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CYTOKINE RESISTIN IN METABOLIC AND CARDIOVASCULAR DISEASE.

Endocrinology

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ABSTRACT

The rise in metabolic syndromes is known to be the root cause of major cardiovascular diseases mainly Coronary Artery Disease (CAD) in India. A biological marker will thus help to determine the disease before its onset and help cure it at early stages, reducing the chances of development of further complications. There are various pro-inflammatory markers (cytokines) which can be used to determine the onset of disease one such marker known is resistin. Resistin is known to be a pro-inflammatory adipokine secreted mainly from Peripheral mononuclear cell (PMNC), bone marrow cells and macrophages in humans [1]. Inflammatory response is generated due to rise in metabolic syndromes which in turn leads to the secretion of various cytokines. The levels of these cytokines released help in determining the severity of disease.

KEYWORDS

CAD, cytokines, resistin, inflammatory response, metabolic syndrome.

INTRODUCTION

Heart is considered to be the most prominent organ of the human body. The major function of heart is to pump blood throughout the body via circulatory system as tissues need to be constantly supplied with nutrients and oxygen for their appropriate functioning. The blood usually flows through the heart via two different pathways the pulmonary pathway in which deoxygenated blood leaves the heart from right ventricle and travels to the lung to become oxygenated while in systematic pathway the oxygenated blood leaves the heart via left ventricle towards aorta travelling to arteries and capillaries which supply the oxygenated blood to various tissues of the body. Apart from supplying oxygenated blood to the various tissues of the body, heart muscles also require oxygenated blood which is provided to the heart via two sets of artery the left coronary artery and the right coronary artery [2]. The left coronary artery arises from the left cusp of aortic wall and supplies blood to the left side of the heart [3] while the right coronary artery differentiates into acute marginal arteries and right posterior coronary artery supplying blood to the right atrium, cells present in right arterial wall and the heart ventricles [4]. The coronary arteries thus play a major role in maintaining the proper functioning of heart. Certain diseases mainly the metabolic diseases may cause damage or alter the functioning of these arteries, which can further lead to various heart diseases and if not treated appropriately may prove fatal. Among the major heart diseases coronary artery disease is one such disease which is mainly caused due to the improper functioning of any two sets of arteries. The arteries are highly affected by the metabolic syndromes such as obesity, diabetes, blood pressure. An obese individual usually as a high amount of fat accumulated inside the body. This accumulated fat also builds up inside the inner lining of arteries and veins because of which the blood flow through them is decreases as there is narrowing of arteries and veins. In certain cases, the blood flow is completely restricted due to the excessive accumulation of fat which then leads to myocardial infraction. Similarly type-2 diabetes mellitus is an another type of metabolic syndrome where there is an increase in blood glucose level as insulin is unable to recognise the glucose molecule circulating throughout the blood as their receptors are blocked by the pro-inflammatory cytokines. Excessive amount of blood glucose levels in turn increases the chances of development of other metabolic and cardiovascular diseases. Also there are various other lifestyle disorders which are caused due to stress, sedentary lifestyle, aging, etc. which further increases the chance of development of cardiovascular diseases [5]. Obesity, diabetes and hypertension are found to be the major cause of development of cardiovascular diseases among all the metabolic diseases so far, also this disease are known to be linked together.

Obesity Linked To Hypertension

The functioning of the heart is mainly disrupted when the level of fat and lipids increases in the body beyond certain limit. Due to obesity there is accumulation of fat in the inner lining of artery, this leads to narrowing of artery because of which the blood flow is decreased or completely blocked. When the fat is accumulated inside the inner lining of heart, pressure is exerted by the blood to flow within the artery and this development of pressure is known as hypertension. Hypertension is a condition in which the blood pressure of an individual rises beyond the prescribed limit. Apart from this, high blood pressure increases the risk of other cardiovascular diseases such as myocardial infraction, left ventricular hypertrophy and ischemic heart disease. Myocardial infraction is caused when the amount of fat increases to such an extent that the fat blocks the passage of blood through the artery and due to insufficient blood supply heart fails to perform its function leading to cardiac arrest. Ischemic heart disease also known as coronary artery disease is one such similar condition to cardiac arrest where the arteries get harden and blocked because of accumulation of fat. Due to this there is an insufficient supply of blood to the heart muscles and thus the heart fails to function. Left ventricular hypertrophy is another such cardiovascular condition which is mainly developed due to hypertension, in which there is an enlargement and thickening of the walls of left ventricle [6,7]. Obesity is therefore highly associated with hypertension while hypertension further increases the chance of development of various other cardiovascular diseases. Resistin also has been detected in serum samples with high cholesterol and triglyceride. Also, certain clinical evidences suggest that resistin levels are associated with hypertension in humans [8]. Hypertension is frequently associated with the several metabolic abnormalities, of which obesity, glucose intolerance, and dyslipidaemia are the most common [9].

Obesity Linked To Type-2 Diabetes Mellitus

The main cause of obesity is the excessive accumulation of fat inside the body because of which stress is generated on to the adipose tissue to process large amount of fat than actual amount. The pressure generated on the adipose tissue gives rise to an inflammation which in turn secretes out certain cytokines. The secreted cytokines thus attach to the insulin receptors blocking the binding of insulin to its receptors. As the receptors are blocked there is an inability of insulin to bind to its receptors making it unable to process the glucose molecule, 4 which generates an insulin resistance also known as type-2 diabetes mellitus [6]. The chances of developing type-2 diabetes mellitus in obese people is high especially when obesity is related to abdomen. Abdominal obesity also known as central obesity is considered to be the major factor responsible for generating insulin resistance as due to abdominal obesity high levels of fats are accumulated. Due to the increase in the level of fat the cells of adipose tissue start secreting pro-inflammatory molecules. This pro-inflammatory molecule then acts as a blocking agent which blocks insulin binding to its receptor and generates an insulin resistance. Insulin plays a vital role in providing energy to the cell by metabolism of glucose but when there is an insulin resistance the body fails to recognise the insulin molecule and the glucose levels thus keep on rising within the blood generating a condition known as type-2 diabetes mellitus [10]. In humans it was also found that, the levels of resistin in blood are increased due to diseases such as obesity and diabetes [11,12].

Proinflammatory Adipokine: Resistin

Resistin is a cysteine rich peptide hormone comprising of various disulfide bonds. Resistin is found to be secreted in both humans and mice but the source from which it is produced is different in both. In mice resistin is secreted by the adipocytes of the adipose tissue. It weighs up to 11kDa and its gene is located on the chromosome number 8. The precursor molecule of resistin in mice is generally made up of 114 amino acids of which 20 amino acids act as signalling sequence while the remaining 94 amino acids are termed as mature segments. While in humans, resistin is not found to be secreted from adipocytes of adipose tissue but it is mainly secreted from the stromal vascular fraction of cells of adipose tissue which comprise of peripheral blood mononuclear cells (PBMC), macrophages and bone marrow cells. All these three kinds of cells from adipose tissue are responsible for

secretion of resistin in humans and generally it weighs about 12.5kDa comprising of 108 amino acid molecules. The gene responsible for resistin in humans is known as RETN gene and is located on the chromosome number 19 [13]. Resistin plays a major role in various diseases such as atherosclerosis, CVD, non-alcoholic fatty liver disease, autoimmune disease, inflammatory bowel disease. In obese people due to excessive accumulation of fat there is a build of pressure onto the arteries which leads to hypertension while the accumulated fat also contributes to the development of insulin resistance leading to inflammation. During an inflammatory response in the adipose tissue, cells of adipose tissue starts secreting cytokines (resistin) which act as a signalling molecule indicating the onset of particular disease. Inflammation is the initial sign of metabolic dysfunction due to which pro-inflammatory molecules are released one such is resistin. Pro-inflammatory molecules released due to inflammation will help to determine the onset of various diseases. Therefore, the pro-inflammatory cytokines can act as a biological marker in determining the disease at its early stage making its prevention easy.

CONCLUSION

Various metabolic diseases especially obesity and type 2 diabetes are majorly contributing to the development of cardiovascular diseases. Early detection of these diseases therefore play a vital role in order to reduce the its fatal outcome. As discussed pro-inflammatory molecules are secreted before the onset of any disease any these molecules may act as a potential biomarker in early prediction of disease. Resistin is one such molecule known to be secreted and is also known as a pro-inflammatory cytokine. A detailed study of this cytokine in human samples might reveal the levels various metabolic disease and its role as a potential biomarker.

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