CHAPTER-2

REVIEW OF

LITERATURE
The Lipids are a group of organic substances of fatty nature in-soluble in water, soluble in organic solvents and basically esters of fatty acids. Lipids are important dietary constituents not only because of their high-energy value but also because of the fat-soluble vitamins and the essential fatty acids contained in the fat of natural food.

- **Biomedical Importance**

  In the body, fat serves as an efficient source of energy both directly and potentially when stored in adipose tissue. It serves as a thermal insulator in the subcutaneous tissues and around certain organs and non-polar lipids act as electrical insulators allowing rapid propagation of depolarization waves along myelinated nerves. A knowledge of lipid biochemistry is important in understanding many current biomedical areas of interest e.g. obesity, atherosclerosis and role of various polyunsaturated fatty acids in nutrition and health. (Harper)\(^{67}\)

- **The Pathologically & Physiologically Significant Blood Lipids are**

  Separation of major lipid classes by thin layer chromatography by taking suitable solvent (Hexane–Diethyl ether formic acid) shows the presence of cholesterol, triglycerides, phospholipids in equal quantity and show existence of much smaller fraction of un-esterified long chain fatty acid. They are called free fatty acid. The free fatty acids (FFA) is found to be most active fraction of plasma lipids. (Godker)\(^{68}\)
Separation of major classes of lipid by thin layer chromatography by taking Hexane – diethyl either – formic acid solvent.

The analysis of blood plasma shown in the major lipid classes that is shown in table with their normal range found in human blood. (Muller)⁶⁹

**TABLE-I**

**LIPIDS OF THE BLOOD PLASMA IN ADULT PERSON**

<table>
<thead>
<tr>
<th>LIPID FRACTION</th>
<th>Normal Values mg PER 100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN</td>
</tr>
<tr>
<td>Total Lipids</td>
<td>625</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>110</td>
</tr>
<tr>
<td>Total Phospholipids</td>
<td>215</td>
</tr>
<tr>
<td>Lecithin</td>
<td>50-200</td>
</tr>
<tr>
<td>Cephalin</td>
<td></td>
</tr>
<tr>
<td>Sphingomyelins</td>
<td>15-35</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>190</td>
</tr>
<tr>
<td>Free Cholesterol</td>
<td>55</td>
</tr>
<tr>
<td>Free Fatty Acids</td>
<td>12</td>
</tr>
</tbody>
</table>

Total fatty acids (as stearic acid) range from 200-800 mg per 100 ml; 45 percent are triglycerides. 35 percent phospholipids; 15 percent cholesterol ester and less than 5 percent free fatty acids.
Since lipids account for much of the energy expenditure of the body. The problem is presented of a transporting a large quantity of hydrophobic material (lipid) in the aqueous environment. This is solved by associating the more insoluble lipids with more polar ones such as phospholipids and then combining them with protein to form a hydrophilic lipoprotein complex. It is in this way that triglyceride derived from intestinal absorption of fat are transported in the blood as chylomicrons and triglycerides derived from the liver are transported as low density lipoproteins. Fat is released from adipose tissue in the form of FFA and carried in the un-esterified state in the plasma as an albumin FFA complex. Many classes of lipids are, therefore, transported in the blood as lipoproteins.

Table II shows the lipids levels of normal and obese persons of different age groups as investigated by [Waxler and Craig. (1964)]70.

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>NORMAL</th>
<th>OBESE</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>477</td>
<td>668</td>
</tr>
<tr>
<td>30-39</td>
<td>565</td>
<td>625</td>
</tr>
<tr>
<td>40-49</td>
<td>605</td>
<td>644</td>
</tr>
<tr>
<td>50-59</td>
<td>612</td>
<td>697</td>
</tr>
<tr>
<td>60-69</td>
<td>635</td>
<td>675</td>
</tr>
<tr>
<td>70 &amp; Above</td>
<td>620</td>
<td>660</td>
</tr>
</tbody>
</table>

- **Fatty Acids**

Fatty acids are synthesized in various tissues including the liver; intestine and adipose cells. The fatty acids are synthesized from glucose through a complex lipogenic pathway that is highly regulated by the hormones insulin, glucagone;
and somatostatin. The availability by initial substrates and products of this pathway also influence lipogenesis. In the liver, fatty acids are incorporated in the triglycerides and secreted in very low density lipoprotein (VLDL) particles. In the intestine triglyceride is secreted in chylomicrons. Enhanced fatty acid synthesis may account, in part, for the hyper triglyceridemia associated with certain obesing associated disorder.[MCNA]^{71}

The free fatty acids are found in combination with albumin in plasma. They are rapidly metabolised so that concentration of FFA is varies in plasma between 0-1 and 2-0 μeq / dl. Low level of FFA is recorded in the fully fed condition that in 0.5 μeq / dl. and raise a level in fasting condition 0.7 to 0.8. The level of FFA reached to 1-2 to 2-0 μeq/dl in obese person which causes certain abnormalities. Fatty acids are found in human body are of two type: (Godker)^{72}

I.  Saturated

II. Unsaturated

Table III

<table>
<thead>
<tr>
<th>I. Saturated Fatty Acids</th>
<th>Good Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td></td>
</tr>
<tr>
<td>1. Butyric Acid</td>
<td>Butter</td>
</tr>
<tr>
<td>2. Laproic Acid</td>
<td>Coconut Oil, Butter</td>
</tr>
<tr>
<td>3. Caprylic Acid</td>
<td>Palm Oil, Coconut oil</td>
</tr>
<tr>
<td>4. Capric Acid</td>
<td>Palm Oil, Coconut oil</td>
</tr>
<tr>
<td>5. Lauric Acid</td>
<td>Palm Oil, Coconut oil</td>
</tr>
<tr>
<td>6. Myristic Acid</td>
<td>Butter</td>
</tr>
<tr>
<td>7. Palmitic Acid</td>
<td>Animal, Plant fats</td>
</tr>
<tr>
<td>8. Stearic Acid</td>
<td>Animal Plant Fats</td>
</tr>
<tr>
<td>II</td>
<td>Unsaturated Fatty Acid</td>
</tr>
<tr>
<td>-----</td>
<td>----------------------------</td>
</tr>
<tr>
<td>1.</td>
<td>Oleic Acid</td>
</tr>
<tr>
<td>2.</td>
<td>Linoleic Acid</td>
</tr>
<tr>
<td>3.</td>
<td>Linolenic Acid</td>
</tr>
<tr>
<td>4.</td>
<td>Arachidonic Acid</td>
</tr>
</tbody>
</table>

**CHOLESTEROL:**

Cholesterol is ubiquitous in the animal body where it acts as stabilizer to the charged phospholipid molecule. In the blood, cholesterol is present as both free and ester cholesterol. About 2/3\textsuperscript{rd} of blood cholesterol is present as ester. In most other tissues, free cholesterol predominates (Khalsa & Sharma 1970)\textsuperscript{73}.

Dietary cholesterol consists of both free and esterified forms. In intestinal lumen ester is hydrolysed to free cholesterol and fatty acids. After entering the mucosa, free cholesterol is re-esterified with fatty acids and passed in the intestinal lymph together with triglycerides and phospholipids in the form of chylomicrons. Bile is necessary for the uptake of cholesterol in the intestinal mucosa. Absorbed cholesterol is mixed with endogenously synthesized cholesterol and delivered to the plasma via intestinal lymph. The liver is another major site of synthesis, the cholesterol pool is further augmented. The liver is a major source of cholesterol degradation (to bile acids and other steroid hormones) and it may also undergo, transformation to sex hormones and also contributes cholesterol to the bile. Some of this cholesterol is reabsorbed and some excreted. The intestine also excretes cholesterol into its lumen from which it is excreted as cholesterol or hydrogenated by the intestinal flora and excreted in faces as Copro-sterol (Kritchivsky 1969)\textsuperscript{74}. 
About 1.5 to 2 g of cholesterol is synthesized by body and about 0.3g / day is provided by the average diet. Cholesterol is eliminated by two main pathways)

A). Conversion to bile acid and

B). By excretion of neutral steroid in the faces. The liver is main site of cholesterol synthesis and other tissues known to be capable of synthesizing cholesterol include the testis, aorta, skin, intestine and the adrenal cortex. Acetyl Co. A is the source of all the carbon atoms in Cholesterol.

The cholesterol is present both in red cells and plasma. The erythrocyte cholesterol is maintained at a relatively constant level and variations are only reflected in plasma cholesterol, hence determinations in it are preferred than the whole blood. The cholesterol is transported from one tissue to another with plasma lipoprotein molecule. Approximately 70 percent of plasma cholesterol is bound in beta lipoprotein and the remaining alpha fraction (Khalas and Sharma 1970).

The concentration of plasma cholesterol in normal healthy persons varies markedly i.e. 150-250 mg per 100 ml of plasma (Khalas and Sharma 1970).

TABLE-IV
SHOWING THE NORMAL LEVELS OF CHOLESTEROL AS FOUND BY DIFFERENT WORKERS

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Cholesterol in mg percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sperry &amp; Webb</td>
<td>1950</td>
<td>200.2 – 210.7</td>
</tr>
<tr>
<td>Carlson</td>
<td>1960</td>
<td>254.0 ± 8</td>
</tr>
<tr>
<td>Bandhyopadhyay &amp; Benerjee</td>
<td>1964</td>
<td>157.0 ± 10</td>
</tr>
<tr>
<td>Hoffman</td>
<td>1964</td>
<td>185.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(135.0 - 260)</td>
</tr>
<tr>
<td>Leonard et al</td>
<td>1965</td>
<td>182.9 ± 23.8</td>
</tr>
<tr>
<td>Dutt</td>
<td>1967</td>
<td>150.0 – 220.0</td>
</tr>
<tr>
<td>Khalsa &amp; Sharma</td>
<td>1970</td>
<td>150.0 – 250.0</td>
</tr>
</tbody>
</table>
60 to 80 percent of the total cholesterol is esterified and remaining is free cholesterol. The ratio of ester cholesterol to total cholesterol appears to be remarkably constant (Borgstrom & Jordan, 1959)⁷⁶. But Leonard et al (1965) have reported that as the total cholesterol level increase in the free cholesterol was proportionally greater than the increase in esterified fraction. Before the age of 20, there is only a slight difference between the serum cholesterol values of girls and boys with slightly higher values for the girls. From the age 20 to 50 years, the plasma cholesterol continues its upward trend with age with higher values for men than women. From then the level of plasma cholesterol in women tends to overtake and surplus that of comparable age probably reflecting the hypercholesterolemic effect of menopause (Lopez et al 1967)⁷⁷. But Khalsa & Sharma (1970) report higher level of cholesterol in females than in male. In older ages (beyond 70 years) the serum cholesterol again decreases in both sexes (Lopez et al 1967)⁷⁷. Several other workers have also reported a significant increase in cholesterol level with age, irrespective of race (Nath et al 1957)⁷⁸.

**TABLE-V**

**SHOWING THE SERUM CHOLESTEROL LEVELS OF NORMAL PERSONS OF DIFFERENT AGE GROUPS**

<table>
<thead>
<tr>
<th>Name of the Author</th>
<th>Cholesterol Levels (mg%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10-19</td>
</tr>
<tr>
<td>Nath et al 1957</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Waxler &amp; Criag (1964)</td>
<td>-</td>
</tr>
<tr>
<td>Rafkind et al 1967</td>
<td>170</td>
</tr>
</tbody>
</table>
In India the normal serum cholesterol level has been shown to vary with socio-economic groups. In the higher income group, Mathur et al 1962 observed a mean concentration of 193 ± 40 mg percent while for low income group the level was 134 ± 32 mg percent.

Padmawati et al (1959)\(^7\) observed that the mean levels of serum cholesterol in the group of industrial worker in Delhi was 168.7 mg percent and it was 179.5 mg percent in general population.

(Niall Jstone 1990)\(^8\) reported that etiology of hypercholesterolemia is not fully understood in assessing this much interest has centered on two principal site of endogenous cholesterol synthesis in vivo i.e. the liver and the intestine, where as the liver is the predominant site of sterologenesis in non diabetic animals.

**TABLE-VI**

**SHOWING THE TOTAL SERUM CHOLESTEROL LEVELS (mg%) IN NORMAL MALE AND FEMALE SUBJECTS OF DIFFERENT AGE GROUPS**

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>SEX</th>
<th>YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Henry</td>
<td>M</td>
<td>110-250</td>
</tr>
<tr>
<td>Schilling</td>
<td>M</td>
<td>199</td>
</tr>
<tr>
<td>et al 1969</td>
<td>F</td>
<td>199</td>
</tr>
</tbody>
</table>

M = MALE    F = FEMALE

With advancing age, there is a trend towards a proportional increase in non-esterified fraction of cholesterol but this is not statistically significant.

**CHOLESTEROL IN OBESE INDIVIDUALS**

In general, the cholesterol level follows the pattern of total body lipids. Therefore, body built influences the serum cholesterol that lean and thin people have lower serum cholesterol than overweight subjects. Increase in serum
cholesterol due to one pound increase in weight is calculated to 1.784 mg per 100 ml (Nath et al. 1957)\textsuperscript{78} Jackson (1969) has reported serum cholesterol levels in obese 220 ± 73 mg percent while Pearson & Mathur (1969) reported 170 – 414 mg percent.

In above individual cholesterol is found to be increased in comparison to normal according to (MCNA – obesity – Vol – 2)\textsuperscript{81}. The hypercholesterolemia found due to increased FFA flux seen in generalised obesity likely contributes, directly or indirectly to these abnormalities.

**TABLE - VII**
**SHOWING SERUM TOTAL CHOLESTEROL IN OBESE INDIVIDUALS OF DIFFERENT AGE GROUPS**

<table>
<thead>
<tr>
<th>AGE GROUPS (IN YEARS)</th>
<th>SERUM CHOLESTEROL (mg%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WAXLER &amp; CRAIG (1964)</td>
</tr>
<tr>
<td></td>
<td>RIFKIND et al (1967)</td>
</tr>
<tr>
<td>10-19</td>
<td>-</td>
</tr>
<tr>
<td>20-29</td>
<td>198</td>
</tr>
<tr>
<td>30-39</td>
<td>198</td>
</tr>
<tr>
<td>40-49</td>
<td>208</td>
</tr>
<tr>
<td>50-59</td>
<td>230</td>
</tr>
<tr>
<td>60-69</td>
<td>215</td>
</tr>
<tr>
<td>70 &amp; Above</td>
<td>213</td>
</tr>
</tbody>
</table>

**PHOSPHOLIPIDS**

Phospholipids are a component of the lipoproteins. They represent about 46 percent of the lipids of alpha lipoprotein and 26 percent of beta lipoprotein (Kritichvsky, 1969)\textsuperscript{82}.

Enzymes which degraded phospholipid are known as phospholipases. These enzymes occur in snake venom, plants and bacteria and recently their
presence in some animal tissues has also been established. There are four major lipases and are designated as phospholipase A.B.C. and D.

In obese persons, (Rifkind et al 1967)\textsuperscript{83} has reported phospholipid levels varying from 204-229 mg percent.

Triglycerides

Triglyceride are major lipids in chylomicron and VLDL and serve as energy substrate in the liver and peripheral tissue particularly muscle energy so, triglyceride is the storage form of fat, this lipid fraction is also present in blood plasma in the form of lipoprotein. Absorption of fat from the intestine occurs as triglyceride in the form of chylomicrons which are then promptly and efficiently removed from the circulation by the parenchymal cells of liver, with a half removal time of about five minutes (Gordon, 1964)\textsuperscript{84} Excluding the post absorptive state, the triglyceride fat circulates in the blood normally in a concentration of about 50 – 150 mg/100 ml. Lipoproteins are produced in the liver from fatty acids glycerol and proteins, after which they are released in blood stream. Under normal conditions, triglycerides are believed not to enter the circulation from adipose tissue, so that their plasma concentration is indicative solely of a function of liver.

The largest contribution to the triglycerides of adipose tissue comes from lipogenesis from carbohydrates. This biochemical transformation occurs with high efficiency in normal animal and human take place at an accelerated rate when large intake of food especially carbohydrate, exceeds the capacity of available mechanisms for utilization through oxidative and storage as carbohydrate (Grodsky et al, 1963)\textsuperscript{85}. 
Perpetuation of these circumstances by habitual consumption of excessive caloric loads leads to adaptive changes which augments the tendency to lipogenesis and storage of body fat (Tepperman, 1958).

**TABLE VIII**
SHOWING THE TRIGLYCERIDE LEVELS IN NORMAL PERSONS AS INVESTIGATED BY DIFFERENT WORKERS.

<table>
<thead>
<tr>
<th>NAME OF THE AUTHOR</th>
<th>YEAR</th>
<th>TRIGLYCERIDE (mg%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Havel and Peterson</td>
<td>1958</td>
<td>112</td>
</tr>
<tr>
<td>Antonis and Bersohn</td>
<td>1960</td>
<td>97 ± 28</td>
</tr>
<tr>
<td>Carlson</td>
<td>1960</td>
<td>112</td>
</tr>
<tr>
<td>Albrink et al</td>
<td>1962</td>
<td>114</td>
</tr>
<tr>
<td>Bandhyopadhyay &amp; Banerjee</td>
<td>1964</td>
<td>125 ± 116</td>
</tr>
<tr>
<td>Hoffman</td>
<td>1964</td>
<td>95 (58-134)</td>
</tr>
<tr>
<td>Harper</td>
<td>1969</td>
<td>142 (80 – 180)</td>
</tr>
<tr>
<td>Dutt</td>
<td>1967</td>
<td>87.04 ± 16.93</td>
</tr>
</tbody>
</table>

**TABLE IX**
SHOWING THE TRIGLYCERIDE LEVELS IN NORMAL PERSONS OF DIFFERENT AGE GROUPS

<table>
<thead>
<tr>
<th>AGE GROUPS (IN YEARS)</th>
<th>SERUM TRIGLYCERIDE (mg%)</th>
<th>Waxler &amp; Craig (1964)</th>
<th>Rifkind et al (1967)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-19</td>
<td>-</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>66</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>75</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>86</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>93</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>101</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>70 &amp; Above</td>
<td>91</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
TABLE-X

SERUM TRIGLYCERIDES LEVELS IN OBESE HEALTHY PERSONS OF DIFFERENT AGE GROUPS

<table>
<thead>
<tr>
<th>AGE GROUPS (IN YEARS)</th>
<th>SERUM TRIGLYCERIDE (mg%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-19</td>
<td>-</td>
</tr>
<tr>
<td>20-29</td>
<td>154</td>
</tr>
<tr>
<td>30-39</td>
<td>132</td>
</tr>
<tr>
<td>40-49</td>
<td>118</td>
</tr>
<tr>
<td>50-59</td>
<td>137</td>
</tr>
<tr>
<td>60-69</td>
<td>124</td>
</tr>
<tr>
<td>70 &amp; Above</td>
<td>115</td>
</tr>
</tbody>
</table>

Lipoprotein

(Godker) A lipoprotein is a complex macromolecule of lipid and protein in which the non-polar lipid core is surrounded by a polar monolayer of phospholipids head of free cholesterol and apolipoprotein. These particles varying in composition; size, density and function, electrophoretic mobility. The major blood lipoproteins are:

1) Chylomicrons (extremely lowdensity lipoprotein derived from triglycerides)

2) Very low density lipoprotein (VLDL)

3) Intermediate – density -- lipoprotein (IDL)

4) Low Density Lipoprotein (LDL)

5) High Density Lipoprotein (HDL)
Plasma lipoproteins are in dynamic state. They are continuously being synthesized and degraded with rapid exchange of protein and lipids. The normal values of lipoprotein in plasma is described as under:

**Table-XI**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of Lipoprotein</th>
<th>Normal range in mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>High density lipoprotein</td>
<td>30 to 60</td>
</tr>
<tr>
<td>II.</td>
<td>Low density lipoprotein</td>
<td>95 to 145</td>
</tr>
<tr>
<td>III.</td>
<td>Very low density lipoprotein</td>
<td>upto 30</td>
</tr>
</tbody>
</table>

These lipoprotein play important role in the regulation of lipid transport and lipoprotein metabolism.

Composition of the lipoprotein in plasma of man

**Table-XII**

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Source</th>
<th>Protein %</th>
<th>Total lipid %</th>
<th>Triglyceride %</th>
<th>Phospholipid %</th>
<th>Free Cholesterol</th>
<th>Ester Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chylomicron</td>
<td>Intestine</td>
<td>1</td>
<td>99</td>
<td>88</td>
<td>8</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2. VLDL</td>
<td>Liver, Intestine</td>
<td>7</td>
<td>93</td>
<td>56</td>
<td>20</td>
<td>0.8</td>
<td>15</td>
</tr>
<tr>
<td>3. LDL</td>
<td>VLDL, Chylomicrone</td>
<td>20</td>
<td>80</td>
<td>20</td>
<td>25</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>4. HDL</td>
<td>Liver Intestine</td>
<td>50</td>
<td>50</td>
<td>5</td>
<td>25</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>

**The Apolipoproteins**

(Godker)\(^7\) The apolipoproteins are the chief structural component of the lipoprotein. Researchers originally speculated that apolipoprotein belonged to distinct families that were identified by an alphabetical nomenclature. Although this hypothesis has fallen out of favour, the naming system it inspired remains. The roman numeral suffix describes the order in which the apolipoproteins emerge from a chromatographic column.
Lipoprotein classes and associated lipids and apolipoproteins are showing in the table. (MCNA - Lipids)\textsuperscript{88}

### TABLE XIII:
LIPOPROTEIN CLASSES AND ASSOCIATED LIPIDS AND APOLIPOPROTEINS

<table>
<thead>
<tr>
<th>Lipoprotein Class</th>
<th>Main Lipids</th>
<th>Apolipoproteins</th>
<th>Electrophoretic Mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicron remnants</td>
<td>Dietary Cholesteryl esters</td>
<td>B-48, E</td>
<td>Origin</td>
</tr>
<tr>
<td>VLDL</td>
<td>Endogenous Triglycerides</td>
<td>B-100, C-I, C-II, C-III, E</td>
<td>Pre beta</td>
</tr>
<tr>
<td>IDL</td>
<td>cholesterol esters</td>
<td>B-100, E</td>
<td>broad - beta</td>
</tr>
<tr>
<td>LDL</td>
<td>cholesterol esters</td>
<td>B-100</td>
<td>beta</td>
</tr>
<tr>
<td>HDL\textsubscript{2}</td>
<td>cholesterol esters</td>
<td>A-I, A-II, C-I, C-II, C-III, E</td>
<td>alpha</td>
</tr>
<tr>
<td>HDL\textsubscript{3}</td>
<td>Cholesteryl esters</td>
<td>A-I, A-II, C-I, C-II, C-III, E</td>
<td>alpha</td>
</tr>
</tbody>
</table>

The surface proteins of the lipoprotein are called apoproteins or apolipoproteins. Beside providing structural stability to the lipoprotein, they play important roles in determining metabolic fate of the particles on which they reside. The apoproteins are named in an arbitrarily alphabetical orders. The nine major apoproteins are listed in Table XIV.
<table>
<thead>
<tr>
<th>Apolipoprotein</th>
<th>Molecular</th>
<th>Lipoproteins</th>
<th>Metabolic Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>apoA-I</td>
<td>28,016</td>
<td>HDL</td>
<td>Structural component of HDL:LACT activator</td>
</tr>
<tr>
<td>apo A-II</td>
<td>17,414</td>
<td>HDL</td>
<td>Unknown</td>
</tr>
<tr>
<td>apo A-IV</td>
<td>46,465</td>
<td>HDL</td>
<td>Unknown: possibly facilitate transfer of other apo-lipoprotein between HDL and chylomicrons</td>
</tr>
<tr>
<td>apo B-48</td>
<td>264,000</td>
<td>Chylomicrons</td>
<td>Necessary for assembly and secretion of chylomicrons from the small intestine</td>
</tr>
<tr>
<td>apo B-100</td>
<td>514,000</td>
<td>VLDL, IDL, LDL</td>
<td>Necessary for assembly and secretion of VLDL from the liver; structural protein of VLDL, IDL, LDL; ligand for LDL receptor</td>
</tr>
<tr>
<td>apo C-I</td>
<td>6630</td>
<td>All major lipoproteins</td>
<td></td>
</tr>
<tr>
<td>apo C-II</td>
<td>8900</td>
<td>All major lipoproteins</td>
<td>Activator of lipoprotein lipase</td>
</tr>
<tr>
<td>apo C-III</td>
<td>8800</td>
<td>All major lipoproteins</td>
<td>Inhibitor of lipoprotein lipase; may inhibit hepatic uptake of chylomicron &amp; VLDL remnants</td>
</tr>
<tr>
<td>apo E</td>
<td>34,145</td>
<td>All major lipoproteins</td>
<td>Ligand for binding of several lipoprotein to the LDL receptor &amp; possibly to a separate hepatic apo E receptor</td>
</tr>
</tbody>
</table>

HDL – High density lipoprotein, LCAT – lecithin cholesterol acyltransferase; VLDL, very low density lipoprotein; IDL – intermediate density lipoprotein; LDL – low density lipoprotein.

apo B-48 is the apoprotein essential for assembly and secretion of chylomicron (Gotto et al, 1986)\(^\text{89}\), Its name derives from the fact that it constitutes 48 percent of the amino terminal end of the apo B-100 (Powell et al, 1987)\(^\text{90}\).
which is the major apoprotein of VLDL, IDL and LDL. It appears that apo B-48 is generated from the same gene and messenger-RNA (m-RNA) as apo B-100, but that only about half of the apo B-100 protein is translated into the protein in the intestine. Once the chylomicron has been secreted by the small intestine. It does not appear that apo B-48 has any other role in the plasma metabolism of this lipoprotein or in the subsequent removal of chylomicrons from the plasma by the liver.

apo B-100 is the largest of apoprotein, having molecular weight of 5,00,000 daltons. In human apo-B-100 appears to be synthesised in significant quantities only in liver. apo B-100 is the major apoprotein of VLDL, IDL and LDL. composing approximately 30 percent, 60 percent and 95 percent of protein in these respective lipoproteins. It is absolutely necessary for the assembly and secretion of VLDL from the liver and serves as the binding protein for the LDL receptor on cells throughout the body. The LDL receptor binding domain of apo B-100 is absent from apo B-48.

There are three C apolipoproteins, which are despite their similar letter names protein with distinct metabolic roles. Liver is the site for synthesis of all three of the C apoproteins.

apo C-I is minor component of VLDL, IDL and HDL whose exact function is unknown.

apo C-II is a constitute of VLDL and is also present in IDL, HDL and chylomicrons. apo C-II is an essential activator of enzyme lipoprotein lipase (LPL), which hydrolyzes triglycerides in chylomicrons and VLDL. Subjects lacking apo C-II have sever hypertriglyceridemia.

apo C-III is a major component of VLDL, in which it accounts for about 40 percent of the protein. apo C-III is an inhibitor of LPL action (Gotto et al 1986)\textsuperscript{89}. 
The subjects lacking C-III were shown to have supranormal rates of lipolysis of VLDL triglyceride (Ginsberg et al. 1986). Several group of investigators have shown that all of the C apolipoproteins may inhibit removal of plasma chylomicron and VLDL remnants by the liver. Transgenic mice that produce excess apo C-III have sever hypertriglyceridemia (Aalto, et al 1992).

apo E is synthesised in the liver and is found in all the lipoproteins. Exact activity of this protein is not known, but it appears to regulate removal of remnants lipoproteins the plasma by the liver. apo-E can bind to both heparin like molecules that are present on the surface of all cells and the LDL receptor. A patient who lacked apo-E was found to have significant elevations of chylomicron remnants and VLDL remnants.

apo A-I is the major protein present on HDL constituting about 70 percent to 80 percent of the protein mass (Gotto et al, 1986) Apo A-1, in synthesised both in the liver and the small intestine. apo A-1 is an activator of the enzyme L-CAT (leicithin cholesterol acyltransferase) which esterifies free cholesterol in plasma (Kostner et al 1987). apo-A-1 also plays role in maintaining integrity of HDL particles in the plasma and thus, prolonging their life time in the circulation. Subjects without apo A-1 have been described and have been shown to lack HDL (Norum et al, 1982), apo A-II is second most abundant apoproteins in HDL, like apo A-1, apo A-II is synthesised in both the liver and the small intestine in human. Function of apo A-II has not been determined.

apo A-IV is a minor component of HDL and chylomicrons (Gotto et al 1986). It is synthesised only in small intestine in humans. apo A-IV may play a role in the activation of L-CAT.
The LDL Receptor

In the ground breaking, noble prize winner work of brown and goldstein, the severe hypercholesterolemia associated with the genetic disorder familiar hypercholesterolemia was attributed to a genetic defect in the cellular receptor for LDL. This LDL receptor is also called the B/E receptor because of its ability to recognized particles containing both apos B and E; Low density lipoprotein receptor activity occurs mainly in the liver; although other body cell are also able to take up LDL. An important feature of the LDL receptor is its Binding selectively; the receptor recognizes apo E more readily than apo B-100 thus accounting for the more rapid clearance from plasma of lipoproteins containing apo E.

Enzymes Involved In Lipid Metabolism

Lipoprotein lipase (LPL) is synthesised in fat and muscle cells. It is a glycoprotein of molecular weight 55,000 kg. After secretion from fat and muscle cells LPL is transported across endothelial cells and binds to their luminal surfaces in the capillary beds of adipose tissue, lung and muscles. Hydrolysis of chylomicron and VLDL triglyceride occur at luminal surface of capillary endothelial cells. LPL then associates with remnant lipoprotein particle and travels with that lipoprotein in the circulation (Goldberg et al 1986).93

In fact, new investigations suggest that LPL bound to chylomicron or VLDL remnants may play an important role in their removal from plasma by the liver. The regulation of LPL synthesis and secretion by fat and muscle cells is complex. Dietary fat seems to stimulate adipose tissue LPL and inhibit muscle LPL, whereas fasting seems to do the opposite. Insulin stimulates the synthesis and secretion of LPL and reduces insulin levels or activity in diabetes mellitus may lead to impaired triglyceride clearance.
Numerous mutations in the LPL gene have been described. Subjects who are homozygous for LPL mutations have severe hypertriglyceridemia, which usually presents in childhood (Type I hyperlipidemia). Individuals who are heterozygous for LPL defects may have only mild to moderate fasting hypertriglyceridemia but almost always have marked elevations of plasma triglyceride after consuming a high fat meal. (Mjesenbock et al., 1993)\textsuperscript{94}.

Hepatic triglyceride lipase (HTGL) is an enzyme and belongs to the same family of lipases as does LPL but which has several unique characteristics. III GL is synthesised in the liver and binds to the luminal surface of endothelial cells in hepatic sinusoids (Gotto et al. 1986)\textsuperscript{95}.

Studies suggest that HTGL plays a role in removing triglycerides from partially catabolised VLDL or IDL and therefore plays a role in the conversion of VLDL to LDL (Goldberg et al 19820)\textsuperscript{93}. There are also some studies suggesting a role for HTGL in the metabolism of chylomicron remnants.

Finally, HTGL may have a role as a lipase for HDL. Absence of HTGL activity has been demonstrated in rare patients. These individuals are usually severally hypertriglyceridemic with an accumulation of chylomicron and VLDL remnants in plasma. In contrast to most patients with elevated triglyceride levels, however, subjects with HTGL deficiency have normal levels of HGL.

L-CAT (lecithin cholestrol acyltransferase) has a molecular weight of about 70,000 Kg, is synthesised in liver. It mediates transfer of linoleate from lecithin of free cholesterol in plasma, resulting in the formation of cholesterol ester. apo A-I is a cofactor for LACT esterification of free cholesterol.

Cholesterol Ester Transfer Protein (CETP) (molecular weight 67,000 Kd) synthesised in the liver and circulation of plasma in association with HDL. CETP mediates the exchange of cholesteryl esters from HDL with triglyceride from
chylomicrons or VLDL (Tall, 1986) \(^{96}\) LDL cholesteryl esters can also be exchanged with triglyceride from chylomicrons and VLDL leading to small, dense LDL. In Japan few individuals were identified with extreme elevation of HDL cholesterol and apo A-I (Inazue et al, 1990) \(^{97}\) These subjects were found to be homozygous for a mutation in the gene for CETP; they have to CETP activity in plasma. Subjects heterozygous for this mutation may have slightly elevated levels in HDL. This genetic disorder demonstrates the important role of CETP in the transport of cholesteryl esters out of HDL. Transgenic mice that over express the CETP gene have low levels of HDL cholesterol. (Havek, et al 1992) \(^{98}\) Subject with hypertriglyceridemia do not, however, have elevated plasma levels of CETP.

**General Lipid Metabolism**

(MCNA-Sheehan) \(^{99}\) The chylomicrons are finally deposited either in the liver or in fat storage depots (adipose tissue) which in health from about 15\% of the body weight role of liver in lipid metabolism.


2. Synthesis of triglycerides


4. Synthesis of phospholipids

5. Synthesis of VLDL and HDL

6. Formation of Ketone bodies.

Like wise lipoprotein lipase in adipose tissue is responsible for the clearance of chylomicrons. Plasma lipoprotein lipase is also responsible for the clearance of small amount of chylomicrons in plasma. The triglycerides undergo hydrolysis by an intercellular lipase to form FFA and glycerol. The released free
fatty acids are carried in the un-esterified state in plasma as albumin – FFA complex, many tissue such as liver, heart, kidney, muscle, lung, testis, brain and adipose tissue have the ability to oxidize long chain fatty acid by β oxidation. By this way long chain fatty acid are degraded completed to acetyl co A which can be oxidise to CO2 and water via the citric acid cycle.

The glycerol which has been released by hydrolysis of fat enters general carbohydrate metabolism via glyceraldehydes and is either converted to glycogen or oxidized. The TG stores in adipose tissue continually undergo lipolysis and re-esterification when the availability of glucose in adipose tissue is reduced rate of lypolysis exceed the rate of esterification with subsequent accumulation of FFA and their release in the plasma. Like wise their are two pathway of lipid metabolism.

I. Exogenous pathway

II. Endogenous pathway

Exogenous Pathway of Lipid Metabolism

Because triglyceride is the chief lipid constituent of these particles, chylomicrons and VLDL are also called triglyceride-rich lipoproteins. chylomicron metabolism characterizes the exogenous pathway of lipid metabolism. Chylomicrons are synthesised by intestinal epithelial cells from fatty acids derived from either diet or catabolism of sugars, certain amino acids, and other fatty acids.

Chylomicrons contain apolipoproteins B-48, A-I, and A-II. They exchange apos A-I and A-II for C apolipoproteins and apo E from HDL as they circulate through the lymphatic system. Also, through the action of cholesteryl ester transfer protein (CETP), chylomicrons exchange triglyceride for cholesteryl esters from
HDL. Cholesteryl ester transfer protein is also called lipid transfer protein I (LTP-I).

In the capillary beds of the arterial system, apo C-II activates lipoprotein lipase (LPL), an enzyme anchored to the capillary endothelium that hydrolyzes the triglyceride content of the chylomicron into free fatty acids (FFA). Free fatty acids obtained in this fashion are either oxidized by muscle cells for energy, stored by adipose tissue, or returned to the liver for oxidation or re-esterification to triglyceride (TG) for VLDL synthesis.

The enzymatic action of LPL and the protein and lipid exchanges with HDL reduce the chylomicron to a smaller particle called a chylomicron remnant. Chylomicron remnants are depleted of TG and apo C, but retain apos B-48 and E and cholesterol from the intestinal lumen. Remnants are cleared from the circulation by uptake into hepatocytes through a chylomicron remnant receptor (possibly an LDL receptor like protein) that recognizes apo E. Apolipoprotein C-III inhibits the uptake of apo E-containing remnant particles by the liver.

Chylomicron expression is closely linked with dietary intake of fat: increased fat consumption leads to increased chylomicron production. Chylomicrons are not found in the postabsorptive state (9 to 15 hour fast) and a high carbohydrate, low fat diet diminishes their formation. Under such conditions, TG transport is achieved through VLDL particles.

Endogenous Pathway of Lipid Metabolism

Very low density lipoprotein (VLDL) is synthesized in the liver from either FFA obtained from chylomicron catabolism or from endogenously produced triglyceride. These particles are smaller and more dense than chylomicrons (Figure 2-5). The apolipoproteins associated with VLDL are apos B-100, C-I, C-II, C-III and E. A high carbohydrate diet can increase VLDL - TG production.
Through the action of CETP, VLDL exchanges triglyceride for cholesteryl esters from HDL. Like chylomicrons, LPL catalyzes the hydrolysis of triglyceride in VLDL to FFA that are either used by muscle or stored in adipose tissue. LPL catalyzed triglyceride hydrolysis reduces VLDL to intermediate density lipoprotein (IDL). Intermediate density lipoprotein can either be taken up by the LDL receptor, or be further reduced to low density lipoprotein (LDL) through the action of hepatic lipase. Intermediate density lipoprotein clearance is mediated by apo E, which has a higher affinity for LDL receptor than does apo B. Of the apolipoproteins, LDL contains only apo B-100. Approximately two thirds of LDL is cleared through the LDL receptor (60% to 70% of the activity of which is located in the liver). Peripheral cells also can take up LDL for use in membrane biogenesis and steroid synthesis. About 70% of plasma cholesterol is carried by LDL particles. The half lives of VLDL and IDL are brief (approximately 12 hours), compared with LDL (2.5 to 3.5 days).

We better understand the roles of LDL in cholesterol transport and atherogenesis than those of the other lipoproteins. Low density lipoprotein is cleared by both receptor mediated and nonreceptor mediated processes.

**Modified LDL**

Low density lipoproteins may be modified through acylation or oxidation, or both. These modified lipoproteins are particularly important in our examination of atherogenesis. First, these molecules are cytotoxic and may damage the vascular endothelium, thus initiating the proliferative process or atherosclerosis. Second, these particles may aggregate in the intima of the vessel wall and are chemotactic to T cells and monocytes. Modified LDL has decreased affinity for the LDL receptor, and may be cleared primarily through a scavenger receptor pathway. These scavenger receptors may explain the mode of transport of lipid into macrophages.
Cholesterol Metabolism

Cholesterol is derived about equally from the diet and from biosynthesis. Acetyl coA is the source of all carbon atom in cholesterol.

Mechanism of Synthesis

Thiolase

HMG-CoA Synthase

3-hydroxy-3-methylglutaryl CoA (HMG-CoA)

HMG-CoA reductase

Prenyl transferase

Squalene Synthase

Squalene epoxidase

Oxidosqualene cyclase

* Cholesterol synthesis is controlled by regulation of HMG CO-A reductase.
* Cholesterol synthesis in cranes by
  1. LDL receptor
  2. ACAT (acyl - COA a cholesterol transferase).
Small Dense LDL

A derangement of LDL metabolism creates a species of LDL particle that has a higher protein to lipid concentration. Elevated concentrations of these small, dense LDL are associated both with increased CHK risk and with elevated triglycerides and low HDL cholesterol. A possible mechanism that would explain the link between these particles and hypertriglyceridermia involves the production of chylomicrons and VLDL that are particularly rich in triglycerides. Catabolism of these TG - saturated VLDL produces LDL that have a higher than normal TG content. These TG - rich LDL are susceptible to further lipolysis by HL, resulting in a decrease in the size and an increase in the density of the particle. Small dense LDL are believed to be more susceptible to oxidative modification and hence are thought to be highly atherogenic. Metabolic disorders accompanied by hypertriglyceridermia, such as diabetes and the insulin resistance syndrome, often produce this lipoprotein profile.

High density lipoprotein cholesterol

The metabolism of HDL is considerably more complex than that of apo-B containing lipoproteins. Nascent HDL particles are secreted by the liver and the intestine and are thought to acquire excess un-esterified cholesterol from peripheral cells cholesterol acyle transferase (LCAT), and as nascent dissociated HDL generate more cholesterol ester; they evolve into spherical HDL particles, form triglyceride rich lipoprotein, HDL acquires additional phospholipids and apolipoprotein as a result of lipolysis and triglycerides by exchange for cholesterol ester through the action of the (CETP). Cholesterol esters are also take up directly from HDL by the liver through a selective uptake pathway that is mediated by an HDL receptor known as SR-BI. The rivers cholesterol transport pathway from tissue to liver promoted by HDL can be direct through SR-BI or indirect through transfer to other lipoprotein with up take by liver. HDL triglyceride and
phospholipid can be hydrolyzed by hepatic lipase leading to smaller HDL particles that may be more rapidly catabolized.

Low level of HDL Cholesterol are presently associated with elevated triglycerid levels and reduction in triglyceride level usually results, In some increase in the HDL cholesterol level. Two notable exceptions to this inverse association between triglycerides and HDL cholesterol exist.

1. Regular alcohol use raises triglyceride levels but also tends to raise HDL cholesterol level.

2. Oral ostrogen replacement therapy tends.

3. Oxidise triglyceride levels but also raises HDL cholesterol levels.

In both cases alcohol and astrogens likely have direct effect on HDL metabolism independent of their effects on triglyceride metabolism.

Guedelines of (NCEP) are that are adult older than age 20 years should be screened not only for total cholesterol levels but also for HDL C level.

Lipoprotein (a)

Lipoprotein (a) [Lp(a)] a particle comparable in size to LDL. It is assembled from an LDL particle and a large, hydrophilic glycoprotein called apolipoprotein(a) [apo(a)]. Apolipoprotein (a) bears little resemblance to the other apolipoproteins. One of its main structural subunits is a kringle, structure that is widely found in the proteins of the fibrinolysis pathway.

The half life of LP(a) is 3.3 days, with cholesteryl ester as its main lipid. Like LDL, it contains apo B-100, which is linked by a disulfide bound with apo(a), a plasminogen like protein. In vitro studies have shown that LP(a) has a reduced affinity for the LDL receptor compared with LDL itself, and once take up
in the cell, may regulate downward de novo cholesterol synthesis. Lp(a) expression appears to be under genetic control, which determines the size of the Lp(a) macromolecule. The plasma concentration varies inversely with the molecular size of the Lp(a) subtype.

Epidemiologic evidence links elevated levels of Lp(a) with increased risk for CHD. The mechanisms for this risk are unclear, although evidence suggests that modified Lp(a) may also be taken up by the macrophage scavenger receptor pathway, thus, contributing to foam cell formation. Lipoprotein (a) also displays structural homology with plasminogen.

**Obesity**

**Definition**: The clinical definition of obesity is controversial. Although the conceptual definition of obesity is simply excessive body fat.

**According to National disease Control Society** "obesity is a condition characterized by excessive body fat."

**According to Goldman 1999** "obesity is a multifactorial condition with excess adiposity."

**According to (Begisson)**: obesity may be defined as a disease process in which excess body fat has accumulated to an extent that health may be adversely affected.

**What leads to obesity?**

(Shankar et al)\textsuperscript{100} Obesity should be considered a multifactorial condition. Genetic, cultural, socio-economic, behavioural and situational factors all play a role in eating and weight control. Most obesity is primary, that is, no obvious cause exists other than an imbalance in energy intake and expenditure.
Recent studies focusing on the Satiety Index (SI) have shed light on 'why people stop eating'. Basically, this index quantifies the duration of hunger suppression by a given amount of food (containing 1000k), plus the amount voluntarily eaten appetite returns. Thus a food which when consumed suppress hunger for a long period and is then succeeded by a small food intake has a high SI. Protein is the most satiating nutrient, followed by carbohydrates. Fat on the other hand is not very satiating at all. Hence, it is not surprising that pursuing a food choice rich in fats can lead to obesity. Fat is poor at switching off appetite and very easy to store.

The brain controls hunger and satiety

In the 1970s, psychologist Richard Keesey hypothesized ('set-point theory') that body weight is strictly controlled by hormones, particularly neurotransmitters. Keesey observed that when loss occurred, resting metabolism declined significantly resulting in a regaining of the weight. Conversely, he observed a dramatic increase in energy expenditure when body weight rose above its 'set' level. According to his theory, the 'set-point' for each individual could be altered by certain foods and pharmacotherapies.

Several animal studies indicate the hypothalamus is the center for weight regulation, and is involved in maintaining the body weight 'set-point' as well as a controlling factor involved in setting the point at which weight is regulated. Recent research has shown that various areas of the hypothalamus are sensitive to at least 13 neurochemicals and that these areas are involved in the regulation of hunger, eating, appetite and satiety. Two of the more significant areas include the ventromedial nucleus and the lateral lobe. The ventromedial nucleus which is activated by serotonin mediates satiety (fullness or satisfaction with what is eaten). The lateral lobe, which is activated by norepinephrine and/or dopamine mediates hunger and hunger and thirst. Thus, stimulation of the ventromedial nucleus may
induce satiety but not relieve hunger. Conversely, stimulation of the lateral lobe only may relieve hunger but leave the person unsatisfied. Hence, combinations of serotonergic and noradrenergic agents have been employed in the management of obesity.

The Burden of Obesity - An Emerging Epidemic in India?

Obesity is a risk factor for many medical illnesses which is discussed elsewhere. Traditionally, obesity was believed to be associated with affluent lifestyles in the West. However, obesity is a fast growing problem in developing countries. Several studies in India have shown that changes in dietary patterns, physical activity levels, lifestyles associated with affluence, and migration to urban areas are related to increasing frequencies of obesity and the risk of diseases, such as coronary heart disease and diabetes. A study was undertaken by the Nutrition Foundation of India (NFI) in which sample selected from among the middle class, consisting of people working as officers, clerks and peons in a large office establishment, and the poor from a slum, in Delhi. The results of the NFI study are outlined below:

Table XV: Prevalence of overweight and obesity in obesity in different income groups of Delhi (NFI STUDY)\textsuperscript{101}

|Ỉ| Prevalence (%) |
|---|---|---|---|
| | Slums | Middle - Class | Total |
| Overweight (BMI > 25) | | | |
| Males | ND | ND | 19.6" |
| Females | ND | ND | 44.5 |
| Obesity (BMI > 30 )" | | | |
| Males | 1 | 32.3 | ND |
| Females | 4 | 50 | ND |
| Abdominal obesity" | | | |
| Males | ND | 49.7 | ND |
| Females | ND | 34.9 | ND |
| ND : Not determined | | | |

\textsuperscript{101}
Also in 5 cities from India similar findings are shown in the table below.

Table XVI: The Five City Study  
n=3257; aged 25-64 yrs  
Cities: Moradabad(n=902), Trivendrum(n=760), Calcutta(n=410), Nagpur (n=405), Bombay (n=780)

<table>
<thead>
<tr>
<th>Social Class</th>
<th>BMI &gt; 27</th>
<th>WHR &gt; 0.85</th>
<th>Sedentary lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n=985)</td>
<td>21.2%</td>
<td>96.9%</td>
<td>92.2%</td>
</tr>
<tr>
<td>II (n=790)</td>
<td>16.4%</td>
<td>57.2%</td>
<td>71.4%</td>
</tr>
<tr>
<td>III (n=674)</td>
<td>8.9%</td>
<td>39.3%</td>
<td>42.3%</td>
</tr>
<tr>
<td>IV (n=602)</td>
<td>3.0%</td>
<td>11.9%</td>
<td>14.9%</td>
</tr>
<tr>
<td>V (n=206)</td>
<td>3.8%</td>
<td>8.7%</td>
<td>8.7%</td>
</tr>
</tbody>
</table>

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The problem of obesity was found to be more prevalent in the middle class than among slum dwellers. Thus, as against the prevalence rate of 1% males and 4% for females in the slums, the corresponding figures among the middle class were 32.3% and 50%, respectively. More females than males have been found to be overweight (BMI>25) in all age groups; 44.5% in females vs. 19.6% in males. It was also seen that the prevalence of overweight/obesity was higher among those aged over 40 years. The prevalence of obesity (BMI > 30) was about 3% in males and about 14% in females above 40 years.

Methods of Measurement of Obesity

Obesity can be measured by measuring the total body fat. There are various methods of measuring Body fat. (Dr. Anoop Mishra et al)\textsuperscript{102}

I Measurement of total body fat

1. Hydrodensitometry
2. Air displacement plethysmography

3. Isotope dilution

4. Dual - Energy X - ray (Absorptiometry DEXA)

II Measurement of Regional fat

1. Computer Tomography (CT)

2. Magnetic Resonance Imaging (MRI)

III Field methods

1. Bioelectrical impedance analysis (BIA)

2. Total body conductivity (TOBEC)

3. Near infrared interactance

4. Skinfold thickness

5. Body mass Index

6. Waist hip ratio

7. Anthropometry

Methods of Estimation Body Composition

Laboratory Methods

The following discussion includes methods that are useful in measurement of total body fat [hydrodensitometry, air displacement plethysmography (Bod Pod), isotope dilution and, dual-energy x-ray absorptionmetry (DEXA) and those
that are useful in the measurement of regional body fat [computed tomography (CT), magnetic resonance imaging (MRI), ultrasound and DEXA].

1. **Measurement of Total Body Fat**

**Hydrodensitometry**

This method has been the 'gold standard' for a long time for estimation of body volume, body density and %BF. Residual lung volume can influence the measurements and need to be determined beforehand. Body volume is determined either by direct measurement of the displaced water as the subject is immersed in water or by weighing the subject underwater. This method however may not be practical for many, as it requires a great deal of cooperation from the subjects.

**Air Displacement Plethysmography (Bod Pod)**

It is a relatively new device (Life Measurement Instruments, Inc., Concord, CA) consisting of a large egg-shaped fiberglass chamber. The relationship between pressure and volume is used to derive body volume of the subject seated inside the chamber, which equals to the volume of air in an empty chamber minus the volume of air remaining in the chamber after placing the subject into it. Temperature, pressure, relative humidity changes and the type of clothing can affect the measurements. Recent studies report it be a highly reliable and valid method for estimation of % BF in humans.

**Isotope Dilution**

This method is based on the dilution principle, which states that the concentration of a compound in a solvent depends on the volume of the solvent and the amount of compound to it, and knowing the concentration and amount of the compound, the solvent can be calculated. Total body water (TBW) can be used to provide an estimate of fat free mass (FFM) and, subsequently, %BF. TBW is
measured by isotope dilution from either mass spectrometry, which is more precise or infrared spectrophotometry, which is quicker and less expensive. The procedure involves ingestion of an isotopic tracer, an equilibrium period, and a sampling period. In past radioactive tritium (3H₂O) has been used frequently, however, D₂O appears to be the tracer of choice now because it is not radioactive, and it has the same distribution properties as 3H₂O. Technical errors could exist due to variations.

Dual-Energy X-ray Absorptiometry (DEXA)

This method used a constant x-ray source to generate two main energy peaks. In this technique the ratio of x-ray beam attenuation at the lower energy relative to that at higher energy is used to distinguish fat from FFM (excluding the bone component It has been observed to be valid accurate method to predict total body fat and to investigate the abdominal on cardiovascular risk factors, compared with other methods.

2. Measurement of Regional Fat

Computed Tomography (CT)

Regional distribution of adipose tissue has effects on the pathological consequences of obesity. Soft tissue depiction is better on CT as it is much more sensitive to slight differences in attenuation and is useful in assessing lean tissue and adipose tissue. Fat has uniquely low attenuation and is readily identifiable. Measurement of total fat area of a single section or combination of areas from successive sections to compute fat volume can be performed. Moreover, differentiation of subcutaneous fat area from intra-abdominal fat area, and quantification of intra-abdominal fat can be performed, as it is highly variable, and may not be accurately predicated by subcutaneous fat measurements such as
anthropometry. More scans increase the precision but also increase exposure to ionizing radiation.

**Magnetic Resonance Imaging (MRI)**

This method involves placing of the subject in a strong magnetic field and application of radio-frequency pulses. Unlike CT, MRI does not involve hazardous ionizing radiation. Protons in water and in the CH$_2$ groups of triglycerides are the main sources of signal and are stored into a computer and processed to an image. The visualization of adipose is based on the fact that it has a considerably shorter longitudinal relaxation time ($T_1$) compared to other soft tissues with higher water content.

**Field Methods**

These methods are cheaper, quicker, and easier to perform in clinical in clinical setting. These again can be categorized into those helpful in measuring total body fat [bio-electrical impedance (BIA), near-infrared interactance (NIR), skinfolds (SKF), and anthropometric measurements] and those helpful in measuring regional body fat (SKF and anthropometric measurements).

1. **Measurement of Total Body Fat**

**Bioelectrical Impedance Analysis (BIA)**

BIA is based on the principle that lean tissue (containing large amounts of water and electrolytes is a good conductor, and fat and bone are poor conductors of electricity. This involves measurement of the impedance to the flow of a low-level electric current (800 A) introduced into the body at a fixed frequency. At present it is the most frequently used method due to its low cost, ease of operation and portability. Measurements can be using single frequency (most common) or using multiple frequencies (Bioelectrical impedance spectroscopy).
Total Body Conductivity (TOBEC)

This is another bioelectrical method to measure body composition. The concept indicates that is relatively insensitive to shifts of fluid and electrolytes between intracellular and extra cellular compartments. This would be helpful in measurement of TBW. This method has been mainly used to monitor changes in body composition in pregnant and lactating women, infants and in childhood obesity.

Near Infrared Interactance

This method originally developed for use in agriculture to assess the composition of grains and seeds uses diffuse reflectance spectrophotometry. This could be used to measure the body composition of human tissues by altering the wavelength used. The shape of the interactance spectrum is a function of the amount of fat, water and protein content of tissues. A strong correlation was observed between % BF estimated from NIR and total water (TBW) (r = 0.84 for men, r = 0.95 for women). Biceps brachii was found to be the most valid site for estimation of %BF and was strongly correlated to total %. However, there is a lack of improved and valid devices for this method.

Skinfolds

This technique measures the thickness of two layers of skin and the underlying subcutaneous fat. Guidelines for the anatomical location of SKF sites and measurement techniques are available to standardize the measurements. SKF is a good measure of subcutaneous fat, however, it cannot provide a measure of visceral adipose tissue when estimating total body fat. There is a good relationship between subcutaneous fat and total body fat. However, SC fat can vary from 20 to 70% of total fat depending on factors such as age, sex and degree of fatness SC fat in the abdominal region may have major impact on the metabolic variables,
leading to resistance to insulin-mediated glucose uptake. The potential sources of error in using this method include variation in SC total fat, variation in SKF thickness to SC fat and technical error in SKF measurement. It is an excellent field method to use on lean subjects, but it is difficult to obtain reliable and accurate on older subjects with loose connective or markedly obese individuals with large folds. However, this is more accurate than BMI in estimating body fat.

**Anthropometry**

Anthropometric measurements are most frequently used for estimation of generalised and regional obesity. Body mass index (BMI) has is a simple measure. It has been shown that obesity-related health risks begin in the BMI range of 25 to 30 kg/m². BMI may not be an ideal tool for evaluating interethnic variations in body composition because of differences in %BF among different populations with similar BMI. The cutoff values of BMI to obesity may vary in different populations. For example, in Asians the cutoffs have to be lower (overweight >23 kg/m² and obese >25 kg/m²) as compared to the conventional cutoffs (overweight >25 kg/m² and obese >30 kg/m²). Various studies, including one by our group have shown that BMI may not be an accurate predictor of % BF in Asian populations.

Measurement of various circumferences is based on the principle that principle that they reflect fat and FFM. Waist circumference has been correlated with the amount of subcutaneous and visceral adipose tissue and hip circumference gives a highly reliable estimate to subcutaneous fat the gluteofemoral region. Other measurements such as waist-hip ratio (WHR) have been used as crude indices of obesity-related health risks. WHR is a good index of central versus peripheral fat distribution although it is a poor index of the amount of VAT.
The indices most frequently used to measure intra-abdominal fat are waist circumference, waist to hip ratio, waist to thigh ratio and truncal skinfolds. But these indirect methods may not be accurate. The imaging techniques are the only reference methods. DEXA is also a fast and precise method but its limit lies in the fact that it informs on truncal fat mass irrespective of its subcutaneous or perivisceral localization.

Body Mass Index (BMI)

In 1998, the US National Heart, Lung and Blood Institute established guidelines to define 'overweight' and 'obesity'. The parameter used is Body Mass Index (also called Quetelet index) and is calculated using the formula given in Table.
Table XVIII

Relationship of life insurance weigh (kg) for 'acceptable range' 'overweight', and 'obese' for men and women Quetelet's index (QI : kg/m²)

<table>
<thead>
<tr>
<th>Height (m)</th>
<th>'Acceptable Range' (kg)</th>
<th>'Overweight' (kg)</th>
<th>'Obese' (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QI</td>
<td>QI</td>
<td>QI</td>
</tr>
<tr>
<td>MEN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6</td>
<td>44-65</td>
<td>17-25</td>
<td>72</td>
</tr>
<tr>
<td>1.7</td>
<td>51-73</td>
<td>18-25</td>
<td>80</td>
</tr>
<tr>
<td>1.8</td>
<td>58-80</td>
<td>18-25</td>
<td>88</td>
</tr>
<tr>
<td>1.9</td>
<td>66-90</td>
<td>18-25</td>
<td>99</td>
</tr>
<tr>
<td>WOMEN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>38-55</td>
<td>17-24</td>
<td>61</td>
</tr>
<tr>
<td>1.6</td>
<td>41-59</td>
<td>16-23</td>
<td>65</td>
</tr>
<tr>
<td>1.7</td>
<td>45-66</td>
<td>16-23</td>
<td>73</td>
</tr>
<tr>
<td>1.8</td>
<td>52-74</td>
<td>16-23</td>
<td>81</td>
</tr>
</tbody>
</table>

Table XIX

Classification of Over weight and Obese by Body Mass Index
BMI = Weight (kg) / [Height (m)]²

<table>
<thead>
<tr>
<th>Obesity Class</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 - 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 - 29.9</td>
</tr>
<tr>
<td>Obese</td>
<td>30.0 - 34.9</td>
</tr>
<tr>
<td>Extremely Obese</td>
<td>35.0 - 39.9</td>
</tr>
<tr>
<td></td>
<td>&gt; 40</td>
</tr>
</tbody>
</table>

Overweight is defined as a BMI of 25 to 29.9 kg/m² and obesity as a BMI of more than 30 kg/m² (Table 1). While BMI is a simple and generally accurate measure, it does not account for weight distribution and lean body mass.
Waist-hip ratio

(Dr. Shasank et al)^103, the waist to hip ratio provides information about the distribution of body fat. To find the ratio, the circumference of the waist at the naval is measured while the patient stands relaxed. The next step is to measure around the hips at the point where the buttocks protrude the most. The waist measure is then divided by the hip measure, resulting in the waist-to-hip ratio.

| Risk increases if waist circumference is > 94 cm in men and > 80 cm in women | Ratio = Waist / Hip Desired Ratio Women ≤ 0.8 Men ≤ 1.0 |

Women should have a waist-to-hip ratio of 0.8 or less, while men should have a ratio of 1.0 or less. Values above this are considered clinical obesity. In men, there is increased risk if the waist if the waist circumference is 94cms or more and substantial risk if it is 102cms or more. For women, the figures are 80cms or more and 88cms or more respectively.

Fat Distribution

There are two major types of fat distribution found in adult obesity

1) Android type-

2) Gynoid Type
Table XX: Classification of Body Fat Phenotype

<table>
<thead>
<tr>
<th>Android (or abdominal or central)</th>
<th>Gynoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Collection of mostly in the abdomen</td>
<td>Collection of fat on hip and buttocks below the waist (above the waist)</td>
</tr>
<tr>
<td>- Apple-shaped -pear-shaped</td>
<td></td>
</tr>
</tbody>
</table>

Showed that in women with obesity-related conditions (i.e. heart disease, diabetes mellitus, stroke), intentional weight loss of 0.5 to 9 kg is associated with a 53% reduction in deaths from obesity-related cancers, a 44% reduction in diabetes-associated mortality, and a 20% reduction in mortality. A retrospective review of patients with type 2 diabetes found that survival increased 3 to 4 months for each kilogram of weight loss. Modest loss of 5% to 10 of body weight has been shown to reduce health risks such as hyperlipidemia, hypertension, and insulin resistance. A study showed a reduction of systolic and blood pressure of 12 and 7 mm Hg respectively, among overweight hypertensive patients who lost as little as 5.1 kg. The results of a meta-analysis of 70 studies showed that for every 1 kg of weight lost, the serum concentration of LDL cholesterol falls by 0.8 mg/dl, while serum concentrations of triglycerides falls by 1.3 mg/dl and of HDL cholesterol rises by 0.36 mg/dl Another 1-year study of obese patients with asthma showed that weight loss was associated with as improvement in lung function and reduction in rescue medication and number of exacerbations. The incidence of other obesity-related health problems, including sleep apnea and osteoarthritis, also decrease with moderate weight.

Mechanisms Regulating food intake

1. Nutrient Intake
2. Hypothalamus
3. Leptin
4. Neuro chemical factors
5. Thermogenesis
1. Nutrient intake

(Dr. Anoop et al) Maintenance of a stable body weight is possible through accurate mechanisms of control of food intake. Appetite is a complex phenomenon arising from a sequence of interactions among peripheral and central mechanisms. The two major variables, which determine the amount of energy intake over 24 hours, are: the size of size of individual meals and the frequency of meals. These variables are regulated by well-defined responses such as hunger and satiety. The mechanisms that promote satiation are different from those that determine the duration of satiety. Macronutrient composition, size and caloric density of the meals and properties such as sight, smell, taste and texture play an important role in the determination of satiation. Proteins have the most potent effect in deploying subsequent nutrient ingestion. Carbohydrates also increase the early satiety period. Lipids however are less potent in inducing satiation. Changes in energy density of the meals results in parallel changes in energy intake. Increasing of the meals leads to excess intake of calories in smaller volume and weight of food.

2. Hypothalamus

Hypothalamus plays important role in controlling feeding behavior, activity level and thermogenesis. Ventromedial hypothalamic (VMH) area has been designated as satiety centre, as stimulation of this area induces termination of food intake. Stimulation of the lateral hypothalamic area triggers food and drink intake. It has been labeled as the feeding centre. Lesions of VMH area in animals lead to development of obesity and hyperinsulinaemia. These changes are mediated by increased vagal activity and a decrease in overall sympathetic activity and brown adipose tissue thermogenesis. Nuclei within the lower brainstem integrate and relay information between peripheral autonomic/endocrine organs and other forebrain structures. Nuclei in pars-midbrain and the thalamus interpret this
information. Hypothalamic nuclei respond to neural inputs as well as to circulating hormones and substrates.

3. Leptin

Recent studies suggest the existence of an adipose tissue mass control. This regulatory loop consists of signals originating from adipose tissue, acting on hypothalamic receptors in the autonomic nervous system. The cloning of the Ob gene and identification of its encoded protein leptin\(^7\) has provided a major breakthrough in obesity research. Several factors such as fasting, feeding play a role in the regulation of leptin production by adipocytes. Food intake increases leptin expression and with prolonged fasting leptin levels tend to decrease.

Leptin acts on hypothalamic leptin-responsive neurons, thereby altering the expression of several genes producing specific neuropeptides that modulate food intake and energy expenditure. One important mechanism may be the inhibition of hypothalamic NPY synthesis and release. Other pathways independent of those using NPY may also exist. Leptin also increases sympathetic nervous system activity. The concentration of leptin is proportional to body adiposity. Leptin concentrations are influenced by the number of adipose cells and the induction of mRNA per cell, with obese individuals having higher values of both. Genetics also affect plasma levels of leptin with women having markedly higher concentration than men for any given degree of fat mass, and it also increases during leuteal phase of menstrual cycle.

4. Neurochemical factors

Recent studies have identified several neuropeptides involved in the regulation of feeding behavior. Neuropeptide Y(NPY) is likely to play an important role in context. It is released from the arcuate nucleus is so far the most potent stimulus for food intake identified within the CNS. Nutrient adsorption
induces a feedback inhibition of NPY NPY inhibits sympathetic stimulation of brown adipose tissue, and thus decreases energy expenditure.

Other increase food intake eg. opioids, galanin, growth hormone releasing hormone and gamma amino butyric acid (GABA) do not cause obesity, another neuropeptide, corticotropin-releasing factor causes reduction in weight gain by decreasing food intake and by enhancing energy expenditure. Glucagon like peptide-1(GLP) is another neuropeptide that has been recently implicated in the central regulation of food intake. It is produced by post-translational processing of proglucagon in the small intestine. Cholecystokinin (CCK) have been proposed as candidate satiety peptides, since administration of CCKa receptor antagonists increases food intake.

5. Thermogenesis and Energy Expenditure

Factors affecting thermogenesis and energy expenditure may be involved in the causation of obesity. Beta-3 adrenergic receptors are present in white and brown adipose tissue of rodents. In human, these are mainly expressed in perirenal and omental adipose tissue. They regulate thermogenesis and lipolysis through increased production of cAMP. In ob/ob mouse, a reduction in the beta-3 adrenergic receptors has been observed. The role of these receptors in human beings needs to be investigated. Recently a missence mutation (Trp64Arg) in the beta-3 adrenergic receptor gene was associated with abdominal obesity, insulin resistance and early onset of 2 diabetes. however the mutation was infrequent in the obese people. Mitochondrial uncoupling protein protein-1 (UCP-1), functions to allow proton re-entry in the mitochondrial matrix. These are activated by beta-3 adrenergic receptors in brown adipocytes, which in turn circumvents ATP synthesis resulting in high catabolic and thermogenesis. The role of UCP-1, UCP-2 and UCP-3 in human obesity needs to be investigated.
Factors Responsible for obesity

1. **Anatomic characteristics of Adipose tissue**

   Adipose tissue of the normal individual grows by an increase in both number and size of its constituent fat cells. Adipose cell number reaches its peak some time in early adult life and thereafter remains constant apparently unchanged.

**Two types of human obesity has been described**

1. Marked increase in the total number of adipose cells is the predominant cellular abnormality. Adipose cell size enlargements is to a lesser degree. It is usually of early onset of severe degree, not easily manageable by usual dietary means. There is weight loss by reduction in cell size, but there is no change in number of cells. There is regain of obesity. the cause of this type of obesity is not known.

2. There is adipose cell size enlargement but number of fat cells remains normal. It is more common and is usually of milder degree onset in adult life. more readily amenable to dietary management. There is weight loss by reduction in cell size, but there is no change in number of fat cells. There is disordered carbohydrate, insulin and triglyceride metabolism in both of these form of obesity.

**AGE**

Obesity can begin at any age. The first appearance of obesity is infancy when body fat rises rapidly. During the first year of life, the size of fat cells increase nearly two folds, but there is no measurable increase in the number of fat cells. A second period of childhood obesity is between the ages of 4 and 11 years. When obesity appears in this age group, there can be a progressive increase
of body weight from the upper limits of normal for height and particular age: this may be called progressive obesity. This type of obesity usually is lifelong and is associated with an increase in the number of fat cells.

**Adult Onset Obesity**

Most obesity develops after the end of puberty. Estimate from several sources have suggested that less than one third of the obese adults were obese in childhood. The early years of life are important for the development of obesity in both men and women.

**SEX**

Sex is another variable with great impact on the development of obesity. From puberty onward. Women are fatter than men and women tend to gain more fat during adult life than men. Yet women have lower risk associated with any degree of extra body fat. This partly may be explained by differences in fat distribution. In one study, an extra 20 kg fat was needed by women to produce the same impairment in glucose tolerance as in a man *(Haffner et al. 1987)*

**Etiologic Factors Obesity**

**Physical Inactivity**

Physical inactivity plays an important role in development of obesity. In one clinical study onset of obesity was associated with inactivity in 67.5 present of patients. In epidemiologic studies the highest frequency of overweight was found in the group with sedentary occupations. These observations suggest the importance of shifting patterns of physical activity in the regulatory systems controlling the storage, distribution and utilization of calories.
OVER NUTRITION AND OBESITY

The composition of diet is another etiologic factor in obesity. Over feeding may be of importance in the onset of childhood obesity. It has been found that infants who gained excessive amount of weight during the first 6 weeks of life had a significantly greater likelihood of being obese later in childhood the available data suggest that infants who grow rapidly in the early weeks of life may be fattest in later childhood.

The relationship of the frequency of eating to the development of human obesity remains an unsettled question. It has been observed clinically that obese individuals frequently eat fewer meals than normal weight people, but this is a difficult point to document. Direct evidence on the relationship of obesity to the frequency of food intake was obtained in a survey of 379 men ages 60 to 64 years (Fabry et al 1964)\textsuperscript{106}. The men who ate one or two meals per day were heavier had thicker skinfolds higher levels of cholesterol and frequently impaired glucose tolerance compared with men who ate three or more meals per day. This finding was confirmed in a study of school children. Children fed only three meals per day tended to gain more weight than children eating five to seven meals per day.

The frequency of eating also changes the metabolism of glucose and the concentration of cholesterol. When normal volunteers ate frequent small meals a day they had lower concentrations of cholesterol than when the same total intake was eaten in a few large meals (Young et al. 19/2)\textsuperscript{107}. The reduction of cholesterol with frequent ingestion of small meals has been confirmed many times. Glucose tolerance curves are also improved when eating three or more meals as compared with one or two large meals.

In one laboratory study (Bray 1972)\textsuperscript{108} six grossly obese patients were fed a 500 calorie as one large meal during the 4 week period. During the other four week the calories were divided into 20 small meals. The period with one large
meal was associated with more rapid formation of fat as measured by incorporation of carbon from glucose into fatty acid in adipose tissue. Recent epidemiologic evidence indicates that in middle aged women there is a positive correlation between fat intake particularly saturated fat and rising BMI. (Romieu et al. 1988)\textsuperscript{109}

\textbf{Drugs and Obesity}

Certain drugs can lead to an increase in body weight. Glucocorticoids are used widely in treating chronic immunologic disease and one of the side effects of the treatment is weight gain. Similarly Amitriptyline antidepressant that is particularly likely to produce weight gain. Cyprohepatadine (Periactin) has been shown to increase food intake in human subject without an alteration in metabolism. Although estrogens alone or in birth control pills have been reported to produce weight gain this largely is the result of fluid retention and probably not the result of increased fat Latino Progestins including medoxyprogesterone are more likely to increase weight.

\textbf{Socio Economic and Psychological Factors in the development of obesity}

Obesity is more prevalent in the lower socio-economic group. Goldblatt and Coworkers (1965)\textsuperscript{110} found that among the highest groups (that is most educated and affluent) only 4 percent were overweight. Whereas in the lowest socio-economic groups 36 percent were overweight. These effects are more prominent in women.

Similar conclusion have been drawn from National Centre for Health Statistics. (Abraham et al. 1983 and Van Itellie 1985)\textsuperscript{111} where there was significantly more obesity as assessed by skinfold thickness in the lower socioeconomic level groups. Psychological factors in the development of obesity are widely recognised. The emotional responses in life stresses affect both the
intake of food and the level of physical and social activity and thus influence both energy intake and output in undesirable directions resulting in obesity. Many psychiatrists have contributed to understanding of emotional aspect of obesity.

**Metabolic and Genetic Factors**

Mayer (1953) has indicated the genetic factor operating in the families as under.

1. In both parents of average body weight have 9 percent obese offsprings.
2. One parent obese and one of normal weight have 50 percent obese offsprings.
3. Both parents obese have 73 percent of obese offsprings.

There are several points that emphasize role of biological inheritance in human body fat variation. *(Claude 1989)* concluded that the additive genetic effect in amount of subcutaneous fat is quite low but that it is highest 25-30 percent) for fat mass and regional fat distribution. These results suggest intraviseeral fat perhaps is more influenced in the genotype than

**Cellular and Molecular Biology of Adiposity and Adipogenesis**

*(Dr. J.S.Bajaj et al)* The last decade has witnessed a quantum leap in our understanding of cellular and molecular biology of obesity. With the cloning of ab (leptin), db (leptin receptor) and agouti genes and the characterisation of melanocortin receptors, the basic cloning of ab(leptin), db(leptin receptor) and agouti genes and the characterisation of melanocortin receptors, the basic physiologic pathways underlying monogenic causes of murine and human obesity have been elucidated and the role of central nervous system, especially the defined areas of hypothalamus, is more precisely delineated. The adipocyte-specific hormone, leptin, regulates mass of adipose tissue not only through major effects on satiety (energy intake), but is also hormone, leptin, regulates mass of adipose tissue not only through major effects on satiety (energy intake), but is also
involved in the regulation of energy expenditure. Likewise, cellular mechanisms that control and regulate energy expenditure through adaptive thermogenesis, have been defined by the recent characterisation of uncoupling proteins, especially UCP-3. Equally significant are the advances in adipocyte biology relevant to molecular basis of pre-adipose cell growth, adipose cell differentiation, and lipogenesis in fat cells. The role of PPAR as a regulator of several fat-specific genes and in 'programming' adipogenesis, seems to be of major clinical and therapeutic significance.

Metabolic Consequences of Overnutrition in Obesity

Overnutrition can induce other, less obvious metabolic alterations that have long term detrimental consequences. Some examples of these effects include high synthetic rates for lipids (i.e., cholesterol, triglycerides). Hyperinsulinemia and resistance to the peripheral action of insulin (Grundy and Barnett. 1990)\(^{114}\). Therefore postulated that responses to overnutrition superimposed on a variety of underlying metabolic defects, whether the latter were inherited or acquired, account for various complications of overnutrition.

Hypertriglyceridemia

Many obese people, but certainly not all, have elevated serum triglycerides. Among obese persons with hypertriglyceridemia the diversity of triglyceride elevation varies greatly. In most overweight individuals caloric restriction reduces triglyceride levels, indicating clearly that obesity contributes to hypertriglyceridemia. Why then does obesity cause hypertriglyceridemia in some people but not in others? To understand the reason, mechanisms for hypertriglyceridemia must be considered. Most hypertriglyceridemia patients have high serum concentrations of very low-density lipoprotein (VLDL) triglycerides, and two mechanisms can underlie raised VLDL triglycerides, and
lipolysis of triglyceride-rich lipoproteins. Both abnormalities have been implicated in the pathogenesis of hypertriglyceridemia.

Overproduction of VLDL Triglycerides

Overproduction of VLDL triglycerides has been postulated to be the genetic defect causing familial hypertriglyceridemia (Chait et al 1980)\(^\text{115}\). This condition may result from a generalized overproduction of lipids in the liver because patients with familial hypertriglyceridemia often have concomitant high synthesis rates for cholesterol and bile acids (Angelin et al 1987 and Grundy et al 1987)\(^\text{114}\). The underlying derangement in this condition is unknown. It could reside in the liver. although many patients with primary hypertriglyceridemia exhibit resistance to the peripheral action of insulin (Reaven et al 1967: Kissebah et al 1976: Garg et al 1989)\(^\text{116}\), this latter abnormality might stimulate hepatic overproduction of VLDL triglycerides by diverting excess substrate to the liver. Thus, whether the molecular defect of familial hypertriglyceridemia occurs in liver or in peripheral tissues remains to be determined.

Defective Lipolysis of Triglyceride-Rich Lipoproteins

(Nikkila and Kekki 1971)\(^\text{117}\) have proposed that clearance capacities for VLDL triglycerides varies considerably in the general population and thus accounts for variable triglyceride levels. Sane and Nikkila (1988) reported that heterogeneity in capacity to clear VLDL triglycerides occurs along genetic lines. Mechanisms responsible for this variability in lipolytic capacity are unknown. but presumably those with low capacities possess abnormalities in the lipolytic that moderate lipolytic defects can be inherited. Dunn et al (1985) reported one family in which several members had hypertriglyceridemia that was the result of defective catabolism of VLDL triglycerides. Whether defects of this type arise from decreased availability of lipase or hepatic triglyceride lipase, polymorphism in lipase structures. or abnormal apo-lipoprotein composition have not been
determined. On the basis of variability in profiles for production rates vs. serum concentrations of VLDL triglycerides in normotriglyceridemic subjects, Grundy Vega (1982) postulated that many individuals have "latent detects in lipolysis of VLDL triglycerides. When people with these "defects" have relatively low production rates for VLDL triglycerides, they do not manifest hypertriglyceridemia, but if production rates rise, serum triglyceride concentrations will increase to the abnormal range.

Effect of Obesity on Triglyceride Metabolism

(Grundy et al 1979)\textsuperscript{114} have shown that overnutrition in obese patients includes overproduction of VLDL triglycerides. High production rates for VLDL triglycerides are present in most obese subjects even in the absence of over hypertriglyceridemia (Grundy et al 1979)\textsuperscript{114}. Many people seemingly respond to obesity by increasing their clearance capacity for VLDL triglycerides and thus avoid hypertriglyceridemia in spite of high input rates for serum triglycerides. These people probably synthesize more lipoprotein lipase in the obese state (Eckel 1987). Other patients, in contrast, develop hypertriglyceridemia when they seemingly fail to respond to overproduction of VLDL triglycerides with a rise in lipolytic capacity. Many of these patients apparently would not manifest hypertriglyceridemia if they remained non-obese; they posses a latent defect in the system for lipolysis of triglyceride-rich lipoproteins. In accord, caloric restriction in these obese patients often normalizes triglyceride levels (Wolf and Grundy, 1983)\textsuperscript{118} although the underlying lipolytic defect probably remains despite caloric restriction. It lies hidden in the absence of overnutrition.

Hypercholesterolemia

Since hypertriglyceridemia generally reflects elevated concentrations of serum low-density lipoprotein (LDL) cholesterol, factors regulating LDL levels must be reviewed. LDL originates from the catabolism of VLDL remnants that in
turn are the catabolic products of newly secreted VLDL. Rate of conversion of VLDL remnants to LDL thus represents one factor determining LDL concentrations. Amounts of VLDL remnants transformed to LDL are determined by two factors: rates of hepatic secretion of VLDL and the fraction circulating VLDL remnants removed directly by the liver. These various rates can be measured by following the Kinetics of VLDL-apo B-100 because every VLDL particle contains one molecule of apo-B. A second major factor affecting serum concentrations of LDL is the rate of clearance of LDL from the circulation. Most circulating LDL particles are removed by hepatic LDL receptors, although peripheral tissues also possess LDL receptors and can remove some LDL (Brown and Goldstein 1983)\(^{119}\). The total number of LDL receptors available in the body thus has a major influence on serum LDL levels. Although most LDL particles disappear via LDL receptors, a small fixed fraction of LDL is cleared by non-receptor pathway (Kesaniemi et al 1983)\(^{120}\) this latter route of removal, however, appears not be a major determinant of LDL concentrations. An elevated LDL cholesterol concentration can result from defects in either input or clearance of LDL. The role of these two abnormalities as causes of hypercholesterolemia can be examined.

**Defective Clearance of LDL**

The most dramatic example of decreased clearance of LDL occurs in hypercholesterolemia (Goldstein and Brown 1974). This disorder results from an inherited defect in the gene encoding for LDL receptors: consequently too few LDL receptors are synthesized. Since one gene for LDL receptors comes from each parent, patients with heterozygous familial hypercholesterolemia manifest half the normal number of LDL receptors and thus have twice normal levels of LDL cholesterol. Another genetic disorder causing defective clearance of LDL is called familial defective apolipoprotein B-100 (Vega and Grundy 1986)\(^{121}\), Innerarity et al 1987 and Soria et al 1989). In this condition the gene encoding for apo-100 is
defective, and thus the apo-B of LDL does not bind to LDL receptors; the clearance of LDL from the circulation consequently is reduced, and LDL cholesterol concentrations are increased.

Although these two monogenic disorders of LDL clearance are well defined most patients with elevated levels of LDL do not have clearly identified genetic abnormalities. Most hypercholesterolemic individuals have a monogenie defects. It has been suggested that many patients with primary moderate hypercholesterolemia have reduced clearance of LDL from the circulation (Grundy and Vega, 1985). Some of these could have less severe toms of defective apo-100. but most probably have reduced activity of LDL receptors. A common cause of the latter may be an increased sensitivity to the action of dietary saturated fatty acids and cholesterol to suppress the activity of LDL receptors. Further it is reported that some individuals are unusually sensitive to dietary saturated fatty acids and they develop clinical hypercholesterolemia only when their intake of saturated fatty acids is relatively high (Grundy and Vega, 1988). Thus many people with hypercholesterolemia may be unusually susceptible fatty acids. and they will remain normocholesterolemic when consuming diets low in saturates.

**Increased Influx of LDL**

Another factor the LDL cholesterol level appears to be enhanced conversion of VLDL to LDL. A high input of LDL can originate from either increased secretion of VLDL or a high fractional conversion of VLDL to LDL. Hypersecretion of VLDL particles has been postulated to be a cause of hypercholesterolemia in the genetic disorder called familial combined hyperlipidemia (Grundy and Chait 1987). The actual metabolic defect causing overproduction of lipoprotein particles has not been determined. but variability in inherent rates of synthesis of apo B-100 by the liver could exist.
A second reason for increased influx of LDL could be a decrease in the direct removal of VLDL remnants that normally occurs before VLDL are converted to LDL. Such could have several causes. One is reduced activity of LDL receptors because VLDL remnants like LDL, are removed by LDL receptors (Brown & Goldstein. 1983). Another cause could be a reduced affinity of VLDL for LDL receptors; this is known to occur with defects in the many structure of apo E (Gregg et al 1989) but other causes for decreased direct removal of VLDL remnants may exist that have not been defined.

Relation of Obesity to Hypercholesterolemia

Although a number of studies have reported that increased body weight is associated with higher levels of total cholesterol, the link between high LDL cholesterol levels and obesity is not so well established as the increase LDL cholesterol accompanying high intake a saturated fatty acids (Gundy and Vega 1988: Carlson and Lindstedt, 1968; Stamler et al 1975). It was suggested that higher LDL cholesterol levels did not accompany increased body weight up to a certain critical weight, or threshold (Garrison et al, 1980). Women may reach this weight threshold before men, because women usually have a higher percentage of body fat. This concept is supported by the finding that LDL levels in women who are less obese show a greater response to weight loss than in women with greater degrees of adiposity (Follick et al 1984 and Thompson et al 1979). In younger age groups, and especially in men the LDL cholesterol level appears more tightly linked to weight than it is in older individuals (Garrison et al. 1980: Keys and Fidanza, 1960). The failure of some studies to uncover a connection between body weight and LDL cholesterol may be partially explained by the tendency of both serum total cholesterol and obesity to increase with age (Carlson and Lindstedt, 1968).
Serum total cholesterol and in some instances LDL cholesterol, has been shown to change in direct proportion to weight gain or loss (Follick et al. 1984, Ashley and Kannel. 1974 : Shekelle et al. f1981 ; Olefsky et al. 1974 and Howard et al 1979). Changes in weight seems to have a more immediate effect on IDI cholesterol levels than degree of adiposity (Albrink et al. 1962)\(^{128}\). An immediate response to weight change, either positive or negative has been observed but not always continue at the same rate: in other words, the rate of changes in serum cholesterol level decreases with continued weight change (Anderson et al. 1957).

In one study. LDL cholesterol levels were observed to decline initially but return to pre-weight loss levels after a period of weight maintenance at a desirable weight. Men appear to have a more striking decrease in LDL cholesterol with weight loss than women do (Brownell and Stunkard. 1981)\(^{129}\) although this possible difference has not been studies systematically.

**Mechanism of Obesity-Induced Hypercholesterolemia**

Overnutrition can affect the metabolism of LDL in several ways that might contribute to raised LDL levels. For one, the high consumption of total food energy in obese subjects seemingly raises hepatic synthesis rated for lipoproteins, notably VLDL (Kesaniemi et al 1985 and Egusa et al. 1985). Overproduction of VLDL leads to increased conversion of VLDL to IDL.

Which in some individuals can increase the LDL cholesterol level. In many obese subjects, however. LDL cholesterol levels are not raised despite increase input of LDL (Kesaniemi and Grundy. 1983)\(^{130}\). There may be at least two reasons for this. First., in obese subjects who are mildly hypertriglyceridemic. the cholesterol esters of LDL particles are partially replaced by triglycerides: consequently. LDL particles are relatively deficient in cholesterol ester. and whereas LDL cholesterol levels may be normal concentrations of LDL particles are raised (Kesaniemi and Grundy. 1983). And second. the activity of LDL
receptors may be stimulated with overnutrition possibly the result of hyperinsulinemia (Howard et al, 1986)\textsuperscript{132} this latter response likewise should partially offset the high input of LDL and mitigate hypercholesterolemia.

When obesity is combined with mild genetic defects in lipoprotein metabolism, the combination can produce a distinct or even marked elevation of serum lipids. In familial combined hyperlipidemia, for example increased serum lipids typically are observed in children, but only in adults (Goldstein et al, 1973)\textsuperscript{132}. This uncovering of a latent defect in lipoprotein metabolism with measuring age could be the result of increasing adiposity. In fact it was recognized early that obese individuals from families affected with combined hyperlipidemia are particularly likely to show elevated serum lipid levels. By the same token, a person with an underlying decrease in LDL receptor activity, other because of excessive consumption of saturated fatty acids and cholesterol or because of an inherited defect in LDL receptor function should be unusually sensitive to the effects of overnutrition and more readily develop hypercholesterolemia in response to obesity than with normal LDL receptor function.

An important but unresolved question is whether overnutrition contributes significantly to the rise of LDL cholesterol levels with age. In the United States for instance. LDL cholesterol concentrations increase by 30 to 50 mg dl from early adulthood to late middle age (Heiss 198). This rise no doubt enhances risk for coronary heart disease in the United States. Mechanisms responsible for gradual but progressive increase in LDL levels with aging are poorly understood. Grudy et al, (1985) have revealed that two factors-measuring production rates of LDL and decreasing fractional clearance of LDL both contribute to the rise in LDL levels with age. The former could be secondary to an enhanced of apo B-containing lipoproteins from overnutrition (Kesaniemi et al 1985 and Egusa et al. 1985). This overproduction itself should cause overloading of LDL receptors, which in turn
should reduce the fractional clearance of LDL (Spady et al. 1986) alternatively, formation of LDL receptors could decline gradually with aging, and this likewise would reduce the fractional clearance of LDL (Miller 1984). Thus overnutrition probably contributes to the rise of LDL with age, but may not be the only factor.

**Hypo Alpha Lipoproteinemia**

A third lipid risk factor for coronary heart disease (CHD) is a low serum level of high-density lipoprotein (HDL) cholesterol (Castelli et al, 1986: Gordon et al 1977: a Miller et al 1977). The reason why HDL predisposes to CHD is scantily comprehended. One possibility is that HDL promotes removal of cholesterol from the arterial wall as part of its function in reverse cholesterol transport (Glomaset 1978). If so, low serum HDL could directly stimulate development of atherosclerosis by failure to mobilize excess cholesterol from within the arterial wall. Other workers speculate that low HDL levels are not directly atherogenic but signify the presence the presence of other atherogenic lipoproteins, such as VLDL remnants (Richards et al, 1989). Although high levels of remnant lipoproteins which are a common cause of low HDL concentrations, almost certainly are atherogenic, the possibility that low HDL levels directly promote atherogenesis has by no means been ruled out.

**Mechanisms For Reduced HDL Levels**

The origins and fates of HDL are not fully understood. Current concepts of the metabolism of HDL and its role in reverse cholesterol transport have been reviewed by (Van. Tol 1989). The liver and gut apparently secrete particles called "nascent" HDL; these particles are disk shaped lipoproteins containing apo A-I and apo A-II as phospholipids. Nascent HDL accept un-esterified cholesterol from tissues and other lipoproteins, and this cholesterol is esterified through the action of and enzyme lecithin cholesterol acetyl transferase (LCAT); acquisition of cholesterol ester converts nascent HDL into small, spherical particles called HDL.
Continuation of cholesterol-ester uptake transforms HDL into a larger species, HDL In term, HDL transfers cholesterol ester to VLDL in exchange for triglyceride this exchange is mediated by cholesterol ester transfer protein (CETP). The cholesterol ester transferred to VLDL makes its way back to the liver with VLDL degradation products VLDL remnants and LDL. This represents one sequence in the reverse cholesterol transport pathway. Alternatively, the various species of HDL probably can be removed directly by liver of other tissues.

Several general mechanisms can be visualized for reduced HDL cholesterol concentrations. First, insufficient synthesis of HDL apolipoprotein apo A-I and apo A-II by liver or gut could yield reduced serum levels of HDL. Indeed genetic disorders are known in which synthesis of A-I is defective and HDL cholesterol concentrations are low (Franceschini et al 1980)\textsuperscript{133} Second, enhanced uptake of whole HDL particles could eliminated them too rapidly from the circulation and thereby reduce their concentrations. The most extreme example of this mechanism is found in Tangier disease, in which markedly enhanced catabolism of HDL is responsible for severe hypoalphalipoproteinemia (Schaefer et al, 1978)\textsuperscript{134}. Increased removal of HDL particles might occur via liver or extrahepatic tissues. Third, small amounts of apo A-I might be transferred to VLDL, and if the VLDL concentrations is high of if flux of VLDL is increased this could drain apo A-I away from HDL; states promote this exchange, resulting in a fall in HDL cholesterol concentrations.

**Effect of Obesity on HDL, LDL And LDL Levels**

An inverse relationship between body weight and HDL cholesterol concentration is well established (Garrison et al, 1980)\textsuperscript{135}. Markedly overweight people have HDL-cholesterol level 8 to 10 mg/dl below normal (Wolf and Grandy, 1983)\textsuperscript{136}. The explicit mechanisms whereby overnutrition or obesity reduced HDL cholesterol level have not been elucidated on the basis of
mechanism fist discussed however it is speculated about possible reasons for fall in HDL cholesterol level in obese patients. It is doubtful that overnutrition reduces the synthesis of apo A-I and A-II. The predominate mechanisms for HDL-cholesterol lowering probably relate to enhanced catabolism of HDL particles or apoA-I increased triglyceride cholesterol ester exchange. The hypertriglyceridemia often present in obese individuals may promote transfer and apo A-I from HDL to VLDL and thus impoverish HDL of apo A-I. Hypertriglyceridemia like wise will promote triglyceride cholesterol ester exchange between VLDL and HDL and thereby deplete HDL of cholesterol ester. It is of interest, however, that in obese patients undergoing weight reduction. Wolf and Grundy (1983) note that the HDL cholesterol levels did not rise immediately after starting caloric restriction even though serum triglyceride levels fell almost immediately to normal; the rapid decrease in triglyceride should have prevented depletion of apo A-I and cholesterol ester from HDL. On the contrary only after weeks and major weight loss did a slow but progressive increase in HDL cholesterol concentration occur. This observation suggests that an excess of adipose tissue, and exclusively high triglyceride level, contributed to reduced HDL-cholesterol level. Perhaps adipose tissue directly removes HDL-particles from the circulation and only when the excess adipose mass is eliminated with the HDL-cholesterol rise to normal.

The concentration of plasma triglyceride is readily increased by diets which are rich in carbohydrate. The magnitude of this increase and its duration are governed by factors such as amount (Lees and Fredrickson, 1965) and the tape (Kuo and Bassett, 1965 and Kaufmann et al, 1966) of carbohydrate, age (Shwartz et al 1967) sex (Beveridge et al, 1964 and Macdonald 1966) the presence of obesity (Schwartz 1967, Albrink, 1964 and Grace & Goldrick, 1968 and the genetic predisposition (Fredrickson et al, 1967). The causal mechanisms have not been established although published reports suggested that measured formation of triglyceride in the liver was of greater importance than diminished from the blood.
(Reaven et al, 1965 and Neatel, 1966). Insulin appeared to be significantly correlated with the degree of hypertriglyceridemia (Farquhar et al, 1966 and Reaven et al, 1967). Oversecretion to insulin was also found in obesity (Bagdade et al, 1967 and Parley and Kipnis, 1967). Which in turn was commonly associated with raised plasma triglyceride levels (Albrink and Meighs,1964 and Grace et al, 1968). Since oculating plasma free fatty acids (FFA) were a major source of plasma triglyceride (Havel, 1961 and Friedberg et al, 1961) and since FFA turnover was also related to overweight (Miller et al, 1968 and Nastel and Whyte, 1968)\textsuperscript{137} excessive production of FFA from carbohydrate has also been considered as a possible causal factor: there was as yet little support for this however, apart from the occasional finding of raised plasma FFA in some hypertriglyceridemic states (Kane et al 1965). Nestel et al, (1970) studied some of these relationship by comparing the differences in the plasma triglyceride concentration, the plasma FFA turnover the rate of appearance of FFA in triglyceride and the insulin responsiveness to glucose under several circumstances: (1) in response to the consumption of carbohydrates: starch glucose or fructose since cash of these carbohydrates has been reported to raise the triglyceride level in plasma though not by identical amount (Kaumfinann et al, 1966 and Macdonald,1966) (2) in response to starvation and overeating and overeating because these procedures might be expected to produce marked changes in FFA and insulin metabolis (Cahill et al, 1966 and solomon 1968) and (3) in response to different kinds of dietars fat since the consumption of saturated and polyunsaturated fat is known mthrence the plasma triglyceride concentration (Ahrens net al, 1957 and Anderson 1967)\textsuperscript{138}

(Ginsberg, et al 1985)\textsuperscript{139} studied and reported in subjects with hypertrgleyeridemia, plasma concentrations of low density lipoprotein (LDL) cholesterol are often normal or reduced. Perturbations that alter plasma very low density lipoprotein (VLDL) concentrations are associated with opposite changes in
L.D.L. levels. To determine the mechanisms regulating plasma LDL levels, they use I VLDL and I LDL to measure the fractional catabolic rates (FCR) production rates (PR), and rates of interconversion of apoprotein B (apo B) in VLDL. Intermediate density lipoprotein and LDL in hypertriglyceridemic subjects pre and post weight reduction. After weight loss, plasma VLDL triglyceride and VLDL apo B concentration were reduced. VLDL triglyceride production rate (PR) also fell after weight reduction.

Plasma LDL cholesterol and apo B levels were low-normal or reduced despite normal or elevated LDL-apo B PR. The reduced cholesterol and apo B levels were associated with increased FCR and reduced cholesterol proteins ratios in LDL. The plasma level of LDL-cholesterol and apo B rose after weight reduction. The changes in LDL catabolism and composition were associated with changes in the source of LDL Apo B. Pre weight loss 73.33 percent of LDL was derived from VLDL while 26.7 percent was directly secreted into plasma. post weight reduction. VLDL -derived LDL- fall to 46.8 percent of total while direct secretion accounted for 53.2 percent of LDL production.

The results indicated that the regulation of plasma LDL levels in hypertriglyceridemic subjects is quite complex and that rise in LDL-levels after weight loss results from reduction in the fractional catabolism of this hypoprotein. The fall in the FCR is associated-with changes in the source of LDL and in its composition.

In contrast to density lipoprotein cholesterol, where high plasma concentration are associated with an elevated risk of developing coronary heart disease (CHD), High level of HDL-cholesterol associated with a decrease rate of CHD (Rhoads et al 1976). The inverse relationship of HDL-cholesterol and CHD prevalence persists with other risk factor like LDL-cholesterol and total cholesterol.
Several authors have noted lower HDL-cholesterol levels in obese individuals (Rhoades et al. 1976 and Carlson and Ericsson, 1975).

(Thompson et al 1979)\textsuperscript{141} studied the effect of weight loss on HDL-cholesterol in obese females. They found that total plasma cholesterol and low density lipoprotein cholesterol (LDL cholesterol) did not change significantly.

Plasma triglyceride level decreased (P<0.05) as did HDL cholesterol (P<0.02) by multiple regression analysis HDL cholesterol decreased with increasing relative weight but also decreased with increase in rate of weight loss. Their result suggested that negative caloric balance produces a decrease in HDL- cholesterol that in prospective studies may obscure the inverse relationship between HDL cholesterol and indices of obesity.

(Kannel et al 1979)\textsuperscript{142} studied and reported that Beta and Pre Beta lipoprotein were positively correlated with relative weight high density lipoprotein cholesterol was inversely correlated. The association was strongest for high density lipoprotein cholesterol, varying little by age and sex in glyeende was a close second but unlike high density lipoproteins. It and other lipids were more closely associated with obesity in men than in women and in younger than in older persons.

(Garrison et 1980)\textsuperscript{143} studied the relationship between obesity and low density lipoprotein (LDL) cholesterol high density lipoprotein (HDL) cholesterol and very low density lipoprotein (VLDL) cholestérol in adult men and women.

There was marked rise in serum total cholesterol level in men during adolescence by age of 40 years (150 mg to over 200 mg/dl). (Tyroler 1975: Johnson 1967) The pattern of increase in women was slightly different, with much rise occurring after age 40. It has been shown repeatedly that as adults change
weight cholesterol levels change in same direction (Mann, Galbraith et al, 1964)\textsuperscript{144}

The strongest association between obesity and LDL-cholesterol was found in 20-20 years old males. The weakest in 40-49 years old males. Conversely in women the relationship between LDL-cholesterol and obesity modest except in the oldest (40-49 years) age group.

In inverse relationship between obesity and HDL-cholesterol was in shape and strength in all sex and specific groups (Garrison et al, 1980)\textsuperscript{41}.

[Kannel et al (1979) and Keys (1980)]\textsuperscript{145} reported that HDL-cholesterol levels were inversely related with body weight and to a lesser extent LDL-cholesterol level was positively correlated with body weight.

[Thompson and Coworkers (1979)]\textsuperscript{146} found an unexpected decrease in the HDL cholesterol level in women completing a behavioral weight control program However all lipid values had returned to baseline at eight month follow up.

[Brownell and Stunkard (1981)]\textsuperscript{147} also found a decrease in HDL cholesterol level in women completing a behavioral weight loss programme but they observed a different pattern of plasma lipid changes in men. Men completing the same programme showed an increase in the HDL-cholesterol level a decrease in the LDL-cholesterol level and a resulting increase in HDL LDL ratio However, Brownell and Stunkard (1981) did not examine changes in HDL and LDL cholesterol levels at follow up. It seems possible that the HDL level might decrease in women undergoing weight loss but may increase after weight loss. when body weigh has stabilised as suggested by Thompson and Coworkers. (1979).

[Follick and Coworkers (1979)]\textsuperscript{148} studied both short and long term sheet of a behavioral weight loss programme, on LDL and HDL cholesterol level There
were significant changes in plasma lipid levels but short and long term effects differed.

Both total and LDL cholesterol levels decrease during weight loss and remained lower at follow up. However, HDL cholesterol level and HDL LDL ratio did not change during (treatment) weight loss but increased significantly above pre-weight loss level at follow up.

Furthermore long term changes in lipoprotein levels were significantly correlated with changes in body mass index even after correction for initial values.

These results showed that weight loss can in the long term have a potentially beneficial impact on lipoprotein levels in women.

[Despres et al (1985)]149 determined body fat from underwater weighing, assessment of 6 subcutaneous skin fold thickness, and a 12 hour fast blood sampling for measurement of serum triglyceride (TG), high density lipoprotein cholesterol (HDL-e) total cholesterol (CHOL) and HDL-C/CHOL ratio in 234 women and 238 man 18-50 years of age. Even though women were significantly fatter than men, they had lower TG, CHOL and higher values of HDL-C/CHOL ratio Correlational and variance analysis showed that body fatness seemed to be more closely associated with serum lipids in men than in women.

Moreover the relationship between skin fold and serum lipids attenuated that subscapular and abdominal fat deposits are more closely attenuated with serum lipids other fat deposits in men.

In women correlation were lower and regional differences attenuated furthermore the regional trend observed in men remained significant after correction for concomitant variables such as age cigarette smoking habitual intake and energy expenditure, maximal aerobic power and alcohol consumption.
However, no effect of increasing body fatness was noted on HDL-C levels in women. Results of this study of this study suggested that measurement of subscapular and abdominal fat should be considered when interpreting the blood lipid, particularly in males. A higher percentage of fat must be present in women than in men to observe alteration in serum lipids.

Adipose tissue lipoprotein lipase (AT-LPL) is rate-limiting enzyme responsible for uptake and storage of lipoprotein triglyceride by adipocyte (Robinson 1970). The enzyme is made in the cytoplasm of the adipocyte and transported to the capillary endothelium, where it hydrolyses fatty acids from the triglyceride circulating it the core of very low density lipoprotein and chylomierons (Robinson and wing 1970. Blanchette-Mackie and Scow 1971)\textsuperscript{151}. the released fatty acids are than taken up by the adipocyte and re-esterified to triglyceride which is stored in the lipid droplet (Robinson, 1970). The unique position of the enzyme AT-PLL with regard to fat storage suggest that it is a factor the development of human obesity and/or maintenance of the obese state.

In obesity AT-PLP activity per cell has been reported to be elevated and was positively correlated with fat cell size as relative weight by actuarial percentage of ideal body weight (Lithel 1978 and Pykalisto et al 1975)\textsuperscript{152}.

[Schwartz and Brunzell (1981)]\textsuperscript{155} studied and reported that obese subjects have elevated adipose tissue lipoprotein lipase activity per fat cell when compared with lean control subject. In persons who lost weight and subsequently regain their lost weight, the enzyme activity increased after weight loss and then returned toward the original basal level with weight gain. Because AT-PLP activity does not "normalize" after weight loss, according to them. This enzyme play a counter regulatory role in resisting deviation from a "set point" for fat mass or fat cell size thereby predispose to re-attainment of the original obese state.
Subjects with a primary form of hyper triglyceridemia have been reported to have either normal (Pykalisto et al, 1975, Guy-Grand and Bigorie 1975)\textsuperscript{154} or low (Larsson et al 1975) level of adipose tissue LPL activity per cell in fasting state. However, the activity of adipose tissue LPL has not been measured in the fed state in primary in primary hypertriglyceridemia the time during which adipose tissue LPL appears to be functionally important in the removal of triglyceride from plasma (Robinson 1970. Tan et al 1977). Although it was presumed that the activity of adipose tissue LPL would be markedly diminished in the post prandial state in patients with primary LPL deficiency this too has not been previously demonstrated.

Walker et al 1953, investigated the influence of weight loss upon serum cholesterol and certain classes of lipoprotein in a group of 39 human subjects. They reported weight loss led to a significant reduction of the total cholesterol in majority of cases. The caloric balance appears to play an important in controlling the serum lipids.

[Newburgh and Conn (1939)]\textsuperscript{155} reported that middle aged obese patients frequently have delayed utilization of carbohydrate and impaired glucose tolerance test. Reversal of weight gain corrected the metabolic defect in more than 90 percent of instances. Subsequently, a number of investigators have reported that greatly increased plasma immuno reactive insulin responses to glucose, tolbutamide and glucagon were observed in these patients which suggested that insulin antagonism was primarily responsible for diabetogenic stress among the over weight (Karam et al 1961 and perley et al 1966).

[Kalkhoff et al (1971)]\textsuperscript{156} assessed oral glucose tolerance and intravenous glucagon and insulin tolerance in obese patients before and after an average weight loss of eighty five pounds and observed a reduction from 83 to 27 percent above ideal body weight.
They observed that fasting plasma glucose, free fatty acids and immunoreactive insulin exceeded normal levels before weight reduction and after weight reduction only minor differences in mean value existed between obese and control groups. Their findings indicated that disturbances in fasting plasma substralte levels as well as plasma insulin and growth hormone responses in obese individuals were reversible after substantial weight reduction.

It has been suggested that obesity has an important causal role in the development of hyperglycemia (Smith and Levine 1964)\(^{157}\), hyperlipemia (Albrink and Meigs 1965; Harlan et al 1967), hyperinsulinemia (Bageade et al 1967)\(^{157}\) and resistant (Rabinowitz and Zieler 1962). Role of obesity in causing the above metabolic abnormalities was controversial (Stunkard and Blumenthal 1972; Drenick et al 1972) and mechanism involved remained quite unclear. Hypertriglyceridemia was one metabolic abnormalities proposed to accompany obesity, and in order to help explain mechanism leading to this abnormality, Olefsky et al (1974) propose the following sequential hypothesis:

\[
\text{Insulin resistance} \longrightarrow \text{hyperinsulineima} \longrightarrow \text{accelerated hepatic triglyceride} \longrightarrow \text{elevated plasma TG concentration.}
\]

To test this hypothesis they studied effect of weight loss on various aspects of carbohydrate and lipid metabolism in normal and hyperlipoproteinemic subjects.

They observed marked decreases after weight reduction in fasting plasma TG mean value pre-weight reduction 319 mg/100 ml post weight reduction 180 mg/100 ml and cholesterol (mean value pre-weight reduction 282 mg% and post weight reduction 223 mg% ) levels with a direct relationship with a magnitude of the fall in plasma lipid values and height of initial plasma TG level.

They also noted significant decant decrease after weight reduction in insulin and glucose responses during oral glucose tolerance test. They observed
significant decreases after weight reduction in both degree of insulin resistance and VLDL-TG production rates. Thus weight reduction has lowered each of the antecedent variables (insulin resistance, hyperinsulinemia and VLDL-TG production) that according to the above hypothesis lead to hypertiglyceridemia. Consistent decreases in plasma TG and cholesterol levels was seen after weight reduction.

[Egusa et al (1985)]\textsuperscript{158} investigated the influence of obesity on the metabolism of apolipoprotein B (apo-B) in very low density lipoprotein (VLDL) intermediate density lipoprotein (IDL), and low density lipoprotein (LDL), in obese and non-obese. Specific activities were measured in apo B isolated from all lipoprotein fractions and triglyceride isolated from VLDL. Transport rates an fractional catabolic rates for apo-B in VLDL, and LDL and triglyceride in VLDL were determined by multicomartmental analysis. This method also allowed the estimation of rates of interconversions of lipoproteins. The two groups had similar ages and height, but the obese group had a higher total body weight and fat free mass than lean controls. Plasma total lipids were found similar for the two group, and apo B concentrations in VLDL IDL and LDL were similar in obese and lean subjects Inspite of similarly in concentrations, obese subjects compared to lean subjects had higher synthetic rates of VLDL triglyceride (62.5=15 vs 26.2=7 g/d, P <0.01). vldl-b (2.241=215vs1.113=72 mg/d p < 0.001) and LDL –B (1.234 = 87 VS 802= 83 MG/D. P<0.01). Furthermore, in obese subjects significantly higher amounts of VLDL-B were removed from circulation without conversion to LDL-B (1.078 : 159 VS 460 34 mg/d p< 0.05), and obese subjects had a either fractional catabolic rate for LDL than the lean controls. The rapid catabolism of LDL and increased of VLDL without conversion to LDL in obese individuals may be mechanism for maintenance of LDL at normal levels despite the overproduction of its precursor.
Obesity has long been recognised to accentuate the known risk factors for atheroslerotic disease–hyperlipidemia hypertension and glucose intolerance. One possible explanation for an excess risk is that obese subjects have abnormalities in lipoprotein metabolism that do not produce hyperlipidemia and yet accelerate atherosclerosis for example obese subjects without hyperlipidemia have been reported to have increase in synthesis of very low density lipoprotein (VLDL) triglycerides (TG) [Olefsky et al 1974, Reaven et al 1978, Grundy et al 1979] apolipoprotein B (Kissebah et al, 1981). low density lipoprotein (LDL-B) (Kesaniemi and Grundy 1983) and total body cholesterol (Miettinen 1971) Any or these abnormalities might enhance the rate of atherogenesis. More over because VLDL is the precursor of LDL (Bilheimer et al 1972: Sigurdsson et al , 1975) there could be aberrations in the interconversion of VLDL to LDL.

One of the other subject comes in light recently. In obese individual raise in free fatty acid level occur. Plasma FFA concentrations are generally higher in obese than in nonobese individual and high FFA concentration are associated with many of the adverse metabolic consequences of obesity. (Sheehan and Jensen 1997)\textsuperscript{159}

**Effect of Obesity on Fatty Acid Metabolism**

(Sheehan and Jensen et al)\textsuperscript{159} Adipose tissue is the main storage depot of fatty acids (in the from of triglycerides) the major lipid fuel in humans. After being released from adipocytes, free fatty acids (FFA) are transported in blood bound to albumin and are rapidly (3 to 4 minutes) removed from the circulation FFA are to fat metabolism as glucose is to carbohydrate metabolism; however, FFA are present in blood at much lower concentrations than glucose (approximately 500 mol/L versus approximately 5 mmol/L) The physiology of FFA uptake and release from adipose is depicted in Figure 1. Adipocytes take up fatty acids from circulating triglycerides present in chylomicron and very-low-
density lipoprotein (VLDL) particles. The action of lipoprotein lipase (LPL) is necessary for this to occur. Once inside the adipocyte, the fatty acids are reesterified to triglycerides for storages. The release of FFA from adipose tissue occurs via hormone-sensitive lipase, which hydrolyzes triglycerides to yield three FFA and one glycerol molecule; the former can be used for fuel and the latter as a substrate for gluconeogenesis (liver and kidney) or triglyceride resynthesis (liver and muscle). Lipolysis is inhibited by insulin and stimulated by catecholamines; cortisol and growth hormone also stimulate lipolysis but to a lesser degree than catecholamines.

Plasma FFA concentrations are generally higher in obese than in non-obese individuals, and high FFA concentrations are associated with many of the adverse metabolic consequences of obesity. Elevated FFA concentrations expose sensitive tissues (skeletal muscle, pancreatic islets, and liver) to excess lipid fuel. There are two possible explanations for above-normal FFA from adipose tissue—a case of fuel availability; (2) decreased uptake of FFA by other tissues—a case of normal or reduced fuel availability. The elevated FFA concentrations reported in obesity in general and upper body obesity in particular could be due to abnormal adipose tissue FFA release or failure of FFA using tissues to remove them normally. Understanding which of these processes involves helps localize the problem. To address this issue, it is necessary to measure the uptake and release of FFA (using isotope dilution techniques), not just FFA concentrations. Measuring FFA release, although not part of clinical practice has allowed investigators to identify excess adipose tissue lipolysis as a reason for higher FFA concentrations in upper body obesity. This increased FFA release in upper body obesity leads to above-normal FFA concentrations especially at times when insulin is increased, such as after meal ingestion. There is strong evidence to suggest that excess FFA contribute to the pathogenesis of the metabolic syndrome.
Free Fatty Acids and Hepatic Insulin Extraction

Normally, approximately 50% of the insulin secreted is removed in the first pass by the liver. Although it is true that the hyperinsulinemia seen in generalized obesity is primarily due to increased insulin secretion upper body obesity is also associated with decreased hepatic insulin extraxtion The mechanism of the abnormality in insulin extraction has been studied in vitro using a rat hepatocyte model system. Exposure of hepatocytes to FFA decreased insulin binding in a manner consistent with decreasing the number of insulin receptors and inhibition of FFA oxidation by etomoxir normalized hepatocyte insulin binding The hyperinsulinemia of upper body obesity is due to increased pancreatic secretion and decreased hepatic insulin extraction. Higher blood concentrations of FFA may contribute to the latter abnormality.

Free Fatty Acids and Endogenous Glucose Production

The liver, using the release of stored glycogen (glycogenlysis) and the synthesis of new glucose (glycogenlysis) is the principal source of glucose production. Insulin is the major hormone the inhibits glucose production and type II DM is associated with hepatic (as well as peripheral) insulin resistance. Increased glucose production, despite hyerinsulinemia, is the cause of fasting hyperglycemia in type II DM. FFA have been implicated in the elevated glucose production associated with diabetes since early studies showed that FFA increased new glucose formation from all precursors in the perfused rat liver.

Type II DM is associated with increased glucose production and this is augmented by obesity Much of excess glucose production is attributed to increased gluconeogenesis. Endogenous glucose production is positively correlated with plasma FFA concentrations in type II DM. The insulin resistance with respect to suppression of glucose production may be mediated in a tonic fashion by elevated FFA because further increasing FFA does not worsen the
ability of insulin to suppress glucose production in type II DM; however, administration of acipimox (which lower FFA) enhances its suppression. Experimental elevations of FFA in lean, insulin-sensitive individuals increases gluconeogenesis and if FFA are increased in the of relative insulin deficiency such as is present in type II DM, glucose production increases Increasing FFA via exogenous lipid emulsion infusions impairs insulin suppression of glucose production in nondiabetic adultic. It has been suggested that visceral fat affects metabolic health by directly releasing FFA into the portal vein, preferentially affecting hepatic metabolism. In support of this theory, decreasing visceral fat of obese rats by caloric restriction or removing it surgically improves the ability of insulin to suppress glucose production.

**Free Fatty Acids and Insulin Secretion**

The development of type II DM requires defects in insulin secretion and insulin action. Many obese individuals are insulin resistant, yet only a subset develop DM. It follows that those who develop type II DM develop pancreatic beta cell decomposition with subsequent hyperglycemia.

Although chronic hyperglycemia itself likely contributes to impaired insulin secretion (glucotoxicity), studies have suggested a process of pancreatic beta cell lipotoxicity is also involved. This model proposes that increased FFA contribute to the insulin secretory abnormalities seen in obesity and ultimately lead to beta cell failure, Evidence for this proposal comes primarily from animal models, given the lack of access to human pancreatic tissue. Plasma FFA concentrations are increased early in the disease process of a model of type II DM (the Zucker diabeticrat). In this prediabetic animal the triglyceride content of pancreatic islet cells is 10-fold greater than control rats, and the islet triglyceride content correlates with plasma FFA and glucose at the onset of hyperglycemia. Furthermore, islets from these animals have impaired glucose-stimulated insulin
secretion, an abnormality that can be reproduced in normal rat islets by incubating them with FFA for 7 days. Increased FFA has been demonstrated to increase basal insulin secretion and reduce glucose-stimulated insulin secretion and insulin biosynthesis. Inhibiting beta cell FFA oxidation with etomoxir can partially reverse the defect in glucose-stimulated insulin secretion. Treatment of this animal model with troglitazone or metformin diminishes the typical rise seen in FFA and prevents the development of diabetes. In vitro studies have shown that increased FFA concentration can induce the beta cell abnormalities seen in diabetes, and blocking the oxidation of FFA can prevent these changes.

In vivo studies involving lipid infusion in rats for 48 hours have generally supported in vitro data. Increasing FFA twofold in these animals increases basal insulin secretion and after 48 hours, glucose-stimulated insulin secretion was blunted. A partial reversal of decreased glucose-stimulated insulin secretion was confirmed in vivo with the addition of etomoxir. Not all studies have confirmed these observations.

The effect of FFA on insulin secretion in humans has not been studied extensively. A threefold increase in plasma FFA concentrations was shown to increase the insulin response to intravenous glucose after 6 hours but to diminish the response after 24 hours. Another study however using a 48-hour lipid infusion to raise FFA did not confirm this observation. The in vivo data in humans is not currently as strong as the in vitro data; it has not yet been studied extensively.

**Free Fatty Acids and Vasoconstriction**

The growing body of evidence that increased FFA may contribute to the hypertension and increased vascular responsivity seen in the metabolic syndrome was the subject of a review. There is a weak but significant correlation between FFA or FFA flux and blood pressure in upper body obesity and obese type II DM. To assess further FFA alters vasoconstriction, the vasoconstrictor response to
thigh cuff inflation (a method of increasing endogenous norepinephrine), lipids were infused to raise FFA in lean, health volunteers. The magnitude and the duration of the vasoconstrictor response was increased when FFA were elevated and the sensitivity to phenylephrine's vasoconstrictor effect was observed, which is consistent with an on-mediated mechanism. This increased vascular sensitivity to an receptor agonist was reproduced in a similar study using changes in systemic blood pressure as the endpoint. Increased FFA are associated with elevated blood pressure in upper body obesity and raising FFA individuals increased the vascular sensitivity to adrenergic stimuli.

Given that increased visceral adiposity is implicated in the development of hypertension, it would be of interest to assess the vascular effects of increased FFA concentration in portal vein. Although not feasible in humans, these studies have been conducted in rats—a significant increase in increase in blood pressure was induced by intraportal lipid infusion. This increase in blood pressure could be blocked by co-administration of an \( \alpha_1 \)-adrenergic antagonist, consistent with the results in humans using systemic lipid infusions. This FFA-induced sensitivity to \( \alpha \)-adrenergic stimuli is not seen with other vasoconstrictor mechanisms, such as angiotensin II.

**Free Fatty Acids and Vasorelaxation**

Nitric oxide is now recognized as a critical component of the human vasodilator system, and insulin has an ability to increase skeletal muscle blood flow that is mediated through an increase in nitric oxide. The ability may have implication for vasoregulation in obesity. Four times more insulin is required to double leg flow in obese, insulin resistant adults than nonobese adults. There is even greater resistance to insulin-induced increase in leg blood in type II DM. The capacity to modulate blood flow appears to be a new role for insulin. FFA may have a role in modulating the insulin and nitric oxide regulation of leg blood
flow. Raising FFA in normal volunteers (as described earlier) diminished the nitric oxide-induced increase in large blood flow. A potential biochemical explanation for this observation has been offered: FFA decrease endothelial nitric oxide synthase activity in a concentration-dependent manner in cultured endothelial cells. FFA appears to interfere with oxide-mediated vaso relaxation and this may contribute the hypertension seen in the metabolic syndrome.

**Free Fatty Acids and Hypertriglyceridemia**

In 1976, Kissebah et al reported that hepatic VLDL-B-apoprotein production was positively correlated with FFA flux. Lewis et al demonstrated that increasing FFA twofold by a lipid infusion increases VLDL triglyceride production 180%. Also several studies have shown that the increase in serum triglyceride concentrations seen in visceral obesity and type II DM is associated with increased VLDL apoB-100 secretion, which in turn is positively correlated with WHR and waist circumference. The positive correlation between VLDL apo-B secretion rate and fasting insulin or C-peptide suggest that resistance to insulin mediated suppression of FFA plays a role in increased VLDL apoB-100 secretion. Hyperinsulinemia decreases VLDL-triglyceride production (in concert with a decrease in FFA) by about 67%, unless the fall in FFA is prevented in which case VLDL-teriglyceride production decreases only modestly. Increased FFA drives VLDL apoB-100 secretion, and insulin acts directly at the liver and indirectly (through decreasing FFA) to diminish this secretion.

The mechanisms by which insulin and FFA exert their effects on VLDL apoB-100 secretion have been unraveled using a cultured hepatocyte cell line (HepG2 cells). The regulation of apoB secretion is a posttranslational process. If FFA is added to the medium of HepG2 cells, a higher proportion of the intracellular apoB is secreted than is degraded. This situation is likely a result of an increase in triglyceride formation stimulated by higher FFA availability.
Furthermore when insulin is added to a culture of rat hepatocytes, there is increased intracellular degradation of apoB-100. FFA stimulate VLDL secretion by increasing triglyceride synthesis which in leads turn leads to a greater secreting of VLDL apoB-100. Insulin antagonizes both of these processes.

**Free Fatty Acids and High-Density Lipoprotein Cholesterol**

The low HDL cholesterol seen in the metadrome appears to be indirectly related to increased FFA. As discussed earlier increased FFA causes increased VLDL-triglyceride secretion. The exchange of HDL cholesterol esters for triglyceride from VLDL or chylomicrons occurs via cholesterol esters transfer protein (CETP). This process is partially controlled by mass action, whereby a larger VLDL-triglyceride pool drives exchange. In addition, CETP mass is increased in obesity and decreased with weight loss. Through increased VLDL-triglyceride and CETP activity, there is an increase in triglyceride-rich αHDL particles. These triglyceride-rich particles are an excellent substrate for hepatic lipase and subsequently become cleared from the blood. This proposed interaction has been experimentally recreated by infusing a lipid emulsion into health men—an increase in the triglyceride content of HDL with a subsequent increase in HDL particle clearance was found.

**Free Fatty Acids and Small, Dense Low-Density Lipoprotein Cholesterol Particles**

An increased concentration of small, dense LDL particles is associated with a threefold increase in the risk of myocardial infarction. Small, dense LDL particles are positively correlated with triglycerides and negatively correlated with HDL cholesterol. Additionally, there are significant positive correlations between fasting insulin and visceral fat and small, dense LDL particles. LDL cholesterol is produced through the metabolism of VLDL particles by LPL. Exchange of triglyceride and cholesterol ester via CETP also occurs between triglyceride-rich
VLDL and LDL particles. Hepatic lipase can act on these triglyceride-rich LDL particles to form small, dense LDL. The increased small dense LDL cholesterol characteristic of the metabolic syndrome is also indirectly related to the increased FFA seen in obesity.

Table XXI (Kushner & Weinsier) 60

<table>
<thead>
<tr>
<th>SYMPTOMS AND DISEASES ASSOCIATED WITH OBESITY</th>
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<tbody>
<tr>
<td>Cardiovascular system</td>
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<tr>
<td>Hypertension</td>
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<td>Congestive heart failure</td>
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<td>Cor pulmonale</td>
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<td>syndrome</td>
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<td>Varicose veins</td>
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<td>Pulmonary embolism</td>
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<tr>
<td>Coronary heart disease</td>
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<tr>
<td>Endocrine system</td>
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<tr>
<td>Reduced insulin sensitivity</td>
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<tr>
<td>Glucose intolerance</td>
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<tr>
<td>Type II diabetes mellitus</td>
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<tr>
<td>Dyslipidemia</td>
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<tr>
<td>Polycystic ovary syndrome</td>
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<tr>
<td>Infertility</td>
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<tr>
<td>Amenorrhea</td>
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<tr>
<td>Musculoskeletal system</td>
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<tr>
<td>Immobility</td>
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</tbody>
</table>
Degenerative arthritis  
Low back pain  
Integument  
Venous stasis of legs  
Cellulitis  
Diminished hygiene  
Intertrigo, carbuncles  

Hypogonadism  
Breast and uterine cancer  
Neurologic  
Stroke  
Meralgia paresthetica  
Idiopathic intracranial hypertension

How Does Excessive Fat Influence Health?

(Dr. A.S. Hakim et al) Obesity can lead to metabolic abnormalities that are considered to be related FFA levels that occur in upper body obesity. The increased FFA levels are thought to be due to either an increased release from adipose tissue or decreased uptake tissue or decreased uptake by other tissues. Elevated FFAs have a multitude of effects. They cause insulin resistance at the level of the skeletal muscle causing decreased glucose uptake into the muscle. FFAs cause an increased release of and triglycerides from the liver with a reduction of insulin clearance and can cause a reduction of pancreatic insulin secretion. Vasoconstriction caused by FFA leads to hypertension.

All these effects ultimately lead to the insulin resistance syndrome or syndrome X (insulin resistance with or without type 2 DM, hypertension, dyslipidaemia and cardiovascular disease).

Mechanical effects such as osteoarthritis and obstructive sleep apnoea can occur and reproductive disorders and psychiatric problems are also associated with obesity.
Hyperinsulinaemia And Diabetes Mellitus

Upper body obesity is associated with hyperinsulinaemia. This is due to insulin resistance at the level of the skeletal muscle as well as increased pancreatic insulin secretion. Insulin resistance in obesity is thought to be due increased FFAs which impair insulin action on the skeletal muscle. Over expression of TNF-from the adiposities (occurring in obese patients) inhibits the action of insulin. This leads to hyperinsulinaemia. The development of 2 diabetes mellitus requires defects in insulin action and secretion. Increased FFA also leads to impaired insulin secretion by the process of cell lipotoxicity. Evidence of this proposal comes from animal models. Systemic hyperinsulinaemia may also be an independent cardiovascular disease risk factor. Among all abnormalities of lipid metabolism / hyperglyceridemia is the commonest in diabetes along with VLX and LDL also increases.

Hypertension

There is a significant positive relationship between FFA and blood pressure in upper body obesity and type 2 DM. This occurs due to FFA increasing the vascular sensitivity to adrenergic stimuli. Furthermore FFA inhibit nitric oxide production causing vasoconstriction and blunt reflex vasorelaxation. Other mechanisms include renal sodium retention secondary to hyperinsulinaemia activation of sympathetic nervous system, excess TNF and angiotensinogen.

Dyslipidaemia

Upper body obesity and type 2 DM are associated with increase in triglycerides, decreased HD, cholesterol and high LDL. This hyperlipidaemia contributes to increased cardiovascular risk. The elevated aVLDL may be caused by increased hepatic FFA delivery, which increased triglyceride synthesis. Low HDL and the increase in LDL are indirect consequences of elevated triglyceride-
rich VLDL. Genetic influences play a significant role in the expression of these abnormalities. Regional distribution of fat plays an important role in the risk factors of obesity. To assess body fat distribution the ratio of waist-hip circumference is a valuable tool for epidemiological studies. For the individual patient the waist circumference is also important. A waist circumference above 100 cms in males and 90cms in females is associated with increased levels of triglycerides and reduced levels of HDL cholesterol. Quantitative estimates of fat distribution can be obtained from MRI or CT scans, these are used more for scientific purposes.

**Cardiovascular Disease**

Obesity causes increased work load on the heart. It is also associated with sudden death probably due to cardiac arthymias precipitated by atherosclerosis. This possibly is a reflection an abnormal lipid profile, diabetes mellitus and hypertension, which are commonly associated with obesity.

**Gall Bladder Disease**

Gall bladder disease increases with obesity and age possibly related to increased excretion of biliary cholesterol. The amount of cholesterol synthesised by the body each increases by 20 mgs for each Kg of adipose tissue. There is approximately a sixfold increase in the incidence of gallstones in patients whose weight is 50% above ideal body weight. Extreme diets that are sometimes used in the treatment of obesity can precipitate cholecystitis.

**Pulmonary Disease**

Pulmonary abnormalities may occur in obese patients. These include decreased total lung capacity, functional residual capacity, reduced chest wall compliance and increased work of breathing. This can lead to reduced effort tolerance and restriction of physical activity. People who are very obese may
develop obstructive sleep apnoea and the obesity hypoventilation syndrome. They can also have central or mixed sleep apnoea. Sleep apnoea can lead to daytime somnolence, depression, hypertension, right heart failure and occasionally fatal cardiac arrhythmias.

Bones and Joints

Increased trauma to weight-bearing joints often leads to osteoarthritis. This commonly involves the knee and hip joints. Obese people are also known to have an increased prevalence of gout.

Skin

Obese people very often have thin friable skin increasing the incidence of fungal of fungal and yeast infection. Other manifestations include acanthosis nigrians where there is darkening and thickening of the skin-folds on the neck and elbows. This is known to reduce with weight loss. Obese people often develop varicose veins and venous stasis.

Cancer

Obesity is linked with a higher incidence of cancer, In obese females there is a higher mortality from cancer of the breast, cervix, endometrium, ovary and gall bladder.

Obesity males have a higher mortality from cancer of the prostate, colon and rectum. Increased cancers in females may be due to increased conversion of androstenedione to estrogen in adipose tissue.

Reproductive Disorders

Women with upper body obesity often have menstrual abnormalities. This is to increased androgen production and increased peripheral conversion of
androgen to oestrogen. Obese women with oligomenorrhoea often have polycystic ovarian syndrome, which is associated with anovulation. An increased incidence of uterine cancer is seen in postmenopausal women with lower-body obesity. The increased conversion of androstendione to oestrogen that occurs to a greater degree in lower-body obesity is thought to be responsible.

Increased adipose tissue distributed in the female pattern is often associated with male hypogonadism. Gynaecomatia may be seen in obese males. Spermatogensis, potency and libido are usually normal in these individuals.

Specific Syndromes Associated with Obesity

Cushing’s syndrome, hypothyroidism, insulinomas and disorders involving the hypothalamus are often associated with obesity. Per cent of men and 17.5 per cent of women were in this category. The characteristics in which they differed significantly from the weight stable members of the population were: a lower level of education chronic disease, little physical activity at leisure, and heavy alcohol consumption. Weight gain was also observed among those who got married or stopped smoking: these predictors applied both to men and to women.

Hiatus and other Hernias:

Hiatus Hernia, reflux esophagitis, are common among the morbidity obese, Hiatus hernia repairs may be requested among the morbidity obese, Hiatus hernia repairs may be requested by the family doctor. This hernia could be dangerous because the combination of a tight gastroesophageal function and small gastric pouch and gastric ruptur.

Psychological problems also related to morbid obesity.
Mechanisms By Which Obesity Causes Disease

(Warrell) A decade ago epidemiologists considered that obesity was not an important cause of disease or mortality, but merely a marker of the true risk factors, such as raised plasma cholesterol, hypertension, and non-insulin-dependent diabetes mellitus. This view was based mainly on multiple regression analyses of the risk factors for total mortality and cardiovascular disease mortality in the Seven Nations Study, which made prospective observations in groups of middle-aged men in the United States, Europe and Japan. Subsequent research has shown that obesity is not merely a marker, but a cause of these risk factors. Cigarette smoking is an important confounder in this association. Figure 6 indicates causative chains between obesity and some important diseases. The links in these chains are discussed further below.

**Insulin Insensitivity And Its Consequences**

Obese people are insulin resistant if their capacity to secrete insulin is limited very liable to develop non-insulin-dependent diabetes mellitus. The definitive demonstration that the obesity causes the insulin resistance was provided by a study in Vermont by signs and colleagues. For 6 moths they overfed 19 young men who had personal or family history of obesity or diabetes. At the end of the overfeeding period, when they were in energy balance again, they had in increased body weight by 21 per cent, of which 73 per cent was fat. Insulin sensitivity, as measured by oral or intravenous glucose tolerance, decreased significantly and there were coincident increases in fasting levels of insulin and glucose as well as in the insulin response. As weight fell towards the original level these changes reverted to normal. We now know that intra-abdominal fat is especially important in causing insulin insensitivity, since its, since its high lipolytic activity releases high concentrations of free fatty acids into the portal circulation. Insulin insensitivity is the key abnormality in the 'syndrome X' described by Reaven, and is associated with hypertension, high low-density
lipoprotein (LDL)-cholesterol, low high-density lipoprotein (HDL)-cholesterol, and an increased risk of atheroma formation. Hypertension is also associated with obesity, and weight reduction has repeatedly been shown to reduce arterial pressure.

Metabolic Effects of Large Adipose Mass

Apart from effects mediated by insulin by insulin insensitivity, a large adipose mass has three other important effects which predispose to diseases:

Aromatase

This is the enzyme system that converts androgens to oestrogens, and in an obese person there is more aromatase in adipose tissue than in the gonds. This probably accounts for the menstrual problems, problems, polycystic ovaries, and infertility which are often seen in obese women; infertility in obese men; and the excess risk of sex-hormone-sensitive cancers: of the colon, rectum, and prostate in men, and of the endometrium, cervix, ovary, and breast in women.

Cholesterol stores

Such stores in adipose tissue greatly increase the rate of cholesterol excretion in the bile, leading to supersaturation of bile in obese people. This predisposes to the formation of gallstones, cholecystitis, and to gallbladder cancer.

The Mechanical Load

This load, represent by the excess weight, decreases exercise tolerance and predisposes to inactivity, although there is little evidence that inactivity is an important factor in causing obesity. Inactivity is itself a contributor to insulin insensitivity, and the increased load contributes to. Other health problems.

(According to Louice J. Aronne M.D.) For maintaining good health Excerisre, balanced diet and Happyness is necessary.

(Slone et al) - The fibrous vegetarian diet have lipid lowering effect it can improve the lipoprotein metabolism.
(Stone et al) The vegetarian diet contain steroles which have been used to lower the blood cholesterol. The comprehensive metanalysis suggest 3g of soluble fiber of Oat can decrease cholesterol and LDL-Cholesterol by 5 mg/di.

(James o Hill et al) Low level of physical activity increase the risk of obesity by stimulating fat deposition and positive emery balance.
In obesity there will be increase in free radical production and so anti-oxidant level is disturbed. So, study of change in anti-oxidant level in obesity will definitely help in treating obesity and associated diseases.

The hazardous effects of reactive oxygen species (ROS) are quite well known. To counteract the potentially hazardous reactions, initiated by oxygen metabolites, and anti-oxidant system is there which encompasses many substances, which are termed as anti-oxidants, free-radical scavengers, chain terminator or reductants. The anti-oxidant system responsible for cellular protection against oxidative stress are as diversified as the free radicals themselves. These anti-oxidant systems have wide distribution in nature. For ex superoxide dismutase (SOD), catalase (CT) and glutathione peroxidase (GSH-Px). Among these anti-oxidants, SOD and catalase are important.

TABLE: Major Biological Anti-oxidant Compounds

<table>
<thead>
<tr>
<th>Enzymatic Systems</th>
<th>Non-Enzymatic Systems</th>
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<tbody>
<tr>
<td></td>
<td>Fat-soluble compounds</td>
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<tr>
<td>Superoxide dismutase</td>
<td>Vitamin E</td>
</tr>
<tr>
<td>Catalase</td>
<td>β-Carotene</td>
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<tr>
<td>Glutathione peroxidase</td>
<td>Bilirubin</td>
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<tr>
<td>Glutathione reductase</td>
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</table>
SUPEROXIDE DISMUTASE (SOD)-

This dismutation of superoxide anion is carried out by the enzyme superoxide dismutase. This enzyme catalyses removal of two molecules of superoxide anion to yield one molecule of oxygen and hydrogen peroxide.

\[ \text{O}_2 + e^- \rightarrow \text{O}_2^- \]
\[ \text{O}_2^- + \text{O}_2^- \rightarrow \text{H}_2\text{O}_2 \]

The activity of SOD is found mainly in liver, adrenal gland, kidneys and spleen. Reduction in the level of SOD invariably leads to impaired protection against toxic effects of \( \text{O}_2^- \) and this might lead to severe cellular damage.

CATALASE-

Catalase is the enzyme which catalyses break down of hydrogen peroxide into water and oxygen.

\[ 2\text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2 \]

This is a tetraheme enzyme and it reduces hydrogen peroxide. Thus it serves a protective role. The increased \( \text{H}_2\text{O}_2 \) concentration and lipid peroxide levels are often associated with a decreased catalase activity. Catalase prevents free radical induced aldehyde, lipid oxidation and DNA scissions caused by \( \text{H}_2\text{O}_2 \)