the control of food intake. Endocannabinoids interact with several anorexic and orexigenic pathways within the CNS, including the central melanocortin and mesolimbic pathways, increasing motivation to eat and stimulating food intake.

Rimonabant, the first CB1-receptor blocker, was initially intended as an antiobesity and smoking-cessation dual-purpose drug; however, the latter development programme has been discontinued.. Rimonabant is a potent CB1-selective ligand, with 1000-fold greater affinity for the CB1 receptor than the CB2 receptor. The drug is hepatically metabolised and excreted in bile. Because of a larger peripheral volume of distribution, obese individuals have a drug half-life that is twice as long (16 days) as non-obese people. Rimonabant produces a dose-dependent reduction in food intake in various rodent models, effects that seem to be both centrally and peripherally mediated. Potential peripheral mechanisms include enhanced thermogenesis via increased oxygen consumption in skeletal muscle, diminished hepatic and adipocyte lipogenesis, augmentation of adiponectin concentrations, promotion of vagally mediated cholecystokin-induced satiety, inhibition of preadipocyte proliferation, and increased adipocyte maturation without lipid accumulation.

**Efficacy :** Four double-blind trials, comprising the Rimonabant In Obesity (RIO) Program, compared rimonabant 5 mg or 20 mg daily with placebo in more than 6600 individuals. RIO-Europe, RIO-Lipids, RIO-North America, and RIO-Diabetes have published 1 year results. RIO-North America also included a second year of follow-up in which rimonabant-treated patients were re-randomised to continue active drug treatment or switch to placebo. The RIO Program enrolled patients with BMIs of 30 kg/m<sup>2</sup> or greater or BMIs of higher than 27 kg/m<sup>2</sup> with dyslipidaemia (predominantly high triglyceride or low HDL cholesterol concentrations), type-2 diabetes, or hypertension. Middle-aged women were most commonly included and enrolment was restricted to highly selected and adherent patients without major comorbidity. Dropout rates at 1 year averaged 40-50%, similar to studies of orlistat and sibutramine. Compared with placebo, rimonabant significantly reduced weight by 4.6 kg (95% CI 4.3-5.0), reduced waist circumference, and improved triglyceride and HDL cholesterol profiles. The proportion of patients achieving 5% and 10% placebo-subtracted weight loss was 29-39% and 17-25% higher with rimonabant treatment than with placebo (p<0.001 in all cases). In RIO-North America, rimonabant-treated patients rerandomised to placebo in year 2 regained weight, whereas those who continued to receive the 20 mg dose maintained their weight loss. Compared with placebo, rimonabant also significantly reduced the placebo-subtracted incidence of metabolic syndrome in all four trials and the placebo-subtracted HbA1c by 0.7% (p<0.001) in RIO-Diabetes. Concentrations of LDL cholesterol did not improve and blood pressure was either unchanged or slightly reduced. No data on cardiovascular morbidity or mortality have been reported, but several

rimonabant studies examining clinical endpoints and surrogate measurements of atherosclerotic burden (eg, intravascular ultrasound) are underway. The largest is the Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) trial, which is investigating the effect of rimonabant on myocardial infarction, stroke, and cardiovascular death in 17 000 obese participants.

**Adverse effects :** The most frequent adverse events are nausea, dizziness, diarrhoea, and insomnia, each occurring 1-9% more frequently than with placebo. Side-effects leading to drug discontinuation occurred in 13-16% of patients taking the 20 mg dose. In RIO-Europe, RIO-North America, and RIO-Lipids, drug discontinuation due to psychiatric disorders (mainly depression) occurred in 6-7% of rimonabant-treated individuals, an absolute increase of 2-5% over placebo.

## HOW TO CHOOSE AN ANTI OBESITY DRUG ?

There are no definitive data showing benefit of one antiobesity drug over another and all three drugs are limited by modest efficacy and low rates of persistence with treatment. Therefore, if drug treatment is to be started, the initial choice is largely based on patients' preference, associated cardiovascular risk factors, and adverse effects. Individual drug-plan and costs are also important. Without definitive head-to-head trials, we suggest the following approach to initial pharmacotherapy on the basis of our review of the evidence and clinical experience.

**Orlistat** reduces LDL concentrations and diabetes incidence, is associated with slight reductions of blood pressure, and is not associated with major systemic toxic effects. Thus this drug might be especially useful in patients at high risk for developing type 2 diabetes, with high LDL cholesterol concentrations, or with pre-existing cardiovascular disease. Orlistat should be avoided in patients with chronic diarrhoea.

**Sibutramine**, because of its satiety-enhancing effects, might be beneficial in cases where a lack of satiety or frequent snacking is a major barrier to weight reduction. Until further efficacy and safety data are available, sibutramine should be avoided in patients with poorly controlled hypertension, pre-existing cardiovascular disease, or tachycardia.

**Rimonabant** may be considered in patients with dyslipidaemia associated with the metabolic syndrome (low HDL cholesterol and high triglyceride concentrations) and in patients who are concurrently attempting to stop smoking. The drug should be used with caution in patients with pre-existing psychiatric illness, particularly depression or anxiety, and in those with liver impairment.

Irrespective of which drug is initially selected, treatment should be discontinued if clinically significant weight loss (ie, at least 5-10% of initial bodyweight or improvement in major obesity-related comorbidity) does not occur within the first 3-6 months. Combination treatment has not been well researched and the existing evidence does not suggest significantly greater weight loss than with single-drug treatment. Furthermore, the optimum duration of treatment is unclear. The longest duration of treatment in clinical trials is 4 years for orlistat and 2 years for sibutramine and rimonabant. Because drug discontinuation invariably leads to weight regain, if clinically significant weight loss is achieved, longer courses of treatment are reasonable to consider.

## CONCLUSION

Orlistat and sibutramine produce average placebo- subtracted weight losses of less than 5%. Orlistat improves cardiovascular risk factors and reduces diabetes incidence in high-risk individuals. The risk-benefit of sibutramine, which can increase blood pressure, is being assessed in a large study of cardiovascular outcomes. Rimonabant is the first of the endocannabinoid receptor antagonists. The weight loss induced by rimonabant appears similar to that of sibutramine, and improvements in HDL cholesterol and triglyceride concentrations have been reported. An increase in the incidence of psychiatric disorders was observed in rimonabant-treated patients. The lack of cardiovascular morbidity and mortality endpoints in obesity drug trials represents a major gap in knowledge. Other endpoints, such as osteoarthritis, gastro-oesophageal reflux disease, sleep apnoea, and quality of life, have also been neglected.

Many other novel potential antiobesity drugs and targets have been identified, including those acting on the central melanocortin pathway, a group of neurons centred in the arcuate nucleus and hypothalamus that control appetite and energy expenditure. Examples include ciliary neurotrophic factor and other melanocortin-4 receptor agonists, ghrelin, neuropeptide Y antagonists, melanin-concentrating hormone antagonists, and peptide YY3-36. Although newer drugs are years away from clinical use, the hope for research investments made to date is translation into safe and effective antiobesity drugs in the future. The neurobiology of obesity is extremely complex, with many overlapping and redundant pathways. This complexity decreases the probability that targeting any single pathway will result in dramatic weight loss and suggests that multiple drugs with different mechanisms will be needed to produce significant and persistent weight loss.

Other than bariatric surgery, which is neither a feasible nor a desirable population-based treatment for obesity, no intervention has remitted in consistent effective long-term weight loss. Treatments targeted at the individual are important, but equally essential is the need to elicit changes in society that address all aspects of the environment thought to be obesogenic. To be successful, such initiatives should involve the concerted efforts of all, from policymakers to the food and drug industries, and from educators to patients and physicians. Even if lifestyle and population-based strategies are creatively and successfully implemented, the large burden of prevalent obesity dictates that many will remain at risk for obesity-related comorbidity and premature death. The search for novel drug treatments for obesity is, necessary. However, in our efforts to fill the therapeutic void that characterises contemporary obesity management, the benefits of obesity pharmacotherapy must outweigh the risks and costs.

## REFERENCES

1. Haddock CK, Poston WSC, Dill PL, Foreyt JP, Ericsson M. Pharma cotherapy for obesity. *Int J Obes Relat Metab Disord* 2002; 26: 262-73.
2. Padwal R, Li SK, Lau DCW. Long-term pharmacotherapy for overweight and obesity. *Int J Obes Relat Metab Disord* 2003; 27: 1437-46.
3. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. Xenical in the prevention of diabetes in obese subjects (XENDOS) study. *Diabetes Care* 2004; 27: 155-61.
4. McNulty SJ, Ur E, Williams G. A randomized trial of sibutramine in the management of type 2 diabetic patients treated with metformin. *Diabetes Care* 2003;
5. Wadden TA, Berkowitz RI, Womble LG, et al. Randomised trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med* 2005; 353: 2111-20.
6. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J, for the RIO-North America Study Group. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients. *JAMA* 2006; 295: 761-75
7. Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF, RIO- Diabetes Study Group. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes. *Lancet* 2006; 368: 1160-72.

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1. Klemmer PJ. Blood Purif. 2005; 23 Suppl 1:12-9  
for bone metabolism and disease in CKD. Am J Kidney Dis. 2003;42(Suppl3):S1-S201

2. Chertow GM, et al. Kidney Int. 2002;62:245-252

3. Chertow GM. J Am Soc Nephrol. 2003;14:S310-S314

4. NKF. Clinical Practice Guidelines

7. Collins AJ. Clin Nephrol 2000;54:334-341

8. Rosenbaum DP. Nephrology Dial Transplant. 1997;12:961-964

5. Maurizio Gallieni, et al. J Nephrol. 2001;14:176-183

6. Bleyer AG, et al. Am J Kidney Dis. 1999;33:694-701

9. Chertow GM, et al. Am J Nephrol. 2003;23:307-314



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## RIMONABANT: A NOVEL BUT CONTROVERSIAL AGENT

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**Abstract:** The treatment strategies for obesity and overweight include increased physical activity, low caloric diet and low fat diet, increased intake of dietary fibers, pharmacological and surgical treatment. Pharmacological management comes very late in the management of obesity. Most of the times this mode is used as an adjunct to diet and exercise. Currently three drugs are being used in the management of obesity: Sibutramine, Orlistat and Rimonabant. Intake of cannabis has been seen to be associated with an increase in appetite. Rimonabant is the first of the new class of agents that act by selectively blocking cannabinoid -1 receptors with resultant central and peripheral metabolic effects. It has a higher affinity for central receptors as compared to peripheral receptors. The drug has a long duration of action and good oral bioavailability. It reduces food intake and increases energy expenditure. The most frequent side effects are nausea, dizziness and upper respiratory infections. The drug has a favorable effect on lipid profile by increasing HDL-C and decreasing LDL-C. In addition to weight loss, Rimonabant has seen to improve HbA1c levels and therefore may be helpful in diabetes. It also prevents weight gain in persons who are quitting smoking and some but not all studies show an increased rate of smoking cessation. Future research and results of ongoing trials are required to establish its long-term therapeutic implications and safety profile.

### INTRODUCTION

The treatment strategies available for obesity and overweight include increased physical activity, low caloric and low fat diet, increased intake of dietary fibers, and other life style modification, pharmacological as well as surgical treatment.

There is no doubt that weight control and weight reduction can reduce the risk of developing diabetes in subjects with impaired glucose tolerance, as shown both by lifestyle interventions<sup>1,2,3</sup> and by use of drugs such as orlistat<sup>4,5</sup>, acarbose<sup>6</sup>, and rosiglitazone<sup>7</sup>. However, the feasibility and benefits by weight reduction in established type 2 diabetes is less well documented and also sometimes hard to achieve if most antidiabetic drugs act by increasing weight, with metformin being the only exception.

The pharmacological intervention comes very late in the management of obesity. It is used in those patients where lifestyle modification and dietary modification have failed to achieve desired reduction in weight. Most of the time this mode of therapy is adjunctive to dietary and regular exercise regimens. Currently three drugs are being used in the management of obesity; these are Sibutramine, Orlistat and Rimonabant

### THE ENDOCANNABINOID SYSTEM

Traditionally in India, there is usage of cannabis in various forms like 'BHANG', 'GANJA' on occasions like 'Holi' festival. It has been observed that after having cannabis there is marked increase in the appetite and thirst along with euphoria and altered behavior. Moreover in ancient India there are references to saints (SADHU) to using marijuana in various forms.

Cannabis sativa is a shrub that abundantly grows in India, being used as source of marijuana. The use of cannabis or hashish as a psychoactive substance reached Europe and the Americas through the Arab world in the 19th century. During the same period, cannabis extracts had gained widespread use for medicinal purposes until 1937, when concern about the dangers of abuse led to the banning of marijuana for further medicinal use in the United States. It has also been noted that cannabis abuse was associated with weight gain.

The active component of marijuana is tetrahydrocannabinol. The endocannabinoid system have several locally produced agonists which act through these receptors, these are anandamide, monoacyl glycerol, 2-arachidonylglycerol and other fatty acid ethanolamides. All these compounds are produced post-synaptically and act on pre-synaptic regions by realizing the neurotransmitters.

Rimonabant is the first in a new class of agents that act by selectively blocking the cannabinoid-1 receptors with resultant central and metabolic peripheral effects, thereby decreasing food intake. Evidence currently exists for two types of cannabinoid receptors: CB1 and CB2. CB1 receptors are present both in the CNS as well as in certain peripheral tissues. The areas in which CB1 receptors are most dense are thought to deal with cognition, motor function and movement. Rimonabant is reported to possess a 1000-fold higher affinity for the CB1 receptor than CB2 receptor. It shows high affinity for the centrally located cannabinoid receptor, while displaying low affinity for the peripherally located receptor. Additionally, it has little or no affinity for non-cannabinoid receptors.

### CHEMICAL STRUCTURE

Rimonabant (SR141716) is a neurokinin-3 antagonist and selective cannabinoid (CB1) receptor antagonist. The chemical name is N-piperino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide<sup>8</sup>.

**Pharmacokinetics:** Rimonabant has demonstrated a long duration of action (8 hours) and good oral bioavailability<sup>9</sup>.

Functional in vitro and in vivo studies have shown that Rimonabant is able to antagonize the pharmacologic effects induced by cannabinoid receptor agonists<sup>10</sup>. It powerfully reduces food intake and increases energy expenditure. It modulates the rewarding properties of food by inhibiting the action of endogenous cannabinoids at specific mesolimbic areas. It alters the variety of signals of peripheral origin (leptin, ghrelin and adiponectin) which modulate the neurochemical activation of hypothalamic neurons and the state of relative energy balance. Rimonabant also inhibits the enzymes involved in lipogenesis<sup>11</sup>. Many rodent model studies have demonstrated a memory enhancing effect due to Rimonabant use<sup>12</sup>.

### ADVERSE EFFECTS

The results of early human trials with rimonabant treatment showed

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an excellent tolerance among patients, except for some mild gastrointestinal adverse effects at the highest dose administered. Some adverse effects on mental function have been noticed in some patients, and that is why this drug should not be prescribed to patients with a medical history of depression or pronounced mental symptoms. Safety data from the preliminary results of the RIO-Lipids, RIO-Europe, RIO-North America and STRATUS-US trials revealed that Rimonabant is well tolerated among patients<sup>13,14,15</sup>. The most frequently reported adverse effects are nausea, dizziness and upper respiratory infections. Diarrhea was seen most commonly in the RIO-Europe trial (2.3%, 5.8% and 7% for placebo, Rimonabant 5 mg/day and 20 mg/day, respectively).

## ADVANTAGES

Rimonabant is reported to increase HDL-C and decrease atherogenic LDL-C levels. The unique property of this drug may, in turn, improve cardiovascular risk factors and metabolic syndrome.

In addition to weight loss, rimonabant is reported to produce improvement in HbA1C levels and may be helpful in diabetes.

It also prevents weight gain in persons who are quitting smoking.

**Evidence:** Clinical studies in obese subjects have documented weight loss, improved glucose metabolism, and lipid control, as well as reduced blood pressure in patients with type 2 diabetes<sup>16, 17, 18</sup>. Other effects seen in some but not all studies include increased rates of smoking cessation. It is important that Rimonabant is currently being evaluated for effects on cardiovascular morbidity and mortality end points versus placebo in a randomized controlled study, the Comprehensive Rimonabant Evaluation Study of Cardiovascular End Points and Outcomes (CRESCENDO) study, with expected results in 2011<sup>19</sup>. This trial is recruiting patients with inclusion criteria: waist circumference >102 cm (40 inches) in males, >88 cm (35 inches) in females, with one coronary heart disease equivalent or two major risk factors for CVD.

## CONCLUSION

Rimonabant, the selective blocker of CB1 receptors, may normalize the activity of the endocannabinoid system, resulting in weight loss, reduced waist circumference, improvement in lipid and glucose metabolism in obese people and may prevent weight gain associated with smoking cessation along with medical nutritional therapy and increased physical activity. The positive effects may, in turn, improve cardiovascular and metabolic risk factors. Future research and the

results of ongoing clinical trials of this exciting drug are required to establish its long-term therapeutic implications and safety profile.

## REFERENCES

1. Lindström J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Uusitupa M, Tuomilehto J, Finnish Diabetes Prevention Study Group: The Finnish Diabetes Prevention Study (DPS): lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* 2003;26: 3230–3236.
2. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002 346:393–403.
3. Indstrom J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemio K, Hannalainen H, Harkonen P, Keinanen-Kiukkaanniemi S, Laakso M, Louheranta A, Mannelin M, Paturi M, Sundvall J, Valle TT, Uusitupa M, Tuomilehto J, Finnish Diabetes Prevention Study Group: Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 2006 368:1673–1679.
4. Holt R: Orlistat reduces features of the metabolic syndrome: the XENDOS study. *Diabetes Obes Metab* 2003; 5:356.
5. Torgerson JS, Hauptman J, Boldrin MN, Sjörström L: XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004;27:155–161.
6. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M: STOP-NIDDM Trial Research Group: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; 359:2072–2077.
7. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccan N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006 ; 368:1096–1105.
8. Iversen L. Cannabis and the brain. *Brain* 2003;126:1252–70.
9. Rinaldi-Carmona M, Barth F, Heaulme M. Biochemical and pharmacological characterization of SR141716A, the first potent and selective brain cannabinoid receptor antagonist. *Life Sci* 1995;56:1941–7.
10. Compton DR, Aceto MD, Lowe J, Martin BR. In vivo characterization of a specific cannabinoid receptor antagonist (SR141716): inhibition of delta-9-tetrahydrocannabinol induced responses and apparent agonist activity. *J Pharmacol Exp Ther* 1996;277:586–94.
11. Cota D, Marsicano G, Tschöp M. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest* 2003;112:423–31.
12. Coizet V, Cassel JC, Kelche C. Effects of the selective CB1 cannabinoid receptor antagonist, SR141716, on cognitive performance in intact, brain-damaged and scopolamine-treated rats. *Behav Pharmacol* 1998;9:25.
13. Van Gaal L. RIO-Europe: A randomized, double-blind study of weight reducing effect and safety of rimonabant in obese patients with or without comorbidity. Program and abstracts from the European Society of Cardiology Congress 2004, Aug 28-Sep1; Munich, Germany; 2004.
14. Press release. [accessed 2004 Nov 9]. Available from: [http://en.sanofi-aventis.com/press/p\\_press\\_2004](http://en.sanofi-aventis.com/press/p_press_2004).
15. Results from the RIO-North America trial show that first year improvements in cardiovascular risk factors are maintained in the second year of treatment. American Society of Cardiology Congress, 2004 Nov 9 (online).
16. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S, RIO-Europe Study Group: Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* 2005; 365:1389–1397.
17. Despres JP, Goyal A, Sjörström L: Rimonabant in Obesity-Lipids Study Group: Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med* 2005; 353:2121–2134.
18. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J, RIO-North America Study Group: Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 2006; 295:761–775.
19. CRESCENDO Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes. *ClinicalTrials.gov Identifier: NCT00263042 (sanofi-aventis)*.

## NOBLE PRIZE IN MEDICINE

Three European scientists who discovered virus that causes cervical cancer and AIDS share this year's Noble prize in Medicine. A German virologist, **Harald zur Hausen**, will receive half the award for discovery of HPV, the human papilloma virus, according to the announcement made on Monday by the Karolinska Institute in Stockholm. The discovery led to the development of a vaccine against cervical cancer, the second most common cancer in women. The institute said the other half of the award will be shared equally by two French virologists, **Francoise Barre-Sinoussi** and **Luc Montagnier**, for their discovery of virus of AIDS. Since its discovery in 1981, AIDS has rivaled the worst epidemics in the history.

An estimated 25 million more are living with HIV. Dr. Zur Hausen of the University of Heidelberg was cited for discovering the first HPV, Type 16, in 1983 from biopsies of woman who had cervical cancer. A year later, Dr. Zur Hausen cloned HPV 16 and another type, 18. The two HPV types are consistently found in about 70% of cervical cancer biopsies throughout the world, the institute said. Of the more than 100 human papilloma viruses now known, about 40 infect the genital tract, and 15 of them put women at the high risk for cervical cancer. Papilloma viruses account for more than 5% of all cancers worldwide. Discovery of HIV led to Blood tests to detect the infection and the infection and to anti-retroviral drugs that are effective in prolonging the lives of the patients. The discovery has also led to an understanding of the natural history of HIV infection, which ultimately lead to AIDS unless treated. "Never before has the science and medicine been so quick to discover, identify the origin and provide treatment for a viral infections," the Karolinska Institute said.

# BARIATRIC SURGERY: CURE FOR MORBID OBESITY

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**Abstract:** Once considered simply a condition of caloric intake exceeding energy expenditure, obesity has come to be known as a complex disease influenced by the interaction of genetic, endocrine, metabolic, and environmental factors. Management of obesity includes life style changes with calorie restriction and vigorous exercise. All patients with morbid obesity do not respond to life style modifications and medical therapy. There is group of patients especially with morbid obesity who in addition to medical management need surgical intervention and bariatric surgery is the answer. Bariatric surgery is the most effective therapy available for the morbidly obese population. It markedly lowers body weight, reverses or ameliorates the myriad of obesity co morbidities, and improved quality of life. Four operative procedures are currently in general use worldwide. These surgical procedures can be divided in to Restrictive (Laparoscopic adjustable gastric banding; vertical banded gastroplasty), Malabsorptive (Biliopancreatic diversion and duodenal switch) and combined restrictive and malabsorptive (Roux en Y Gastric bypass). There is an ever-increasing effort to match a particular patient to a particular operation. In this review we will discuss various surgical procedures available for morbid obesity and their success rates.

## INTRODUCTION

Obesity has become a health problem worldwide encompassing 1.7 billion people. According to World Watch Institute, the number of overweight people is approximately equal to the number of under weight people in the world. Prevalence of obesity is particularly high in many ethnic minority women, such as African, Mexican and Pacific Islander American women.

Obese patients are at increased risk of illness from coronary artery disease, hypertension, type II diabetes, respiratory insufficiency, venous stasis or thromboembolic disease, debilitating arthritis of weight bearing joints, depression, as well as from uterine, ovarian, colon, breast, and prostate carcinoma. Obesity, in particular morbid obesity, is also a social and economic problem. Practical social implications of morbid obesity are manifold, e.g., inability to ambulate, limited selection in clothing, stress incontinence, difficulty in personal hygiene and depression.

The impact of obesity on longevity has been well documented. In the world, over 2.5 million deaths annually can be attributed to obesity. There is direct relationship between increasing BMI and relative risk of dying prematurely as evidenced in the Nurses Health Study with a > 100% increase in relative risk as BMI increased from < 19 Kg/m<sup>2</sup> to > 32 kg/m<sup>2</sup>. In the morbidly obese populations, average life expectancy is reduced by 9 years in women and 12 years in men. The financial burden of obesity is more the \$117 billion annually in the United States. Bariatric surgery is the most effective therapy available for the morbidly obese population. It markedly lowers body weight, reverses or ameliorates the myriad of obesity co morbidities, and improved quality of life.

## DEFINITIONS AND RISK FACTORS

In 1998, the NIH established federal guidelines for identification, evaluation and treatment of overweight obese adults. Whereas being overweight is having a body mass index

(BMI) greater than 25 kg/m<sup>2</sup> Obesity is having a BMI greater than 35 kg/m<sup>2</sup>. Severe obesity is having a BMI greater than 30 kg/m<sup>2</sup>, and morbid obesity is having a BMI greater than 40 kg/m<sup>2</sup>, or a BMI greater than 35 kg/m<sup>2</sup> with concomitant obesity related morbidity. (Figure)

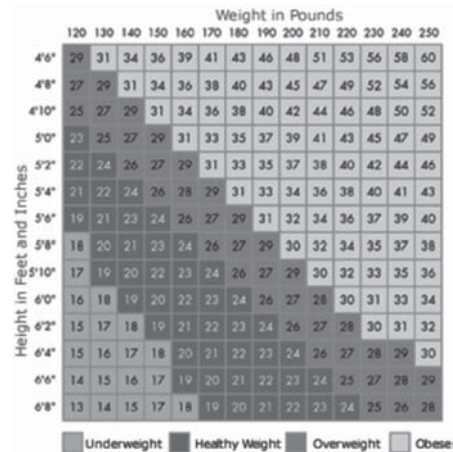


Fig.1 : Obesity evaluation

BMI is only one measurement technique of obesity and has limitation. Other techniques such as waist-to-hip ratio of 1.0 or higher in males and 0.8 or higher in females defines upper body obesity and in an independent predictor of disease risk. Obese patients have an increased risk of coronary artery disease. Complications related to obstructive sleep apnea are 12 to 30 fold higher in the morbidly obese than in the general population. Morbidly obese patients may experience 12-fold reduction in life expectancy in comparison with age-matched controlled subjects.

## ETIOLOGY OF OBESITY

Once considered simply a condition of caloric intake exceeding energy expenditure, obesity has come to be known as a complex disease influenced by the interaction of genetic, endocrine, metabolic, and environmental factors. Mutations in human obesity gene and leptin receptor gene have been identified in obese family members.

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## CONSEQUENCES OF MORBID OBESITY

Hypertension is the most common co-morbidity of obesity. The risk of coronary artery disease is higher in obese population. Obesity itself increases metabolic and mechanical load on the heart, predisposing the heart to left ventricular hypertrophy and congestive failure. Venous stasis disease cause significant chronic morbidity in obese patients. Obese patients have an increased incidence of IDDM. Obesity with NIDDM is susceptible to coronary artery disease, renal insufficiency, and cerebral vascular disease.

Adipose tissue acts as endocrine organ, converting 17- beta-hydroxysteroid to androstenedione and estradiol. The hormones lead to feminization in men and masculinization, polycystic ovarian disease, amenorrhoea and infertility in women. The incidence of obstructive sleep apnea is 12-30 folds higher in morbidly obese patients. Obese patients are also at higher risk for hypoventilation syndrome and restrictive lung disease.

A relative hyperandrogenism and elevated estrogen blood levels are hypothesized to be the reason for an increased risk towards the development of hormonally sensitive tumor (e.g., breast, ovary, endometrial, and prostate cancer) in obese patient.

## NONOPERATIVE TREATMENT OF MORBID OBESITY

Nonoperative treatment includes *caloric restriction, exercise, behaviour modification, and drug therapy*. Weight lost on low caloric diets of approximately 800 calories per day is typically regained within 18 months to 4 years after initiation if weight loss program. Exercise programs without some type of caloric restrictions are generally ineffective beyond the loss of 6 to 10 pounds. Long-term success with behavior modification program is also lacking. Pharmacologic programs use appetite-suppressing medications, inhibition of lipase, and metabolic enhancers, though popular but are equally ineffective as a treatment for morbid obesity.

## OPERATIVE TREATMENT FOR MORBID OBESITY

**Bariatric surgery** is the most effective therapy available for the morbidly obese population. It markedly lowers body weight, reverses or ameliorates the myriad of obesity co morbidities, and improves quality of life.

### **Patient selection**

The 1991 NIH Consensus Conference weight criteria for bariatric surgery of a BMI > 40 kg/m<sup>2</sup> or a BMI of 35.0 kg/m<sup>2</sup> to 39.9 kg/m<sup>2</sup> in the presence of severe comorbidities are still reasonable today. High-risk comorbid conditions that can justify reducing the BMI to 35 kg/m<sup>2</sup> include type 2 diabetes, life-threatening cardiopulmonary problems (e.g. severe sleep apnea, Pickwickian syndrome, obesity-related cardiomyopathy), obesity-induced physical problems

interfering with a normal lifestyle (eg, joint disease treatable but for the obesity), and body size problems precluding or severely interfering with employment, family function, and ambulation. Certain data demonstrate that bariatric surgery can ameliorate obesity co-morbidities (e.g. type 2 diabetes) in patients with a BMI > 35 kg/m<sup>2</sup>.

Four operative procedures are currently in general use worldwide. These surgical procedures can be divided in to *Restrictive* (Laparoscopic adjustable gastric banding; vertical banded gastroplasty) *Malabsorptive* (Biliopancreatic diversion and duodenal switch) and *combined restrictive and malabsorptive* (Roux en Y Gastric bypass). There is an ever-increasing effort to match a particular patient to a particular operation.

## LAPAROSCOPIC ADJUSTABLE GASTRIC BANDING

Gastric banding is the least invasive of the purely restrictive bariatric surgery procedures. It consists of a small pouch and a small stoma created by a band high on the stomach. Laparoscopic adjustable gastric banding was first introduced in the early 1990s. Today, there are six adjustable bands available worldwide and one approved by the FDA (June 2001) for use in the United States. Laparoscopic adjustable gastric banding is the most common procedure performed outside of the United States, primarily in continental Europe, Australia, and South America. It is the second most commonly performed procedure worldwide.

**Current techniques:** (Fig.2) The upper gastric pouch is made very small (the "virtual pouch"), approximately 15 mL in volume, and placed primarily anteriorly. The dissection on the lesser curvature of the stomach includes the neurovascular bundle of the lesser omentum—the *pars flaccada* approach. Suture fixation of the anterior wall of the stomach, with at least four gastrogastic sutures, completely imbeds the anterior band. The system is assembled and the port for inflation and deflation of the band is secured onto the rectus fascia of the anterior abdominal wall. Adjustment of the band through the access port is an essential part of laparoscopic adjustable gastric banding therapy.

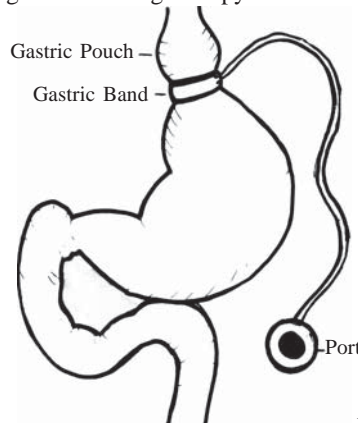


Figure 2: Gastric Banding

**Weight loss:** Weight loss after laparoscopic adjustable gastric banding is about 50% of the EBW and about 25% of the BMI at 2 years.

**Operative mortality and morbidity:** Operative (30-day) mortality for laparoscopic adjustable gastric banding when performed by skilled surgeons is about 0.1%. Operative morbidity is about 5%.

**Longterm complications:** There are unique longterm complications of laparoscopic adjustable gastric banding, which include gastric prolapse, stomal obstruction, esophageal and gastric pouch dilation, gastric erosion and necrosis, and access port problems. Experience has markedly reduced the incidence of these complications.

**Reversal and revision:** Laparoscopic adjustable gastric banding can be completely reversed with removal of the band, tubing, and port. For failed weight loss, revision procedures include removal of the device and performance of a restrictive-malabsorptive procedure (eg, gastric bypass) or a primarily malabsorptive procedure (eg, biliopancreatic diversion and duodenal switch).

**GASTRIC BYPASS**

It is a combined restrictive and malabsorptive procedure and is currently the most popular procedure performed in the United States and worldwide. The restrictive element of operation consists of the creation of a small gastric pouch with a small outlet. The intestine tract bypassed consists of the distal stomach, entire duodenum and 40 cm proximal jejunum. The Roux limbs vary from 75 cm – 150 cm.

**Current Techniques:** (Fig.3) RYGB can be performed by either open or laparoscopic techniques. The upper pouch (15-25 ml) is constructed horizontally with distal stomach separated from this pouch by four rows of staples of totally divided from the upper gastric pouch. Gastrojejunostomy can be performed with the end-to-end circular stapler, linear stapler or hand sewn.

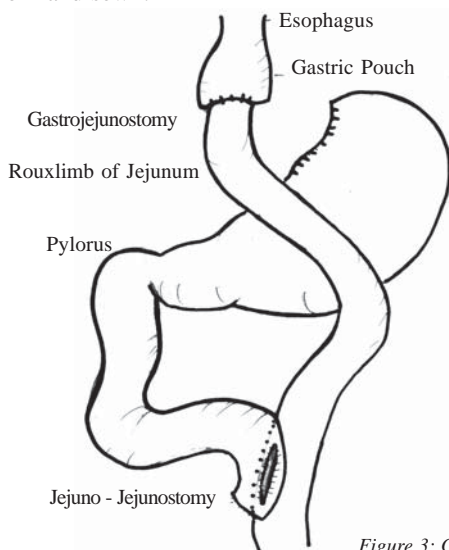


Figure 3: Gastric Bypass

**Weight loss:** Weight loss after a standard 75 cm Roux gastric bypass usually exceeds 100 lb, or about 65% to 70% of the excess body weight (EBW) and about 35% of the BMI.

**Operative mortality and morbidity:** Operative (30-day) mortality for gastric bypass when performed by skilled surgeons is about 0.5%. Operative morbidity (eg, pulmonary emboli, anastomotic leak, bleeding, wound infection) is about 5%.

**Longterm complications:** Gastric bypass can be associated with the dumping syndrome, stomal stenosis, marginal ulcers, staple line disruption, and internal hernias. Life-long oral or IM vitamin B12 supplementation, and iron, vitamin B, folate, and calcium supplementation is recommended to avoid specific nutrient deficiency conditions, such as anemia.

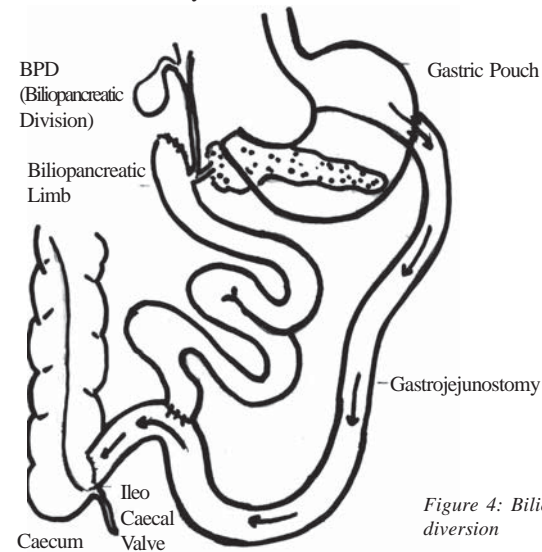


Figure 4: Biliopancreatic diversion

**BILIOPANCREATIC DIVERSION AND DUODENAL SWITCH**

Biliopancreatic diversion and duodenal switch are primarily malabsorptive procedures. The biliopancreatic diversion originated in Genoa, Italy and is widely used in Europe and sparingly in the United States. Both procedures involve a partial gastrectomy leaving a gastric pouch of 100 to 150 mL, which is considerably larger than that of gastric bypass or the restrictive procedures and, thereby, allows larger meals in comparison with those of the other bariatric operations. Both procedures avoid leaving a nonfunctioning intestinal segment by dividing the intestine into a long enteric limb joining a long biliopancreatic limb to form a common channel 50 to 150 cm from the ileocecal valve. This modification avoids the toxic problems seen with the old jejunoileal bypass procedure

**WEIGHT LOSS**

Weight loss after biliopancreatic diversion and duodenal switch is about 70% of the EBW and about 35% of the BMI. Weight loss with these procedures is at the upper end of the

efficacy range. Weight loss may be sustained without a rise from the weight nadir.

## OPERATIVE MORTALITY AND MORBIDITY

Operative mortality for biliopancreatic diversion and duodenal switch when performed by skilled surgeons is about 1%. Operative morbidity is about 5%.

## LONGTERM COMPLICATIONS

On occasion, these procedures are associated with diarrhea. Some patients report malodorous stools and flatus. Long-range complications can consist of vitamin, mineral, and nutrient deficiencies, in particular, protein deficiency. These contingencies need to be anticipated and properly managed by dietary supplements with about 75 to 80 g of dietary protein and B vitamins, calcium, and iron. Biliopancreatic diversion may be associated with postoperative dumping; the duodenal switch is not.

## PREOPERATIVE CARE

The bariatric surgery patient needs to be well-informed, motivated, willing to participate in longterm care, change dietary patterns, and embrace a revised lifestyle. The bariatric patient is best evaluated and subsequently cared for by a team approach involving the surgeon, a nurse practitioner or nurse, a dedicated dietician, office personnel (scheduling and triage), and other specialists when needed. Availability of a support group is recommended, as is distribution of literature describing procedures, postoperative diets, exercise, and so forth. Availability of a full spectrum of expert consultants (eg, cardiologists, pulmonologists, psychiatrists and psychologists) is mandatory.

## PERIOPERATIVE CARE

Expert anesthesiology support, knowledgeable in the specific problems of the bariatric patient, is necessary. The anesthesiology support includes an understanding of patient positioning, blood volume and cardiac output changes, airway maintenance, and drug pharmacokinetics in the morbidly obese. It is advisable to have preoperative, intraoperative, and

postoperative written protocols. The bariatric surgeon must be able to manage, and have coverage to manage, the postoperative patient and any problems and complications that may occur. A facility that practices bariatric surgery must be equipped with appropriate operating room equipment, including operating tables that can handle large patients; bariatric instruments, including large retractors, special staplers, long laparoscopic instruments; special equipment to transfer the patient; extra-large beds, commodes, chairs, and wheelchairs; and diagnostic facilities and equipment that can accommodate the morbidly obese patient.

## POSTOPERATIVE CARE

Care of the postoperative bariatric surgery patient is recommended for the lifetime of the patient with at least three followup visits with the bariatric surgery team within the first year. Laparoscopic adjustable gastric banding will require more frequent visits for band adjustment. Postoperative dietary (including vitamin, mineral, and possibly liquid protein supplementation), exercise, and lifestyle changes should be reinforced by counseling, support groups, and working with the family physician. Favorable outcomes of bariatric surgery can lead to socioeconomic advancement, which may require patient guidance. Postoperative care may include planning for reconstructive operations after weight stabilization for certain patients.

## CONCLUSION

Bariatric surgery, involving either open or laparoscopic techniques, is the most effective weight loss therapy available for patients with morbid obesity. Bariatric surgery results in marked and long-lasting weight loss and elimination or improvement of most obesity-related medical complications.

## RECOMENDED READING

1. *Bussen DH. Update on obesity. J Clin Endocrinol Met 2008; 248: review*
2. *Cunneen. Review of meta analysis of comparison of bariatric surgery with a focus on laparoscopic adjustable gastric banding. Sur Obstet Realt Dis 2008; 4(3 supplement) S47-55.*
3. *Khalileh A, Malot I, Schwurger C et al. Laparoscopic Roux-en-Y gastric bypass for treatment of morbid obesity; experience with 50 patients. Isr Med Assoc J 2008; 10(50):350-5.*
4. *Gonzalez-Sanchez JA et al. Bariatric surgery patients: reasons to visit emergency department after surgery. Bol Asoc Med P R. 2007 Oct-Dec;99(4):279-83.*
5. *Hutter MM et al. Laparoscopic versus open gastric bypass for morbid obesity: a multicenter, prospective, risk-adjusted analysis from the National Surgical Quality Improvement Program. Ann Surg. 2006 May;243(5):657-62; discussion*

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