CHAPTER 2

REVIEW

OF

LITERATURE
AETIOLOGY OF ESSENTIAL HYPERTENSION

Various non-modifiable and modifiable risk factors have been identified as causative agents of Hypertension based on cross-sectional, longitudinal and experimental studies conducted in human populations across the world. The major non-modifiable and modifiable causative agents are listed below:

A. Non-Modifiable Risk Factors

1. Ethnicity
2. Genetic Influence
3. Age
4. Gender

B. Modifiable Risk Factors

1. Unhealthy Life Style
   i. Inappropriate Diet
   ii. Sleep Disorders/ Inadequate Sleep
   iii. Physical Inactivity
   iv. Smoking
   v. Excess Alcohol Intake
2. Obesity
3. Intrauterine Growth Retardation
4. Adverse Environmental Climate
Ethnic Influence on Blood Pressure

Epidemiological studies report differences in the incidence and prevalence rate of Hypertension amongst different ethnic groups living in the same environmental conditions and sharing similar lifestyle. Epidemiological studies report that the Black Americans showed a higher prevalence of Hypertension as compared to the Whites.\textsuperscript{(13,14)} This difference is linked to the differences in the renal handling of sodium in these ethnic populations with blacks being more salt sensitive as compared to whites.\textsuperscript{(15,16,17)}

However, ethnicity not only influences the physiological determinants of blood pressure directly but also influences the association of other risk factors with blood pressure. Studies conducted on the Pima Indians show that despite having a high body fat content, the Pima Indians show a relatively very low prevalence of hypertension as compared to Caucasian population. The lack of an increase in Sympathetic Nervous activity with increasing adiposity and insulinemia observed in Pima Indians is believed to be responsible for the low prevalence of hypertension despite high prevalence of obesity.\textsuperscript{(18,19)}

Genetic Influence on Blood Pressure

Population studies show that hypertension is about twice as common in subjects who have one or two hypertensive parents as compared to those who have normotensive parents. Family studies and twin studies suggest that about 30\% of blood pressure variance is attributable to genetic factors and 50\% to environmental factors.\textsuperscript{(20)} The phenotypic variations observed are not due to a single gene but it is due to a complex interplay of various genes. Most of the genes that are found to be involved in pathogenesis of essential hypertension are
directly or indirectly, coupled to salt handling of the kidney, being included in the renin-angiotensin system (RAS), steroid-hormone metabolism, and renal sodium transporters.\(^{(21)}\) Though some familial concordance is reported to be due to shared lifestyle factors like dietary pattern, studies indicate that genetics plays a critical role in affecting the blood pressure not only in individual but in ethnically diverse populations.

**Influence of Age on Blood Pressure**

In the past, essential hypertension was recognized as a disease of late middle age and/or old age. But with changing lifestyle essential hypertension has now become a disease that starts affecting individuals as early as first decade of life. However, the type of essential hypertension and therefore the pathogenesis differs in the young, middle age and old age.

In young populations (17 to 25 years), Isolated Systolic Hypertension is found resulting from sympathetic overactivity, an increase in cardiac output and aortic stiffness. In middle age (30 to 50 years) Isolated Diastolic Hypertension or Combined Systolic-Diastolic Hypertension is found. This has been linked to middle age weight gain and is more common in men. The fundamental haemodynamic abnormality is an elevated systemic vascular resistance coupled with an inappropriately normal cardiac output. In old age (after 60 years) Isolated Systolic Hypertension predominates. It occurs due to deposition of collagen in the vessel walls that adversely affects the collagen to elastin ratio in the vessel wall causing a decrease in vascular compliance as evident by the widening of the pulse pressure.\(^{(22)}\)
Influence of Gender on Blood Pressure

Studies have reported gender differences in the incidence and prevalence of essential hypertension with women showing lower incidence and prevalence as compared to men especially during the premenopausal years. One of the earlier explanations for these findings was that the monthly menses keeps the fluid volume slightly lower in women before menopause so that the hemodynamic cascade towards hypertension is slowed.\(^{(23)}\)

However, studies report that premenopausal women with hypertension usually have a higher heart rate and cardiac output with low peripheral resistance in comparison to men with similar degrees of hypertension suggesting differences in pathogenesis of essential hypertension between genders.\(^{(24)}\) These differences are postulated to be due to the effect of the sex hormones.

It has been found that estrogen decreases while testosterone increases the levels of plasma endothelin, which is thought to be involved in the pathogenesis of atherosclerosis and hypertension.\(^{(25)}\) Another mechanism, which could be responsible for the lower blood pressure among premenopausal women in comparison to men of similar age group, is a higher level of endogenous nitric oxide production in women as compared to men.\(^{(26)}\) Muscle sympathetic nerve activity has also been found to be lower in women in comparison to men of similar age, which may also contribute to the low level of blood pressure in women as compared to men.\(^{(27)}\)
Influence of Life Style on Blood Pressure

Meal Frequency and Blood Pressure

Though it is thought that lowering the dietary intake or regularizing the dietary pattern may have a beneficial effect on health, very little is reported regarding the effect of meal frequency on health.

Fabry and Tepperman, 1970 have reported the findings of various studies conducted in animals and man to find the effects of meal frequency on various physiological functions. The most important effect of meal frequency was found to be observed on the body composition, plasma Insulin levels and serum cholesterol levels. The major changes in morphology and functioning of body tissues observed experimental animal viz., rats, mouse, chicks, rabbits and monkeys are shown in the Table 2.1.

It was proposed that the morphological and functional changes observed with intermittent feeding were possibly a part of an adaptive process which would equip the body tissues to meet the increased needs for dissimilation, interconversion and deposition of biological materials supplied by the periodic loads of food. An important adaptive process which was observed in experimental animals was “Adaptive Hyperlipogenesis” where in there was found an increase in the capacity for fat formation from carbohydrate sources in the liver and adipose tissue.
Table 2.1: Functional and Morphological Changes Due to Intermittent Food Intake in Experimental Animals.

<table>
<thead>
<tr>
<th>Morphological or Functional Change</th>
<th>Experimental Animal</th>
<th>Intermittent Feeding Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophy of stomach and small intestine</td>
<td>Rat, Mouse</td>
<td>I, H</td>
</tr>
<tr>
<td>Increased Activity of Pancreatic Enzymes</td>
<td>Rat</td>
<td>H</td>
</tr>
<tr>
<td>Enhanced Lipogenesis in liver and Adipose Tissue</td>
<td>Rat, Chick</td>
<td>H, I</td>
</tr>
<tr>
<td>Increased activities of lipogenic enzymes in liver and adipose tissues</td>
<td>Rat</td>
<td>H, FF</td>
</tr>
<tr>
<td>Increase Total Body Fat</td>
<td>Rat, Mouse</td>
<td>FF, I</td>
</tr>
<tr>
<td>Enhanced synthesis of cholesterol in liver</td>
<td>Rat, Chick</td>
<td>H</td>
</tr>
<tr>
<td>Greater increase of serum cholesterol or more advanced vascular changes, or both, when feeding atherogenic diets</td>
<td>Chick, Rabbit, Monkey</td>
<td>H</td>
</tr>
<tr>
<td>Hypertrophy of the Gall Bladder</td>
<td>Mouse</td>
<td>I</td>
</tr>
<tr>
<td>Enhanced intestinal absorption of glucose</td>
<td>Rat</td>
<td>I, H</td>
</tr>
<tr>
<td>Increased Post-prandial level of serum Insulin</td>
<td>Rat</td>
<td>H</td>
</tr>
<tr>
<td>Increased sensitivity of adipose tissue to Insulin</td>
<td>Rat</td>
<td>H</td>
</tr>
<tr>
<td>Increased Sensitivity of the animal to diabetogenic agents</td>
<td>Rat</td>
<td>H, FF</td>
</tr>
</tbody>
</table>

1 = Intermittent Feeding (alternating 1-3 day periods of fasting with periods of refeeding)
H = Feeding 1-2hrs/day, FF = Forced Feeding twice a day by gavage

An important biological determinant of adaptive hyperlipogenesis was found to be Insulin, as the adipose tissue of intermittently fed animals was found to be more sensitive towards lipogenic stimulating effects of Insulin and that Insulin levels were found to be higher in these animals as compared to controls. However, though the changes associated with intermittent feeding reflected an adaptive process, it was said that certain effects of this adaptive process like increase total fat mass, increase total cholesterol and hyperinsulinaemia would lead to pathological states like obesity, Diabetes (Beta-cell exhaustion) that could be detrimental to health.
Learning from various animal experiments, researchers have conducted various studies on humans as reported by Fabry and Tepperman. Studies conducted in humans also revealed results similar to animals.

One of the study conducted showed that subjects with the smallest number of meals (3-1 meals/day including snacks) were found to be more overweight, showed a greater skin fold thickness and a higher cholesterol-phospholipid ratio in comparison to those subjects who had 4-5 meals/day and 5-6 meals/day.

Another study showed that overweight, hypercholesterolemia and glucose intolerance tend to decrease as the meal frequency increases. It was reported that in some hyperlipidaemic patients the level of serum lipids declined when the diet, otherwise unchanged was divided into a greater number of small portions. Another study reported that the fall in serum cholesterol in obese patients treated with 1000 kcal diet was greater during the periods when they the daily food intake was divided into eight portions in comparison to when the daily intake was taken at two times with each intake equivalent to 500 kcal. Glucose tolerance was also found to be lower when hospitalized patients were having a single large meal over a period of 2-3 weeks as compared to the period when the meal was given in 10 portions.

A study conducted by Fabry et al showed that in comparison to those men who were having a meal frequency of = 3 meals/day men who were having a meal frequency of =5 meal/day showed lower prevalence of overweight (57.2% vs. 28.8%), hypercholesterolemia ( 51.2% vs 17.9%), glucose intolerance (42.9% vs 19.4%) and ischaemic heart disease (30.4% vs 19.9%).
On the basis of the findings of animal and human studies it was concluded by Fabry and Tepperman that an infrequent meal pattern is associated with a tendency towards obesity, hypercholesterolemia, glucose intolerance and ischaemic heart disease. However, infrequent meal pattern was indirectly linked to the causation of cardiovascular disease by causing an increase in the prevalence of cardiovascular risk factors viz., overweight/obesity, hypercholesterolemia and glucose intolerance.

Recently in 2007 Stote et al reported the findings of a randomized cross-sectional study they conducted to determine the role of meal frequency independent of calorie intake in the maintenance of health. The study showed that a 1 meal/day diet without calorie restriction was associated with a decrease in total body weight, total fat mass, RBC count, Hemoglobin level, hematocrit, Blood Urea-Nitrogen (BUN) and serum cortisol levels in comparison to a 3 meal/day diet regime. However, individuals on a 1 meal/day diet showed a significantly higher level of SBP, DBP, Total Cholesterol, LDL and HDL in comparison to individuals on a 3 meal/day diet. There were no significant differences in total body water, fat free mass, heart rate, body temperature blood glucose, serum total proteins and serum electrolytes viz., sodium, potassium and calcium. There was no effect of meal frequency on the physical activity level. The 1 meal/day diet was however associated with a significantly higher desire to eat, hunger and prospective consumption and a significantly lower feeling of fullness than the 3 meal/day diet. However, authors report that the differences observed in blood pressure levels between the two groups were probably due to the diurnal variation in blood pressures as the blood pressure measurements were taken at two different times of the day in the two groups.
Figure 2.1 shows the interrelationships of various changes which occur in the body due to infrequent meal pattern that may lead to a pathological state as proposed by Fabry and Tepperman.

Figure 2.1: Multiple Effects of Infrequent Feeding
Sleep Duration and Blood Pressure

Very recently published longitudinal, population-based studies are bolstering the relationship between sleep and hypertension. Gangwisch et al used NHANES I data to show significant increases in incident hypertension over 10 years in those who reported sleep durations of 5 hours or less per night. This relationship was minimally attenuated after controlling for obesity and diabetes. The cross-sectional Sleep Heart Health Study reported by Gottlieb et al showed that the highest odds of hypertension were seen in those reporting less than 6 hours per night. Reporting more than 8 to 9 hours per night also conferred a higher risk for hypertension, although lower than in those who had the shortest sleep duration.

Although the development of Hypertension in sleep deprived individuals may be occurring due to comorbid obesity, experimental and observational studies indicate sleep debt as an independent risk factor for Hypertension. This hypothesis is biologically logical due to various reasons. The cumulative blood pressure load and exposure to an activated sympathetic nervous system is increased as time awake is prolonged, whereas the protective effects of reduced blood pressure and sympathetic withdrawal during sleep are curtailed.

Researchers across the globe have studied various cardiac and non-cardiac physiological variables which may be influenced by sleep duration and consequently lead to development of hypertension.

Heart rate, as an index of cardiac sympathetic activity is one cardiac measure which has been studied extensively in cross-sectional, longitudinal and experimental studies to determine the association of sleep duration with blood pressure. Bonnet and Arrand have reported the findings of various research studies conducted to find the relationship of sleep duration with sympathetic activity and blood pressure. (34) An early cross-sectional study reported that poor sleepers have an elevated heart rate as compared to good sleepers (7bpm higher 30 minutes before sleep, 6bpm higher on average during 30 minutes before sleep and 4bpm higher during the sleep period) with both presleep differences being statistically significant. Stepanski et al reported a significantly higher heart rate in Insomniacs in comparison to normal with a significant consistent increase in heart rate throughout the awake state, Non-Rapid Eye Movement (NREM) sleep and Rapid Eye Movement (REM) sleep. Bonnet and Arand have also reported results similar to those of Stepanski et al (Table 2.2) However; they also studied the relationship of sleep duration with heart rate variability and found that the ratio of low to high frequency power was significantly greater in insomniac patients both during the wake and across the sleep stages when compared with normal subjects.

Some studies also reported the relationship of sleep duration with cardiovascular variables during stressful conditions. In one study insomniacs showed a significant and constant elevation in heart rate compared with normal throughout
Haynes and colleagues reported a significant increase in heart rate amongst insomnia patients in comparison to normal before and after but not during a mental arithmetic task presented to the subjects while in bed.

Table 2.2: Heart rate by sleep stage in primary insomnia and controls

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stepanski et al</th>
<th>Bonnet and Arand</th>
<th>Bonnet and Arand</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart rate</td>
<td>Heart rate</td>
<td>Low/high power</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Normal</td>
<td>Insomnia</td>
<td>Normal</td>
</tr>
<tr>
<td>Wake</td>
<td>70.5 (9)</td>
<td>64.5 (7.3)</td>
<td>68.8 (9)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>66.0 (9.1)</td>
<td>59.8 (7.9)</td>
<td>65.6 (9.1)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>62.3 (8.6)</td>
<td>59.2 (8.6)</td>
<td>65.6 (9.1)</td>
</tr>
<tr>
<td>SWS</td>
<td>68.4 (7.2)</td>
<td>57.9 (6.3)</td>
<td>68.3 (8.3)</td>
</tr>
<tr>
<td>REM</td>
<td>64.8 (8.3)</td>
<td>60.9 (8)</td>
<td>68.3 (8.3)</td>
</tr>
</tbody>
</table>

Abbreviations: REM, rapid eye movement; SWS, slow wave sleep

Studies done on Insomnia patient indicate various significant differences in physiological parameters apart from elevated heart rate in comparison to normal that may be responsible for elevated blood pressure observed in Insomnia patients. Other significant differences in these patients include elevated 24-hour whole-body metabolic rate (as measured by VO₂); elevated brain metabolic rate (positron emission tomography results); increased cortisol and adrenocorticotropic hormone secretion; increased interleukin-6; and increased beta electroencephalogram (EEG) activity. Another study has shown that increasingly poor sleep in insomnia patients is correlated with norepinephrine, epinephrine, and dopamine precursors and metabolites. All of these results are consistent with sympathetic or hypothalamic-pituitary-adrenal (HPA) activation.
Primary insomnia is frequently a chronic condition, and this implies that patients may remain in a sympathetic dominant or HPA-activated state for many years. As such, these patients might be expected to develop cardiovascular problems secondary to the arousal that also produces poor sleep.

However, though cross-sectional and longitudinal studies indicate heightened sympathetic tone associated with short sleep duration or Insomnia to be responsible for rise in blood pressure observed in those who sleep less, Zhong and colleagues reported that experimental total or partial sleep deprivation and sleep restriction studies show variable results as shown in Table 2.3. (35) Combined Data compiled from Total Sleep Deprivation studies indicated a non-significant 0.5 bpm decrease in heart rate during sleep deprivation. However, the combined data of these studies indicated a significant increase in blood pressure after total sleep deprivation. (Table 2.4)

Partial sleep deprivation studies show a significant increase in heart rate, systolic and diastolic blood pressure. But, these studies were conducted on people who were already having a stressful life (alcoholics or diagnosed case of hypertension). Therefore, the significant difference observed between the results of partial sleep deprivation and total sleep deprivation is attributed to the existing stress amongst the subjects of the former study group.
Table 2.3: Studies of cardiac variables during total sleep deprivation, partial sleep deprivation, and sleep restriction

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Position</th>
<th>Heart rate</th>
<th>Systolic pressure</th>
<th>Diastolic pressure</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSD study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 YA</td>
<td>Supine</td>
<td>Decrease</td>
<td>NS</td>
<td>NS</td>
<td>HRV NS</td>
</tr>
<tr>
<td></td>
<td>Sitting</td>
<td>Increase</td>
<td>NS</td>
<td>NS</td>
<td>HRV NS</td>
</tr>
<tr>
<td></td>
<td>Sitting RT</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>HRV Significant</td>
</tr>
<tr>
<td>4 YA</td>
<td>Sitting</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>19 YA</td>
<td>Supine</td>
<td>NS</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>6 YA</td>
<td>Sitting</td>
<td>NS</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>8.40-YO</td>
<td>Supine</td>
<td>NS</td>
<td>Increase</td>
<td>Increase</td>
<td>MSNA decrease</td>
</tr>
<tr>
<td>12 YA</td>
<td>Supine</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>15 YA</td>
<td>Sitting</td>
<td>Decrease</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>21 YA</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>10 YA</td>
<td>—</td>
<td>NS</td>
<td>Increase</td>
<td>NS</td>
<td>CRP increase</td>
</tr>
<tr>
<td>12 YA</td>
<td>Supine</td>
<td>Decrease</td>
<td>—</td>
<td>—</td>
<td>SNS decrease</td>
</tr>
<tr>
<td>6 YA</td>
<td>Supine</td>
<td>NS</td>
<td>NS</td>
<td>Increase</td>
<td>MSNA decrease</td>
</tr>
<tr>
<td><strong>PSD study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36 HTN</td>
<td>Sitting</td>
<td>Increase</td>
<td>Increase</td>
<td>Increase</td>
<td>EPI increase</td>
</tr>
<tr>
<td>18 YA, 1 3.6-h sleep</td>
<td>Ambulatory</td>
<td>NS</td>
<td>Increase</td>
<td>Increase</td>
<td>HRV EPI Increase</td>
</tr>
<tr>
<td>18 YA, 1 5-h sleep</td>
<td></td>
<td>Increase</td>
<td>Increase</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>36 44-YO</td>
<td>Supine</td>
<td>NS</td>
<td>Increase</td>
<td>Increase</td>
<td>NE EPI NS</td>
</tr>
<tr>
<td>36 alcohol dependent</td>
<td>Supine</td>
<td>Increase</td>
<td>Increase</td>
<td>Increase</td>
<td>NE EPI increase</td>
</tr>
<tr>
<td><strong>Sleep restriction study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 YA, 10 4.2-h sleep</td>
<td>—</td>
<td>Increase</td>
<td>NS</td>
<td>NS</td>
<td>CRP increase</td>
</tr>
<tr>
<td>11 YA, 6 4-h sleep</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>HRV Significant</td>
<td></td>
</tr>
<tr>
<td>10 60-yr-old F, 3 4-h sleep</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Cholesterol, LDL increase</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CRP, C-reactive protein; EPI, epinephrine; HRV, heart rate variability; HTN, hypertension; LDL, low-density lipoprotein; MSNA, muscle sympathetic nerve activity; NE, norepinephrine; NS, nonsignificant; PSD, partial sleep deprivation; RT, with performance; SNS, sympathetic activity; TSD, total sleep deprivation; YA, young adult; YO, year-old.
### Table 2.4: Group analysis of cardiac measures

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Baseline</th>
<th>Sleep Deprivation</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total sleep deprivation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>76</td>
<td>68.5 (4.03)</td>
<td>68.0 (3.78)</td>
<td>-0.999</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>36</td>
<td>117.2 (8.8)</td>
<td>122.3 (8.8)</td>
<td>2.459</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>42</td>
<td>63.9 (6.88)</td>
<td>67.2 (6.7)</td>
<td>2.360</td>
</tr>
<tr>
<td><strong>Partial sleep deprivation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>126</td>
<td>61.2 (12.97)</td>
<td>67.9 (8.48)</td>
<td>4.855</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>126</td>
<td>119.0 (16)</td>
<td>132.1 (7.5)</td>
<td>8.419</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>54</td>
<td>86.9 (7.2)</td>
<td>90.5 (6.8)</td>
<td>2.668</td>
</tr>
</tbody>
</table>

* a P<0.05

Sleep restriction studies on the other hand showed a significant increase in heart rate but not in blood pressure. Though it is believed and indicated by various studies that sleep duration may be affecting blood pressure through its effect on sympathetic activity, a recent study has been reported by Kato et al (2000), which showed an increase in resting blood pressure among sleep deprived individuals along with a decrease in muscle sympathetic nerve activity and no change in heart rate. This study also indicates that the pressor response to sleep deprivation is not mediated by either sympathetic vasoconstriction in muscles and/or tachycardia.
Sleep deprivation per se has also proven to be an independent risk factor for metabolic syndrome due to its effect on metabolism. Gangswich et al and Vorona et al have reported that reduction in sleep quantity is associated with overweight and obesity, with obese subjects showing a linear relationship between weight and sleep time.\(^{(37, 38)}\) Although the exact mechanism underlying this relationship is not clear, studies conducted by Spiegel et al (1999, 2004 and 2005) indicate sleep deprivation has neurohumoral consequences like sympathovagal imbalance, excess Cortisol levels, changes in Leptin and Ghrelin level which are probably responsible for sleep deprivation induced weight gain and obesity.\(^{(39,40,41)}\) However, apart from causing obesity, sleep deprivation is also linked to Glucose intolerance (Spiegel et al 2005 ), dyslipidaemia (Kaneita et al 2008) and activation of systemic inflammatory states (Vgontzas et al 1999) which are all risk factors for Hypertension.\(^{(41,42,43)}\)

**Sleep Duration and Blood Pressure in Adolescents**

Although a substantial amount of information is available regarding the effect of sleep duration on blood pressure amongst adult, there is scant literature which reports about the relationship of sleep duration with blood pressure amongst children and adolescents.

Sampei, Murata, Dakeishi and Wood reported the relationship between Total sleep Duration (TSD) and blood pressure amongst Japanese children of age group 5-6 years. TSD showed a significant correlation (\(r=0.265\)) with SBP but not with DBP.\(^{(44)}\)
Javaheri, Storfer-Isser, Rosen and Redline studied the relationship of inefficient sleep with Prehypertension amongst healthy adolescents. Analysis of their study revealed that after adjusting for gender, BMI and socioeconomic status, the odds of Prehypertension increased 3.5 fold for low sleep efficiency and 2.5 fold for short sleep. The study showed that adolescents with low sleep efficiency had on average a 4.0 +/- 1.2 mmHg higher systolic blood pressure than those who had a better sleep efficiency.

**Influence of Physical activity on Blood Pressure**

Earlier reports regarding the association of physical activity with health were by reported by Morris et al (1950) and Paffenberger et al (1970). Since then a large number of cross-sectional, longitudinal and experimental studies have been conducted across the globe to detect the effect of physical activity or exercise on health. Studies have indicated that physical activity and physical fitness are inversely related to the relative risk of death and that a dose-response relationship exists between physical activity/fitness and risk of premature deaths from any cause and cardiovascular disease among asymptomatic men and women.

Longitudinal studies report that people who engage in regular sweat-Inducing physical activity reduce their risk of developing hypertension by almost 50% in comparison to those who were physically inactive (Lowry et al 1995, Appel et al 2003). (47, 48)

George et al conducted a meta-analytic study which indicated that aerobic exercise reduces resting systolic and diastolic blood pressure in adults
independent of changes in body weight and percent body fat. \(^{(49)}\) However, Stamler et al reported that the reduction in blood pressure due to aerobic exercise is more amongst hypertensives in comparison to normotensives. \(^{(50)}\) The Systolic Blood Pressure (SBP) was found to be reduced by 6mmHg (4\%) and 2mmHg (2\%) in hypertensives and normotensives respectively while the Diastolic Blood Pressure (DBP) reduced by 5mmHg (5\%) in hypertensives and 3mmHg (1\%) in normotensives. This shows the important role that physical activity plays in controlling blood pressure as it is reported that a 2mmHg reduction in resting SBP is associated with a reduction in mortality by 4\% from Coronary Artery Disease (CAD), 6\% from Stroke and 3\% from all causes.

Exercise lowers blood pressure through multiple mechanisms which include decrease in sympathetic nerve traffic, potentiation of baroreceptor reflex, reduced arterial stiffness, increase total systemic arterial compliance, increase release of endothelium-derived nitric oxide and increase insulin sensitivity (Warburton et al 2006, Kaplan 1998, Winnick et al 2008). \(^{(46, 51, 52)}\)

One of the major mechanisms through which physical activity probably affects blood pressure is through its effects on metabolism. The metabolic effect of physical activity is indicated by the improvements in body composition with a decrease in abdominal adiposity observed amongst people who increase their physical activity level as reported by Gutin et al and Saelens et al. \(^{(53, 54)}\) Physical activity also prevents the rise of blood pressure in obese individual due to various other mechanisms as depicted in Figure 2.2.
Another metabolic effect through which physical activity is believed to affect blood pressure is by improving the Insulin sensitivity as reported by Carrel et al. \(^{(55)}\) Insulin Insensitivity is found to cause an increase in sympathetic activation which leads to vasoconstriction in the systemic vasculature and a rise in blood pressure (Straznicky et al.) \(^{(56)}\)

A Study conducted by Yang et al has shown that a single exercise session acutely enhances insulin-induced and IGF-1-induced vasorelaxation in rat aorta. \(^{(57)}\) It is therefore believed that one of the mechanisms through which physical activity lowers the blood pressure is by reducing the peripheral resistance through its effects on Insulin sensitivity.

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**Figure 2.2: Mechanisms by which physical activity controls blood pressure in obesity.**

Another metabolic effect through which physical activity is believed to affect blood pressure is by improving the Insulin sensitivity as reported by Carrel et al. \(^{(55)}\) Insulin Insensitivity is found to cause an increase in sympathetic activation which leads to vasoconstriction in the systemic vasculature and a rise in blood pressure (Straznicky et al.). \(^{(56)}\)

A Study conducted by Yang et al has shown that a single exercise session acutely enhances insulin-induced and IGF-1-induced vasorelaxation in rat aorta. \(^{(57)}\) It is therefore believed that one of the mechanisms through which physical activity lowers the blood pressure is by reducing the peripheral resistance through its effects on Insulin sensitivity.
Physical activity also corrects Dyslipidaemia, a risk factor for Hypertension. A dose-response relationship exists between volume of physical activity and the change in blood lipids. Physical activity mainly increases the High Density Lipoproteins (HDL) levels and decreases the Triglyceride (TG) levels without altering the Total Cholesterol and Low Density Lipoproteins (LDL) in both genders. However, the improvement in lipid profile seems to occur only when a threshold volume of physical activity is achieved. Cross-sectional studies reveal that training volumes of 24 to 32 km (15 to 20 miles) per week of brisk walking or jogging with energy expenditure ranging between 1200 to 2200 kcal/wk lead to an improvement in lipid profile. Such level of physical activity may cause a rise in HDL levels in the range of 2 to 3 mg/dl and reduce the TG by 8 to 20 mg/dl. (Durstine et al).\(^{58}\)

Yet, another possible link between increase physical activity and low blood pressure is the independent effect of physical activity on the vascular endothelial function. Endothelial function (Endothelial Nitric Oxide production) is found to change and improve with regular aerobic activity as an adaptive response independent of the effects of physical activity on other risk factors. Physical activity is said to cause a Shear-Stress mediated improvement in endothelial function that protects against Hypertension. The increase in blood flow, and change in haemodynamics that occur during acute exercise is thought to provide a stimulus for both acute and chronic changes in vascular function.

Majorana et al and Green et al demonstrated that exercise training involving repetitive bouts of exercise done over weeks or months up-regulates endothelial NO bioactivity.\(^{(59,60)}\) Majorana et al also showed that the short-term functional adaptation in the form of enhancement of NO bioactivity that occurs with
exercise training is followed by NO-dependent structural changes, leading to arterial remodeling and structural normalization of shear if the exercise training is maintained over a longer period. However, the improvement in endothelial function with regular physical activity is found to be more in individuals who have endothelial dysfunction and a cardiovascular risk profile in comparison to those who are normal.

Physical activity is now also believed to play an important role in reducing the low grade systemic inflammation associated with chronic non-communicable diseases like Hypertension, Type-II Diabetes Mellitus and Cancer (Mathur et al). With the identification of skeletal muscle to be an endocrine organ which releases cytokines called Myokines, it has been postulated that the exercise induced release of cytokine mainly IL-6 from skeletal muscle in response to exercise may decrease the chronic low grade systemic inflammation and protect the vasculature from insulin resistance and atherosclerosis (Febbraio & Pedersen 2005, Pedersen & Fischer 2007). This is also supported by the fact that insulin sensitivity is enhanced during the post-exercise period as reported by Jennings et al. However, controversies exist regarding the relationship of IL-6 with insulin sensitivity since it is found that IL-6 levels are often high in patients suffering from metabolic disease.

Improvement in autonomic tone to heart and vasculature is also one of the major mechanism by which Physical activity seems to lower blood pressure. Study conducted by Jennings et al indicated that physical activity decreases sympathetic activity as indicated by the decrease in Norepinephrine Spill over rate, an index of sympathetic activity.
Collier et al found that aerobic exercise increases the vagal tone, reduces sympathovagal balance and increases baroreceptor sensitivity in prehypertensive individuals.\(^{65}\)

A recent study conducted by Ino-Oka et al indicated a negative correlation between daily physical activity and LF/HF ratio (Index of sympathetic tone) and that appropriate level of physical activity is required to cause sympathetic relaxation.\(^{66}\)

Though most of the effects discussed above indicate the beneficial chronic adaptations that take place in the body with regular physical activity or exercise which keep the blood pressure in check, recent study indicates that even the acute effects of physical activity tend to control blood pressure. It has been found that acute dynamic exercise result in transient changes in physiological variables that lead to reduction in blood pressure for 12 to 16 hours following the exercise act (Thompson et al, 2001).\(^{67}\)

**Physical Activity Status and Blood Pressure in Adolescents**

Although a large number of studies have been conducted in various populations across the globe to determine the association of physical activity with blood pressure amongst children and adolescents, however unlike adults the results of these studies do not indicate a definite role of physical activity in reducing blood pressure amongst children and adolescents.
Kelley et al conducted a meta-analysis of Randomized Control Trials (RCT) to determine the effect of exercise on resting blood pressure in children and adolescents showed that there was only a marginal effect of short-term exercise on systolic blood pressure (3% reduction) and diastolic blood pressure (1%). This meta-analysis was done using the outcomes reported by 12 RCT between 1981 and 1999. It was concluded by the meta-analysis that short-term exercise did not affect the blood pressure amongst adolescents. The findings of the

Brage et al reported the findings of European Youth Heart Study which indicated that physical activity was not associated with Systolic and Diastolic blood pressure amongst the Danish children. Instead, it was the physical fitness of the adolescents which showed a significant association with the systolic blood pressure. Rizzo et al also reported the findings of European Youth Heart Study and found that it is the cardio respiratory fitness rather than physical activity that has a strong corollation with the risk of metabolic syndrome amongst adolescents and the association of both physical activity and cardiorespiratory fitness with the metabolic risk is reduced when body fat percentage is taken into consideration. Similar results have also been reported from study conducted in Finland and Ireland as reported by Raitakari et al and Boreham et al respectively. Recently, the results of Oslo Youth Health study have also been reported by Kvaavik et al. The study found that physical activity levels do not show any significant relationship with blood pressure amongst adolescents. Ravaja et al also reported that there was no association between the development of metabolic syndrome in young adult and the level of physical activity during adolescence.
However, a cross-sectional study conducted by Leary et al on 5505 children of mean age 11.8 years showed that there existed a weak but significant association of physical activity level and blood pressure. It was found and reported that it is the volume of physical activity rather than the intensity of activity that seems to reduce the blood pressure.

The Dietary Intervention Study in Childhood (longitudinal study) also showed a significant association between physical activity and systolic blood pressure amongst children over a period of 3 years. It was found that for every 100 estimated-metabolic-equivalent hours of physical activity, the systolic blood decreased by 1.15mmHg.

The Young-Hunt study conducted on Norwegian adolescents showed that low physical activity was associated with higher mean diastolic blood pressure amongst both boys and girls. Although the amount of reduction in blood pressure due to physical activity was found to be small it was independent of other confounding factors like BMI.

The National Health and Nutrition Examination Survey (NHANES) 1999-2002 showed that in adolescents of age group 12-19 years, the prevalence of each metabolic syndrome component (Central obesity, Impaired Fasting Glucose, High Triglyceride level, low-HDL-C level and Elevated Blood Pressure) was found to be low in physically active adolescents. It was reported that adolescents with low physical activity levels had the highest rates of all the metabolic syndrome components.
Another longitudinal study conducted in the North Carolina state of United States has also reported findings similar to those reported from NHANES1999-2002. It showed that adolescents with metabolic syndrome were five times more likely to have a low physical activity levels during childhood and six times more likely to have a low aerobic fitness. (79)

Mark et al reported a dose-response relationship between physical activity and blood pressure amongst adolescent. According to this study the chances of developing hypertension decreased in a curvilinear manner with increasing minutes of PA. At 30 and 60 min.d of moderate-to-vigorous PA, the odd ratios (95% confidence intervals) for hypertension were 0.50 (0.28-0.64) and 0.38 (0.17-0.52), respectively, in comparison to no PA. (80)

Studies conducted on Indian adolescents also show variable results regarding the relationship between physical activity and blood pressure. Thakkor et al conducted a study on Indian adolescents which showed a weak negative correlation between outdoor playing and blood pressures. However, the correlationship disappeared when gender and age were adjusted. (81)

Soudarssanane et al conducted a study amongst Indian adolescents of age group 15-19 years in Pondicherry and found an insignificant relationship between physical activity level and blood pressure. (82)
Influence of Body composition on Blood Pressure

Body composition especially the amount of adipose tissue has a significant effect on blood pressure. Obesity is now recognized as one of the major risk factor for essential hypertension. The increasing incidence and prevalence of hypertension has been attributed to the parallel rise in the incidence and prevalence of obesity across the globe.

The Framingham study showed that 70% of hypertension in men and 61% in women was directly attributable to the excess adiposity; with a 4.5-mmHg average increase in systolic blood pressure for every 10-pound weight gain.\(^{(63)}\)

The Intersalt cross-sectional survey of 52 populations worldwide showed a strong association of Body Mass Index (BMI) with blood pressure, independent of dietary sodium and potassium intake.\(^{(84)}\) It has been reported that the upper body obesity (Android or visceral) rather than the lower body obesity (Gynoid or Peripheral) is associated with higher cardiovascular morbidity and mortality, insulin resistance, dyslipidaemia and hypertension.\(^{(85)}\)

A number of studies have been carried out to understand the pathophysiological mechanisms that may underlie to cause hypertension in obese individuals. The major pathophysiological changes that are found in obese individuals and which may be responsible for hypertension are Insulin resistance, an increased activation of Renin-Angiotensin-Aldosterone system (RAAS) and Sympathetic Nervous System (SNS) activation. However, apart from these major mechanisms the other mechanisms which may lead to hypertension in obese individuals are leptin resistance, high resistin levels, low adiponectin levels, increase free fatty acid levels and increase endothelium -1levels. (Kurukulasuriya et al 2008).\(^{(86)}\)
Relationship of Insulin Resistance & Hyperinsulinaemia with Hypertension in Obesity:

Although many people believe that insulin resistance observed in obesity may be responsible for causing hypertension in obese individuals, controversies still exist regarding this issue. Hall et al conducted a study on obese dogs and reported that despite the obese dogs being resistant to metabolic and vasodilatory effects of insulin they did not show any rise in blood pressure when exposed to chronic hyperinsulinaemia. *(87)*

Studies conducted by Anderson et al showed that in both normotensive and borderline hypertensive human subjects, high and low doses of Insulin resulted in an increase in sympathetic neural outflow but did not cause a rise in arterial pressure. In fact, in borderline hypertensive subjects the SBP and DBP fell by approximately 3mmHg and 6 mmHg respectively during insulin infusions. *(88, 89)*

Yet another study conducted on patients having Insulinoma showed that patients with insulinoma have high levels of plasma insulin levels but do not differ from normal control subjects in blood pressure levels and surgical removal of Insulinaemia does not reduce their blood pressure despite causing a fall in plasma insulin levels. *(90)*

However, though hyperinsulinaemia associated with obesity may not be directly causing hypertension, insulin resistance observed in obese individuals has been proposed to cause hypertension by mechanisms such as inflammation, oxidative stress, activation of sympathetic nervous system, renal sodium retention, vascular smooth muscle growth and remodeling and vasoconstriction. *(91)*
Relationship of Renin-Angiotensin-Aldosterone System (RAAS) Activation with Hypertension in Obesity:

Studies have shown that RAAS is often activated in obese individuals as indicated by high levels of plasma Angiotensinogen and Aldosterone levels in obese individuals.

A study of postmenopausal women showed that obese women had higher circulating angiotensinogen, renin, aldosterone, and ACE levels than lean women. Weight reduction by 5% reduced plasma angiotensinogen by 27%, renin by 43%, aldosterone by 31%, ACE activity by 12%, and angiotensinogen expression by 20% in adipose tissue (all \( P < .05 \)). The decrease in plasma angiotensinogen levels was highly correlated with the waist circumference decline (Engeli et al 2005). (92)

Another study showed that obese individuals (body mass index > 31) had significantly higher serum ACE and angiotensinogen levels and the relationship persisted for ACE in multivariate analyses controlling for BP, hypertension status, age, and gender (Cooper et al 1997). (93)

Kim et al (2006) conducted a study on three different mouse models based on the expression of Angiotensinogen levels in the adipose tissue i.e., mice lacking angiotensinogen, Agt (Agt-KO), mice expressing Agt solely in adipose tissue (aP2-Agt/Agt-KO), and mice overexpressing Agt in adipose tissue (aP2-Agt). The study was based on the fact that adipose tissue renin-angiotensin system (RAS) contributes to regulation of fat mass and that it may also impact systemic functions such as blood pressure and metabolism. The study showed that the Total body weight, epididymal fat pad weight, and circulating levels of leptin,
insulin, and resistin were significantly decreased in Agt-KO mice, while plasma adiponectin levels were increased. aP2-Agt mice exhibited increased adiposity and plasma leptin and insulin levels compared to wild type (WT) controls. Angiotensinogen and type I Ang II receptor protein levels were also elevated in kidney of aP2-Agt mice. It was concluded from the study that alterations in adipose RAS activity significantly impact both local and systemic physiology.\(^{94}\)

It is also said that in contrast to rodents where the local angiotensin II released from adipocytes help in preadipocyte recruitment and adipocyte growth, in humans' angiotensin II acts as an antiadipogenic substance. This has important consequences since obese individuals may be producing higher amounts of local angiotensin II which may lead to hypertension as an endocrine effect and insulin resistance (Engeli et al 2003).\(^{95}\)

Plasma Aldosterone levels are higher in obese subjects. Goodfriend et al (1998) studied some predictors of plasma aldosterone include abdominal obesity, measured as waist/hip ratio or by CT scan, and insulin resistance measured by glucose tolerance tests or euglycemic clamp techniques. The study suggested that aldosterone participates in hypertension associated with insulin resistance, both components of the cardiometabolic syndrome (CMS).\(^{96}\)

Aldosterone increases BP in obesity by its action on both mineralocorticoid and glucocorticoid receptors located in different tissues, including brain, heart, kidney, and vasculature (Rahmouni et al 2005).\(^{97}\)

In a study of 223 obese patients, lisinopril was shown to be as effective as hydrochlorothiazide in treating obese subjects with hypertension. This study
also showed that ACE inhibitors may show greater efficacy as monotherapy at lower doses (compared with thiazide diuretics), may have a more rapid rate of response, and may offer advantages in patients at high risk of metabolic disorders (Reisin et al 1997).\(^{(98)}\)

De Paulo et al (2004) found that Aldosterone antagonist eplerenone markedly attenuates glomerular hyperfiltration, sodium retention, and hypertension associated with chronic dietary-induced obesity in dogs fed with a high fat diet.\(^{(99)}\) Together, these data indicate that aldosterone plays an important role in the pathogenesis of obesity hypertension.

**Relationship of Sympathetic System Activation with Hypertension in Obesity:**

There are several proposed mechanisms linking obesity with Sympathetic Nervous System activation. These include baroreflex dysfunction, hypothalamic-pituitary axis dysfunction, hyperinsulinemia/insulin resistance, hyperleptinemia, and elevated circulating angiotensin II concentrations (Davy et al 2004 and Alvarez et al 2002).\(^{(100,101)}\)

Study conducted by Alvarez et al 2004 showed that Muscle sympathetic nervous system activity (MSNA) in men is more closely associated with the level of abdominal visceral fat than total fat mass or abdominal subcutaneous fat. MSNA did not differ in subcutaneous obese and nonobese men with similar levels of abdominal visceral fat.\(^{(102)}\)
It is also proposed that the increase renal sympathetic activity observed in obesity may possibly be necessary for the development of HTN in obese individuals, but not a sufficient cause, as it is present in both normotensive and hypertensive obese individuals.

However, the discriminating feature of obesity-related hypertension has been shown to be an absence of the suppression of the cardiac sympathetic outflow seen in normotensive obese individuals (Rumantir et al 1999). \(^{(103)}\)

Another interesting finding that indicates the role of sympathetic activation in causing hypertension in obesity is the findings of Weyer et al (2000) who carried out a study on Pima Indians. The study found low prevalence of hypertension in this population despite having high prevalence of obesity and hyperinsulinaemia. The lack of increase in SNS activity with increasing adiposity and insulinemia in the Pima Indians was thought be responsible for the low prevalence of hypertension in that population. \(^{(104)}\)

Nevertheless, increased renal sodium absorption associated with increased renal SNS activity appears to contribute to obesity-related hypertension in many individuals. A study of both lean and obese hypertensive has shown that BP is more sensitive to alpha and beta adrenergic blockade in obese than in lean hypertensive patients, and suggests that increased sympathetic activity may be an important factor in the development and maintenance of hypertension in obesity (Wofford et al 2001). \(^{(105)}\)
Role of Adipocytes in Causation of Hypertension:

Expansion of adipose tissue is a hallmark of obesity, however the location and adipocyte morphology of the expanded adipose tissue differs among individuals. The presence of large adipocytes is associated with functional and structural abnormalities of adipose tissue. These include: (1) the increased production of bioactive molecules, such as leptin, resistin, angiotensinogen, proinflammatory cytokines, and reactive oxygen species (ROS); (2) an insufficient capacity to accommodate excess energy-intake related increases in serum lipids, leading to ectopic fat storage in tissues such as skeletal muscle and liver, which, in turn, enhances insulin resistance and hyperinsulinemia; (3) augmented macrophage infiltration of the adipose tissue enhancing the production of proinflammatory cytokines and ROS. This "dysfunctional" adipose tissue may, in turn, induce activation of the sympathetic nervous system and RAAS, and enhance systemic oxidative stress, all of which promote the development of obesity-associated Hypertension (Pausova 2006). \(^\text{106}\) Figure 2.3 shows the complex actions of various adipokines on the cardiovascular system (Katagiri, Yamada & Oka 2007). \(^\text{107}\)

Ehrhart-Bornstein et al have shown that secretory products from human adipocytes stimulate steroidogenesis in human adrenocortical cells with a predominant effect on mineralocorticoid secretion, suggesting a direct link between obesity, RAAS activation, and hypertension. \(^\text{108}\)
Figure 2.3 Adipocytokines interact in a complex way to regulate vascular function and ultimately the development of cardiovascular diseases.

Role of Leptin in causing Hypertension in Obesity:

Leptin is important in regulating appetite, body weight, and energy balance. It is secreted by adipocytes and acts as a signal by which adipose tissue communicates with the brain. It acts as the afferent component of a negative feedback mechanism that helps in controlling adipose tissue mass. Apart from its action in brain, leptin also affects the sympathetic nervous system, glucose and insulin metabolism, lipolysis, vascular tone, the hypothalamic-pituitary-adrenal axis, and reproduction. Normally, leptin alters energy intake by decreasing appetite and increasing energy expenditure via sympathetic nervous system stimulation (Haynes et al.).(109)
Plasma leptin levels are typically elevated in obese people and are positively correlated with the amount of adipose tissue. Study conducted by Correia et al showed that Leptin-induced decrease in food intake and body weight were less in agouti obese mice than in lean littermates while leptin-induced increases in sympathetic nerve activity did not differ in obese and lean mice. These findings supported the concept of selective leptin resistance in obesity, with resistance to the metabolic actions of leptin but preservation of the sympathoexcitatory actions.\(^{110}\)

The cardiovascular effects of leptin have recently been reviewed by Katagiri et al and Yang & Barouch.\(^{107, 111}\) Figure 2.4 demonstrates the various actions of leptin in obese individuals. (Yang & Barouch).\(^{111}\)

The mechanisms of leptin's vascular effects are complex. However, the predominant vascular effect of chronic hyperleptinemia is a pressor effect mediated by increased SNS activity. Leptin infusion in animal models causes increases in arterial BP, heart rate, and sympathetic nerve signals in several tissues (Haynes et al 1997, Dunbar, Hu & Lu 1997 and Shek, Brands & Hall 1998).\(^{109, 112, 113}\) Finally, leptin is also thought to cause hypertension by stimulating the production of ROS and endothelin-1(Bouloumie et al 1999 and Quehenberger et al 2002).\(^{114, 115}\)
Figure 2.4 Systemic leptin function. Chronic hyperleptinemia impairs the centrally mediated metabolic actions of the hormone, although its activation of sympathetic outflow is preserved. Selective central leptin resistance results in obesity and adverse effects on the cardiovascular system including hypertension, atherosclerosis, and LVH.

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Role of Resistin in Causing Hypertension in Obesity:

Resistin is a recently discovered polypeptide that antagonizes the action of insulin and thus is thought to play a part in the pathogenesis of insulin resistance. Resistin is increased in diet-induced and genetic forms of obesity (Steppan et al).\(^{(116)}\)

A Chinese study showed resistin gene polymorphism to be an independent factor associated with elevated SBP and DBP in patients with type 2 diabetes. These findings suggest that resistin may play a part in the pathogenesis of type 2 diabetes and insulin resistance-related hypertension (Tan et al).\(^{(117)}\)

Role of Adiponectin in causing Hypertension in Obesity:

Low plasma adiponectin level is considered as an independent risk factor for hypertension (Iwashima et al 2004).\(^{(118)}\) Since plasma levels of adiponectin are found to decrease in obesity, this may be one of the potential mechanism through which obesity may lead to hypertension (Katagiri et al 2007).\(^{(107)}\)

Adiponectin is thought to protect against hypertension through its various positive actions on the vascular endothelium and vascular wall remodelling. Adiponectin induces nitric oxide production and increases nitric oxide bioavailability by up-regulating eNOS expression and reducing ROS production in endothelial cells (Chen et al 2003 and Hattori et al 2003).\(^{(119,120)}\)

It has been shown in both human beings and adiponectin-deficient mice that
hypoadiponectinemia is associated with endothelial dysfunction and impaired endothelium-dependent vasodilatation (Ouchi et al 2003). (121)

It is also believed that Adiponectin may be modulating smooth muscle cell proliferation during the development and progression of vascular lesions. Arita et al showed that in physiological concentration, adiponectin significantly suppresses both proliferation and migration of human aortic smooth muscle cells in vitro by directly binding with platelet-derived growth factor-BB. (122) Adiponectin is also found to inhibit smooth muscle cell proliferation through its ability to interfere with receptor-mediated cellular responses (Wang et al 2005). (123)

**Role of Endothelin in causing Hypertension in Obesity:**

Some hypertensive patients have increased endothelin-1 (ET-1) dependent vasoconstrictor tone. It has been shown in subjects with a BMI of over 25 kg/m², that DBP is significantly associated with G/T polymorphism of ET-1 (Asai et al 2001). (124) Endothelin antagonism unmasks or augments nitric oxide synthesis capacity in obese patients (Mather et al 2004). (125) Thus, in addition to direct vasoconstrictor effects of endothelin, impaired nitric oxide bioavailability as a result of elevated endogenous endothelin may also contribute to endothelial dysfunction in obesity.
Role of Free fatty acids in causing Hypertension in Obesity:

It has been shown that increases in portal venous delivery of FFA (i.e., oleic acid - a cis unsaturated nonesterified fatty acid or NEFA) to the liver, stimulates a neurally mediated reflex that results in an increase in vascular sympathetic tone and an increase in BP (Grekin, Vollmer and Sider 1995). In vivo data from both animal and human studies support the notion that acute plasma NEFA elevation leads to an increase in BP levels. Epidemiologic evidence suggests a link between increased NEFA levels and HTN. Accumulating evidence indicates the existence of several pathways through which NEFA could promote BP elevation. These include alpha (1)-adrenergic stimulation, endothelial dysfunction, increases in oxidant stress, and stimulation of vascular smooth muscle cell growth and remodeling. Collectively, these data support a possibly important role of NEFA in the development of HTN in patients with obesity and CMS (Sarafidis and Bakris 2007).

Figure 2.5 illustrates the diverse effects of obesity particularly visceral obesity on the physiological functions which may lead to hypertension. To summarize, Insulin resistance, sympathetic activation, renal sodium retention, dyslipidaemia, Leptin resistance and impaired vasodilation are the major mechanisms through which obesity induces hypertension.

Figure 2.6 shows the interplay of various genetic, environmental, physical and hormonal factors that affect the blood pressure through their influence on cardiac output and peripheral resistance.
OBESITY + Androgen 

Increased Abdominal Fat 

Dyslipidaemia 

Release of Free Fatty Acids 

Type II Diabetes Mellitus 

Peripheral Insulin Resistance 

Increased Pancreatic Insulin Secretion 

Decreased Hepatic Insulin Extraction 

Hyperinsulinaemia 

Attenuated Vasodilation 

Sympathetic Overactivation 

Sodium Retention 

Vascular Hypertrophy 

HYPERTENSION 

Figure 2.5: Mechanisms of Hypertension in Obesity
Figure 2.6: Genetic, Environmental, Physical and Hormonal influence on cardiac output and peripheral resistance.