REVIEW OF LITERATURE

Oxidative stress and human hypertension

Oxidative stress is a multisystem phenomenon in hypertension and involves the heart, kidneys, nervous system, vessels and possibly the immune system (Biswas et al; 2016).

In a recent study the responses of A, B, O blood groups to oxidative stress induced through storage has been carried out and the author observed that blood group O endured oxidative insult more efficiently than A and B. (Carl et al; 2016).

Increased oxidative stress in a hallmark of many chronic disease including hypertension. It occurs as a consequence and altered balance between the production and elimination of reactive oxygen species via antioxidative enzymes (Mihalj et al, 2016)

It has been found that essential hypertension is associated with increased oxidative stress and reduced antioxidative status. (Kwamoteetal 2016, Rodrigo et al.; 2013)

In some studies oxidative stress has been proposed as the cause of hypertension (Ceriello; 2008).

In different studies of human essential hypertension and various animal models of hypertension, alterations of antioxidative enzymes have been
demonstrated and correlated with an increase in ROS production. *(Rodrigo et al; 2011, Tanito et al; 2004)*

Altered oxidant and antioxidant status was analyzed in 30 patients with essential hypertension and compared with 21 healthy control men. The activity of catalase was found to be significantly decreased (27.92±14.08, 19.81±9.7; P=0.019; 95% CI lower=1.41 and 95% CI upper = 14.81) *(Nadeesha et al; 2007)*.

In another study 31 hypertensive male patients and 35 healthy normotensive subject of age group 35 and 60 years were taken. Parameter measured in blood plasma were plasma antioxidants status and lipid per oxidation products. The authors found that systolic and diastolic blood pressures of hypertensives were negatively correlated with plasma antioxidant capacity (r = 0.46, P < 0.009) and hypertensives showing higher level of oxidative stress. *(Rodrigo et al; 2007)*

*Valko et al; 2007*, found that over production of reactive oxygen species could be an important mediator of damage to cell structure including lipids, membrane proteins and DNA.

*Tandon et al; 2005* analyzed serum malondialdehyde and superoxides dismutase in fifty patient with essential hypertension. The mean (SD) serum malondialdehyde was found to be significantly increased (0.33 [0.07] mmol/L)
in patient with hypertension compared with controls (0.21/[0.05] mmol/L ; P < 0.01). The activity of serum superoxide dismutase was significantly lower in patients (6.93 [1.35] mg protein/ml of serum) compared with controls (20.12 [3.65] mg protein/ml serum ; P<0.001) These findings suggest relationship between oxidative stress and essential hypertension.

Clinical studies have demonstrated increased ROS production in patients with essential hypertension, renovascular hypertension, malignant hypertension and preeclampsia (Lee et al; 2003, Higashi et al; 2002). These findings are based, in general or increased levels of plasma thiobarbituric acid reactive substances and 8-epi-iso prostanes, biomarkers of lipid peroxidation and oxidative stress. (Redon et al; 2003).

All the major classes of biomolecules are attacked by the free radicals but lipids are the most susceptible. Lipid peroxides are derived from the oxidation of polyunsaturated fatty acid (PUFA) of membranes and are capable of further lipid per oxidation by a free radical-chain reaction (Kaur et al; 2008, Cheesman and Slater; 1993).

To prevent an overload of free radicals the human body utilises sophisticated complex defence system of, antioxidative enzymes; superoxide-dismutase, catalase, glutathione per oxidase and glutathione reductase which decreases the concentration of the harmful oxidants in the tissues by functioning as free radicals scavengers and they are found to be preventive for the
pathophysiological and metabolic disorder including cardiovascular diseases; atherosclerosis, hypertension ([Fukai and Ushio-Fukai; 2011]), coronary artery disease, arthritis, neurological damage and cancer which may even lead to death.

**Blood groups**

The role of blood groups in the etiology of essential hypertension has long been suspected ([Varghese et al 2015]).

Blood groups are genetically transmitted biochemical expressions with antigenic (agglutinogen) properties located within red blood cells.

Individuals belonging to group A have A antigen in the red blood cells and b-antibodies and B group people have B antigen in the red blood cells and a-antibodies in the plasma.

Those belonging to blood group AB have both A and B antigen and no antibody (a or b). They are the universal recipient.

Group O have no reactive antigens but have both a and b antibodies in the plasma and called as universal donors.

**Biochemistry of ABO blood groups**

Biochemically the defining sugars in blood groups A, B, AB and O are nitrogenous substance, neutral heteropolysaccharide containing D-galactose, methyl pentose fucose, D-glucosamine, D-galactosamine present as N-acetyl derivatives and other amino acids such as threonine, serine etc. ([Morgan and Watkins; 1953]).
According to theories of inheritance genetic material consists of DNA which is arranged in such way as to provide information of amino acid for a given protein. This would mean that proteins are the only direct result of gene action. The difference between A, B, H substance does not; however, seem to be in their protein structure but in the carbohydrate portion of the molecule.

This suggest that blood group substances are not the direct product of the gene but that the blood group gene produce protein enzyme which act at late stage upon basic mucopolysaccharide to give blood group specificity (Carton et al; 1980). It is suggested that a common blood group substance exists which is converted though a series of stages to the final specific blood group products. The conversions are almost certainly affected by specific enzymes the synthesis of which is controlled be genes.

The biochemistry of the A and B antigens was elucidated by the astonishingly early and brilliant work from the group of Kabat; 1956 and Morgan and Watkins; 1953

The A, B and H determinants were hypothesized to reside on water-soluble glycoprotein. A precursor substance H was hypothesized as a building structure for A and B. (Morgan and Watkins; 1948)

An H gene codes for a fucose transferase that parts, a fucose on the end of the glycoprotein, forming the H antigen that is usually present in individuals of all blood type (Storry and Olsson; 2009).
The basic structure of antigen H is given below.

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**Fucose-Gal-GalNAc – Protein**

The presence of A and B glycosyl transferase was first predicted by Watkins in 1967 and then experimentally established by other workers (Hearn *et al*; 1967).

Individuals who are type A have a gene which code for a transferase (N-acetyl-galactosaminyl transferase) that catalyze placement of a terminal N-acetylgalactosamine on the H-antigen where as individuals who are type B have a gene which codes for a transferase (galactosyl transferase) that place a terminal galactose (Pattenaude *et al*; 2002)

\[ \text{A antigen : Fucose Gal NAc – Protein} \]
\[ \text{GalNAc} \]

\[ \text{B antigen : Fucose – Gal-GalNAc – Protein} \]
\[ \text{Gal} \]

Individuals who are type AB have both the transferases and who are type O have neither, so the H antigen persists.

Thus A and B glycosyl transferase use UDP-Gal NAc and UDP Gal respectively as substrates (Pattenaude *et al*; 2002). Both require the H
determinant as acceptor. The O protein is nonfunctional leaving the H-defining terminal Fuc unaltered.

Apart from their matching role in blood transfusion these specific antigens are known to play their important role in regulation of various biochemical and immunological reactions in the body.


**Blood Groups, Hypertension and Cardiovascular Diseases**

The extensive studies carried out by numerous authors over a long period of time have made it possible to establish convincing correlation between different types of hypertension, cardiovascular disease and their important etiological factor that is lipid profile with each type of blood group (A, B, AB & O).

The details of basic information regarding blood groups and presence of hypertensive condition in their each class as suggested by the results produced in the comprehensive studies carried out by a large number of authors who
established a positive correlation between the hypertension and the individual class of blood groups has been discussed in this section.

In most of the studies carried out in large population shows the direct correlation between blood group A, hypertension and the changes in serum lipids viz. triglycerides (TGs), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), which are increased and associated decrease in high-density lipoprotein cholesterol (HDL-C). However, in certain studies the hypertension has not been evaluated but nevertheless these changes certainly would be taken as predisposing factors in the development of hypertension at some stage of the life. However, several other reports correlating hypertension and lipid profile are available in blood group A subjects.

In a recent study it was found that blood group A is related to the higher incidence of high serum cholesterol level and hypertension (*Zera et al; 2015*)

It has been found that there is a positive correlation between diastolic blood pressure and blood group and the author suggested that screening of various blood groups might help in identifying the risk factor for hypertension. (*Varghese et al; 2015*)

A study of potential mechanisms of future role of blood groups in identifying those at risk of arterial and venous disease found that ABO (H) antigens affect arterial disease with a consistent effect observed in peripheral vascular disease and the higher risk was associated with non-O group individuals (*Clark et al; 2011*)
The relationship between ABO blood group and total serum cholesterol level was examined in a Japanese population to determine whether elevated cholesterol levels are associated with blood group A. Their results showed that cholesterol levels were very significantly elevated in the blood group A compared to non-A group (Reid; 2009).

A study by Wu et al.; 2008, revealed the relationship between non 'O' group entities with numerous forms of vascular involvement viz intravascular thrombosis etc.

Saha et al; 2006, studied serum lipid profile of hypertensive patients. It was concluded that hypercholesterolemia, hypertriglyceridaemia and LDL are the main lipid abnormalities in the incidence of hypertension and these may be due to genetic factors, increased consumption of dietary animal fat, lack of physical exercise, severe stress, metabolic disorder, increased age and sex.

Nemesure et al in 2006, explored correlation between hypertension and blood groups.

Since blood pressure is multifactorial, perhaps the ABO antigens play a role of influencing renin levels and affecting plasma angiotensin and aldosterone secretion thus indirectly influencing arterial hypertension.

In a study it has been observed that ABO blood groups are the factors codetermining the plasma ACE activity. ACE molecules in the circulation were suggested as the carrier of the antigenic determinants A, B or O. These
oligosaccharide components some how affects ACE activity in the plasma and differences in ABO antigen might alter the state of ACE glycosylation and thus affect the functions of ACE. *(Cidi et al; 1996)*

An adverse lipid profile with elevated serum TG/TC/LDL-C along with low HDL-C was found to be an additional risk factor for coronary heart diseases *(Kanbay et al; 2006).*

*Nazir et al; 2006,* studied prevalence and possible relationship between ABO rhesus blood group and hypertension. The prevalence of hypertension was greatest among rhesus positive male subjects having blood group A (30.1%), followed by B group (18%) and prevalence rate of about (17%) each in subjects having blood group O and AB.

In an another study the authors explained the association of blood group A with increased risk of coronary heart disease. *(Wazeralli et al; 2005).*

*Alam and Haq; 2004,* found that B and O phenotypes had relatively higher tendency of developing adverse lipid metabolism.

*Friedrich; 2004,* in a genetic study concluded that the subjects with blood group A are more prone to coronary disease.

*Alberto et al; 2001,* explored various risk factors on cardiovascular events in the hypertensive patients. The males were statistically at more risk for cardiovascular events. The age factor suggest that these events are more
prevalent at or beyond 65 years. Many authors assessed the role of lipid profile in the pathogenesis of hypertension and their relation with different blood groups (Marques-Vidal; 2000, Horby et al; 1989, Galeazzie et al; 1975).

The bulk of evidences support the role of oxidative stress in hypertension. The hypertensives are found with an excess of generation of ROS/free radicals may be involved with endothelial dysfunction, no bioavailability, decreased vasodilation in them. The literature search also supports that hypertension in patients is a function of their blood group and this may be affected by some other pathophysiological factors in them. (Varghese et al; 2015, Clark et al; 2011, Reid, 2009, Nazir et al; 2006)