Effect of Obesity on Cardio Vascular System

by

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<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
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<tr>
<td>AgRP</td>
<td>Agouti-related peptide</td>
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<tr>
<td>a-MSH</td>
<td>a melanocyte-stimulating hormone</td>
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<tr>
<td>AngII</td>
<td>Angiotensin II</td>
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<tr>
<td>AP-1</td>
<td>Activator protein-1</td>
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<tr>
<td>ARC</td>
<td>Arcuate nucleus;</td>
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<tr>
<td>ASCVD</td>
<td>Atherosclerotic cardio vascular disease</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<td>BP</td>
<td>Blood pressure</td>
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<td>CHD</td>
<td>Coronary heart disease</td>
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<tr>
<td>CHF</td>
<td><em>Congestive heart failure</em></td>
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<tr>
<td>CO</td>
<td><em>Cardiac output</em></td>
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<td>CR</td>
<td>Concentric remodeling</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>EKG</td>
<td>Electrocardiogram</td>
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<tr>
<td>eNOS</td>
<td>endothelial NO synthase</td>
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<tr>
<td>ER</td>
<td>Endoplasmic reticulum</td>
</tr>
<tr>
<td>ERK1/2</td>
<td>Extracellular signal-regulated kinase-1/2</td>
</tr>
<tr>
<td>ET-1</td>
<td>Endothelin-1</td>
</tr>
<tr>
<td>FFAs</td>
<td>Free-fatty acids</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Glycated haemoglobin</td>
</tr>
<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
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<tr>
<td>HF</td>
<td>Heart failure</td>
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<tr>
<td>HTN</td>
<td>Hypertension</td>
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<tr>
<td>ICAM-1</td>
<td>Intracellular adhesion molecule-1</td>
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<tr>
<td>IGT</td>
<td>Impaired fasting glucose</td>
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<tr>
<td>IL-1</td>
<td>Interleukin-1</td>
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IL-1b            Interleukin-1b
IL-6             Interleukin-6
IRS-1            Insulin receptor substrate 1
LA                Left atrial
LDL               Low density lipoprotein
LV                 Left ventricular
LVH               Left ventricular hypertrophy
MAPK            Microtuble associated protein- kinase
MC3/MC4 receptor   Melanocyte receptor-3/4
MC3R             Melanocortin 3 receptor
MC4R             Melanocortin 4 receptor
MF                Myocardial infarction
mmLDL           Minimally modified LDL
Na/K-ATPase     Sodium- potassium-ATPase
NADPH            Nicotinamide adenine dinucleotide phosphate
NCEP            National Cholesterol Education Program
NEFA            Non-esterified fatty acids
NF-kB          Nuclear factor k light-chain enhancer of activated B cells
NF-Kb            Nuclear factor kappa B
NHANES III    Third national health and nutrition examination survey
NLRP3          Nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor-3
NO               Nitric oxide
NP              Natriuretic peptides
NPY             Neuropeptide Y
O2–             Superoxide
OSA             Obstructive sleep apnea
oxLDL          Oxidized LDL
PAI-1          Plasminogen activator inhibitor-1
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<tr>
<th>Acronym</th>
<th>Abbreviation</th>
<th>Full Name</th>
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<tr>
<td>PDK-1</td>
<td>Phosphoinositide-dependent kinase 1</td>
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<td>PI3K</td>
<td>PI3-kinase</td>
<td></td>
</tr>
<tr>
<td>PK-B</td>
<td>protein kinase B</td>
<td></td>
</tr>
<tr>
<td>PMNs</td>
<td>Polymorphonuclear leukocytes</td>
<td></td>
</tr>
<tr>
<td>POMC</td>
<td>Proopiomelanocortin</td>
<td></td>
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<tr>
<td>RAGE</td>
<td>Receptor to advanced glycation endproduct</td>
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<tr>
<td>RAS</td>
<td>Renin-angiotensin system.</td>
<td></td>
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<td>ROS</td>
<td>Reactive oxygen species</td>
<td></td>
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<td>SNS</td>
<td>Sympathetic nervous system</td>
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<tr>
<td>TF</td>
<td>Tissue factor</td>
<td></td>
</tr>
<tr>
<td>TGRLPs</td>
<td>Triglyceride-rich lipoproteins</td>
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<tr>
<td>TLR3</td>
<td>Toll like receptor-3</td>
<td></td>
</tr>
<tr>
<td>TLR4</td>
<td>Toll like receptor-4</td>
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<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
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| TNFa    | Tumor necrosis factor-
| Tx-A2   | Thromboxane A2 |
| TXNIP   | Thioredoxin-interacting protein |
| VCAM-1  | Vascular cell adhesion molecule-1 |
| VLDL    | Very low density lipoprotein |
| VSMC    | Vascular smooth muscle cell |
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Figure 1. Mechanisms of insulin-mediated nitric oxide (NO) and endothelin 1 (ET-1) production leading to vasodilation and vasoconstriction, respectively

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Objectives

General objectives

To provide full knowledge about effect of obesity on cardiovascular system.

Specific objectives

To know the different clinical consequences of obesity associated with cardiovascular system.

To explain the mechanisms by which obesity will cause cardiovascular diseases.
Summary

The aim of this review is to provide full knowledge about effect of obesity on cardio vascular system to the general population and to offer the greatest possibility for reducing the cardiovascular risk that accompanies obesity since obesity causes cardiac and vascular disease through well-known mediators such as hypertension, type II diabetes, and dyslipidemia as well as chronic inflammation and hyper coagulation. Obese individuals (BMI of 30 kg/m2 and above) are at increased risk for physical ailments such as:

- High blood pressure, or hypertension
- High blood cholesterol levels
- Type 2 (non-insulin dependent) diabetes
- Insulin resistance, or glucose intolerance
- Coronary heart disease
- Cardiac arrhythmias
- Congestive heart failure
- Stroke
- ECG abnormalities
- Obstructive sleep apnea
- Venous disease

Key words: Obesity, heart, blood vessel
Introduction

Obesity can be defined as an excess of body fat. A surrogate marker for body fat content is the body mass index (BMI), which is determined by weight (kilograms) divided by height squared (square meters) and waist-to-hip-ratio. In clinical terms, a BMI of 25–29 kg/m² is called overweight; higher BMIs (30 kg/m²) are called obesity. A better way to define obesity would be in terms of percent total body fat. This can be measured by several methods (skin-fold thickness, bioelectrical impedance, underwater weighing). In terms of percent body fat, obesity can be defined as 25% or greater in men and 35% or greater in women (Scott et al, 2004).

The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. Globally there has been: an increased intake of energy-dense foods that are high in fat, salt and sugars but low in vitamins, minerals and other micronutrients and decrease in physical activity due to the increasingly sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization (WHO, 2012). Obesity is a common disorder that develops from the interaction between the genotype and the environment and involves social, behavioral, cultural, physiological, metabolic and genetic factors (Vasilios et al, 2010).

Over the last decades, obesity and its consequences worldwide have become a major health problem. Between 1976 and 2002, the prevalence of overweight [body mass index (BMI) ≥ 25 kg/m²] in the USA has increased from 46 to 66% of the population and that of obesity (BMI ≥ 30 kg/m²) from 15 to 31% (Hedley et al, 2004).

The increase in obesity worldwide will have an important impact on the global incidence of cardiovascular disease, type 2 diabetes mellitus, cancer, osteoarthritis, work disability, and sleep apnea. Obesity has a more pronounced impact on morbidity than on mortality. Disability due to obesity-related cardiovascular diseases will increase particularly in industrialized countries, as patients survive cardiovascular diseases in these countries more often than in nonindustrialized countries. Disability due to obesity-related type 2 diabetes will increase particularly in industrializing countries, as insulin supply is usually insufficient in these countries. As a result, in these countries, an increase in disabling nephropathy, arteriosclerosis, neuropathy, and retinopathy is expected. Increases in the prevalence of obesity will potentially lead to an increase
in the number of years that subjects suffer from obesity-related morbidity and disability. A 1% increase in the prevalence of obesity in such countries as India and China leads to 20 million additional cases of obesity. Prevention programs will stem the obesity epidemic more efficiently than weight-loss programs. However, only a few prevention programs have been developed or implemented, and the success rates reported to date have been low. Obesity prevention programs should be high on the scientific and political agenda in both industrialized and industrializing countries.

During the past few decades, the prevalence of obesity has grown to epidemic proportions, and this condition is now known to be a major contributor to the global burden of disease (WHO, 1997). Currently, more than 50% of the US population is overweight and approximately 20% is extremely overweight, or obese (Flegal et al., 1998). Obesity prevalence is still increasing rapidly, not only in industrialized countries but also in nonindustrialized countries, particularly in those undergoing economic transition (Seidell et al., 2000). Worldwide, around 250 million people are obese (WHO, 1998).

In recent years, overweight and/or obesity among children and adolescents have emerged as a global epidemic (WHO, 2013). Adolescence is a vulnerable period for the development of obesity and weight of adolescent tracks strongly into adulthood (Tsiros MD et al., 2011). The WHO estimated that by 2005, at least 1.6 billion and 400 million people aged above 15 years were overweight and obese respectively. It further projected that by 2015, these statistics will increase to 2.3 billion for overweight and 700 million for obesity, unless drastic measures are taken to mitigate this burgeoning problem (Freedman DS et al., 1999). The fastest overweight and obesity growth rates are found in Africa – the number of overweight or obese children in 2010 was more than double that in 1990 (de Onis M et al., 2010). In Africa, despite a high prevalence of under nutrition, the prevalence of overweight is increasing at an alarming rate. It is estimated that 25% to 60% of urban women are overweight (Caleyachetty R et al., 2012). In Ethiopia, one study conducted in Addis Ababa in 2007 reported that the prevalence of overweight and obesity on elementary school students were 7.6% and 0.9% respectively (Alebachew Z et al., 2009). Attitudes toward obesity differ across populations and, with economic changes, may change within populations over time. In industrialized countries, obesity is most common among those with low socioeconomic status. The opposite is true in nonindustrialized countries, where obesity
is most often seen among individuals with high income and may be considered a status symbol. This may change as nonindustrialized countries become more affluent and obesity is seen increasingly in those with low socioeconomic status (Seidell et al, 1997). Diabetes is by far the most expensive public health consequence of obesity (Wolf et al, 1998).

In industrialized countries, severe forms of type 2 diabetes are controlled relatively well by insulin therapy. However, the industrializing countries in which a huge obesity-linked diabetes epidemic is expected will not be able to afford sufficient insulin therapy. Under such circumstances, uncontrolled glucose levels would lead to millions of patients developing nephropathy, arteriosclerosis, neuropathy, retinopathy, and related disability. The increase in disability due to obesity-induced diabetes will, therefore, be larger in industrializing than industrialized countries.

The direct costs of obesity are now estimated to be around 7% of total health care costs in the United States (Colditz et al, 1999) and around 1%–5% in Europe (Seidell et al, 1995). Narbro calculated that approximately 10% of the total costs of loss of productivity due to sick leave and work disability might be attributable to obesity-related diseases (Narbro et al, 1996). Because of the increasing prevalence and costly consequences, obesity is now being recognized not only as a risk factor in the clinical setting but also as an important threat to public health.
1. Literature review

This review provides a brief description about effect of obesity at the level of heart and blood vessels aimed at reduction or modification of dietary fat intake as an important tool in reducing obesity.

1.1 Systemic hemodynamic changes

The hemodynamic profile of obese subjects is characterized by high intravascular volume, high cardiac output, and inappropriately norm-al peripheral resistance (Frohlich et al, 1983, Messerli et al, 1981). Because heart rate remains unchanged, the increase in cardiac output in response to the elevated metabolic requirement and expended intravascular volume occurs chiefly through increased stroke volume.

In the lean subject with HTN, the hemodynamic profile is characterized by high total peripheral resistance and contracted circulating intravascular volume. Cardiac output increases in the early stage of HTN development, but tends to decrease thereafter with established HTN (Terazi et al, 1983).

The hemodynamic changes in obese-hypertensive subjects have a mixed profile resulting from the interplay of the individual components of obesity and HTN. In the obese-hypertensive patient, intravascular volume, total peripheral resistance and cardiac output are all elevated. However, due to the effect of the obesity component, total peripheral resistance is less elevated than would be expected in the lean hypertensive subject, and may be completely normal in some obese-hypertensive patients (Schmieder et al, 1993, Licata et al, 1990).

Obesity also appears to change the normal circadian variation of BP. In a recent study, we found that up to 70% of obese-hypertensive subjects failed to show an appropriate fall in both systolic and diastolic pressures during sleep (Weir et al, 1998). There also are important hemodynamic differences in response to stress between obese and nonobese hypertensive patients. When subjected to mental stress, obese hypertensives responded with a higher increase in total peripheral resistance and lower increases in heart rate, stroke volume, and cardiac output compared with non obese counterparts.
When exposed to isometric handgrip stress, obese individuals responded with an exaggerated increase in BP and heart rate (Rockstroph et al, 1992). These maladaptive hemodynamics and abnormal responses to stress also contribute to the development of HTN in obesity.

1.2. Vascular changes

Cellular metabolism of cations and other molecules may be altered in obesity and lead to changes in vascular responsiveness (Rocchini et al, 1992). Insulin has been shown to be a vasodilator that regulates peripheral vascular resistance. Insulin not only inhibits voltage-gated Ca\textsuperscript{2+} influx, but also stimulates glucose transport and phosphorylation of glucose to glucose-6-phosphate, which further activates Ca\textsuperscript{2+} ATPase transcription and increases cellular Ca\textsuperscript{2+} efflux. Both actions result in a net decrease in intracellular Ca\textsuperscript{2+} and, therefore, decrease vascular resistance. These effects are blunted in obesity due to insulin resistance, leading to increased vascular resistance (Zemel et al, 1998). With the use of magnetic resonance imaging to evaluate the aorta of normal and hypertensive subjects, Resnick et al(1997) found that increased abdominal visceral fat, decreased intracellular magnesium and advanced age were closely associated with reduced aortic distensibility vessels. Obesity is often accompanied with structural changes in peripheral resistance vessels; the nature of such changes remain to be known (Boechringer et al, 1982).

Possible mechanisms for obesity-associated micro vascular dysfunction

There may be several mechanisms involved in the development of obesity-associated micro vascular dysfunction. In the following subsections, we will discuss two main mechanisms.

Intracellular signaling

The metabolic action of insulin to stimulate glucose uptake in skeletal muscle and adipose tissue is mediated through stimulation of PI3-kinase-dependent signaling pathways. These pathways involve the insulin receptor, insulin receptor substrate 1 (IRS-1), PI3- kinase, phosphoinositide-dependent kinase 1 (PDK-1), and protein kinase B (PK-B) (Kim et al, 2006). The vasodilator actions of insulin require highly parallel PI3-kinasedependent insulin-signaling pathways. Insulin
induced stimulation of Akt directly increases endothelial NO synthase (eNOS) activity, leading to increased NO production (Kim et al, 2006) (Figure 1).

In addition to its vasodilator actions, insulin also has vasoconstrictor effects. These vasoconstrictor effects are mainly mediated by the vasoconstrictor peptide endothelin-1 (ET-1) (Kim et al, 2006). ET-1 is produced in the vascular endothelium through stimulation of the intracellular MAP-kinase signaling pathway and the extracellular signal-regulated kinase-1/2 (ERK1/2) (Eringa et al, 2004). The PI3-kinase pathways are not involved (Figure 1). Thus insulin has opposing endothelial derived vasodilating and vasoconstrictor effects, with the net effect being dependent on the balance between these two. Normally, the net result is either neutral or vasodilatory. Obesity-associated microvascular dysfunction may be caused by cellular defects that influence this balance.

First, obesity is associated with an increased production of reactive oxygen species (ROS) (De Keulenaer et al, 1998, Laigh et al, 1998, Perticone et al, 2001). ROS limits the bioavailability of NO via reduced NO production and direct inactivation of NO by superoxide (O2–) (Landmesser et al, 2006). Second, muscle and kidney eNOS expression and activity are diminished in obesity (Hickner et al,2006,Li et al,2005,Roberts et al,2005), resulting in blunted NO production. Finally, the intracellular insulin signaling transduction pathway is impaired (Wassink et al, 2007). Fatty acid elevation induces phosphorylation of IRS-1 that interferes with insulin-receptor mediated phosphorylation of IRS-1, and in turn results in impaired activation of PI3-kinase (Shulman et al, 2004). As a consequence of these cellular defects,endothelium-derived vasodilation, including insulin mediated dilation, is blunted in obesity. In contrast, the signaling pathways for insulin-mediated vasoconstriction seem to be intact or only selectively impaired in obesity. Cardillo et al (2004) demonstrated impaired MAP-kinase pathway activity in obese rats, whereas Jiang et al (1999) showed intact MAPkinase pathways in the vasculature of obese Zucker rats. However, ERK1/2 activation remains intact in obesity (Jiang et al, 1999). Therefore, insulin-induced vasoconstriction can be demonstrated. In line with this, insulin induced ET-1-dependent vasoconstriction has been shown in skeletal muscle arterioles of obese rats (Eringa et al, 2006). Thus there is an imbalance between NO and ET-1 production in obesity, where in the vasoreactivity is shifted from vasodilation toward vasoconstriction. This is further demonstrated in Cardillo’s study in which obese, hypertensive individuals showed insulin-induced
vasoconstriction and increased ET-1-dependent vasoconstrictor tone as well as decreased NO-dependent vasodilator tone (Cardillo et al, 2004, Gudbjornsdottir et al, 1996). This endothelial dysfunction may contribute importantly to obesity-associated insulin resistance and obesity associated hypertension.

Endocrine signaling

Adipokines. The fact that measures of adiposity and microvascular function are closely linked is strongly suggestive for signaling pathways between adipose tissue and the microcirculation. Adipose tissue functions not merely as a passive storage depot but as a highly active endocrine organ. Adipose tissue, and in particular visceral adipocytes, secretes a variety of bioactive substances called adipokines. In the case of obesity, there is an enhanced production of free fatty acids (FFA) (Piatti et al, 1996), angiotensinogen, leptin, resistin, and several inflammatory cytokines such as tumor necrosis factor (TNF)-a and interleukin-6 (IL-6) (Hotamisligil et al, 1995, Singhal et al, 2005, Yudkin et al, 1999), whereas the production of adiponectin, an anti-inflammatory adipokine, is reduced (Arita et al, 1999).

FFA and TNF-a elevation impair insulin sensitivity and increase blood pressure through mechanisms that are not completely understood but do involve microvascular function (Clerk et al, 2002, de Jongh et al, 2004, Youd et al, 2000). In lean rats, acute FFA elevation impairs insulin-mediated capillary recruitment and muscle glucose uptake (Clerk et al, 2002). In addition, human studies also demonstrate endothelial dysfunction in response to FFA exposure. Steinberg et al (Steinberg et al, 1997) and Watanabe et al (2005) demonstrated a reduction in endothelium-dependent vasodilation with intralipid infusion in resistance vessels. In another study, elevation of FFA levels in lean subjects resulted in impaired basal and insulin-induced skin capillary recruitment and endothelium-dependent vasodilation, which was associated with reduced glucose uptake. Conversely, obese women showed improved basal and insulin-mediated skin capillary recruitment and glucose uptake in response to lowering FFA levels (de Jongh et al, 2004). In this study, approximately 29% of the effects of FFA elevation or lowering on insulin-induced glucose uptake could be explained by changes in microvascular function, which is consistent with a role for FFA induced microvascular dysfunction in the development of obesity-associated disorders (de Jongh et al, 2004).
Figure 1. Mechanisms of insulin-mediated nitric oxide (NO) and endothelin 1 (ET-1) production leading to vasodilation and vasoconstriction, respectively (Amy et al, 2007)

cause vascular endothelial dysfunction indirectly via increased release of the vasoconstrictor substance ET-1 (Piatti et al, 1996).

Increased production of the proinflammatory cytokine TNF-a is associated with obesity-related insulin resistance and hypertension (Hotamisligil et al, 1993, Pausova et al, 2000, Togashi et al, 2000). It has been suggested that the vasculature is an important target of TNF-a (Youd et al, 2000, Zhang et al, 2003). Indeed, in a rat in vivo clamp study, acute administration of TNF has been shown to inhibit insulin-mediated increases in femoral blood flow and muscle capillary recruitment, leading to a marked decrease in insulin sensitivity. The inhibitory effect of TNF-a appeared to be wholly hemodynamic in that insulin-mediated increases in femoral blood flow and capillary recruitment were totally blocked (Youd et al, 2000). Furthermore, in a human study, weight loss resulted in significant amelioration of endothelial function that closely correlated with a reduction in circulating TNF-a (Ziccardi et al, 2002). Circulating TNF may impair insulin-mediated effects on microvascular function by impairing the balance between endothelial-derived vasodilator and vasoconstrictor substances. TNF-a downregulates the expression of eNOS (Rask-Madsen et al, 2007, Yoshizumi et al, 1993) and upregulates ET-1 expression in human endothelial cells (Mohamed et al, 1995). Furthermore, it may directly activate NAD(P)H oxidase and increase ROS production in the endothelial and vascular smooth muscle cells (De Keulenaer et al, 1998, Inoguchi et al, 2000). More importantly, adipose tissue-derived TNF-a may suppress insulin-mediated hemodynamic and metabolic effects through inhibition of IRS-1 phosphorylation (Hotamisligil et al, 1996, Williams et al, 2003). In addition to these direct effects of TNF-a, it may also induce microvascular dysfunction indirectly through stimulation of lipolysis, thereby leading to an increased release of FFAs (Figure 1).

Leptin is another adipocyte-derived hormone that rises with increasing percentage of body fat (Singhal et al, 2005, Williams et al, 2002), which is likely to be the result of resistance to its appetite-suppressing effects in obesity. Leptin plays an important role in vascular physiology, as leptin signaling in skeletal muscle activates various kinases including PI3-kinase (Dyck et al, 2006). Therefore, decreased leptin signaling leads to impaired insulin-induced microvascular function and, as a consequence, decreased insulin-mediated glucose uptake. Furthermore, increased levels of leptin have been shown to increase ROS production in endothelial cells (Singhal et al, 1999).
Adiponectin is unique amongst the adipokines in that increasing fatness is associated with a lower concentration (Arita et al, 1999). Adiponectin affects glucose uptake and vascular endothelium via increased phosphorylation of IRS-1 and other molecules in the insulin-signaling cascade (Chandran et al, 2003).

In conclusion, several adipose tissue-derived factors, in particular FFA and TNF-a influence insulin signaling and, thereby, insulin-mediated vasodilation. These endocrine factors therefore provide a potential link between obesity-associated microcirculatory dysfunction and obesity-related hypertension and insulin resistance. Besides these endocrine factors linking obesity to impaired insulin-induced vasodilation, recently a Vasoregulatory role for local deposits of fat has been postulated (Yudkin et al, 2005). Obese Zucker rats are characterized by a well circumscribed depot of fat cells around the origin of the nutritive arteriole supplying the cremaster muscle, whereas lean rats are not. Adipokines released by these fat cells may inhibit directly vasodilatory pathways distal in the arteriole and thereby cause loss of blood flow in the nutritive capillary network supplied by this arteriole. In this hypothesis, adipokines released from fat depots have local rather than a systemic vasoregulatory effect, a mechanism that is termed “vasocrine”signaling.
1.3. Cardiac changes

In nonobese hypertensive patients, cardiac adaptation is “concentric” hypertrophy due to the elevated peripheral resistance, increased ventricular afterload, and wall stress. Contractile elements are added in parallel, resulting in the thickening of chamber walls, partially at the expense of chamber volume. Cardiac dilation is not observed until the later stages when cardiac decompensation eventually occurs due to uncontrolled progressive disease (Frohlich et al, 1992). As opposed to the “concentric” cardiac hypertrophy seen in essential HTN, the characteristic finding in obese individuals is “eccentric” cardiac hypertrophy (Simon et al, 1994) due to increased intravascular and left ventricular volume or filling pressure. This eccentric hypertrophy can be demonstrated by echocardiographic studies. An earlier autopsy study of obese subjects showed increased heart weight–associated thickening and hypertrophied ventricles (Amad et al, 1965). Not surprisingly, congestive heart failure has been documented as a common
complication of morbid obesity, regardless of the presence of HTN (Messerli et al, 1986, Drenick et al, 1980).

The coexistence of both obesity and HTN in the same patient results in a mixed “eccentric–concentric” hypertrophy (Messerli et al, 1983). Obesity-HTN produces an extensive rise in left ventricular stroke work, as the result of increased afterload associated with HTN and increased preload associated with obesity. The combined hemodynamic burden increases the risk for congestive heart failure. Autopsy data from the Mayo Clinic revealed that the average heart weight was 467 g in obese hypertensive subjects, compared with 367 g in obese individuals without heart disease and only 272 g in nonobese hypertensive subjects (Smith et al, 1933). These hypertrophic changes in obesity may provide the basis for the development of cardiac arrhythmias (Lip et al, 1994).

A recent study of obese individuals showed the presence of mononuclear cell infiltration in and around the sinoatrial node, with marked fat throughout the conduction system (Bharati et al, 1995). Lipomatous hypertrophy of the interatrial septum has also been noted in obesity (Basa et al, 1994) Such changes may contribute to the high rate of sudden cardiac death in morbidly obese patients (Duflou et al, 1995).

In summary, obesity can cause marked changes in systemic hemodynamics as well as structural adaptations in blood vessels and in the heart. Coexistence of obesity and HTN exerts a double burden on the heart, resulting in distinct cardiac pathologic changes, which increase the risk for congestive heart failure and sudden cardiac death. Fig. 3 summarizes the effects and consequences of obesity-HTN on the cardiovascular system.
1.4. Pathophysiology of obesity

Obesity increases total blood volume, cardiac output and cardiac workload. Typically, obese patients have a higher cardiac output caused by stroke volume but, a lower level of total peripheral resistance at any given level of arterial pressure (Alpert et al, 2001), although, heart rate is typically mildly increased because of increased sympathetic activation (Messerli et al, 1987). This is associated with increase in filling pressure and volume, thus increasing CV work developing left ventricular (LV) chamber dilation.
Alpert et al, 2001, Messerli et al, 1987). Obese patients are more likely to be hypertensive than lean patients, and weight gain is typically associated with increase in arterial pressure (Messerli et al, 1987). Independent of arterial pressure and age, obesity increases the risk of left ventricular hypertrophy (LVH) as well as other structural abnormalities, including concentric remodeling (CR) and concentric LVH (Lavie et al, 2007). In addition to LV structural abnormalities, obesity also leads to left atrial (LA) enlargement, both from increased circulating blood volume as well as abnormal LV diastolic filling (Alpert et al, 2001). These abnormalities not only increase the risk of HF but LA enlargement may increase the risk of AF thereby morbidity (Wang et al, 2004). In addition, obesity has adverse effects on diastolic and systolic function (Alpert et al, 1997 & 2001).
Figure 4. Pathophysiology of obesity and cardiomyopathy (Alpert et al, 2001)
1.5. Clinical consequence of Obesity

1.5.1. Obesity and Hypertension (HTN)

Obesity increases the risk of developing hypertension (HTN), which is a strong risk factor for atherosclerotic cardiovascular disease, left ventricular hypertrophy (LVH), heart failure, chronic renal failure and cerebrovascular accident (CVA). A 10-kg weight gain is associated with an increase of 3.0 mm Hg in systolic and 2.3 mm Hg diastolic blood pressure, which translates to a 12% increased risk for ASCVD and a 24% increased risk for CVA (National Institutes of Health, 1998).

The development of obesity-induced hypertension is multifactorial and includes an increase in peripheral vascular resistance via endothelial dysfunction, activation of the sympathetic nervous system, direct and indirect renal effects, sleep apnea, and other vasoactive effects of peptides released from adipocytes (Poirier et al, 2006, Grundy et al, 2004).

1.5.1.1. Mechanisms of obesity-induced Hypertension

The mechanisms through which obesity directly causes hypertension are still an area of research. Activation of the sympathetic nervous system has been considered to have an important function in the pathogenesis of obesity-related hypertension. The arterial-pressure control mechanism of diuresis and natriuresis, according to the principle of infinite feedback gain, seems to be shifted toward higher blood-pressure levels in obese individuals. During the early phases of obesity, primary sodium retention exists as a result of increase in renal tubular reabsorption. Extracellular-fluid volume is expanded and the kidney-fluid apparatus is resetted to a hypertensive level, consistent with a model of hypertension because of volume overload. Plasma renin activity, angiotensinogen, angiotensin II and aldosterone values display significant increase during obesity. Insulin resistance and inflammation may promote an altered profile of vascular function and consequently hypertension. Leptin and other neuropeptides are possible links between obesity and the development of hypertension (Vasilios et al, 2010).
1.5.1.1. Sympathetic activation in Obesity

Activation of the sympathetic nervous system (SNS), measured with direct or indirect methods, has been considered to have a crucial function in the pathogenesis of hypertension among obese individuals.

Microneurographic techniques, a direct method of measuring increased SNS activity, provide evidence of high muscle SNS activity in obese subjects (Grassi et al, 1995). High-caloric intake increases norepinephrine turnover in peripheral tissues, raises resting plasma norepinephrine concentrations, an indirect measurement of SNS activity and amplifies the rise of plasma norepinephrine in response to stimuli such as upright posture (Landsberg et al, 1989). High dietary content in fat and carbohydrate has been suggested to acutely stimulate peripheral α1- and β-adrenergic receptors, leading to elevated sympathetic activity and hypertension (Rocchini et al, 2004).

The mechanisms that have been proposed to be responsible for an increased sympathetic activity in obesity include impaired function of the baroreceptor sensitivity, increased levels of circulating free-fatty acids (FFAs), angiotensin (Ang) II, insulin and leptin. The arterial baroreceptors acutely respond to increases in BP by parasympathetic activation and sympathetic inhibition. A reduced sensitivity of the arterial baroreflex manifested as a diminished response in heart rate to BP changes may occur in long-standing hypertension and obesity, presumably because of various mechanisms, including a concomitant increase in central sympathetic outflow and the effects of arteriosclerotic lesions leading to an increased stiffness of the large arteries in which the receptors are located. We have earlier reported an increased carotid arteries intima media thickness in obese subjects independently of the BP levels, even in a normotensive BP range, suggesting an early course of the atherosclerotic process in obesity (Kotsis et al, 2006). Impaired baroreflex sensitivity leads to withdrawal of parasympathetic cardiac modulation, which occurs in obesity even in the absence of an elevation in arterial pressure.

Elevated levels of FFAs have been reported in obese hypertensive subjects. Abnormal distribution of FFAs in obese patients has been found to enhance vascular α-adrenergic sensitivity and consequently to increase α-adrenergic tone (Stepniakowski et al, 1995).
The exact mechanisms through which endogenous FFAs exert this effect have not been thoroughly investigated. Lysophospholipids and FFAs inhibit Na+, K+-ATPase and the sodium pump raising vascular smooth muscle tone and resistance (Oishi et al, 1990). Binding of lysophospholipids and FFAs to Na/K-ATPase changes the interaction of the enzyme with neighboring membrane proteins and induces the formation of multiple signaling modules. As a result, the epidermal growth factor receptor is activated and production of reactive oxygen species is increased. Another target system of the FFAs is the calcium-independent isoenzyme of protein kinase C, which is a vital element in mediating signal transduction and cell regulation. FFAs act as potent activators of phosphorylation of protein kinase C (Khan et al, 1993). Other studies have reported a direct action of FFAs released from phospholipids on ion channels at the cellular membranes of smooth muscle cells and other tissues (Ordway et al, 1991). (Hall et al, 1993) have reported that plasma renin activity displays a significant increase during obesity, despite extracellular-fluid volume expansion and sodium retention in dogs fed with a high-fat diet. Moreover, studies in patients under sodium restriction, which activates the rennin–Ang system (RAS), provided evidence for a presynaptic potentiating effect of Ang II on sympathetic neurotransmission (Taddei et al, 1995).

### 1.5.1.1.2 Renal mechanisms

**Impairment of pressure natriuresis**

The arterial pressure control mechanism of diuresis and natriuresis according to the principle of infinite feedback gain seems to be shifted toward higher BP values in obese patients (Guyton et al, 1990). Abnormalities in these mechanisms that would tend to raise BP increase sodium and water excretion through pressure natriuresis and diuresis. As long as excretion exceeds intake, extracellular-fluid volume decreases reducing venous return and cardiac output until BP returns to normal. Conversely, when BP decreases, the kidney retains salt and water until arterial pressure returns to normal. Thus, pressure natriuresis acts as the key component of the feedback system that normally stabilizes BP and body-fluid volumes. During the early phases of obesity, before loss of nephron function because of glomerular injury, primary sodium retention occurs as a result of increase in renal tubular reabsorption. This may be compensated by renal vasodilation, increased glomerular filtration rate and increased filtered amount of water and electrolytes. As a
consequence of an incomplete compensation, however, extracellular-fluid volume is expanded, resulting in a hypertensive adjustment of the pressure natriuresis. This resetting of the kidney-fluid apparatus to a hypertensive level is consistent with the model of hypertension because of volume overload. Another significant cause of shift of pressure natriuresis toward higher BP levels in obesity is the possibility of alterations in intrarenal forces caused by histological changes in the renal medulla that may compress the loops of Henle and vasa recta (Hall et al, 1997).

**Function of RAS in obesity hypertension**

Several studies have shown predominantly high levels of plasma rennin activity, plasma angiotensinogen, Ang II and aldosterone values in association with human obesity (Ruano et al, 2005). Hall et al (1997) reported a more than twofold increase in plasma rennin activity after a 5-week period of high fat diet administration in conscious dogs. Moreover, fat restriction succeeded in diminishing the values of the RAS components, indicating the possibility that the degree of adiposity might have a direct influence in this BP-regulating system. Under normal conditions, the RAS represents a regulatory mechanism, which prevents extreme variations in arterial pressure evoked by changes in salt intake. Cessation of Ang II formation during high-salt intake results in a decreased rate of BP elevation, as indicated by the leftward shift in the renal function curve closer to the initial BP level.

Despite remarkable volume expansion and sodium retention in obesity, several mechanisms are responsible for the RAS activation. Renin secretion by the kidney seems to be induced by changes in intrarenal physical forces, generating from fat accumulation around and into the renal medulla. Owing to the actual histologic changes that cause compression of the medulla, flow rate of the filtrate is diminished at the loop of Henle leading to prolongation of the time given for sodium reabsorption (Rocchini et al, 2002). Detection of the decreased amount of sodium, reaching the distal tubular cells, by the macula densa leads to a rise in renin secretion, through tubuloglomerular feedback. Recent studies elucidated the potent function of the adipose tissue’s physiology in BP elevation. Adipose tissue-derived angiotensinogen can enter the circulation. Adipose cells may represent a major site in which all components of the RAS are formed. Renin, Ang II, angiotensinogen and Ang II receptors are found in abundance in adipose mass suggesting that a local tissue Ang system is settled at the adipocytes level (Campbell et al, 1987).
The tissue RAS and the circulating RAS are in a state of constant interaction. Angiotensinogen and Ang I and II are locally produced and at the same time are taken up by the cells, in which Ang II receptors are overexpressed. Angiotensinogen production serves as both a cause and effect of adipocyte hypertrophy and leads to elevation of BP through the actions of Ang II, which induce systematic vasoconstriction, direct sodium and water retention and increased aldosterone production. Consequently, Ang II determines a high-salt-sensitive BP condition in obesity as it is produced at high rates and is not suppressed by volume expansion. Another potential mechanism of RAS activation could be a chronic elevation of sympathetic tone, causing renal vasoconstriction and renin-dependent chronic hypertension.

**Structural changes in the kidney**

Among the multiple causes of renal function impairment, relatively recent data have revealed the implication of a large number of factors provoking changes in renal structure, which, in turn, seem to be a predominant cause of gradual nephron loss, having a great impact on the alteration in pressure natriuresis (Hall et al, 1997). Physical compression of both kidneys seems to generate from accumulation of adipose tissue around the organs emphasizing the crucial function of visceral obesity in the development of renal disease (Hall et al, 2002).

Deposition of extracellular matrix throughout the renal medulla is greatly expanded and the tissue surrounding the ducts of Bellini at the vascular pole tends to prolapse. Increased numbers of interstitial cells and an increase in material rich in lipids and proteoglycans compresses the renal parenchyma toward the pole of the kidney resulting in the formation of round-shaped, enlarged kidneys in obese subjects (Dwyer et al, 2000, Kambham et al, 2001).

Renal compression affects both vascular (mainly the vasa recta) and tubular (the Henle’s loops) elements causing activation of the RAS and increased sodium reabsorption. Renal injury in obesity seems to be directly dependent on body weight, as dietary fat restriction can ameliorate the renal histology (Deji et al, 2009).

The primary histologic features are relatively few lesions of focalsegmental glomerulosclerosis, profound glomerulomegaly because of glomerular hyalinosis and fibrosis, as well as lipid accumulation in the glomeruli and adhesion to Bowman’s capsule (Chalmers et al, 2006, Hall et al, 2006).
Some studies suggest that lipid accumulation is a result of alterations in fat metabolism. Whether upregulation of lipogenic enzymes and decreased amounts of lipolytic factors could imply direct lipotoxicity remains an area of active investigation (Kume et al, 2007).

Glomerulomegaly was observed in 100% of renal biopsies in a clinicopathologic study of obesity glomerulopathy. Despite the observed high incidence of glomerulomegaly, glomerular changes in obesity-induced renal injury are incomparable with those of diabetic nephropathy, mainly because of the lower severity of changes in the mesangial space. Other causes of renal injury, apart from high-fat intake, could possibly include overexpression of Ang II with a consequent increase in proliferative factors such as transforming growth factor-b and plasminogen activator inhibitor, high protein diet, as well as hyperinsulinemia giving genesis to insulin growth factors. All of the above may lead to changes in the glomeruli. There is also evidence that SNS response to hypoxia may affect the renal circulation in patients with obstructive sleep apnea, an abnormality often seen in the obese population (Grassi et al, 1995). Hyperfiltration as a result of heightened blood flow to the kidney is always present in obesity, long before glomerulopathy occurs. It is, therefore, the primary cause of gradual sclerosis of the glomeruli wall because of physical stress and eventually of a vicious circle in which nephrons are injured, sodium retention worsens and arterial pressure reaches higher values to maintain sodium balance.

1.5.1.1.3. Function of hormones

Insulin

Obesity is a state of impaired glucose tolerance, high levels of circulating insulin and reduced sensitivity to the metabolic actions of insulin. This condition is defined as insulin resistance. Whether hyperinsulinemia or insulin resistance is the primary disorder has not yet been clearly delineated. It has been proposed that hyperinsulinemia could compensate for decreased sensitivity to insulin. Normally, insulin exhibits a sodium retaining effect through its direct action on the renal tubules. A potential enhancement of sodium retention because of hyperinsulinemia could lead to a rise in BP. (Sechi et al, 1999) have shown that high dietary salt in normal Sprague–Dawley rats causes a dose-dependent downregulation in the number of insulin receptors in the kidney. However, in genetically predisposed hypertensive rats, this autoregulative response was blunted. The same effect was also present in fructose-fed
hypertensive rats, suggesting a possible function for hyperinsulinemia in the pathogenesis of sodium retention and hypertension in the obese.

Insulin has also been proved to have an acute sympathoexcitatory action in both normotensive and borderline hypertensive subjects, as indicated by increased muscle SNS activity and heightened norepinephrine levels after insulin administration in several studies (Anderson et al, 1992, Gudbjör et al, 1996). Insulin release leads to hypoglycemia, which serves as an activator of the SNS. Moreover, vasodilator responses to increased muscular glucose uptake and oxygen demands lead to activation of the baroreceptor reflex and to enhanced muscle SNS activity. Insulin might also have a sympathoexcitatory effect directly on the central nervous system (Landsberg et al, 1986). However, in a study by (Sakaguchi et al, 1987) insulin injection into the ventromedial hypothalamus produced centrally controlled decreases in sympathetic nerve activity. Another aspect of insulin infusion is the simultaneous depressor effect of peripheral vasodilation (Hall et al, 1993, Creager et al, 1985) mediated by a b-adrenergic mechanism. Moreover, tachycardia induced by insulin release suggests a withdrawal of parasympathetic tone. Chronic hyperinsulinemia has been associated with impairment of the vasodilator action of insulin (Hall et al, 1995). Vasoconstriction in the forearm was reported during insulin infusion in severe insulin resistance. This finding suggests that hyperinsulinemia promotes an altered profile of vascular function. Vascular dysfunction seems to be the important factor in understanding the long-term implication of insulin in the causation of hypertension. Whether hypertension is caused by excessive amounts of insulin, resistance to its action or chronically induced trophic vascular effects remains to be uncovered. Finally, insulin resistance has also been exhibited as an effect of heightened sympathetic drive, through b-adrenergic stimulation and/or vasoconstriction with subsequent reduction of muscular blood flow (Julius et al, 1994, Masuo et al, 2000).

**Leptin and neuropeptides**

Hyperleptinemia is another possible link between obesity and the development of hypertension. Leptin is a peptide hormone secreted from adipose tissue in direct proportion to adipose tissue mass (DeCourten et al, 1997). The amount of leptin secreted from the adipocytes into circulation binds to its short-form receptors and is transported across the blood brain barrier to the arcuate nucleus, a hypothalamic region of high significance for the transmission of appetite controlling neuropeptides to peripheral tissues. Leptin’s primary effects on the hypothalamic neuronal
systems include a decrease in food consumption and upregulation of thermogenesis and energy expenditure, through stimulation of sympathetic activity (Wynne et al, 2005). These effects are mediated by two major pathways, one posting a positive-regulating action through expression of the propiomelanocortin-derived peptides a melanocyte-stimulating hormone (a-MSH) driven by high leptin levels, and the other exhibiting the opposite actions through the expression of agouti-related peptide and neuropeptide Y (NPY). a-MSH molecules bind to melanocortin 3 and 4 receptors (MC3R and MC4R), act as agonists, stimulate the SNS, increase energy expenditure and activate the hypothalamus–pituitary–adrenal axis. Studies in mice and human beings with leptin deficiency because of mutations of the leptin expressing gene (ob gene) show high incidence of obesity. The increase in SNS activity develops slowly (hours after infusion of leptin), and in the long term, it may induce sympathetic-mediated hypertension development through raised tubular sodium reabsorption and volume overloading. The cardiovascular actions of leptin are utterly prevented during combined a- and b-adrenergic blockade. In addition, the chronic pressor effects of leptin are supposed to be simultaneously controlled by endothelial nitric oxide (NO) production (Engeli et al, 2002, Kuo et al, 2001). Deprivation of the endothelium-derived NO markedly promotes BP elevation.

On the other hand, agouti-related peptide is an antagonistic ligand of the MC3/MC4 receptor system. Agouti-related peptide is expressed during fasting and leads to increased food consumption. Although obese individuals have high levels of circulating leptin, the expected metabolic actions of leptin leading to reduction in food intake and increased energy expenditure are absent. Selective resistance to the metabolic actions of leptin seems to be present in obesity (Correia et al, 2002), whereas its action in stimulating the sympathetic tone remains unaltered. An impairment of leptin’s transport to the hypothalamus could be a possible reason. Moreover, overexpression of the suppressor of cytokine signaling 3 by high-circulating leptin, which serves as a feedback mechanism, has been suggested to have a function in the pathogenesis of leptin resistance(Denis et al,2004).

The close relationship of hyperleptinemia with hypertension is further supported by observations obtained in obese leptin-deficiency mice, which are obese, but do not exhibit hypertension. Obesity does not invariably increase BP in mice and probably also in human beings and the
arterial pressure response to obesity may depend critically on the underlying genetic and neuroendocrine mechanisms (Mark et al, 1999).

Mutations might reduce the functional activity of leptin. MC4R deficiency abolished the cardiovascular and metabolic actions of leptin in obese MC4R mice and possibly in human beings. BP levels have been reported significantly lower in MC4R-deficient subjects than in control subjects (Greenfield et al, 2009). Thus, a functional MC4R is essential for the chronic cardiovascular and metabolic actions of leptin (Tallam et al, 2006). MSHs have important function in feeding, energy metabolism and inflammation. Both α- and γ-MSH acutely elevate BP and heart rate through central stimulation of sympathetic nervous outflow (Humphreys et al, 2007).

This action of α-MSH is mediated by the MC4R, whereas γ-MSH deficiency or disruption of MC3R in rodents leads to salt-sensitive hypertension possibly through a central mechanism. This salt-sensitive hypertension is accompanied by the development of insulin resistance. SNS-stimulating actions of leptin are mainly shown in the kidneys, adrenal glands and brown adipose tissue. SNS stimulation is not the only mediator through which hyperleptinemia leads to cardiovascular reactions. Endothelial dysfunction has also been reported as another important aspect of leptin’s effects (Knudson et al, 2008, Korda et al, 2008). Leptin is believed to promote direct endothelium toxicity by causing an alteration in the expression of endothelial NO synthase. Finally, it should be considered that perivascular adipose tissue is an additional source of leptin. NPY is a neurotransmitter also being expressed in the hypothalamic arcuate nucleus at high rates during fasting, having an orexigenic effect combined with reduction in thermogenesis and downregulation of the sympathetic neurons. All the above actions are mediated by the binding of the NPY to receptors Y1–Y6 in the hypothalamus. Normally, NPYexpression is suppressed by high leptin levels. In the leptin resistant state in which leptin’s metabolic effects are blunted, NPY should rather be considered over expressed. NPY released from neural sites by sympathetic activation acts as a vasoconstrictor and could have a function in obesity-related hypertension (Lundberg et al, 1987).

Leptin action, when associated with the leptin receptor in the vascular endothelium, enhances endothelin-1 production, elicits oxidative stress, and promotes angiogenesis (Singer et al, 2007, Knight et al 2007). Leptin has also been shown to enhance platelet aggregation, which may lead
Leptin levels are directly proportional to adiposity and leptin is capable of exerting a vasodilatory effect on coronary and resistance arteries through endothelium-dependant phosphorylation of eNOS at Ser1177 or directly through uncharacterized endothelium independent mechanisms (Nakagawa et al, 2002, Matsuda et al, 2003). Interestingly, leptin levels are elevated in human obesity leading some scientists to postulate the existence of leptin resistance, with C reactive protein (CRP) identified as a possible source of disruption of intracellular leptin signaling (Eringa et al, 2007). IL-6 is the primary regulator of CRP, with elevations in IL-6 leading to CRP mediated inhibition of eNOS, angiotensin-stimulated production of reactive oxygen species, increases in vascular permeability, elevated expression of adhesion molecules and thrombus formation (Singer et al, 2007, Knight et al, 2007). IL-6 levels are directly proportional to adiposity and elevations result in direct impairments of endothelial function (Singer et al, 2007).

Figure 5. Overview of Leptin Resistance and Hyperleptinemia in Obesity-related Cardiovascular Disease (Lavie et al, 2008)
**Corticosteroids**

The hypothesis that the hypothalamic–pituitary–adrenal axis could possibly take part in the pathophysiology of obesity-related hypertension is supported by similarities in phenotype between Cushing’s syndrome and visceral obesity-associated disease. Glucocorticoids increase food intake, reduce energy expenditure and they promote insulin resistance, fat accumulation (Kellendonk et al, 2002) and hypertension (Saruta et al, 1996, Whitworth et al, 2001).

Many rodent models of obesity, which are characterized by hypercorticosteronemia with weight gain, displayed body weight normalization after adrenalectomy and reinstated by glucocorticoid replacement. Although plasma glucocorticoid levels are normal in human idiopathic obesity (Flier et al, 2004), it has been proposed that intra-adipose glucocorticoid action is increased. Obese individuals have selectively increased adipose levels of 11b-hydroxysteroid dehydrogenase1 (Michailidou et al, 2007, Lindsay, 2003), an enzyme that regenerates active cortisol from inactive 11-keto forms. The aP2- HSD1 mice, with relative transgenic overexpression of this enzyme in fat cells, develop visceral obesity with insulin resistance, dyslipidemia and hypertension. These mice have increased sensitivity to dietary salt and increased plasma levels of angiotensinogen, Ang II and aldosterone. Hypertension in aP2-HSD1 mice was abolished by selective Ang II receptor antagonists at a low dose (Masuzaki et al, 2003). These findings propose that a local activation of the adipose glucocorticoid action induce an activation of the RAS, which mediates a salt-sensitive form of hypertension in obesity.

**1.5.1.1.4. Endothelial dysfunction and changes in vascular structure**

There is increasing evidence supporting the significance of vascular endothelial dysfunction in the pathogenesis of hypertension. Obesity represents a state of inflammation (vascular and systemic) that can cause endothelial dysfunction. Insulin resistance, low levels of adiponectin, high plasma leptin, increased levels of plasma glucose and FFAs are considered as indices of an inflammation compatible profile.

A series of insulin signaling pathways are instructed to function in favor of inflammation and uncontrolled endothelial growth causing endothelial dysfunction and finally hypertension. NO, which derives from the vascular endothelium, promotes vasodilation, whereas at the same time
protects from inflammation and platelet aggregation. Insulin-dependent phosphoinositide 3-kinase activation normally leads to phosphorylation of endothelial NO synthase and a subsequent increase in NO production. In the presence of insulin resistance, this pathway is downregulated leading to impairment of NO synthesis, whereas hyperinsulinemia increases vasoconstrictor endothelin-1 levels (Kim et al, 2006, Montagnani et al,2000), as the mitogen-activated protein-kinase pathway mediating endothelin-1 production remains unaltered. As a result, an imbalance between vasodilator and vasoconstrictor actions in the vascular endothelium is provoked. Another mitogen-activated protein -kinase controlled pathway is the production of adhesion molecules, vascular cell adhesion molecule-1, intercellular adhesion molecule-1 and E-selectin by the endothelial cells, promoting monocyte adhesion to the vascular wall. Similar mechanisms are brought into operation because of elevated serum levels of glucose and FFAs.

A variety of biologically active derivatives generate from adipose cells, including reactive oxygen species, proinflammatory and inflammatory molecules (interleukin-1b, interleukin-6, tumor necrosis factor- a, C-reactive protein), angiogenetic factors (vascular endothelial growth factor) (Ledoux et al, 2008),hemostasis modulating compounds (plasminogen activator inhibitor-1, thromboxane A2) and acute phase reaction proteins (serum amyloid A proteins, C-reactive protein). Activation of nuclear factor k light-chain enhancer of activated B cells (NF-kB) and IkB kinase (Kim et al, 2008) because of fat accumulation is of great significance for the establishment of a proinflammatory and prothrombotic state, indicating the presence of altered vascular function that predisposes to the development of hypertension.

Earlier studies had also reported that the mean intima media thickness of the internal carotid arteries was increased from the lowest to the highest quartile of BMI. Intima media thickness was found significantly higher in obese compared with normal weight subjects in groups of patients matched for age, sex and ambulatory BP levels (Kotsis et al, 1995). These results suggest that obesity per se may be a major risk factor for carotid atherosclerosis. Intima media thickness in obese subjects was independently associated with fasting serum glucose levels, suggesting that obesity-induced hyperglycemia is an important predictor of carotid atherosclerosis. As atherosclerosis progresses, large arteries become stiffer. Increased pulse wave velocity and arterial stiffness may contribute to obesity hypertension. Long-term sympathetic and RAS activation leads to small artery vasoconstriction and remodeling, which increases wall to
lumen ratio and may act synergistically with large artery damage to raise BP. In obese patients, aortic pulse wave velocity rises not only because of aortic stiffening, but also possibly because of remodeling of the small and medium sizes arteries. As a result of these changes, the amount of the reflected pressure waves in the periphery arrives back earlier at the central arteries augmenting systolic BP.

**Atherogenic dyslipidemia**

This condition is characterized by an increase in elevated triglycerides (and increased VLDL particle number), increased small LDL particles, and low HDL cholesterol (NCEP, 2002). It is commonly present in obese persons. The increased number of VLDL and LDL particles accounts for the increased level of total apo B usually observed with atherogenic dyslipidemia. The atherogenic potential of each lipoprotein abnormality has long been a topic of great interest but one that is not fully resolved.

For many years triglyceride-rich lipoproteins (TGRLPs) were thought not to be atherogenic. Nonetheless, there is growing evidence that smaller TGRLP (remnant lipoproteins) are in fact atherogenic (Krauss et al, 1998).

This evidence comes from studies in laboratory animals, patients with genetic disorders causing remnant accumulation, meta analysis of epidemiological studies, and clinical trials (Grundy et al, 2004). TGRLPs as a class are a mixture of lipoproteins, and it has been difficult to differentiate between atherogenic and nonatherogenic forms of TGRLPs. Nonetheless, there is a growing consensus among investigators that TGRLP fraction definitely contains atherogenic lipoproteins. The LDL particles associated with the metabolic syndrome theory widely held is that smaller LDL particles are more atherogenic than larger LDLs (Krauss et al, 1995). Smaller LDLs may filter more readily into the arterial wall. They further may be more prone to atherogenic modification. Even so, not all investigations are convinced that small LDL particles are unusually atherogenic, compared with other apo B-containing lipoproteins. Nonetheless, when small LDLs are present, the total number of lipoprotein particles in the LDL fraction usually is increased (Blake et al, 2002). Most researchers will agree that the higher the number of LDL particles present, the higher will be the atherogenic potential. In other words, small LDL particles are often a surrogate for an increased LDL particle number (Blake et al, 2002). A simple strategy for assessing the sum of atherogenic particles is measurement of either LDL,
VLDL cholesterol (non-HDL cholesterol) or total apo B (NCEP, 2002). In persons with metabolic syndrome and atherogenic dyslipidemia, LDL, VLDL cholesterol and total apo B typically are elevated. These measurements should be used increasingly both in risk assessment and as targets of therapy in persons with the metabolic syndrome (Grundy et al, 2002). A low HDL level is another characteristic of atherogenic dyslipidemia. As a risk predictor, a low HDL rivals an elevated total apo B (or VLDL-LDL cholesterol). This fact has led to the concept that HDL is intimately involved in the atherogenic process. The theories abound as to the mechanisms whereby HDL is antiatherogenic, e.g. enhanced reverse cholesterol transport, antiinflammatory properties, ability to protect against LDL modification, among others. Although HDL in fact may be directly antiatherogenic, it also is a marker for the presence of other lipid and nonlipid risk factors. Obesity itself reduces HDL levels (National Institutes of Health, 1998), and obese patients with metabolic syndrome and atherogenic dyslipidemia almost always have low HDL levels. Thus, the association between low HDL and ASCVD risk is complex (NCEP, 2002), and the various components of this association are difficult to differentiate. Regardless of mechanism, however, the presence of a low HDL level carries strong predictive power for development of ASCVD.

**Proinflammatory state**

Obesity is associated with an increase in both oxidative stress and the proinflammatory effects of certain cytokines. Interleukin-6 is produced in adipocytes, and increasing adipocyte mass causes an elevated production of IL-6 (Papanicolaou et al, 2000). These higher levels of IL-6 subsequently stimulate production of CRP in the liver and both play a role in endothelial dysfunction by decreasing nitric oxide (NO), leading to vasoconstriction and increasing vascular resistance (Papanicolaou et al, 2000, Poirier et al, 2006).

The finding that elevations of serum CRP carry predictive power for the development of major cardiovascular events led to the concept that advanced and unstable atherosclerotic plaques are in an even higher state of inflammation than stable plaques (Ridker et al, 2003). It is of interest that obese persons (Visser et al, 1999) and particularly those with the metabolic syndrome (Ridker et al, 2003) also have elevated levels of CRP. This finding has suggested that obesity is a
proinflammatory state and is somehow connected with the development of unstable atherosclerotic plaques.

Attempting to understand the relationship between obesity and inflammation can be a daunting task in that inflammation is simultaneously its own independent risk factor while also being an integral component in the pathways by which other obesity related risk factors manifest themselves as disease. Adipokines, cytokines secreted by adipose tissue, released in excess in an obese state can create an environment susceptible to inflammation. In obese animal models, many adipokines are amplified above a normal level, but are lower than a traditionally described inflammatory state, leading many investigators to describe a chronic state of low-grade obesity-associated inflammation (Eringa et al, 2007). These white adipose derived signaling molecules can be classified as non-esterified fatty acids (NEFA), cytokines, chemokines, or hormones and can influence insulin dependent and independent signaling, insulin mediated glucose uptake and numerous aspects of vascular function( Singer et al,2007). The inflammatory markers include: TNFα, endothelin, angiotensinogen, adiponectin, MCP-1, IL-1β, IL-8, Leptin, IL-6, and resistin.

Levels of TNFα correlate strongly with adiposity and are associated with impaired capillary recruitment in man, diminished vasodilatory effect in muscle resistance arteries of rats, diminished insulin-mediated glucose uptake in rat skeletal muscle, elevated adhesion of polymorphonuclear leukocytes (PMNs) to microvessels, induction of oxidative stress, upregulation of endothelial cell adhesion molecules, and reduced barrier function (Singer et al,2007). TNFα is produced by neutrophils, macrophages and adipocytes with its production apparently elevated in perivascular adipose tissue leading researchers to believe that the measurements of circulating TNFα may give deceptively low concentrations relative to true site-of-action concentrations (Eringa et al, 2007). TNFα, which works primarily by modifying the effects of insulin, is one of a group of signaling molecules capable of acting directly on the vascular endothelium and the net effect of its apoptotic and pro-inflammatory properties is endothelial dysfunction and decreased insulin sensitivity by the vascular endothelium.

Adipocytes store excessive nutrient load and progressively become hypertrophic. Cell hypertrophy leads to a proinflammatory response mainly through hypoxia and endoplasmic
reticulum (ER) stress-related mechanisms. Eventually, this may lead to adipocyte death. Furthermore, stressed adipocytes produce a wide range of cytokines and chemokines, including TNF-α, that in turn promote immune cell accumulation and activation in adipose tissue. Therein, numerous macrophages create a local proinflammatory loop with adipocytes. Other immune cells, such as T cells, might also contribute to inflammation. In parallel, circulating FFAs and mLDL particles may directly bind to TLR2 and TLR4, inducing NF-κB activation and production of various proinflammatory factors including pro-IL-1β. In the meantime, hyperglycemia promotes the activation of the NLRP3 inflammasome through the binding of TXNIP in macrophages. Lipid species such as ceramides may directly activate the inflammasome. The NLRP3-caspase-1 complex promotes IL-1β secretion through cleavage of the proform. IL-1β strongly contributes to adipose tissue inflammation through autoamplification and paracrine activation during obesity (Marc et al, 2013).

Figure 6. Activation of the immune System in adipose tissue during obesity (Marc et al, 2013)
Circulating LDL undergo oxidation in the subendothelial space, from minimally modified LDL (mmLDL) to extensively oxidized LDL (oxLDL). Uptake of oxLDL through scavenger receptors leads to the intracellular storage of cholesterol crystals that can activate the NLRP3 inflammasome through the transcription factor Nrf2, leading to IL-1β secretion. FFAs and mLDL particles can also bind directly to TLRs, leading to the expression of numerous proinflammatory genes such as cytokines and chemokines. These factors, including IL-1β, activate endothelial cells of the vasculature, triggering the production of chemokines and adhesion molecules and, subsequently, other immune cell migration which in turn leads to vascular inflammation that promotes atherosclerosis (Marc et al, 2013).

Figure 7. Activation of Immune Responses in the Atheroma( Marc et al, 2013)
**Prothrombotic state**

Obesity is accompanied by a large number of coagulation and fibrinolytic abnormalities (De Pergola et al, 2002). This suggests that obesity induces a prothrombotic state. What is not known at present is how a prothrombotic state will either promote the development of atherosclerosis or participate in the development of acute ASCVD events. Perhaps the most attractive candidate for enhanced atherogenicity associated with coagulation and fibrinolytic abnormalities is endothelial dysfunction. It is believed by many workers that endothelial dysfunction is somehow involved in the atherogenic process (Widlansky et al, 2003). Several pathways have been proposed; so far, however, none of these have been substantiated. Perhaps more likely, the obesity-induced procoagulant and antifibrinolytic factors contribute to a worsening of acute coronary syndromes. Thrombosis occurring with plaque rupture or erosion is a key element in determining the severity of the syndrome. If normal coagulation and fibrinolysis are impaired at the time of plaque rupture or erosion, then a larger thrombus should form. An attractive hypothesis is that acute plaque disruption is common, but only when thrombosis is large is there a significant acute coronary syndrome. If so, such could make the presence of a prothrombotic state important for determining the clinical outcome.
1.5.2. Obesity-induced metabolic syndrome as multidimensional risk factor for ASCVD and type 2 diabetes

Several recent reports (Isomaa et al, 2001) indicate that the presence of the metabolic syndrome is associated with increased risk for both ASCVD and type 2 diabetes. Persons with the metabolic syndrome have at least a 2-fold increase in risk for ASCVD, compared with those without. Risk for type 2 diabetes in both men and women is increased about 5-fold (Grundy et al, 2004). The risk for diabetes is highest in those with impaired fasting glucose or IGT. Once a patient develops type 2 diabetes, risk for ASCVD is enhanced. Not only is relative risk for coronary heart disease (CHD) raised by 2- to 3-fold, but once CHD becomes manifest in a patient with diabetes, the prognosis for survival is greatly reduced (NCEP, 2002). In addition, diabetes is accompanied by microvascular disease, which is a common cause of chronic renal failure. The relationship between the metabolic risk factors and development of ASCVD is
complex and certainly not well understood. Nonetheless, a brief review of hypothesized mechanisms may be of interest.

**Figure 9:** The fundamental metabolic abnormalities in diabetes mellitus activate adverse protein kinase C, increase the production of advanced glycation endproducts, and amplify superoxide anion production. In turn, endothelial homeostatic mechanisms are co-opted, including vasodilation, attenuation of inflammation, and platelet antagonism (Creager et al, 2003)

1.5.3. Obesity and congestive heart failure (CHF)

Heart Failure in obesity is multifactorial. Systolic and diastolic dysfunction are caused by 1) the ischemic effects of coronary artery disease, 2) the usually eccentric but at times concentric LVH caused by hypertension, 3) the increase in LV dilatation caused by an increased stroke and blood
volume and cardiac output, and 4) the contribution of RV dysfunction from sleep apnea and pulmonary hypertension. Combined with fatty infiltration of cardiomyocytes, these effects lead to a form of apoptosis and subsequent left ventricular dysfunction. With the increased incidence and prevalence of congestive heart failure (CHF), associated mortality rates are climbing. Despite new pharmacologic and device therapies, the 5-year survival rate for CHF is estimated at 50%. The risk of CHF increases 5% for men and 7% for women for each increment of BMI, representing a linear increase which does not plateau. The finding that ejection fractions of <40% are seen in 42% of obese as compared to 54% of normal-weight patients with heart failure confirms that diastolic heart failure is the more common type of dysfunction among the obese (Poirier et al, 2006).

In a study of 5,881 Framingham heart study participants, Kenchaitah et al, (2002) showed that during 14 year follow up, for every 1kg/m2 increment in BMI, the risk of HF increased 5% in men and 7% in female. In fact a graded increase in the risk of HF was observed across all categories of BMI. In a study of 74 morbidly obese patients, nearly one-third had clinical evidence of HF. The probably of increased HF increased dramatically with increasing duration of morbid obesity (Alpert et al, 1997).

Left ventricular hypertrophy is common in patients with obesity and to some extent is related to systemic hypertension (Messerli FH et al, 1982). However; abnormalities in left ventricular mass and function also occur in the absence of hypertension (Alpert MA et al, 1993) and may be related to the severity of obesity (Duflou J et al, 1995).

Increased left ventricular volume and wall stress in addition to increased stroke volume and cardiac output are commonly seen in systemic hypertension (Messerli FH et al, 1995). The hypertrophy of the left ventricle is both concentric and eccentric, and diastolic dysfunction is common. When obesity is present but systemic hypertension is absent, left ventricular volume is often increased, but wall stress usually remains normal. However, in obese patients without hypertension, increases in stroke volume and cardiac output as well as diastolic dysfunction are seen. These changes in the left ventricle are related to sudden death in obese patients.

When 22 patients with severe obesity were examined postmortem, dilated cardiomyopathy was most frequently associated with sudden death (n=10), with severe coronary atherosclerosis (n=6),
concentric left ventricular hypertrophy without dilatation (n=4), pulmonary embolism (n=1), and hypoplastic coronary arteries (n=1) also found. Thus, dilated cardiomyopathies, presumably with concomitant cardiac arrhythmias, may be the most common cause of sudden death in patients with severe obesity. The prolonged QT interval also seen in obesity (Frank S et al, 1986) may predispose to such arrhythmias.

Changes in the right heart also occur in obesity. The pathophysiology is related to obstructive sleep apnea and/or the obesity hypoventilation syndrome, which produce pulmonary hypertension and right ventricular hypertrophy, dilatation, progressive dysfunction, and finally failure (Burwell et al, 1956, Menashe et al, 1965). However, right ventricular dysfunction can also occur as a consequence of left ventricular dysfunction, and the heart failure that develops is often biventricular (Alpert MA et al, 1993).

### 1.5.4. Obesity and coronary heart disease (CHD)

Obesity is probably an independent risk factor for atherosclerosis and CHD events (Lavie et al, 2005). Additionally, excess adiposity has been strongly related to first non ST segment myocardial infarction (MF) occurring at younger age (Mdala et al, 2008).

Obesity is an independent predictor of coronary artery disease, as observed in the Framingham heart study (Hubert et al, 1983), Manitoba study (Rabkin et al, 1977) and Harvard public health nurses study (Manson et al, 1990). In the Framingham cohort, patients aged 28 to 62 years were followed for a mean of 26 years. Among men younger than 50 years, the heaviest group experienced twice the risk of coronary disease compared with the leanest group. The risk was increased 2.4-fold among obese women of similar age, and this was after adjusting for the influence of other major cardiovascular risk factors. Autopsy among 15 to 34 year olds who died from accidental causes revealed plaques and ulceration in the coronary arteries and abdominal aorta, the extent of which correlated with the amount of abdominal fat and BMI (PDAY study) (McGill et al, 1995). Obesity accelerates atherosclerosis decades before clinical manifestations appear and this remained significant even after adjustment of other risk factors like high cholesterol, hypertension, smoking, and increased HbA1c. The density of macrophages per mm2 of plaques also correlated with visceral obesity. After coronary artery bypass surgery also there are more adverse outcomes in obese patients (Marik et al, 1998).
1.5.5. Obesity and stroke

Numerous studies have reported an association between BMI and stroke. For each 1 -U increase in BMI, there was an increase of 4% in the risk of ischemic stroke and 6% for hemorrhagic stroke (Kuth et al, 2002).

This increased risk of stroke may be attributable to a higher prevalence of HTN, a prothrombic /proinflammatory state that accompanies excess adipose tissue accumulation, as well as increased AF.

1.5.6. Obesity and arrhythmias

Visceral adiposity and obesity have complex effects on the cardiac conduction system. Even in the absence of left ventricular dysfunction, there is a significant increase in the incidence of sudden cardiac death and arrhythmias in obese patients. Several mechanisms account for these associations: 1) increased free fatty acids, which are plentiful in obese patients, may affect depolarization; 2) an increase in plasma catecholamines may decrease the threshold for arrhythmias particularly in patients with obesity-associated cardiomyopathy (Corbi et al, 2002); 3) elevated glucose concentrations may cause an increase in vasomotor tone and a decrease in nitrous oxide (NO) availability, thus increasing ventricular irritability (Marfella et al, 2000); 4) the autonomic nervous system and obesity are closely related. A 10% increase in body weight is accompanied by a decline in parasympathetic tone and heart rate modulation, which leads to an increase in heart rate and decreased heart rate variability, both factors contributing to increased mortality (Kannel et al, 1987).

Atrial fibrillation (AF) is the most common dysrhythmia in obesity and is associated with significant morbidity and mortality. Obese men and women are significantly more likely than the general population to develop AF (men 52%; women 76%). Obese patients with paroxysmal AF are more likely to progress to permanent AF which leads to a 3-5 fold increase in the risk of stroke and a 2-fold increase in risk of death (Wang et al, 2004). There are multiple causes for the increased incidence of AF in the obese population. Diastolic dysfunction from longstanding hypertension leads to concentric or eccentric left ventricular hypertrophy with associated transmural stresses and ultimate left atrial (LA) enlargement. Other structural changes include
LV dilatation, which can subsequently lead to mitral regurgitation and LA enlargement, further worsening risk. Other contributing mechanisms are the effects of systemic inflammation and sleep apnea with associated autonomic imbalances and hypoxic periods. The prevalence of AF increases with obesity, and is expected to increase 2.5 fold by 2050. Although the increase in AF may be attributable to the aging of our population combined with the impaired prognosis of HTN, CHD and HF, conditions that increase the risk of AF, the epidemic obesity, with its hemodynamic attendants hemodynamic effects and impact on LV and LA structure and function, may also contribute to higher prevalence of AF. In a sub group of 5 population based studies enrolling 78,602 patients, obese patients had a nearly 50% increased risk of developing AF that escalated with increasing BMI (Wanahita et al, 2008).

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Finally, in obese patients a metaplastic, not infiltrative, phenomenon occurs in the heart causing a significant increase in fat content within the tissue. Various tissues such as the sinus node, atrioventricular node, right bundle branch, and the myocardium at the atrioventricular ring are replaced by fat cells. The end result is a constellation of conduction defects like sinoatrial block, bundle branch block, and rarely, atrioventricular block. Irregular bands of adipose tissue may also cause pressure-induced atrophy of adjacent myocardial cells and secrete adipokines that may be injurious to normal myocytes. The high levels of triglycerides in these patients can also cause lipotoxic-induced cell dysfunction (Balsaver et al, 1967).

There is an increase in the incidence of sudden cardiac death and arrhythmias in obesity (Kannel et al, 1988). Fatal arrhythmias may be the most frequent cause of death among obese patients. According to the Framingham data, sudden cardiac death was 40 times higher in obese men and women (Kannel et al, 1988). In another study of severely obese individuals, this was 6-fold and
12-fold higher in those aged 25 to 34 years and 35 to 44 years, respectively (Drenick et al, 1980). In the NHANES III study, 30% of obese patients with glucose intolerance had a prolonged corrected QT (QTc) interval. Schouten et al (Schouten et al, 1991) found that 8% of obese individuals had a QTc interval of more than 0.44 seconds and, in 2%, it was more than 0.46 seconds. A QTc interval of more than 0.42 seconds was associated with increased mortality in “healthy” obese patients followed for 15 years. QT dispersion, which measures the difference in duration between the maximum and the minimum QT interval in different leads in the EKG is a good noninvasive measurement for quantifying the degree of myocardial repolarization inhomogeneity, which was also increased in the obese. Both QTc interval and QT dispersion are mediated by changes in sympathetic-vagal balance. Catecholamine levels are increased in the obese (Esposito et al, 2002). In addition, increased free fatty acid levels in the obese may also affect repolarization. In patients with myocardial infarction, there is a relation between ventricular arrhythmias and long chain saturated fatty acid level. Various changes occur in the autonomic system with weight gain. A 10% increase in body weight causes a decrease in parasympathetic tone and increase in heart rate. On the other hand, heart rate decreases with weight reduction. There is a significant improvement in heart rate variability with 10% weight loss. Both increased resting heart rate and decreased heart rate variability are predictors of mortality, independent of the ejection fraction (Scareccia et al, 2001).

In a study of obese patients without clinical heart disease, the prevalence of late potentials (high-frequency, low-amplitude signals at the terminal part of the QRS complex demonstrated using high-resolution signal averaged recording) are seen to be increased proportionately with BMI. The presence of late potentials has been documented to be associated with increased risk of ventricular arrhythmias in several cardiac conditions and is present in less than 3% of normal controls. In those with a BMI score between 31 to 40, 41 to 50, and >50, the incidence of late potentials were 35%, 86% and 100%, respectively. This increased frequency may be related to fat and mononuclear infiltration, fibrosis, focal myocardial disarray, or myocyte hypertrophy (Lalani et al, 2000).
1.5.7. Obesity and Echocardiography

Large accumulation of sub epicardial fat can mimic pericardial effusion (pseudopericardial effusion). Lipomatous hypertrophy caused by fat deposition in the interatrial septum can cause it to be up to more than 20 mm thick and can even suggest a tumor (Alpert et al, 1986). Left ventricular diastolic dysfunction is very common. When compared with normal people, Subclinical changes in the structure and function of the left ventricle, such as differences in the regional or global strain, were identified in asymptomatic obese patients.

1.5.8. Obesity and Electrocardiogram

Interplay between several factors, such as horizontal displacement of the heart by the elevated diaphragm, cardiac hypertrophy, increase in the distance between the heart and the electrodes, and coexisting sleep apnea/obesity/hypoventilation syndrome, tend to modify the EKG in obese patients. The EKG may show low voltage, leftward axis, flat inferolateral T waves, left atrial enlargement, increased false positive criteria for inferior wall myocardial infarction, and less prevalence of left ventricular hypertrophy than that based on echo criteria (only around two thirds)(Alpert et al,2000). The left ventricular forces are more posteriorly and laterally oriented with deep S waves in V3 and tall R waves in aVL. The sum of R wave in aVL and S wave in V3, if more than 35 mm in men and 25 mm in women, has a sensitivity of 49% and a specificity 93% when compared with echo in diagnosing left ventricular hypertrophy and is more helpful than many of the more commonly used voltage criteria.

1.5.9. Obesity and sleep apnea

Obesity is a classic cause of alveolar hyperventilation and the obstructive sleep apnea (OSA) syndrome (Trollo et al,1996). In fact OSA may contribute to the pathogenesis of HTN and increased inflammation and CRP (Shamsuzzaman et al,2002). Clearly patients with OSA have increased risk of hypertension, dysrhythmias, pulmonary hypertension(present in 15%to 20% with OSA), HF, MI, stroke and overall mortality(Partinen et al,1988).
OSA is associated with systemic hypertension, pulmonary hypertension and cor pulmanale. Obesity is probably the important risk factor for OSA. Several studies have shown an association between an increased body mass index (BMI) and risk of OSA (Young et al, 2005). Significant OSA is present in 40% of obese individuals (Vgontzas, et al, 1994) and 70% of OSA patients are obese (Vgontzas, et al, 1994). A mere 10% increase in body mass has been shown to increase an individual’s risk of developing OSA by 500% (Peppard et al, 2000). Conversely, weight loss in OSA patients leads to a significant decrease in apnea frequency.

1.5.10. Obesity and venous disease

The combination of increased intravascular volume and high volume lymphatic overload, as well as reduced physical activity, often lead to venous insufficiency and edema with increasing obesity (Sugerman et al, 2001). Additionally, obesity is associated with an increased risk for venous thromboembolism and pulmonary embolism, especially in women (Tsai et al, 2002).

2. Conclusion

The increase in obesity worldwide will have an important impact on the global incidence of cardiovascular disease, type 2 diabetes mellitus, cancer, osteoarthritis, work disability, and sleep apnea.

Disability due to obesity-related cardiovascular diseases will increase particularly in industrialized countries, as patients survive cardiovascular diseases in these countries more often than in nonindustrialized countries.

Disability due to obesity-related type 2 diabetes will increase particularly in industrializing countries, as insulin supply is usually insufficient in these countries. As a result, in these countries, an increase in disabling nephropathy, arteriosclerosis, neuropathy, and retinopathy is expected.

Increases in the prevalence of obesity will potentially lead to an increase in the number of years that subjects suffer from obesity-related morbidity and disability.
3. Recommendation

Prevention programs will stem the obesity epidemic more efficiently than weight-loss programs. However, only a few prevention programs have been developed or implemented, and the success rates reported to date have been low. Obesity prevention programs should be high on the scientific and political agenda in both industrialized and industrializing countries.

Obesity has a devastating effect on cardiovascular system. Therefore, further studies are necessary to better understand the deleterious effects of obesity on cardiovascular system in order to improve health care, help to reduce body weight as prevention and treatment of CV diseases.

Health professionals should provide patient-centered counseling and health education to the general population including reduction or modification of dietary fat intake and exercise as an important tool in reducing obesity.
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