A Review on Obesity its pathophysiology, and role of Serum lactate and Cystatin C Biomarkers in obesity

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Abstract

Obesity and its prevalence is rising continuously in developed as well as developing countries. High body mass index is a risk factor for various metabolic derangements which includes hypertension, dyslipidemia, stroke, gall bladder disease, diabetes and coronary artery disease and therefore the associated morbidity, mortality and medical costs are expected to increase as well. Lactate and Cystatin C are known to release from adipose tissues and may both contribute to metabolic derangements in obese patients. So, the aim is to study the role of serum Lactate and Cystatin C in obesity. In this article we will review 1) The pathophysiology of obesity 2) role of lactate and Cystatin C in obesity.

Keywords- Serum lactate, Cystatin C, Obesity, BMI, Metabolic derangements

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Introduction:

Obesity is one of the growing epidemics which have been found to be associated with various metabolic derangements such as dyslipidemia, hypertension, diabetes mellitus, stroke, coronary artery disease, gall bladder stones. Obesity is a multifactorial disease i.e. there is no. of factors involved in the progression of obesity and its associated health problem. According to National Health Association Nutrition and Examination Survey (NHANES) in 2015- 2016, the prevalence of obesity has been found to be 39.8% and 18.5% in United States adults and youth respectively.
Obesity is a major worldwide public health problem with rising incidence and severity both in developing and developed countries. Obesity is of multifactorial origin, that is genetic, behavioral, environmental, metabolic, cultural, Psychological, and physiological factors. Obesity is one of the leading preventable causes of death. When excess of body fat has been accumulated to the extent that it may have an adverse effect on health is termed as obesity. According to National Health and Nutrition Examination Survey (NHANES) in 2015-2016, the prevalence of obesity was 39.8% in adults and 18.5% in youth. Obesity is emerging as an important health problem with 25.6% of men and 44% of women being obese in Indian population.

Obese patients has an increased risk of cardiovascular diseases through various factors such as increased fasting plasma triglycerides, high LDL cholesterol, elevated blood glucose, insulin levels and high blood pressure and low serum high density lipoproteins. These abnormalities are clinically important because of their causal relationship with coronary heart disease. Obesity or excess fat has serious effect on public health, increasing the risk of type 2 diabetes, dyslipidemia, hypertension, coronary artery disease, renal insufficiency, degenerative changes of joints, cholethiasis, gall bladder disease, the increased risk of CVD disease.

Various biomarkers have been reported to play an important role in obesity associated oxidative stress. Lactate is the one marker of decreased oxidative capacity. Lactate is an anion that results from dissociation of lactic acid, intracellular metabolites of glucose; specifically it is the end product of anaerobic glycolysis the final step of which is conversion of pyruvate to lactate by the enzyme lactate dehydrogenase. Lactate is a marker of decreased oxidative capacity which may further contributes to insulin resistance, alters serum triglycerides levels, which may further contributes to major cardiovascular risks. When oxidative capacity decrease, lactate levels increases as a consequence of increased flux through glycolytic pathway. Previous studies have suggested that lactate levels increases in insulin resistance. Higher levels of lactate in blood leads to decreased oxidative capacity which may leads to obesity and obesity which further contributes to hypertension and insulin resistance and other major health related problems. High carbohydrate diet may significantly increase the activity of serum lactate dehydrogenase which leads to increase in lactate levels. (Lucia Marsegelia, Sara Manti et al; 2015)

Cystatin C is a monomer, 13.3 kDa globular, and nonglycosylated protein. Its isoelectric point is high i.e. pI=9.3, is positively charged and found in all body fluids and cells. The primary biological function of cystatin C is to inhibit
cysteine proteinases of host and microbial origin present in extracellular fluids (Barrett et al., 1984). Cystatin C is expressed and released by human preadipocytes differentiated in vitro (Taleb et al., 2006). The epidemiological studies have demonstrated that obesity is indicator for cardiovascular diseases (Francisco B. Ortega, Carl J. Lavie et al., 2018). It is reported that increased adiposity and obesity has been found to be associated with higher waist circumference, an index of visceral adiposity, and increased percent of body fat is associated with higher serum cystatin C in apparently healthy subjects (Ichihara et al., 2008). In American adults the higher BMI has been found to be also associated with increased cystatin C levels (muntner et al., 2008). Cystatin C regulates the enzymatic activity of cathepsins. The increase Cystatin C levels may be due to regulatory mechanism in order to control the proatherogenic capacity of cathepsin (Lafarqe JC et al., 2010). This shows that adipose tissues may directly contribute in enhanced Cystatin C levels in condition like obesity (Christine Poitou, Arnaud Basdevant et al., 2005). Obesity is a medical condition which contributes to metabolic derangements which includes hypertension, insulin resistance, coronary artery disease, Cystatin C levels were found to be increased in patients with metabolic syndrome and it increases as the number of components of metabolic syndrome increases. Cystatin C and serum lactate are known to be clearly affected by metabolic status of the body. Thus, the present study is aimed to assess the role of Cystatin C and lactate levels and its association with obesity.

Obesity is one of the growing epidemic which has been found to be associated with various metabolic derangements such as dyslipidemia (Klop Boudewijn, Jan Willem F. Elte et al., 2013), hypertension (Kotchen Theodore A.et al., 2010) diabetes mellitus (Baird JD. 1973), stroke (Goyal, M., Mohr, J.P, Calle et al., 1978, 2015), coronary artery disease (Lavie CJ, De Schutter et al., 2014), gall bladder stones (Everhart JE et al., 1993). Obesity is a multifactorial disease i.e. there is no. of factors involved in the progression of obesity and its associated health problem (MB Chalk , 2004). According to National Health Association Nutrition and Examination Survey (NHANES) in 2015-2016, the prevalence of obesity has been found to be 39.8% and 18.5% in United States adults and youth respectively.

Obesity is a term characterized by alterations in metabolic function resulting from an increase in body fat mass as well as the visceral distribution of adipose tissues and there have been a close association between metabolic alterations and development of important co-morbid diseases eg; dyslipidemia, insulin resistance, ischemic heart disease (Muoio DM, Newgard CB et al., 2006). Obesity is a medical condition in which excess of fat has been

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gathered in the body due to imbalance between food intake and energy homeostasis over many years and thus affecting the health of individual. Obesity is a term derived from Latin word “obesus” which means by eating much and doing less physical activity one becomes plump, which also means “coarse” or “vulgar”.

**PREVALENCE AND INCIDENCE**

The prevalence of obesity is rising in both developed as well as developing countries. In recent years, morbidity and mortality is increasing day by day due to obesity (Sari et al., 2004). As per HMSO report, 32% of women and 39% of men in United Kingdom were overweight and obese in 1980, and the percentage is increased to 44% and 52% respectively in 1991 (HP Ferrer, A Moore, GC Stevens - 1977).

According to the National Health and Nutrition Examination Surveys (NHANES), the prevalence of obesity increased gradually from 1960 to 1980, but in the period from the second survey (NHANES II: 1976 to 1980) until the third (NHANES III: 1988 to 1994); it increased markedly, from 14.5% to 22.5% (Flegal et al., 1998). The combined prevalence of overweight and obesity also increased dramatically, from 46.0% to 54.4% in the period from the second to third NHANES Surveys. Even in India, obesity is emerging as an important public health problem with 25.6% of men and 44% of women being obese and overweight in urban Indian population.
Table-1: International Classification of adult underweight, overweight and obesity according to BMI (World Health Organization):

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m^2)</th>
<th>Principal points</th>
<th>Additional cut-off points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.50</td>
<td>&lt;18.50</td>
<td></td>
</tr>
<tr>
<td>Severe thinness</td>
<td>&lt;16.00</td>
<td>&lt;16.00</td>
<td></td>
</tr>
<tr>
<td>Moderate thinness</td>
<td>16.00 - 16.99</td>
<td>16.00 - 16.99</td>
<td></td>
</tr>
<tr>
<td>Mild thinness</td>
<td>17.00 - 18.49</td>
<td>17.00 - 18.49</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>≥ 25.00</td>
<td>≥ 25.00</td>
<td></td>
</tr>
<tr>
<td>Pre-obese</td>
<td>25.00 - 29.99</td>
<td>25.00 - 27.49</td>
<td>27.50 - 29.99</td>
</tr>
<tr>
<td>Obese</td>
<td>≥ 30.00</td>
<td>≥ 30.00</td>
<td></td>
</tr>
<tr>
<td>Obese class I</td>
<td>30.00 - 34.99</td>
<td>30.00 - 32.49</td>
<td>32.50 - 34.99</td>
</tr>
<tr>
<td>Obese class II</td>
<td>35.00 - 39.99</td>
<td>35.00 - 37.49</td>
<td>37.50 - 39.99</td>
</tr>
<tr>
<td>Obese class III</td>
<td>≥ 40.00</td>
<td>≥ 40.00</td>
<td></td>
</tr>
</tbody>
</table>


TYPES OF OBESITY

The distribution of adipose tissues around the body is also important. There are two types of fat distribution viz: Android and Gynoid type.

Fig-1: (a) Android type

(b) Gynoid type
(a) Android type: In android type (apple shape), fat is doling out around the abdomen and viscera, is also
called as truncal obesity or abdominal obesity.

(b) Gynoid type: Where as in gynoid type (pear shape), the fat is distributed more peripherally, especially around
the hips and buttocks and mostly prevalent in women.

PATHOPHYSIOLOGY OF OBESITY

The etiology of obesity is complex, with environmental influences acting on genetic or biologic predisposition.
The various mechanisms involved in pathophysiology of obesity are as follow:

FOOD INTAKE

Food intake is a multiplex behaviour that addresses acute and long term energy needs of body. There are many
different levels and types of control. While the timing of food ingestion is largely related to environmental
factors and learned behaviour which is highly variable, the amount of food consumed over long intervals is
regulated to maintain adiposity at a constant level.

ADIPOSITY SIGNALS

Various hormones have been reported to be currently available but the two major hormones that are involved in
adiposity are insulin and leptin. Both leptin and insulin circulate in the body at concentrations proportional to
body fat content, and enter the central nervous system proportional to their plasma levels. Receptors of insulin
and leptin are present in the areas of brain involved in the control of energy intake. When peptide enter directly
into the brain, there is decrease in the energy intake in CNS(JE Blevins, F Kim,2009) and deficiency of either
hormone or central blockade of their action has the opposite effect. The mechanism by which these two
hormones link with adipose tissues is different.

CENTRAL MEDIATORS OF ADIPOSITY SIGNALS

Several distinct hypothalamic pathways containing different neuropeptides mediate the response to insulin and
leptin. Few are as follows:

- Orexigenic peptides
- Anorexigenic peptides

• Monoamines and appetite control
• Endocannabinoids
• Peripheral hunger and satiety factors

RISKS ASSOCIATED WITH OBESITY

1. Coronary artery disease
2. Type 2 diabetes mellitus and insulin resistance
3. Hypertension
4. Stroke
5. Breast, endometrial and colon cancers
6. Varicose veins
7. Increase in all-cause mortality
8. Dyslipidemia
9. Cholelithiasis
10. Sleep apnoea syndrome
11. Osteoarthritis
12. Depression
13. Deep vein thrombosis
Obesity has become a major worldwide health problem. In every single country in the world, the incidence of obesity is raising continuously and therefore, the associated morbidity, mortality and both medical and economical costs are expected to increase as well. The majority of these complications are related to co-morbid conditions that include coronary artery disease, hypertension, type 2 diabetes mellitus, respiratory disorders and dyslipidemia.

**HYPERTENSION**

In previous studies, it has been stated that each Kg increase in body weight leads to increase the risk for developing hypertension by 4.4%. In previous study it has been shown that with increase in body weight the
prevalence of hypertension is also increasing particularly among individuals aged less than 55 years. Similarly, in postmenopausal women, with high BMI or waist hip ratio (WHR), the risk of developing high blood pressure has been doubled. Overall, it is found that the prevalence of hypertension increases with relatively small increases in body weight (Dyer and Elliott, 1994)

**DYSLIPIDEMIA**

The greater association between plasma lipoproteins and body weight has been found in various observational studies. Novel lipid dependent, metabolic risk factors associated to obesity are the presence of the small dense LDL phenotype, postprandial hyperlipidemia with accumulation of atherogenic remnants and hepatic. Over production of apoB containing lipoproteins. All these lipid abnormalities are typical features of the metabolic syndrome and may be associated to a pro-inflammatory gradient which in part may originate in the adipose tissue itself and directly affect the endothelium

An important link between obesity and dyslipidemia seems to be the development of insulin resistance in peripheral tissues which leads to an enhanced hepatic flux of fatty acids from dietary sources, intravascular lipolysis and from adipose tissue resistant to the antilipolytic effects of insulin. In the Framingham Heart study, increase in weight gain was observed to be associated with adverse lipid profiles and weight loss was observed to be associated with improvements in cholesterol levels (Kannel et al., 1996). Some other studies also reported that increase in body weight was associated with changes in lipid profile.

**GALL BLADDER DISEASE**

Some patients develop other gastrointestinal syndrome such as “dumping syndrome” or gallstones. Obese people have a higher output of cholesterol in bile, with a lower concentration of bile salts, so their bile is constantly in danger of forming gallstones. Release of cholesterol from adipose tissues increases, with the reduction in weight loss and hence increases the load to be excreted in bile.

**Role of Lactate and Cystatin C in obesity:**

The various biomarkers for decreased oxidative capacity was found which includes Malonyaldehyde, Acrolein, Advanced oxidation protein products (e.g asymmetric Dimethyarginine) Advanced glycosylation end products,  

Lactate etc.

Lactate is an anion that results from dissociation of lactic acid, intracellular metabolites of glucose; specifically it is the end product of anaerobic glycolysis the final step of which is conversion of pyruvate to lactate by the enzyme lactate dehydrogenase. Lactate is an organic compound with the formula CH₃CHCOOH. In its solid state, it is white and water soluble. In its liquid state, it is colorless; it is produced both naturally and synthetically. During the 1980's and 1990's a number of animal and small clinical studies showed that lactate, a marker of decreased oxidative capacity and increased glycolytic flux, is also associated with less extreme states of disordered energy homeostasis, such as obesity. Lactate's association with obesity may be linked to underlying defects in mitochondrial function leading to insufficient oxidative capacity in skeletal muscle and other tissues. Obesity is also associated with increased fat free mass, fat mass, oxidative stress along with increase in body weight and vice versa.

Lactate is utilized as a substrate for gluconeogenesis, a process which generates new molecule of glucose for energy metabolism, essentially reversing the reactions of glycolysis (Carl and Gerty Cori, 1929). In tissues with insufficient availability of oxygen or cells with few mitochondria, glycolysis is the final step in the production of ATP. Pyruvate is shunted away to form lactate via the enzyme lactate dehydrogenase instead of being transported to mitochondria. However, it is demonstrated that adipose tissues may be an important source of lactate production as well.

In adipose tissues, lactate production may also be increased in states of high energy demand, such as obesity. For example, Di Girolamo(1992) showed that high fat diet fed by rats showed an increased rate of glucose conversion to lactate, suggesting that larger fat cells with low oxygen availability is associated with increase lactate production. Obesity results from an imbalance in energy intake leading to increased metabolic demand and disordered energy homeostasis. A significant correlation between BMI and peripheral lactate levels had been shown in small clinical studies by comparing lean and obese subjects, and a growing body of evidence demonstrated that lactate may play an active role in the disordered energy homeostasis of obesity and its metabolic derangements (Kopelman PG, Albon L. 1997, Krotkiewski M. et al.,1983).

Due to increased production by adipocytes lactate may be elevated in obesity. 5 to 15% of glucose metabolized by adipose tissues is converted to lactate for hepatic gluconeogenesis, glycogen storage and oxygen storage, and...
oxidation by the heart and other tissues in the lean state. However 70% of glucose is converted to lactate in obese patients. Increased lactate production in adipose tissues may be related to oxygen availability. Larger cells are much sensitive to hypoxia; therefore, lactate production and release increases as adipocyte size increases.

Hence, in obesity, increased body mass index leads to decreased oxidative capacity which tends to increase lactate levels and also the decreased oxidative capacity further contributes to insulin resistance which in further increases triglyceride levels and also large proportion of plasma glucose is converted into plasma lactate, which correlates with lipid oxidation. When oxidative capacity decrease, lactate levels increases as a consequence of increased flux through glycolytic pathway.
Fig 3: Obesity, lactate and associated risks
Role of biomarkers in Obesity:

Previous studies had suggested that lactate levels increases in insulin resistance (Lovejoy J., 1992). Higher levels of lactate in blood leads to decreased oxidative capacity and this may leads to obesity, hypertension and insulin resistance (Massie et al. 2007). High carbohydrate diet may significantly increase the activity of serum lactate dehydrogenase which leads to further increase in lactate levels.

CYSTATIN C:

Cystatin C is a 122 amino acid protein with a molecular mass of 13 kDa. Cystatin C has been thought of as produced at a constant rate by a “housekeeping” gene expressed in all nucleated cells. Because of its small size and basic pH, Cystatin C is freely filtered at the glomerulus. Cystatin C is found in a variety of body fluids including the blood and is produced throughout the body by all cells that contain a nucleus. Some studies suggests that levels of Cystatin C may increase by inflammation, adiposity, thyroid diseases, certain malignancies, use of glucocorticoids and smoking (Naour N, Fellahi S, Renucci JF et al., 2009). Adipocytes secrete proinflammatory cytokine and adipokines in response to hypoxic stress. These adipokines are linked to genesis of endothelial dysfunction, insulin resistance and metabolic syndrome. Increased serum Cystatin C levels may be associated with the presence of early signs of atherosclerosis and cardiovascular disease. A previous study has reported positive associations of cystatin C with BMI in different populations (Salgado JV et al 2014).

The primary biological function of cystatin C is to inhibit cysteine proteinases of host and microbial origin present in extracellular fluids. The epidemiological studies have demonstrated that obesity is an indicator for cardiovascular diseases (Tan, B.K., 2010). It has been reported that increased adiposity and obesity is associated with higher waist circumference, an index of visceral adiposity, and increased percent of body fat is associated with higher serum cystatin C in apparently healthy subjects (Ichihara et al., 2007). Cystatin C is expressed and released by human preadipocytes differentiated in vitro (Taleb et al., 2006). In American adults the higher BMI is also associated with increased cystatin C levels (muntner et al., 2008).

Cystatin C regulates the enzymatic activity of cathepsins. The increase Cystatin C levels may be due to regulatory mechanism in order to control the proatherogeniccapacity of cathepsin (Sukhova et al., 1998). This shows that adipose tissues may directly contribute in enhanced Cystatin C levels in condition like obesity (Taleb et al., 2005).
Studies have showed that higher waist circumference; an index of visceral adiposity, and increased percent of body fat was associated with higher Cystatin C in apparently healthy subjects. Increased BMI leads to decreased oxidative capacity which further leads to insulin resistance due to which there has been increased TG and LDL levels which further involved in metabolic derangements. (Sokol et al., 2004) demonstrated the insulin resistance, inflammation, endothelial dysfunction and activation of the rennin-angiotensin systems are integrated and explain the link between Cystatin C and adipose tissue. Cystatin C and serum lactate are known to be clearly affected by metabolic status of the body.

**Conclusion:** In conclusion, this study suggested that there was a significant role of Serum Lactate and Cystatin C levels in obesity and they are highly associated with increased body mass index. Furthermore, these two biomarkers are highly associated with various metabolic derangements in obesity. So, a thorough medical assessment is required for identifying patients who are obese so that early assessment of serum lactate and Cystatin C levels in obese patients may provide beneficial effect for early prevention of metabolic derangements and further development of cardiovascular risks.

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