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STUDY OF BIOMARKERS TO ASSESS THE CARDIOVASCULAR RISK IN OBESE PATIENTS UNDERGOING BARIATRIC SURGERY

[1]HARSHAL NAIK, [2] DR. GEETA IBRAHIM, [3] DR. SANJAY BORUDE, [4] DR. SHUBHA CHOGLE

[1] Researcher, Institute of Science Department of Biochemistry, Mumbai
[2] Principle, Nirmala Niketan, College of Home Science, Churchgate, Mumbai
[3] Bariatric Surgeon, Bariatrics by Borude's 21, Prabhuta Villa, Kemps Corner, Mumbai
[4] Head, Biochemistry Department, Breach Candy Hospital, Mumbai

Abstract

Due to changes in lifestyle, dietary habits and reduction in physical activity owing to urbanization, modernization and westernization, obesity seems to increase at an alarming rate right from childhood. Modernization has brought along with it the fast food culture, high intake of fatty food consumed due to the taste factor that comes along with it, increasing levels of stress, depression, etc. leading to a large population being prone to obesity with a high risk of developing cardiovascular diseases. Therefore, people prefer opting for Bariatric Surgery in order to lose weight. The biomarkers- Leptin, Adiponectin, Small Dense LDL and Leukocyte telomere length have been studied to predict the risk of Cardiovascular Diseases. It would also help in providing scope for future research in the overall management if risk factors associated with Cardiovascular Diseases.

I INTRODUCTION

Cardiovascular diseases (CVD) encompass any medical conditions related to the heart and blood vessels. CVD is the main cause of disability and premature death worldwide, and is projected to remain the leading cause of death. Persons with high levels of cholesterol in blood, a condition called as hypercholesterolemia, are more prone to atherosclerosis. It is not a disease but a metabolic derangement that can be caused by many diseases, notably cardiovascular disease. "Hyperlipidemia" (elevated levels of lipids in the blood) and "hyperlipoproteinemia" (elevated levels of lipoproteins in the blood) are the other factors responsible for CVD. Elevated cholesterol in the blood is due to abnormalities in the levels of lipoproteins, the particles that carry cholesterol in the bloodstream. Cholesterol contains various subtypes that include very-low-density lipoprotein cholesterol (VLDL-C), low density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). The normal cholesterol range in human body should be below 200 mg/ dl and is good for body to function normally and anything over 240 mg/ dl indicates risk for developing CVD. Relative risk of all lipoproteins in CVD has been extensively studied and till now LDL-C, known as bad cholesterol, is considered as a marker for cardiovascular risk assessment. The LDL-C level in human body should be below 130 mg/dl. High density lipoprotein cholesterol, which is known as good cholesterol and have antioxidant property, should range between 35-40 mg/dL. The high level of HDL-C (~60 mg/dL) has the benefit of reducing the chances of heart attack. Moreover, there are several amendable risk factors that include hyperlipidemia, dyslipidemia and have higher incidence of deranged lipid profile. The various study established that elevated LDL-C and increased ratio of LDL/HDL (high density lipoprotein) is the most important lipid derangement making those subjects more susceptible to atherosclerosis.

II OBESITY AND CARDIOVASCULAR DISEASE

Obesity is recognized as a classic risk factor for atherosclerosis and subsequent cardiovascular disease. It is becoming a global epidemic in both children and adults. It's a known fact that obesity can take a toll on our heart health. And there's a plethora of research to back it up. For instance, a recent study published in April 2018 in the journal JAMA Cardiology concluded that adults between ages 40 and 59 who are overweight or obese have a significantly increased risk (ranging from 21 to 85 percent higher) of developing cardiovascular disease as compared with their normal weight peers. Individuals who are overweight, defined as having a body mass index (BMI) between 25 and 29.9, or are obese (a BMI of 30 or higher), also have a much greater risk of developing cardiovascular disease at a younger age. Obesity is associated with an increased risk of morbidity and mortality as well as reduced life expectancy. The research showed that individuals who are obese had a shorter lifespan. In fact, obesity is an independent risk factor for CVD, and CVD risks have also been documented in obese children. Reducing cardiovascular (CV) disease (CVD) risk is a primary public health imperative given the substantial morbidity and mortality associated with the disease. The most effective nonpharmacologic means of achieving such risk reduction is weight loss. Even a moderate 5% to 10% weight loss through diet and lifestyle interventions has been shown to decrease the risk for conversion from impaired glucose tolerance to overt diabetes and can maintain blood pressure reductions over prolonged periods of follow-up.

More dramatic weight loss after bariatric surgery has been associated with even greater benefits, such as reduced CV mortality and total mortality in obese patients, particularly those with diabetes.

Health service use and medical costs associated with obesity and related diseases have risen dramatically and are expected to continue to rise. Besides an altered metabolic profile, a variety of adaptations/alterations in cardiac structure and function occur in the individual as adipose tissue accumulates in excess amounts, even in the absence of comorbidities. Hence, obesity may affect the heart through its influence on known risk factors such as dyslipidemia, hypertension, glucose intolerance, inflammatory markers, obstructive sleep apnea/hypoventilation, and the prothrombotic state, in addition to as-yet-unrecognized mechanisms. On the whole, overweight and obesity predispose to or are associated with numerous cardiac complications such as coronary heart disease, heart failure, and sudden death because of their impact on the cardiovascular system. However, the cardiovascular clinical evaluation of obese patients may be limited because of the morphology of the individual. In this statement, we review the available evidence of the impact of obesity on CVD with emphasis on the evaluation of cardiac structure and function in obese patients and the effect of weight loss on the cardiovascular system.

Overweight and obesity is a complex disease itself and is linked to more deaths worldwide than underweight. Obesity is now recognized as the first leading cause of premature mortality followed by cancer and DM, and the biggest issue behind this incidence is the association between obesity and CVD. Obesity has long been considered as an established risk factor for CVD. For instance, in a Framingham cohort study, relative weight (i.e., percentage of desirable weight) was found to be positively and independently associated with a 26-year incidence of CAD, stroke, HF, and CVD-related death. Recent studies have further investigated how both the duration and degree of obesity affect the risk of different CVDs. Data from the Coronary Artery Risk Development in Young Adults study showed that, for every 2 years lived with obesity, the risk of CVD mortality significantly increased by 7%. As for the risk of different types of CVD, another meta-analysis revealed that the relative risk (RR) of stroke with obesity was 1.3, and that of VTE with obesity was 2.4. The risk of HF increased 5% for men and 7% for women per 1 unit increase in BMI (27–30).

THE SOCIOECONOMIC BURDEN OF OBESITY AND IMPACT ON THE OVERALL HEALTH

Being overweight or obese refers to the condition that a person's weight is higher than what is considered as a healthy weight for a given height. BMI has been conventionally used as an indicator to define overweight and obesity. This is a person's weight in kilograms divided by the square of height in meters. For adults, Centers for Disease Control and Prevention and World Health Organization (WHO) define BMI of 18.5 to 25 as the normal range, 25 to 30 as overweight, and 30 or higher as obesity, while age also needs to be taken into consideration for children. Although BMI is not a perfect index to assess the relationship between the body weight and health of an individual for its incapability of diagnosing the body fatness, it is still considered the most useful screening tool at an individual level worldwide.

Overweight and obesity are growing global issues, in terms of prevalence, health risks, and socioeconomic impact. Globally, more than 1.9 billion adults aged 18 years and older, nearly 40% of the world's population, were overweight in 2016. Over 650 million people—approximately 13% of the adult population— were obese. The worldwide prevalence of obesity nearly tripled between 1975 and 2016. If this rate is kept constant, almost half of the world's adult population will be overweight or obese by 2030.

As another important part of the obesity epidemiology, the prevalence of obesity in a country does not directly correlate with its economic status. When the countries were categorized according to the income level as low-income, lower middle income, higher middle-income, and high-income, the prevalence of obesity increased up to upper middle-income countries, however the high-income countries came to the second among the 4 categories (20). Low socioeconomic status of individuals has been associated with a higher prevalence of obesity regardless of the nation's economic status, whether it is developing, transitional, or developed. Larger disparities in individual access to better quality diet (e.g., fresh fruits, vegetables, and fish) were observed especially in countries with developing or transitional economies as they faced the globalization of food markets. This is likely due to greater economic inequality, under-established healthcare systems, and poorer education on diet .Development of strategies to address overweight- and obesity-related health problems is therefore warranted worldwide regardless of the nation's economic status.

Besides physical health problems, the economic impact of obesity has been an important public health issues. Obesity imposes large socioeconomic costs not only to the healthcare system but also to the society. Recent studies on the association between BMI and costs attributable to obesity have described that the burden comes in the form of the individual's lost productivity as a result of lost work days, lower productivity at work, mortality, and permanent disability. All of these could lead to a loss of economic growth nationwide. Above all, medical costs for obesity-related diseases have been the biggest global concern. Medical costs are typically divided into direct costs and indirect costs. Direct costs include costs for the treatment and management of the diseases—e.g., inpatient and outpatient care. An example of direct non-medical costs is

transportation to healthcare providers. Indirect costs include early mortality costs and morbidity costs due to sickness absence and informal care costs. Costs of obesity have been calculated in several studies. In the US, the direct per-capita costs over a lifetime amounted to US$171,482 in 2010, and the total 10-year per-capita costs were predicted to be US $70,200 in 2013 (33). Costs of obesity on the individual ,families ,and nations have been more enormous than ever, calling not only for global healthcare policy reforms but also for better treatment and preventative interventions on individual basis.

III TELOMERE LENGTH AND CARDIOVASCULAR DISEASES

Telomeres are structures composed of deoxyribonucleic acid repeats that protect the end of chromosomes, but shorten with each cell division. They have been the subject of many studies, particularly in the field of oncology, and more recently their role in the onset, development and prognosis of cardiovascular disease has generated considerable interest. It has already been shown that these structures may deteriorate at the beginning of the atherosclerotic process, in the onset and development of arterial hypertension or during myocardial infarction, in which their length may be a predictor of outcome. As telomere length by its nature is a marker of cell senescence, it is of particular interest when studying the lifespan and fate of endothelial cells and cardiomyocytes, especially so because telomere length seems to be regulated by various factors notably certain cardiovascular risk factors, such as smoking, sex and obesity that are associated with high levels of oxidative stress. The dysfunction of telomere has been reportedly the most important reason behind cardiac failures as is evident from animal studies as well as human heart samples. Telomere shortening in animal models has showed inhibition to proliferation of myocytes coupled with myocyte hypertrophy and an enhanced rate of apoptosis. Cardiovascular disease patients show 40% reduction in their telomere lengths when compared with the healthy normal human beings and that the shorter the length of the telomere, more is the disease severity. In addition, shortened telomeres were linked to reduction in renal function. Higher lengths of telomere are responsible for an increase of 5% ejection by the left ventricle. In the aged population the variation in the ejection capability is highly dependent on the telomere length. Also in the same population, heart related ailments show characteristics of moderate to low dilation and hypertrophy with an overall increment in the cell death. The cells exhibiting the characteristics followed the p16INK4a path and presented shorter telomeres. Besides, the patients with heart diseases and shortened telomeres have the risk of being anemic with compromised prognosis. In a study carried out by the New York Heart Association, it was observed that short telomere containing patients with heart failure (Class II-IV) were more at risk of death within a period of about 18 months. Therefore, shortened telomere lengths might be used as successful predictors of death in chronic cardiovascular disease patients.

IV SMALL DENSE LDL: A NEW MARKER

Sd LDL cholesterol is a subtype of LDL cholesterol, one of the lipoproteins. Lipoproteins transport lipids in the blood stream and are characterized depending on size and weight. LDLs vary in size through genetic determination and dietary lipid intake. They range from small dense through normal size to big buoyant LDL. They all transport triglycerides and cholesterol to the tissues, but their atherogenesis varies according to size. Smaller particles such as sdLDL more readily permeate the inner arterial wall and they are also more susceptible to oxidation.

Modern research on CVD decode several new risk factors that include elevated lipoprotein(a), high sensitivity C reactive protein (hs- CRP), fibrinogen and hyperhomocysteinemia etc., an important one of which is estimation of small dense LDL cholesterol (sd LDL-C). Lipoprotein profiles that are relatively rich in sd-LDL particles are associated with up to a 3-fold greater risk of myocardial infarction than those mainly consist of large buoyant (lb)-LDL particles. Currently published report established that predominance of sd-LDL-C is a major component of an atherogenic lipoprotein phenotype, and a source of increased risk for coronary heart disease. The ratio of sd-LDL-C to LDL-C plays an important role in assessing CVD.

V APOLIPOPROTEIN B AND APOLIPOPROTEIN A-I :

Although LDL cholesterol (LDL-C) is associated with an increased risk of coronary heart disease, other lipoproteins and their constituents, apolipoproteins, may play an important role in atherosclerosis. Elevated levels of apolipoprotein (apo) B, a constituent of atherogenic lipoproteins, and reduced levels of apo A-I, a component of anti-atherogenic HDL, are associated with increased cardiac events. Apo B, apo A-I and the apo B/apo A-I ratio have been reported as better predictors of cardiovascular events than LDL-C and they even retain their predictive power in patients receiving lipid-modifying therapy. Measurement of these apolipoproteins could improve cardiovascular risk prediction.

VI ADIPONECTIN:

A protein hormone produced and secreted exclusively by adipocytes that regulates the metabolism of lipids and glucose. Adiponectin influences the body's response to insulin. Adiponectin also has anti-inflammatory effects on the cells lining the walls of blood vessels.

High blood levels of adiponectin are associated with a reduced risk of heart attack.

Low levels of adiponectin are associated are found in people who are obese (and who are at increased risk of heart attack).

VI LEPTIN:

A hormone produced mainly by adipocytes (fat cells) that is involved in the regulation of body fat. Leptin interacts with areas of the brain that controls hunger and behaviour and signals that the body has had enough to eat. A small number of people have genetic mutations in the leptin gene, leading to a greater demand for food, resulting in obesity.

Obesity is a risk factor for cardiovascular diseases. Leptin levels are increased in obesity and leptin exhibits cardiovascular actions that may contribute to increased cardiovascular risk.

In patients with acute myocardial infarction, obesity is related to increased leptin. The subcutaneous fat compartment seems to be an important determinant of plasma leptin , concentration. Leptinemia is associated with several biochemical disorders suggesting that leptin may be pathogenetic factor in cardiovascular disease.

VII BARIATRIC SURGERY:

Traditional treatments to achieve weight loss such as diet, lifestyle, and behavioural therapy have proven relatively ineffective in treating obesity and associated cardiovascular risk factors in the long term, especially when used in isolation, but have demonstrated some metabolic and cardiovascular benefits when they are used together as combination strategies. It is important to note that these treatments have been specifically ineffective on the morbidly obese subgroup of patients (BMI _40 kg/m2) and have led to development of operations in the form of "bariatric surgery" to treat obesity and its comorbidities.

Bariatric surgery is a type of surgery performed on morbidly obese individuals to achieve weight loss. Weight loss is achieved by reducing the size of the stomach with a gastric band or through removal of a portion of the stomach (sleeve gastrectomy or biliopancreatic diversion with duodenal switch) or by resecting and re-routing the small intestine to a small stomach pouch (gastric bypass surgery). The U.S. National Institutes of Health recommends bariatric surgery for obese people with a body mass index (BMI) of at least 40, and for people with BMI of at least 35 and serious coexisting medical conditions. The selection of the type of bariatric operation performed depends on surgical and patient preference. These procedures can be classified into 3 categories: restrictive malabsorptive, or combination procedures. Restrictive operations literally decrease the size of the stomach (either by a synthetic gastric band, stapling, or size reduction by "sleeve gastrectomy"), leading to satiety with smaller volumes of food that eventually leads to food intolerance and weight loss. Malabsorptive operations consist of bypassing segments of bowel, which thereby cause malabsorption of nutrients (such as the biliopancreatic diversion with or without duodenal switch and ileal interposition). The combination group of operations involves both aspects of restriction and malabsorption such as the Roux-en-Y gastric bypass, which is considered as the "gold standard" bariatric operation and is currently the most commonly performed procedure for weight loss worldwide. These bariatric operations demonstrate the most encouraging results for rapid weight loss and subsequent improvements in overall morbidity and life expectancy in obese patients. Long-term follow-up of bariatric patients reveals significant reductions in mortality from heart disease, diabetes mellitus, and cancer. This leads to a decrease of any-cause mortality by 40% while also cutting long-term healthcare costs. Consequently, these operations have found a role in decreasing cardiovascular risk in asymptomatic obese patients but can also reduce cardiac mortality and morbidity in obese patients with established cardiac pathology.

VIII METHODOLOGY:

1. Around 20-25 obese patients in age group 16-65 years males & female have been recruited. These patients have been admitted in various hospitals in Mumbai under bariatric surgeon Dr. Sanjay Borude.

2. An informed consent is obtained from all subjects to be participants in the study. Ethical clearance is obtained from the Ethics Committee of Breach Candy Hospital for carrying out the study.

3. Blood samples of the patients is collected and Leukocyte telomere length would be estimated using PCR, small dense LDL using ELISA kit, Leptin using Human leptin ELISA kit and Adiponectin using Human Adiponectin ELISA kit.

4. All participants were questioned about previous and current diseases, use of medications. BMI waist circumference & waist to hip ratio were measured & calculated.

5. Measurement of Telomere Length (Δ value) by qPCR
   Genomic DNA is extracted from blood samples by standard procedures of chloroform extraction .Purified DNA samples is diluted in a TE buffer (PH7.5) It is dissolved by heating at 95 °C for 5min.in dry bath & quick chilled by transfer to an

ice/water bath for 5 min.& stored at 4 °C until the time of assy. The purity & concentration of extracted DNA is checked on spectrophotometer by taking ratio of 260/280.This DNA is used for checking the expression of telomere gene. (A quantitative PCR method for measuring telomere length)

6. Statistical Analysis: Data obtained will be analyzed by SPSS package. Version II

Mean, I.S.D. Students t-test and Pearson's correlation coefficient will be also done.

RESULTS:

The analysis for Leptin, Adiponectin and Small Dense LDL has been carried out using ELISA Kits. However, statistical analysis results are pending, post which comparative study will be done.

IX EXPECTED RESULTS AND OUTCOME:

There are various studies in the past in India (Ref:-Small Dense LDL: New Marker for Cardiovascular Risk Assessment and its Therapeutic Inflection by M Salman Khan* Department of Biotechnology, Integral University, Lucknow- India) as well as abroad (Ref:- Small, Dense Low-Density Lipoprotein Particles as a Predictor of the Risk of Ischemic Heart Disease in Men carried out in Canada, Ref:- The rate of leukocyte telomere shortening predicts mortality from cardiovascular disease in elderly men by Richard Cawthon et.al in the University of California) that have identified biomarkers such as Role of Leukocyte Telomere Length, small dense LDL cholesterol, apolipoproteins apoB and apoA-I (Ref:- Apolipoprotein B and apolipoprotein A-I: risk indicators of coronary heart disease and targets for lipid-modifying therapy by G. wallidus at Sweden), Leptin and Adiponectin and have shown promising results in affirming risk related to CVD. However, no study has shown the correlation between these biomarkers and their role in the early diagnosis of CVD. Traditional biomarkers like the Lipid Profile Test are used for routine screening, however, they underestimate the cardiovascular risks. These novel biomarkers are stronger and stable predictors which would provide more accurate results and therefore, this study would be immensely helpful in evaluation of risk in young age group which would help detection, followed by treatment, modification of lifestyle, which would ultimately decrease the onset of CVD. In addition, numerous conventional cardiovascular risk factors are associated with telomere length. If telomeres can be proven to be not only associated but also causally involved in the pathogenesis of cardiovascular disease, it might provide exciting new avenues for the development of future preventive and therapeutic strategies of cardiovascular diseases.

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