Metabolic complications of obesity

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- Overweight refers to a weight above the "normal" range.
- calculation of the body mass index (BMI, defined as the weight in kilograms divided by height in meters squared) .
- is widely accepted for the determination of underweight, normal weight, overweight, and obesity.
- Overweight is defined as a BMI of 25 to 29.9 kg/m2,
- obesity as a BMI of >30 kg/m2.
- Severe obesity is defined as a BMI >40 kg/m2 (or ≥35 kg/m2 in the presence of comorbidities).

- Adult obesity is associated with a striking reduction in life expectancy for both men and women.
- It has been suggested that the steady rise in life expectancy seen during the past two centuries may end because of the increasing prevalence of obesity .
- Individuals with obesity who smoke have a substantially greater reduction in life expectancy than smokers without obesity or nonsmokers with obesity .

- "Metabolically healthy" obese patients.
- — The term "metabolically healthy" obese and overweight refers to individuals who do not have clear adiposity-associated cardiometabolic abnormalities ,
- (ie, hypertension, hypertriglyceridemia, low high-density lipoprotein [HDL] cholesterol, impaired fasting glucose and/or evidence of insulin resistance, diabetes mellitus, abnormal C-reactive protein or abnormal liver function tests suggesting fatty liver disease) .

- Despite the lack of metabolic abnormalities in a subset of obese patients, there is evidence of increased mortality.
- In a pooled analysis of four studies with 10-year follow-up, "metabolically healthy" individuals with obesity had a significantly increased risk of mortality compared with metabolically healthy normal-weight individuals .

- It is evident that obesity varies in its impact on metabolic health ,
- and may often require many years to render measurable deleterious effects.

- three main metabolic complications of obesity;
- diabetes and dysglycemia; metabolic syndrome; and polycystic ovary syndrome.

- As many of these complications can go unnoticed for years without overt clinical complications,
- awareness of both patients and health care professionals is essential such that appropriate screening and diagnostic strategies can be undertaken.

- insulin resistance being the common denominator in these conditions.
- Dysglycemia:
- Impaired blood glucose regulation is one of the most important of these complications, and includes type 2 diabetes mellitus (T2DM), prediabetes, and gestational diabetes.

- Chronic hyperglycemia is associated with an increased risk of development of microvascular complications in T2DM,
- diabetic retinopathy, nephropathy, and neuropathy.
- These complications are often subclinical at the onset,
- being detected through regular screening, which is an important part of overall diabetes management.

- However, in more severe cases, these complications can progress to cause end organ damage,
- diabetes is a leading cause of blindness, kidney failure, and peripheral limb amputation.
- The time from the onset of disease to end stage complications varies, being accelerated by poor glycemic control;
- with good control, it is entirely possible to have a lifetime of diabetes without developing clinically relevant complications.

- Chronic hyperglycemia is also associated with an increased risk of macrovascular complications,
- ischemic heart disease, stroke, and peripheral vascular disease.

- Many patients with T2DM also have several additional risk factors for macrovascular disease,
- including hypertension and dyslipidemia ,
- As for microvascular complications, good glycemic control, blood pressure control, lipid management, and abstinence from smoking are key factors in preventing or delaying the onset or progression of macrovascular disease.

- Metabolic syndrome ;
- Metabolic syndrome describes a constellation of features including;
- insulin resistance, hypertension, dyslipidemia, and abdominal obesity

Diagnostic criteria for the metabolic syndrome.

Parameter	NCEP[a] criteria	IDF[b] criteria
Required		Waist ≥94 cm (men) or ≥80 cm (women)[c]
Number of abnormalities required	≥3 of:	And ≥2 of:
Glucose	≥5.6 mmol/L or drug treatment for elevated blood glucose	≥5.6 mmol/L or diagnosed diabetes
HDL cholesterol	<1.0 mmol/L (men); <1.3 mmol/L (women); or drug treatment for low HDL	<1.0 mmol/L (men); <1.3 mmol/L (women); or drug treatment for low HDL
Triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)	
Hypertension	≥130/85 mmHg or drug treatment for hypertension	≥130/85 mmHg or drug treatment for hypertension

[a] NCEP = National Cholesterol Education Program.[44]

[b] IDF = International Diabetes Federation.[45]

[c] For South Asian and Chinese patients, waist ≥90 cm (men) or ≥80 cm (women); for Japanese patients, waist ≥90 cm (men) or ≥80 cm (women).

- Obese persons undoubtedly release;
- an increased amount of nonesterified fatty acids (NEFA) into the circulation,
- and this increase could supply excess fatty acids to skeletal muscle.
- Increase insulin resistant.
- lipoprotein lipase rapidly hydrolyzes much of the triglycerides, markedly raising NEFA levels.
- NEFA utilization evokes a striking reduction in insulin sensitivity.

- Excessive secretion of NEFA by an expanded pool of adipose tissue remains an attractive mechanism for the insulin resistance of obesity.
- There is relation between distribution of body fat and insulin resistance.
- There is a marked difference in insulin sensitivity in skeletal muscle,
- depending on whether fat is located predominantly in the trunk of the body or mainly in peripheral tissues, particularly the gluteofemoral region.
- Insulin resistance is highest when weight gain occurs predominantly in the trunk .

- There appears to be a fundamental difference in the metabolism of adipose tissue depending on whether it is located in the upper or lower body.
- The triglycerides of upper body fat turn over more rapidly than does fat in the lower body .
- Consequently, plasma NEFA rises to higher levels with upper body obesity than with lower body obesity.
- Seemingly, upper body fat is more insulin resistant than lower body fat, which accounts for differences in NEFA release.

- One hypothesis holds that most of the metabolic consequences of upper body obesity result from increased visceral fat.
- Visceral adipose tissue drains its NEFA directly into the portal circulation and thus could overload the liver with lipids .
- According to this theory most of insulin resistance in muscle is secondary to metabolic changes in the liver, perhaps hepatic glucose overproduction.

- ***Obesity and Fatty Liver:***
  Obesity predisposes to fatty liver.
- **The prevalence of obesity is rising and has brought greater attention to the problem of fatty liver.**

- One route to elevated hepatic triglyceride is through increased synthesis of fatty acids in the liver.
- Another is through inhibition of assembly and secretion of triglyceride-rich lipoproteins (TGRLPs);
- failure to normally secrete TGRLPs leads to a retention of triglycerides in the liver.
- A third mechanism is defective oxidation of fatty acids.

- The primary cause of the fatty liver of obesity appears to be an increased plasma level of NEFA resulting from excess adipose tissue.
- The liver seemingly “sops up” excess NEFA; that is, it removes NEFA that were not taken up by skeletal muscle and other tissues.

- In most nonobese persons, the influx of NEFA into the liver is low enough that fatty acids can be oxidized and/or resecreted (as TGRLP-triglyceride) without appreciable triglyceride accumulation.
- In the presence of obesity, however, the influx of NEFA exceeds the liver's ability to dispose of them, and triglycerides accumulate.
- This basic mechanism accounts for the fatty liver of obesity.

- Even so, the amount of triglycerides that accumulate in the liver of obese persons vary depending on several factors.
- The magnitude of the plasma NEFA flux undoubtedly is one.
- Persons with upper body obesity are more prone to fatty liver than are those with lower body obesity.
- The former likewise has a higher flux of NEFA than does the latter.

- The excess visceral adipose tissue accompanying upper body obesity likely accentuates the amount of NEFA entering the liver.
- If an increased influx of NEFA coexists with a defect in fatty oxidation in the liver, triglyceride accumulation will be accentuated;
- Minor genetic defects in fatty acid oxidation may be relatively common and could contribute to fatty liver, as could an excess consumption of alcohol.

- Polycystic ovarian syndrome;
  Polycystic ovary syndrome (PCOS) consists of a constellation of clinical features including ;
- ovulatory dysfunction, clinical evidence of hyperandrogenism (hirsutism and/or acne), and subfertility.
- PCOS is the most common endocrinopathy in reproductive aged women, affecting between 6.5% and 8% of women overall.

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