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Abdominal Obesity, Adipokines and Non-communicable Diseases

Deepika Dhawan [a,b,*], Sheel Sharma [b]

[a] Department of Dietetics and Applied Nutrition, Amity University, Haryana, Gurgaon, India
[b] Department of Food Science and Nutrition, Banasthali Vidyapith, Rajasthan, India

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ABSTRACT

Abdominal obesity may be defined as excess deposits of fat in the abdominal region. It is a common health condition seen in South Asians and is positively related to non-communicable diseases (NCDs). It is independent of body mass index and measured by raised waist circumference for men≥90 cm and women≥80 cm. The reason for its prevalence being common in Indians finds its root from pregnancy, during fetal period and has emerged as a concept of 'Thin Fat Indian'. Malnutrition in such a critical period of growth has consequences in the form of reduced basal metabolic rate (BMR), reduced blood flow to growing tissues, reduced functional ability of vital organs, endocrine changes and reduced capacity of primary adipose tissue. However, excess of visceral fat facilitates high dosage of adipokines in the portal vein to liver and other body tissues having serious implications seen in the form NCDs like diabetes, hypertension, heart diseases, non-alcoholic fatty liver diseases, kidney disorders, cancer and other health problems. Abdominal obesity should be addressed before it has progressed further to defined health issues by exercise and diet, so that people can live a quality life.

1. Introduction

Abdominal Obesity (AO) has seen a remarkable increase over the years and its consequences have been reported in the form of NCDs in many studies. However, AO has remained a neglected factor and studies show that even (body mass index) BMI <20Kg/m^2 may suffer from AO and NCDs. This makes it important to study about how AO is associated with pathogenesis of NCDs [1,2].

AO is observed to be an adverse form of obesity with serious implications [3]. It is the presence of excess fat deposits in the abdominal region [4]. The latest guidelines for South Asians define AO as large waist circumference (WC) ≥90 cm in men and ≥80 cm in women independent of BMI [5]. AO is an indicator of accumulation of triacylglycerols in the liver and muscles [6]. Hence, it has been strongly linked to given common NCDs in particular: cardiovascular diseases (CVDs), diabetes, hypertension, cancer, kidney diseases and non-alcoholic fatty liver diseases (NAFLDs) [3].

2. Materials & Methods

A literature review was done to obtain relevant information, searching the online databases- PubMed, Medline, Google scholar and NCBI (National Center for Biotechnology Information) and related books. Research articles such as cross-sectional, prospective and longitudinal studies and reviews were identified. Following keywords: 'Abdominal Obesity', 'Non-communicable diseases', 'BMI norms', 'In utero malnutrition', 'Thin Fat Indian', 'Pathophysiology of visceral obesity', 'Cardiovascular diseases', 'Diabetes', 'Hypertension', 'Cancer', 'Liver Disorders', 'Kidney diseases' ', 'Diet' and 'Exercise' were used in search strategy. This review explains in detail about how abdominal obesity is related to non-communicable diseases.

3. Different BMI norms for Asians, Asian Indians, Europeans and Pacific Islanders

The international classification for BMI given by WHO (World Health Organization) is followed worldwide, though due to differences in proportion of lean body mass and fat mass in the ethnic groups; recommendations have been given to be used by researchers to understand the relation of obesity with NCDs. In the Table 1, BMI cut off points are tabulated as given by WHO [7]. However, apart from this, another classification for adult Asians has been given in Table 2; according to the "WHO expert consultation, 2004". Studies done in Asian countries indicate high body fat mass even when populations fall under normal BMI category. WHO also suggested that in Asian countries, 23 kg/m^2 is a cut off point where special attention should be given. Above this point,

* Corresponding author at: Department of Dietetics and Applied Nutrition, Amity University, Haryana, Gurgaon, India.
E-mail address: deepikadhawan10@gmail.com (D. Dhawan).

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Table 1
International classification of BMI, WHO [7].

Category	BMI range (kg/m^2)
Underweight	≤18.50
Severe underweight	<16.00
Moderate underweight	16.00-16.90
Mild underweight	17.0-18.49
Normal range	18.5-24.9
Overweight	≥25.00
Pre-obese	25.00-29.90
Obesity	≥30.00
Obese class I	30.00-34.90
Obese class II	35.00-39.90
Obese class III	≥40.00

population is at a high risk of NCDs. Another cut off point identified posing a higher risk than the former is ≥27.5 kg/m^2 as presented in Table 3. Waist circumference cut off also vary in Asians ≥90 cm for men and ≥80 cm, while for Europeans ≥94 cm for men and ≥80 cm for women being indicators of abdominal obesity and NCDs [8,9].

Higher BMI cut offs have been given for Pacific Islanders due to greater lean body mass at a given BMI as compared to Europeans who follow international WHO classification. They have been categorized overweight for BMI range 26.0-32.0 and ≥32 indicate obesity for them [10].

4. Concept of "Thin Fat Indian"

Malnutrition in India especially during pregnancy and fetal period has a long-term consequence and not just as low birth weight baby whose health may be improved through nutrition and medicine to achieve a normal weight. With urbanization and advancement, in undernourished infants, with affluences coming in later years may develop into unhealthy and overweight adults [11].

During fetal growth period, if there is deficit of nutrients; human body will adjust to a thrifty metabolism to save body's fuel and survive starvation condition. However, this same thrifty phenotype is programmed and is prevalent today. But the environmental conditions are not same now, having abundant food available despite low energy output as programmed in-utero save guarding the body's fat leading to obesity in Indians, such an individual is said to be "Thin Fat Indian" [12].

The thin fat Indian may or may not have normal BMI but as discussed, this phenomenon of under nutrition during critical growth period and an abundance later may have serious consequences as discussed in Table 4 [12,13].

5. Abdominal obesity

Within the period of 1960-2000, there has been expansion in the size of waist circumference, especially in women. Also, AO has seen higher shift than generalized obesity owing to higher risk of NCDs, even in people within the normal BMI range [14]. WC is seen to be a better predictor of dyslipidemia, hypertension and metabolic syndrome as indicated in a study conducted by National Health and Nutrition Examination Survey (2004). Abdominal obesity may be determined by WC, is seen to be a useful tool to forecast NCDs [15]. The question is how AO causes metabolic disorders and this may be unmasked by understanding the pathophysiology of it. White adipose tissue mass contributes to proinflammatory cytokines and their level may rise in excess adiposity implicated in the development of atherosclerosis, CVDs, insulin resistance and other NCDs. Studies show high level of proinflammatory cytokines in subjects suffering from abdominal obesity [16].

Table 2
BMI classification for Adult Asians of obesity, WHO [8].

Category	BMI range (kg/m^2)
Underweight	<18.50
Normal range	18.50-22.90
Overweight	≥23.00
At risk	23.00-24.90
Obese I	25.00-29.90
Obese II	≥30.00

5.1. Adipose Organ

Adipose organ is about 20% of total body weight in a healthy human being. It has been neglected part of body since historic times. However, it contributes to the regulation of body's homeostasis, if disturbed for prolonged period may lead to severe illness and lifestyle disorders. Adipose organ has two types of tissues namely, white adipose tissue (WAT) and brown adipose tissue (BAT) performing different body functions.

Function of WAT is to act as a reservoir of high energy molecules (fatty acids) and supply it as a fuel when the need arises. While BAT uses the same high energy molecules to produce heat in thermogenesis to maintain body temperature. Hence there should be a balance between the accumulated fatty acids in WAT and its usage in various metabolic functions. If this balance is altered, WAT metabolism will be disturbed. WAT, apart from being source of energy also plays important role in the regulation of lipid and glucose metabolism. Energy obtained from food is stored by WAT in the form triacylglycerol (TAG). Mobilization of fat stores and its storage are also regulated by WAT and various other hormones. This tissue also produces very important hormone- leptin, which controls food intake behavior [14].

5.2. Pathophysiology of abdominal obesity

Mesenteric fat consists of adipose tissues which attaches to the intestine covering posterior portion of abdominal wall and is formed by double folding of peritoneum. It allows storage of fat in the abdominal region and consists of a network of blood vessels for a constant flow of fatty acid and lipid molecules [17]. Studies demonstrate high lipogenic activity in mesenteric fat tissues than subcutaneous fat and other regions of the body, with high calorie diet and sedentary lifestyle. This portion of the body is metabolically very active and may have constant uptake of fat than any other part of the body. With excess fat deposition, there is a higher release of free fatty acids in circulation leading to atherogenesis, hyperlipidemia, hypertension and CVDs. Also, excess of free fatty acid level in blood may enhance lipid biosynthesis in the liver causing insulin resistance [18].

5.3. Endocrine and cell signaling activity of abdominal adipose tissue

Adipose organ not just functions to store fat but possess endocrinal ability to produce, secrete and act as a receptor for metabolic compounds, responsible for homeostasis of the body. As discussed earlier, WAT perform various physiological functions which may help to understand the progression of abdominal obesity [19]. Proteins related to adiposity produced by adipose tissue and its health implications have been discussed as follows:

5.3.1. Proinflammatory Cytokine and cytokine-related proteins

- Leptin: It is an anti-obese hormone which reduces food intake and its deficiency is linked to obesity [20].
- TNF α (tumor necrosis factor alpha): Performs diverse cell signaling and its excess may be a cause of insulin resistance as it inhibits insulin signaling [21].
- IL-6 (interleukin 6): Elevated level of IL-6 produced by adipose cells has been reported in CVDs, diabetes in visceral obesity [22,23].

Table 3
BMI Cutoff point indicating high risk of NCDs in Asians, WHO [9].

BMI range (kg/m^2)	Category of risk
18.50-23.00	Acceptable normal range
23.00-27.50	Moderate increase in risk of NCDs
>27.50	High increase in risk of NCDs

5.3.2. Other immune related proteins

- MCP-1 (monocyte chemoattractant protein-1): It is a chemokine produced by adipose cells, inducing increased level of monocytes. Large adipocytes (in obesity) in hypoxia and cellular stress cause inflammation leading to insulin resistance and development of atherosclerosis [24].
- MIF (macrophage migration inhibitory factor): Expansion of adipose cells due to excess energy intake may cause release of MIF by adipose organ, resulting in inflammation and then progression of type 2 diabetes, NAFLDs and atherosclerosis [25].

5.3.3. Proteins involved in coagulation & fibrinolytic system

- PAI-1 (plasminogen activator inhibitor-1): Level of PAI-1 is elevated in obesity and leads to formation of atherosclerotic plaque causing CVDs and is associated with diabetes [26,27].
- Tissue factor: Elevated level of tissue factor secreted by adipose tissue (in obesity) is associated with inflammation and then, diabetes [28].

5.3.4. Complement Proteins

- Adipsin and ASP (acylation-stimulating protein): High level of adipsin and ASP has been linked to obesity and CVDs, as it enhances the uptake of glucose and fatty acids and activity of lipoprotein lipase [29].
- Adiponectin: Low level of adiponectin has been associated with prognosis of insulin resistance, CVDs, and atherosclerosis, whereas its level may balance with weight loss and improve insulin sensitivity [30].
- Adipophilin: It surrounds lipid molecule allowing storage of lipids, functions to increase uptake of fatty acids. Enhanced expression of this protein will lead to fatty liver, heart diseases and type2 diabetes [31].

Table 4
Consequences of under nutrition during in-utero period.

Consequence	Discussion
Reduced BMR (basal metabolic rate) and growth	Lack of availability of essential nutrients may slow down BMR resulting in lowered cell division of tissues and growth of vital organs. This may have long term implications in later life.
Redistribution of blood flow	Brain being a larger and important organ for survival, in starvation condition growing body may maximize blood flow towards brain and not to other body tissues.
Reduced abdominal circumference at birth	Under nutrition may lead to low birth weight infant having lower abdominal circumference. This also may indicate impaired growth of liver during critical period of growth and as an adult may have reduced functional ability, hence liver and other metabolic disorders.
Endocrine changes	Since vital organs are poorly developed due to under nutrition, there may be permanent programming of endocrine system affecting body homeostasis, leading to NCDs in later life.
Reduced capacity of primary adipose tissue: "The adipose overflow hypothesis"	Primary adipose is the first superficial adipose tissue to develop and mature present all over the body, in undernutrition, it has reduced capacity to store excess fat. So, this may cause higher storage of fat in secondary depot (deep subcutaneous and inta-abdominal tissue) which is more metabolically active and present majorly in abdominal area leading to abdominal obesity in adult life and along with other metabolic disorders.

5.3.5. Proteins for lipid metabolism or transport

- LPL (lipoprotein lipase): LPL is an enzyme which hydrolysis triglycerides to lipoprotein and is linked to NCDs [32].
- CETP (cholesteryl ester transfer protein): CETP is produced by adipose tissue transfers cholesteryl ester and triglyceride to lipoprotein. It is considerably important in progression of atherogenesis [33].

5.3.6. Enzymes involved in steroid metabolism

- Cytochrome P450-dependent aromatase: It is an enzyme responsible for conversion of androgens to estrogens and its level if elevated with relation to total adipose mass locally may lead to polycystic ovary syndrome, breast and other related cancers [34,35].

5.3.7. Protein of RAS (renin-angiotensin system)

- Angiotensinogen: One third of this protein is produced by adipose tissue and seen elevated in obesity and possible cause of chronic inflammatory diseases [36].

5.3.8. Other regulatory proteins

- Resistin: Another cytokine highly expressed in abdominal obesity, elevated level of resistin suppresses insulin signaling and induces hepatic injury. It may lead to insulin resistance and NAFLDs [37,38].
- TGF_{β} (transforming growth factor beta): In obesity, level of TGF_{β} rises and it is related to diabetes and progression of cancer [39].
- IGF-1 (Insulin like growth factor 1): Abdominal obesity is linked to lower IGF-1 levels and increases the risk of metabolic disorders. As IGF-1 level rises with protein rich diet and improved body composition, better liver and mitochondrial function is seen which may reduce risk of CVDs and diabetes [40,41].

5.4. Consequences of abdominal obesity

Adipose organ has been regarded as a powerhouse of energy. It is now seen as an interactive unit of the body involved in inflammatory system and the vascular wall. It not only manages energy flux but also is involved in homeostasis of the body interplaying with sympathetic nervous system, rennin-angiotensin pathway, liver metabolic pathways and other vital organ systems. It has an easy access to liver via the portal circulation. In case of hyperlipolytic conditions in adipose tissue present in abdominal region (abdominal obesity), it may deliver excess amounts of non-sterified free fatty acids to the liver. Excessive uptake of free fatty acids by the liver leads to biosynthesis of VLDLs (very low density lipoproteins) and LDLs (low density lipoproteins). Hence, plasma concentrations of triglycerides, LDLs and VLDLs rises remarkably. If such conditions prevail in the body for long duration of time, it may lead to hyperlipidemia, insulin resistance, CVDs, hypertension and other related health problems. Also, people suffering from AO are seen to have low level of HDL (high density lipoprotein) cholesterol. Visceral adipose depots secrete large amount of interleukin-6, leading to production of C-reactive protein (CRP) being strongly associated with heart diseases. Studies also show CRP levels are high in populations with AO with

excess visceral adipose tissue, leading to athero-inflammatory processes [42].

5.5. Abdominal obesity, a potential risk factor for NCDs

About 50 years ago, central adiposity was linked to the increase in risk of diseases that are now profoundly known as NCDs [43]. Later, various population studies were aimed at delineating association of AO with hypertension, type2 diabetes, cardiovascular diseases, cancer, kidney, and liver diseases [1,44–48]. Studies revealed that greater hip circumference means higher lean body mass reduces the risk of NCDs. Hence, solely BMI or body weight may not accurately predict health risk than what is done by WC. Hence, abdominal obesity seems to be positively related to risk of NCDs which need to be studied and controlled at population levels [15].

5.5.1. CVDS

As discussed before, excess adipose tissues contribute to proinflammatory cytokines which pose high risk of CVDs. Meta-analysis done by C.M.Y. Lee et al supports abdominal obesity as an important factor for heart health [49]. Even distribution of fat in abdominal compartments is associated with markers of cardiovascular diseases. High deposits of VAT (visceral adipose tissue) is linked to high triglycerides and low HDL cholesterol levels, while high SAT (subcutaneous adipose tissue) is linked to high LDL and low HDL cholesterol levels [45]. Visceral fat deposits is considered the most baneful owing to greater supply of free fatty acids through portal vein to liver. Thus, increasing the risk of cardiovascular disorders. South Asians are seen to have thrifty phenotype- "Thin Fat Phenotype", i.e. increased body fat percentage specifically at abdominal region. Even in people falling in normal BMI ranges, become prone to cardio-metabolic stresses [50]. Deaths due to CVDs have been reported to be 24% in India (2008), while substantial increase is predicted by 2030 to be 35.9% [51].

5.5.2. Diabetes

Excess abdominal fat increases risk of insulin resistance, hyperinsulinemia and glucose intolerance [52]. Glucose intolerance is a state of unstable blood glucose levels (dysglycemia) often called pre-diabetic stage. Release of excess free fatty acids and adipokines cause oxidative stresses and abnormal endothelial function leading to preliminary stage of type2 diabetes [53]. High level of circulating adipokines from abdominal adipose tissue reduces expression of insulin receptors of body inhibiting insulin pathways and phosphorylation processes leading to insulin resistance [54]. While, Hyperinsulinemia is linked to excess free fatty acid release from abundant abdominal adipose tissue leading to reduced hepatic clearance of insulin in the body [55].

Many studies also report relationship of central obesity and prevalence of diabetes. Misra et al (2005) reported that people having central obesity had diabetes of about 10.1% (male) and 25.9% (female) in a study conducted in North India [56]. A study in urban population in New Delhi found out the prevalence of diabetes to be 50.2% (male) and 50.0% (female) in people suffering from abdominal obesity [57]. Another study in South India indicates the prevalence of abdominal obesity as well as diabetes at 32.4% (male) and 41.4% (female) levels [58].

5.5.3. Hypertension

Obesity is strongly linked to increase in sodium and water retention causing activation of rennin-angiotensin-aldosterone and sympathetic nervous system. Visceral obesity may also enhance cardiac output with continuous release of adipokines and cytokines into the bloodstream leading to hypertension and other related heart problems [59,60]. Marker et al reported in a study conducted in Pune, India that abdominal obesity has link between hypertension, wherein prevalence of hypertension was found to be 25.6% while of abdominal obesity was 38.2% [61]. Another cross-sectional study found high blood pressure was related to raised waist circumference in young population [62].

5.5.4. Cancer

Excess adiposity causes enhanced activity of fatty acid synthase and increased free fatty acids production. High amounts of free fatty acid sensitize oncogenic signals and act as fuel for cancer cells promoting tumor cell growth. Dysfunctional large adipose organ contains large amounts of penetrated immune cells with altered function and causes chronic inflammation with increased supply of pro-inflammatory cytokines which lead to tumor growth. Along with this, excess body fat may lead to constant supply of adipose tissue and tumor-related macrophages, abnormal levels of hormones like estrogen, adiposity related insulin-resistance factors and oxygen deprived tissues, and they all lead to an environment which initiates, promotes and regulates various types of cancer [63,64]. Studies implicate that populations suffering from various types of cancer do have high fat deposits on the abdomen. The cancer research institute however, states that excess fat in the body may increase the risk of 12 types of cancers specific to its sites- stomach, esophageal, liver, pancreatic, gall bladder, colorectal, kidney, breast, ovarian, endometrial, prostate and mouth related cancers. Hence, raised WC pose a high risk for cancers [65].

5.5.5. NAFLDs

NAFLDs refer to multiple disorders associated with liver including fatty liver, nonalcoholic steatohepatitis and with progression of liver damage, cirrhosis. The strong link between abdominal obesity and NAFLD points at the inclusion of this component among risk factors of metabolic syndrome [66]. With excess fat deposition at abdomen, there is a constant release of adipokines to the blood circulation which is harmful and causes liver damage leading to NAFLDs. Also, people with abdominal obesity have high deposit of fat in liver, due to persistent high cholesterol levels in the body [37].

5.5.6. Kidney diseases

Increased energy intake and excretory load in abdominal obesity may cause severe damage to kidney. These changes include glomerulosclerotic damage, hyperperfusion and hyperfiltration and eventually a gradual decline in glomerular filtration rate with time. This poses severe risk of renal injury, chronic kidney disease and end-stage renal disease [67]. Study also reported high fat intake causes structural changes in renal organ and it is evident that renal hypertrophy occurs before hyperglycemia in diabetes [68].

6. Conclusion

In this persisting communicable COVID-19 pandemic, amalgamated with obesity and Non-communicable Diseases, has put populations at higher risk of mortality. The pandemic has disturbed the current health infrastructure with delayed surgeries and poor delivery of health care facilities to non-COVID-19 patients. Individuals with obesity and other metabolic co-morbidities as discussed in the present article, if infected with novel COVID-19 require thorough health care facilities and hospitalization as they have a poor immune system and suffer from severe symptoms. Their health problems like diabetes, hypertension, cardiovascular diseases and other NCDs also must be addressed along with this infection [69]. Health organizations have been targeting quantitative improvement in health to decrease the mortality rates, overlooking qualitative aspects of health. Today's trend in Asian Indians show fall in birth and death rates, while progressive aging goes on in populations owing to faulty lifestyle habits. This points to the need of more population-based studies so that these health factors can be identified and real time data about abdominal obesity and NCDs can be recorded. Hence, abdominal obesity should be further studied so that better kinetics of this endocrine organ can be acknowledged, and possible solutions can be drawn for the betterment of health of population.

Declaration of Competing Interest

The authors report no declarations of interest.

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