INSULIN RESISTANCE, ALCOHOL AND CORONARY HEART DISEASE (CHD) MORTALITY

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ABSTRACT

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The classical understanding of insulin resistance is the blunted response to insulin-mediated glucose uptake. It is not simply a problem of deficient glucose uptake in response to insulin, rather, a multifaceted syndrome that increases significantly, cardiovascular disease risk. The pathogenic mechanism of insulin resistance as a cardiovascular risk factor is considered to be through the direct atherogenic action of insulin on vessel wall cells and indirect through upper body obesity, blood pressure, lipids and homeostasis. Alteration in insulin sensitivity is postulated as a potential intermediary through which alcohol exerts its pro and anti-atherogenic effects. This study was aimed at finding the correlation between insulin resistance, alcohol and coronary heart disease (CHD) mortality. The subjects consisted of middle-aged men in a longitudinal study and data on alcohol, insulin resistance and other variables were obtained at baseline. CHD mortality was linked with the Finnish national discharge register. Our results showed that the risk of CHD mortality in men in the upper median of alcohol consumption was 1.99 fold and 1.79 fold using the fasting serum insulin and HOMA-IR respectively. Insulin resistance is therefore, directly associated with CHD mortality and this was further enhanced by alcohol consumption. The presence of alcohol in the equation resulted in a U-shaped relationship between insulin resistance and CHD. Hence, we conclude that even though insulin resistance is an independent risk factor for CHD mortality, alcohol consumption modifies this relationship.

CONTENTS

1 INTRODUCTION

The epidemic of coronary heart disease in the 20th century are among the worldwide leading causes of shorter life expectancy and loss of quality of life and is largely a consequence of lifestyle; marked by high fat diet, cigarette smoking, uncontrolled weight gain and physical inactivity which promote atherogenic risk factors thereby accelerating the rate of atherosclerotic cardiovascular disease development (Kannel et al 1996).

Cardiovascular diseases are the leading causes of morbidity and mortality in insulin resistant individuals. Insulin resistance which is known to be a cardinal feature in diabetes, obesity and dyslipidemia is also a prominent component of hypertension, coronary heart disease and atherosclerosis with endothelial dysfunction as a characteristic feature (Muniyappa et al, 2007). Endothelial dysfunction precedes the formation of atheromatous plaque which is predictive of cardiovascular diseases (Schachinger et al, 2000) and its impaired response is associated with risk factors for cardiovascular diseases (Vapaatalo and Mervaala, 2001).

Insulin resistance has been found to be the single most important cause of coronary artery disease, responsible for about 42% of myocardial infarction in the U.S. (Eddy 2009). The pathogenic mechanism of insulin resistance as a cardiovascular risk factor is considered to be through the direct atherogenic action of insulin on vessel wall cells and indirect through upper body obesity, blood pressure, lipids and homeostasis (Janku 1994). Insulin resistance and hyperinsulinaemia have been associated with higher levels of triglycerides, lower levels of high density lipoprotein-cholesterol (HDL-C), elevated blood pressure, Non-Insulin Dependent Diabetes Mellitus (NIDDM) and Coronary Heart Disease (CHD) (Mayer et al 1993).

Secreted by pancreatic B-cells, insulin is released in response to elevation of blood glucose levels and insulin resistance can be defined as a decrease in the ability of insulin to stimulate glucose uptake normally at a given insulin concentration in an individual. Other risk factors of insulin resistance include obesity, race, sex, physical inactivity, age and genetic factors (Ausk 2010).

Another common feature of daily living is the consumption of alcoholic beverages which proffer both adverse and favorable effects on cardiovascular disease outcomes (Kannel et al 1996) like the proverbial double-edged sword. Alcohol, when consumed in excess amounts for years is toxic to almost every tissue in the body and these are due to disturbances of a wide variety of metabolic and organ damage. Amongst other things, with heavy alcohol consumption, there is the risk of; mood changes, depression, loss of inhibition, violent/self-destructive behavior, liver disease, heart disease, peptic ulcers, certain types of cancers, complicated pregnancies, birth defects and brain damage. Respiratory depression and death could also follow heavy or binge drinking (Agarwal 2002).

One of the most investigated behavior is the cardioprotective effects of light to moderate alcohol consumption (Kiechl et al 1994, 1998); and attempts to shed more light on the mechanisms has resulted amongst others, findings suggesting; alterations in high density lipoproteins (HDL) levels, low density lipoproteins (LDL) levels (van Tol et al 1998), LDL oxidation (van Golde et al 1999 and Trevithick et al 1999), blood pressure (Rywik at al 2000 and Friedman 1998) and coagulation fibrinolytic factors (Djousse et al 2000 and Dimmitt et al 1998). Alteration in insulin sensitivity which is less studied is postulated as a potential intermediary through which alcohol exerts its pro and anti- atherogenic effects (Flanagan et al 2000, van de Wiel et al 1998 and Lazarus et al 1997). The target of important mediating pathways such as oxidative stress, insulin resistance and lipoprotein of differential ethanol concentrations is the vascular endothelium. However, synthesis of several markers like nitric oxide, cortisol, endothelin-1, adhesion molecules, tumour necrosis factor alpha, interleukin-6, C-reactive protein and haemostatic factors are all related to alcohol-induced endothelial damage or protection and their expression is consistent with the J-shaped curve between alcohol consumption and cardiovascular health (Bau et al, 2007).

The paradox linked to alcohol use with respect to insulin resistance and cardiovascular diseases are the diverse associations between acute and chronic intake of alcohol; as well as abstinence/excessive intake; and moderate intake of alcohol. While consistent reports show that alcohol acutely induces a state of insulin resistance following an oral and /or intravenous glucose load, a large range of epidemiological studies show evidence that long moderate

exposure to alcohol (chronic) could in fact be protective from insulin resistance and other associated cardiovascular diseases (Renate 2003). The association between insulin and alcohol may explain to an extent, the reported associations between alcohol and the components of the metabolic syndrome (Mayer 1993). The evidence suggests a J- or U-shaped relationship between alcohol, insulin resistance and coronary heart disease mortality (Agarwal 2002).

This prospective study is aimed at finding the role of insulin resistance, alcohol intake and coronary heart disease mortality.

2 LITERATURE REVIEW

2.1 Insulin

2.1.1 Physiology and functions of Insulin

Insulin is synthesized in the beta cells of the pancreas in the form of proinsulin which is the precursor; and the prohormone convertase 2 and 3 and carboxy peptidase H convert proinsulin to insulin. It is secreted in response to glucose (major physiological determinant) stimuli (Shashank et al 2007).

The physiological effects of insulin in addition to its crucial metabolic actions range from cell growth to regulation of cognitive functions such as learning and memory (Zhao et al 1999, Sundell et al 2003). It acts in the brain, pancreatic cells and the cardiovascular system contributing to its overall regulation of glucose and lipid homeostasis in muscles, liver and adipocytes (Potenza et al 2009). Therefore, it enhances cholesterol transport into arteriolar smooth-muscle cells and subsequently, increases endogenous lipid synthesis in these cells; stimulates the proliferation of cells in the arteriolar smooth-muscles; augments collagen synthesis in the vascular wall, increases the formation of and decreases the regression of lipid plaques, and stimulates a variety of growth factors (Defronze 1992).

In the cardiovascular system, the hemodynamic action of insulin is through multiple mechanisms, one of which is the associated increase in sympathetic nervous system activity and plasma norepinephrine levels with insulin increase and may result in either vasoconstriction (Sartori et al 1999) or vasodilation (Creager et al 1985); depending on the preexisting vascular tone and vascular bed. The hemodynamic actions of insulin largely depends on its ability to stimulate the release of mediators like Nitric oxide (NO), endothelin-1 (ET-1) and reactive oxygen species (ROS) with opposing properties on vascular tone, hemostatic process and vascular permeability from the endothelium; and their balanced activity ensures dynamic control of vascular function (Potenza et al 2009). Increasing evidence indicate that by its action on the endothelium, it also facilitates its own transendothelial transport which is a rate limiting factor for its action in stimulating glucose uptake (Barrett et al 2009, Miles et al 1995, Yang et al 1989).

Insulin also favors renal sodium reabsorption with a resultant extracellular fluid expansion and invariably, an increased systemic blood pressure (Potenza et al 2009).

2.2 The endothelium

The endothelial layer of the vascular wall is the largest endocrine organ in the body producing substances that act both locally and remotely in several parts of the organism (Furchgott and Zawadzki, 1980; Vapaatalo and Mervaala, 2001). It is a semipermeable barrier that prevents the leaking of excessive plasma fluid through the monolayer and regulates selective delivery of nutrients and hormones to underlying tissues (Potenza et al 2009). The endothelial cells serve as both sensory and effector cells, playing a major role in vascular remodeling and lesion formation; they provide an interface with the bloodstream, sensing changes in flow, pressure, inflammatory signals or levels of circulating hormones (Gibbons 1997); and has the capacity to integrate hemodynamic and humoral signs as well as modulate the vasomotor tone in response to local tissue metabolic needs (Baua et al, 2007). They play major roles in four cellular processes: cell growth, programmed cell death (apoptosis), cell migration, and modulation of extracellular matrix composition by releasing or activating substances that regulate these processes (Gibbons 1997).

The endothelium contributes to vascular hemostasis by the release of mediators with a wide range of vasodilator/vasoconstrictor, procoagulant/fibrinolytic, permeability/adhesion, and growth/differentiation properties; which not only exert independent vascular effects, but also modulate one another's actions; in general, the vasodilators inhibit cell growth while the vasoconstrictors induce cell growth (Potenza et al 2009, Gibbons 1997). A balance between vasoconstrictors like angiotensin II and vasodilators like nitric oxide (NO) is maintained by the normal homeostasis such that an imbalance between these substances with perturbations in the regulation of tone, hemostasis and vessel structure is characteristic of endothelial dysfunction. Flow-dependent vasodilation is mediated in part by NO and as such, its synthesis by the vascular endothelium regulates arterial blood pressure (Huang et al 1995). The clinical markers of endothelial dysfunction have been suggested to be due to NO and its metabolites (Raitakari and Celermajer, 2000; Vallance and Chan, 2001). However, most of

the cytotoxicity is by peroxynitrite, a product of the reaction between NO and super oxide and is implicated in the pathogenesis of cardiovascular diseases (Pacher et al, 2007). Since it is the first tissue encountered by molecules released into the vascular system, this exposes the cells to effects of composition/concentration of circulating factors that may stimulate the cells abnormally resulting in impaired function (Potenza et al 2009).

Characterized by abnormal endothelium-dependent vasorelaxation and increased adhesiveness, endothelial dysfunction can induce clinically significant vascular diseases like hypertension, coronary artery disease, chronic heart failure, peripheral artery disease, diabetes and chronic renal failure by promoting vasospasm, thrombus formation, atherosclerosis or restenosis after angioplasty; that is a shift of its actions toward reduced vasodilation, proinflammatory state, and prothrombic properties (Gibbons 1997, Endemann and Schiffrin 2004). Mechanisms that participate in this reduced vasodilatory response include reduced NO generation, oxidative excess and reduced production of hyperpolarizing factor: upregulation of adhesion molecules, production of plasminogen activator inhibitor-1 (PAI-1) and generation of chemokines such as macrophage chemoattractant peptide-1 participate in the inflammatory response and contribute to the prothrombotic state. However, altered insulin signaling, vasoactive peptides like angiotensin II and endothelin-1 (ET-1), the accumulation of dimethylarginine (an endogenous nitric oxide inhibitor), hypercholesterolemia, hyperhomocysteinemia and hyperglycemia contribute to these mechanisms (Endemann and Schiffrin 2004, Kielstein et al, 2004).

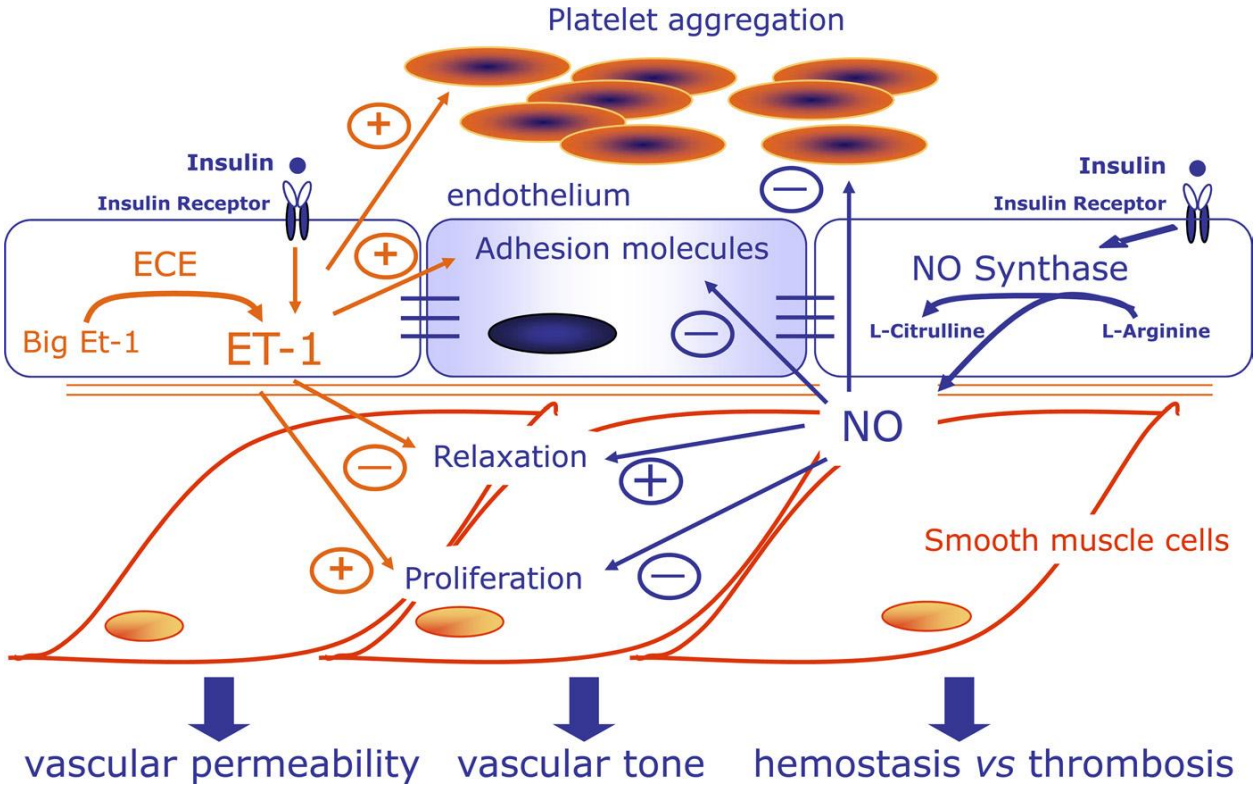
Results from several studies show that the impairment of endothelium-dependent vasodilation occurs in coronary and peripheral conductance and resistance vessels (Vita 1990, Anderson et al 1995) which correlates with an increased risk for cardiovascular events and independently predicts vascular morbidity and mortality (Sydow et al 2005). Moreover, the severity of endothelial dysfunction has been shown to have prognostic value for cardiovascular events and correction of endothelial dysfunction associated with reduced cardiovascular risk **(**Endemann and Schiffrin 2004).

2.3 Vascular actions of insulin

Recent findings indicate that insulin plays an important role in normal vascular function. Insulin binding to insulin receptors exerts its vascular actions through two major branches of transduction cascade; the metabolic signaling pathways mediated by phosphatidylinositol 3-kinase (PI3K) and the mitogenic signaling pathway mediated by mitogen-activated protein kinase (MAPK) (Muniyappa and Quon, 2007). Hence, one of the key vascular actions of insulin is to stimulate production of the potent vasodilator nitric oxide (NO) from the endothelium via the PI3K pathway which in turn, enhances glucose uptake in skeletal muscles but the pathways regulating endothelial production of NO exhibit striking parallels with metabolic insulin signaling pathways in skeletal muscles and adipose tissue (Muniyappa and Quon, 2007). Simultaneously, insulin also stimulates the production of endothelin-1 (ET-1), a potent vasoconstrictor that opposes the actions of NO and has been implicated in the development of hypertension from the endothelium via the MAPK pathway (Muniyappa and Quon, 2007).

Insulin regulates the endothelial function through the aforementioned mediators with opposite hemodynamic action on vascular tone, vascular permeability and haemostatic processes. While NO reduces the expression of adhesion molecules in the endothelium, inhibits adhesion and proliferation of vascular smooth muscle cells (VSMC), promotes vasorelaxation, activation, secretion and aggregation of platelets; the ET-1 on the other hand increases expression of adhesion molecules, favour platelet aggregation and promotes VSMC contraction, migration and proliferation (Potenza et al 2009 and Mather et al 2001) (fig.1). Insulin, therefore, modulates hemodynamics through changes in both flow and capillary recruitment by its action in the endothelium and vascular wall (Muniyappa et al, 2007); such that PI3K dependent pathway regulates vasodilator actions of insulin while the MAPK dependent actions of insulin promote the prohypertensive actions of insulin in various tissues (Muniyappa and Quon, 2007).

Figure 1. Vascular actions of insulin



Adopted from Potenza et al. Vascular actions of insulin with implications for endothelial dysfunction. Am J Physio Endocrinol Metab 297: E568-E577, 2009
ECE, endothelin-converting enzyme

Studies have shown that inhibitors of PI3K, nitric oxide substrate (NOS) block insulin-mediated capillary recruitment, blood flow and glucose disposal whereas, ET-1 infusion inhibits the insulin-induced capillary recruitment and is associated with decreased muscle glucose uptake; and inhibition of the MAPK blocks the vasoconstrictor effects of insulin and increase vasodilation suggesting that the vasodilator actions of insulin help couple the metabolic and hemodynamic homeostasis (Muniyappa and Quon, 2007; Ross et al, 2007). However, in the normal endothelium, the vasodilator PI3K/AKt/nitric oxide pathway is more robust than the vasoconstrictor MAPK/ET-1 pathway but an imbalance in these pathways results in impaired vascular and metabolic actions of insulin (Muniyappa and Quon, 2007). Various experimental studies have shown that insulin- mediated cardiovascular protection

against reperfusion injury of the heart is via the PI3K/Akt signaling pathway and has therefore been termed a 'survival pathway' (Hausenloy and Yellon 2004).

2.4 Insulin resistance

A condition in which normal levels of insulin are not adequate to produce the expected biologic effect in the target tissues such as adipose tissue, muscle and liver is called insulin resistance (Ausk 2010). Characterized by an inadequate glucose uptake in peripheral tissues at a given concentration, insulin resistance involves an impairment of the nonoxidative (glycolytic) pathways of intracellular glucose metabolism (Ferrannini et al, 1987).
The classical understanding of insulin resistance is the blunted response to insulin-mediated glucose uptake. It is not simply a problem of deficient glucose uptake in response to insulin, rather, a multifaceted syndrome that increases significantly, cardiovascular disease risk (Ginsberg 2000). Insulin resistance, however, may involve any of its other biological effects (Sundell et al 2003). Vascular insulin resistance appears to be an important mediator in the vascular pathophysiology (Mather et al 2001) of cardiovascular diseases and its regulation is different from the insulin resistance on glucose metabolism (Sundell et al 2003).

In general, the abnormality in insulin resistance can be due to a pre-receptor, receptor or post-receptor malfunction and one signaling pathway for both insulin and Insulin-like Growth Factor-I (IGF) is the phosphatidyl inositide 3-kinase (PI 3-kinase) system (Hunter et al 1998). Insulin and IGF-I stimulation increases the amount of PI 3-kinase associated with the insulin receptor substrate (IRS) resulting in increased activity of the enzyme in cardiovascular tissues and insulin sensitive tissues (Hunter et al 1998). Increases in NO, sodium (Na^+) pump, potassium (K^+) channel, and calcium (Ca^{2+}) myofilament sensitivity are mediated by the PI3-kinase by increasing the trafficking and translocation of NO synthase and cation pump units and glucose transporters (Hunter et al 1998, Zeng et al 1996).

Therefore, an interruption or reduction in the PI 3-kinase pathway creates a resistance to the actions of insulin and IGF-I in stimulating vascular NO production (Zeng et al 1996, Bengum et al 1998), cardiovascular cat-ion transport mechanisms (Sowers et al 1998) and glucose

transport (Hunter et al 1998) in classically sensitive tissues such as muscle and adipose tissue. The pathway specific impairment in phosphatidylinositol 3-kinase-dependent signaling characterizes insulin resistance, such that, vascular endothelium contributes to a reciprocal relationship between insulin resistance and endothelial dysfunction (Muniyappa et al, 2007). Consequent to insulin resistance, there is an increased formation of advanced glycation end products (AGEs), which play a major causative role in cardiovascular diseases through an increase in endothelial dysfunction, inflammatory responses, and increased oxidative stress (Vasdev et al., 2006)

Hyperinsulinaemia which often accompanies insulin resistance in the early stages as a result of a physiological response to maintain euglycaemia raises insulin levels and contributes to the maintenance of the insulin resistance (Wheatcroft et al 2003). In as much as hyperinsulinaemia compensates for resistance to some biological actions of insulin, it results in overexpression of actions of insulin in tissues that retain normal or minimal impairment in insulin sensitivity. In addition, high concentrations of insulin in the system can stimulate receptors for IGF-I (Sowers 1996). Thus diverse clinical manifestations occur with accentuation of some actions of insulin and resistance to others and a sequel of insulin resistance syndrome (Mcfarlane et al 2001).

Insulin resistance may be associated with other components of the metabolic syndrome (dyslipidemia with increased triglycerides and decreased HDL-cholesterol, central obesity, hypertension and progressive glucose intolerance) except hyperuricaemia. These components are markers for an increased risk of atheroma and type 2 (non-insulin-dependent) diabetes. Consequently, insulin resistance/hyperinsulinaemia results in a series of hypertensiogenic and atherogenic side effects, aggravating the individual components of the metabolic syndrome (Rett 1994) and an increased risk of cardiovascular diseases.

2.4.1 Insulin resistance and endothelial dysfunction

The endothelium is thought to play a critical role in maintaining vascular homeostasis: a process dependent on the balance between the production of nitric oxide (NO), superoxide and other vasoactive substances and its dysfunction which occurs early has been demonstrated

in insulin-resistant states in both humans and animals alike (Wheatcroft et al 2003, Sydow et al 2005): leading to an increased susceptibility to accelerated atherosclerosis, coronary heart disease and hypertension. At normal physiologic levels, insulin increases blood flow to skeletal muscles and other insulin sensitive tissues via the endothelium-derived nitric oxide synthase (NOS) in healthy insulin sensitive individuals and its effect to vasodilate skeletal muscle vasculature is directly proportional to its ability to increase glucose uptake (Laakso et al 1992, Vincent et al 2003). Consequently, there is inhibition of NOS in insulin resistant individuals with a resultant impairment of skeletal blood flow as well as peripheral glucose uptake, even in the face of high insulin concentration (Laakso et al 1990, Vincent et al 2003). Perturbed insulin signaling is often characterized by loss of endothelial-derived NO bioavailabilty, increased production of reactive oxygen species (ROS) and enhanced release of ET-1 (Potenza et al 2009).

A number of mechanisms like disturbances of subcellular signaling pathways common to both insulin action and nitric oxide, the roles of oxidant stress, endothelin, the renin angiotensin system and the secretion of hormones and cytokines by adipose tissue may link insulin resistance to endothelial dysfunction (Wheatcroft et al, 2003).

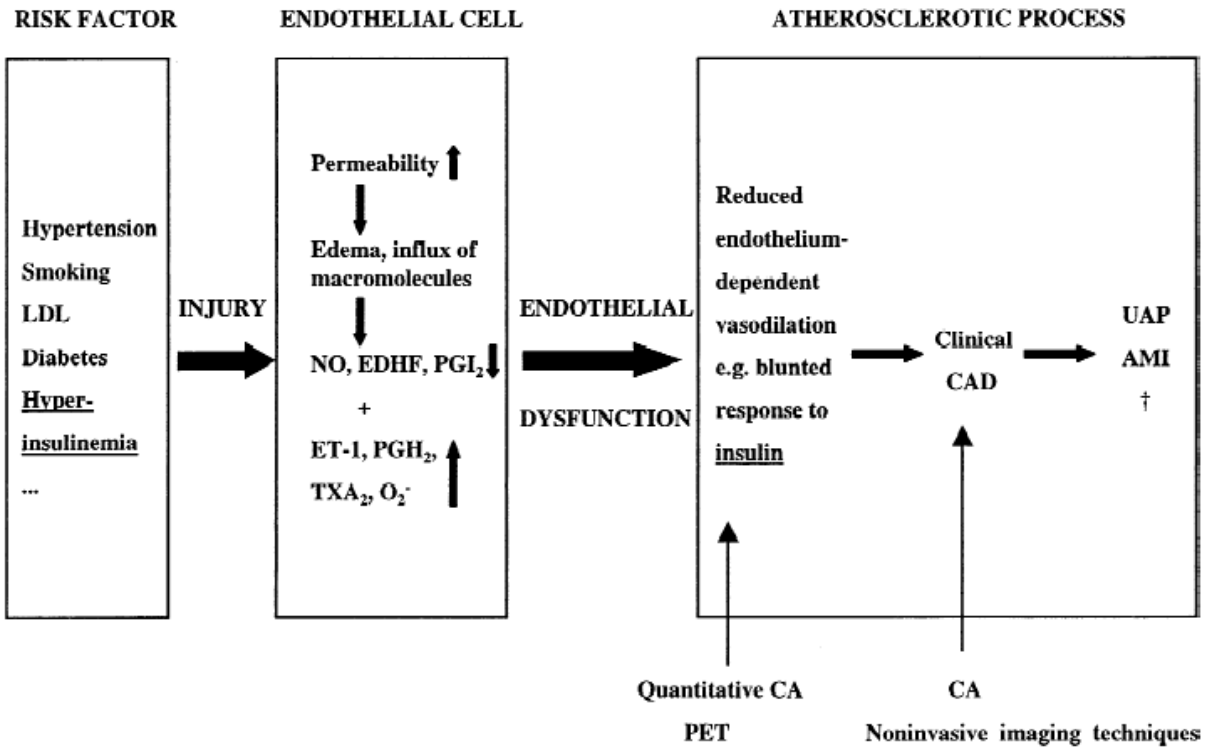
One key feature of insulin resistance is that it is characterized by the specific impairment of PI3K- dependent signaling pathway while other insulin-signaling pathways including the Ras/MAPK-dependent pathways are unaffected (Jiang et al 1999, Cusi et al 2000). The pathophysiologic implication of this is based on the fact that metabolic insulin resistance is accompanied by compensatory hyperinsulinemia to maintain euglycemia such that, in the vasculature and elsewhere, hyperinsulinemia overdrives the unaffected MAPK-dependent pathways resulting in an imbalance between the PI3K and MAPK-dependent functions of insulin (Kim et al 2006). Therefore, decreased PI3K signaling and increased MAPK-signaling in the endothelium, in response to insulin could result in decreased production of NO and increased secretion of ET-1 which is characteristic of endothelial dysfunction (Kim et al 2006, **J**ansson 2007).

As aforementioned, the MAPK signaling pathway control the prohypertensive effects of insulin and its preferential signaling contribute to the progression of atherosclerosis by

promoting the secretion of ET-1, activation of cation pumps, increase in vascular smooth muscle cell (VSMC) migration in the expression of cell adhesion molecules (vascular cell adhesion molecules - VCAM-1, E-selectin) and cell interactions between vascular cells and macrophage/ monocytes (Montagnani et al 2002, Kim et al 2006). Stimulated VSMC increase the production of plasminogen activator inhibitor type 1 (PAI-1) leading to a reduced fibrinolysis and increased vascular occlusion (Nigro et al 2006).

Thus, under conditions of insulin resistance, the antihypertensive effects of insulin to produce NO are reduced leading to the atherosclerotic process (fig 2).

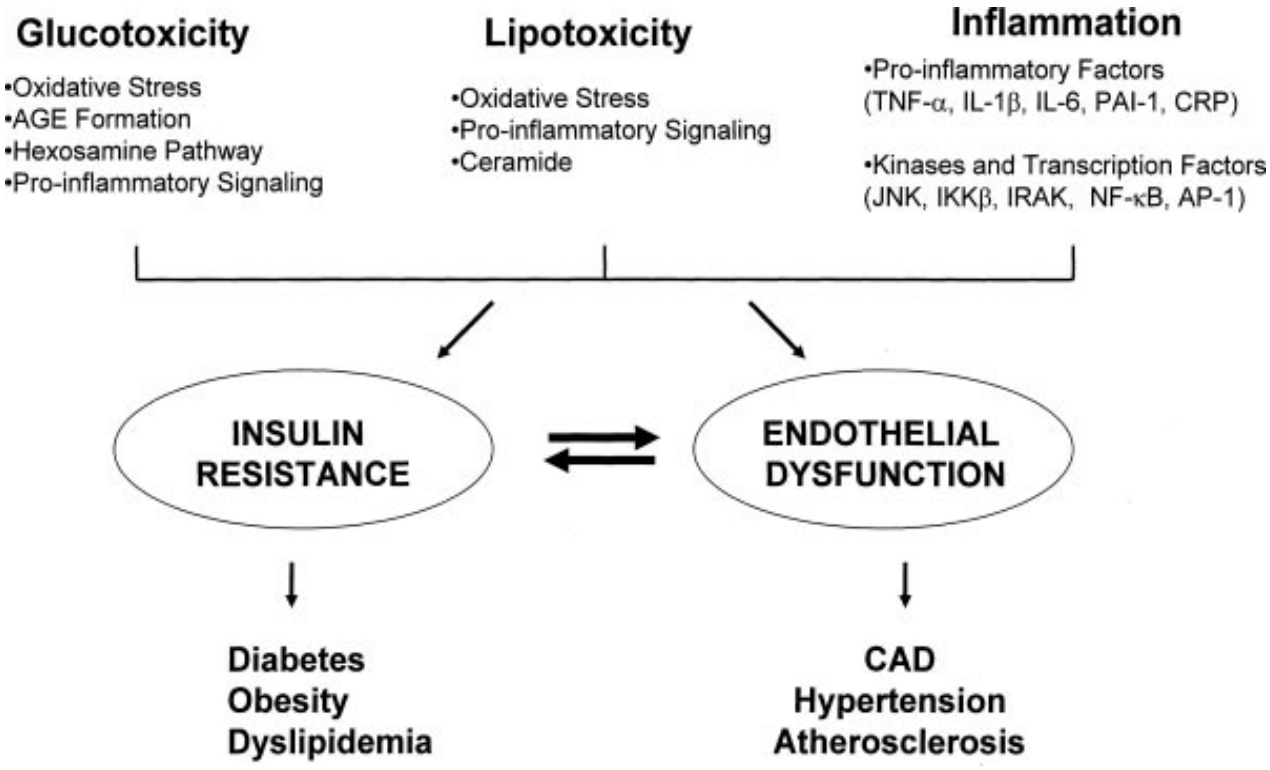
Figure 2



Risk factors for coronary artery disease damage endothelial cells leading to endothelial dysfunction
LDL; low densisty lipoproteins, NO; nitric oxide, EDHF; endothelium-derived relaxing factor, PGI_2; prostacyclin I_2, ET-1; endothelin-1, PGH_2; prostaglandin H_2 , TXA_2; thromboxane A_2 , O_2^-; superoxide anions, PET; positron emission tomography, CA; coronary angiography, CAD; coronary artery disease, UAP; unstable angina pectoris, AMI; acute myocardial infarction, †; ischemic sudden death.
Adopted from Sundell and Knuuti. Insulin and myocardial blood flow Cardiovascular Research 57 (2003) 312–319

Impaired microvascular recruitment is a direct pathophysiological consequence of reduced NO production under insulin resistant state (Potenza et al 2009). This ultimately leads to reduced glucose delivery and uptake in skeletal muscles due to reduced capillary perfusion with decreased surface area for nutrient absorption and exchange (Clark et al 2003). However, not only does this impaired capillary recruitment reduce glucose uptake, it also impairs insulin's own transendothelial transport to muscles; the rate limiting step for its metabolic actions (Barrett et al 2009). Furthermore, insulin resistance and endothelial dysfunction exhibit a reciprocal relationship chiefly determined by the shared and interacting mechanisms of glucotoxicity, lipotoxicity and inflammation which contribute to the linkage between metabolic and cardiovascular diseases (fig 3) (Kim et al 2006).

Figure 3



Adopted from Kim et al. Reciprocal Relationships Between Insulin Resistance and Endothelial Dysfunction Molecular and Pathophysiological Mechanisms. Circulation 2006, 113:1888-1904: CAD; coronary artery disease

The presence of a strong association between insulin resistance and endothelial dysfunction supported by several lines of evidence; measured in terms of impaired endothelium-dependent vasodilation; coupled with chronology of this association in animal studies (Katakam et al 1998) leads to the hypothesis that insulin resistance promotes endothelial dysfunction which in turn accelerates the development of cardiovascular diseases. Petrie et al (1996) found in healthy volunteers, a close correlation between insulin sensitivity and basal NO production. In a study by Piatti et al (1996), they showed that insulin resistant patients had elevated plasma ET-1 levels, and hyperinsulinemia increase ET-1 levels in humans. In otherwise healthy insulin-resistant humans, they were found to have impaired endothelium-dependent vasodilatory responses assessed using a variety of techniques (Laine et al 1998, Steinberg et al 1996). Furthermore, insulin resistance correlates with abnormal endothelium-dependent coronary artery response in subjects with cardiovascular risk factors but with angiographically normal coronary arteries (Inuoe et al 2000).

One notable feature in these studies is that the relationship between insulin resistance and endothelial dysfunction is independent of the traditional cardiovascular risk factors like blood pressure, plasma cholesterol and triglycerides (Wheatcroft et al, 2003).

2.4.2 Insulin resistance and coronary heart disease

Researches have shown that the common features in a widespread of diseases are the reduced insulin-stimulated glucose metabolism in skeletal muscles (insulin resistance) and hyperinsulinism, hence; have being implicated in adverse health outcomes such as hypertension, cardiovascular disease, cerebrovascular disease, peripheral vascular disease (atherosclerosis), congestive heart failure, non-alcoholic fatty liver disease, android obesity and a variety of malignancies (Pederson 1992 and Ausk 2010). After correction for traditional risk factors like hypertension, hyperlipidaemia and family history, insulin resistance has been accepted to be an independent risk factor for ischaemic heart diseases (Despres et al, 1996 & Pyorala et al 2000) and represent a major underlying abnormality driving cardiovascular diseases, the major cause of morbidity and mortality in developed world (Ginsberg 2000).

The first step in the atherosclerotic process has been suggested to be endothelial dysfunction consistent with the fact that impaired coronary endothelium derived vasodilation seems to be one of the earliest abnormality associated with coronary artery disease (CAD) (Vita et al 1990). However, Ross (1993) hypothesized that risk factors for coronary artery disease (insulin resistance/hyperinsulinemia inclusive) damage endothelial cells and impair its function leading to increased release of endothelium derived vasoconstrictory factors.
As previously mentioned, insulin, a predominantly endothelium-dependent vasodilator (Scherrer 1995, Sobrevia et al 1996) acts in the endothelium and the vascular wall to modulate hemodynamics through changes in blood flow and capillary recruitment; suggesting that insulin enhances myocardial blood flow in the heart (Lautamaki et al 2006, Scognamiglio et al 2006, Sundell and Knuuti 2003, Sundell et al 2002, Iozze et al 2002, Laine et al 2000, Rogers et al 1977) alongside increasing cardiac contractility; with a resultant increased work and oxygen consumption (Baron 1994) and decrease coronary vascular resistance (Laine et al 2000). Conversely, when myocardial oxygen consumption increases, myocardial hyperemia is initially associated with increased capillary blood flow velocity and followed by capillary recruitment (Wei and Kaul 2004).

Recent studies (Salomaa et al 1995, Agewall et al 1995, Shinozaki et al 1996, Suzuki et al 1996) have shown a relationship between carotid wall atherosclerotic lesions, angina, and insulin levels/resistance. Furthermore, evidence from large prospective studies (Pyorala 1979, Welborn and Wearne 1979, Ducimentiere et al 1980, Fontbonne et al 1991) has shown that high fasting insulin is a predictor of CAD, and clearly an independent predictor in the study by Despre´s et al (1996). Therefore, it can be hypothesized that insulin resistance provides a novel mechanism in the progression towards CHD.

2.5 Alcohol intake and insulin levels

Improved insulin sensitivity has been associated with moderate alcohol consumption (Bell et al 2000, Flangan et al 2000, Lazarus et al 1997), through its limitation of advanced glycation end products (AGEs) formation, their subsequent cardiovascular complications and also, through lowering of plasma-free fatty acids (Avogaro et al, 2002); which partly explains the

cardioprotective effect of alcohol. Consumption of ethanol has been however, reported to decrease glucose uptake and utilization with the subsequent development of insulin resistance, a central component of diabetes and cardiovascular diseases (Onishi et al 2003). Furuya et al (2003) analyzed the effect of the intake of various ethanol concentrations in rats and showed an inverted U-shaped relationship between alcohol intake and insulin sensitivity.

The biological mechanisms underlying the association between alcohol consumption and insulin sensitivity are not known, however, suggestions indicating the alterations in hepatic glucose metabolism with decreased gluconeogenesis (Krebs 1968, Flanagan et al 2002), alteration of the counter regulatory hormones actions (Lecavalier et al 1989, Kirkman and Nelson 1988, Jenjins and Connolly 1968, Eisenhofer et al 1983), a direct effect on beta cells of the pancreas (Flanagan et al 2000), or through a reduction in the sympathetic activity (Flanagan et al 2002); have being made. Also, it has being proposed by McCarty (2001) that improved insulin sensitivity maybe due to the metabolism of acetate in the peripheral tissues which generate sufficient levels of AMP to temporarily stimulate the AMP-activated protein kinase; this in turn induces the synthesis of certain long-lived proteins that act to boost insulin sensitivity and possibly aid the efficiency of fat oxidation as well. Large quantities of ethanol, either acute or chronic have been reported by Onishi et al (2003) to induce insulin resistance as evidenced by decreased glucose utilization and impaired insulin suppression of hepatic glucose production. As opposed to Yeon et al (2003) who suggested reduced phosphorylation of insulin receptor IRS-1 levels and lower activities of PI3K/Akt in the liver alongside the insulin resistance, Onishi et al (2003) reported an enhanced phosphorylation of insulin receptors IRS-1 and IRS-2 levels and increased PI3K activity. Thus, the mechanism underlying ethanol-induced insulin resistance remains controversial.

2.6 Insulin resistance, alcohol and coronary heart disease (CHD)

The evidence that moderate intake of alcohol may be associated with reduced insulin resistance and insulin resistance associated with increased risk for coronary heart disease implies that insulin resistance may in part explain the apparent protective effect of moderate alcohol intake (Lazarus et al 1997). Most studies have suggested a J-shaped curve as regards

the health effects of ethanol which is dependent on the amount of alcohol consumed as well as the pattern of drinking; such that, while moderate drinkers have less risk than abstainers, heavy drinkers are at the highest risk (O'keefe et al, 2007).

The suggested protection conferred by light to moderate alcohol consumption appear to be most important on the cardiovascular system showing a CHD risk reductions of about 30% to 35% (Kabagambe et al, 2005, Mukamal et al, 2005); which is predominantly through the enhancement of insulin sensitivity and elevation of HDL cholesterol; and less predominantly through improvements in inflammation and abdominal obesity (Keichl et al, 1993; Freiberg and Samat, 2005). The major factor conferring this benefit is the ethanol itself rather than the specific component of wine, spirits or beer (Mukamal, Jensen et al, 2005, Mukamal et al, 2003) because in as much as red wine has been shown to have higher levels of bioflavonoids (with anti-oxidants, anti-endothelin-1, and anti-platelets effects) compared with other forms of alcohol (Corder et al, 2006), most studies show equal cardiovascular protection from all types of alcohol (O'keefe et al, 2007).

The biochemical mechanism of the differential effect of low as opposed to high doses of ethanol was suggested by Vasdev et al (2006) as attributable to the ability of low doses of alcohol to increase the antioxidant activity, lower insulin resistance and reduce advanced glycation end products (AGEs) thereby preventing hypertension and atherosclerosis, whereas, the reverse is the case for high doses. Also, low dose alcohol exerts its beneficial effect on the cardiovascular system through the release of nitric oxide (Puddey et al, 2001) which explains the vasodilator effect of alcohol. This hypothesis is supported by Abou-Agag et al (2005) when they found in rats that moderate doses of ethanol increased the expression of eNOS and the resulting vascular relaxation caused by the nitric oxide could explain in part, the cardioprotective benefits of moderate alcohol consumption. Hence, the specific alcoholic beverage is less important than the quantity and pattern of consumption (Ellison RC, 2005).

The favorable changes conferred by alcohol on insulin sensitivity, HDL cholesterol and inflammation are transient, reverting back to baseline within 24 hours (Veenstra et al, 1990). This may explain the superior health benefits shown in daily moderate alcohol consumption compared with less frequent consumption in both men and women alike (Mukamal, Jensen et

al, 2005, Mukamal et al, 2003, Veenstra et al, 1990, Rehm et al, 2003, Mukamal, Maclure et al, 2005). In the study by Mukamal, Jensen et al (2005), 37% decrease in CHD risk was present in those who drank 5 to 7 days per week as opposed to those who drank less than once a week. Furthermore, alcohol is shown to be most cardioprotective when consumed before or during a meal (Rehm et al, 2003) which correlates with improvements in postprandial glucose metabolism found in light to moderate alcohol consumption (Greenfield et al, 2005). However, cardioprotective alcohol intake is generally defined as 1or 2 drinks per day for men and 1 drink per day for women (DiCastelnuovo et al, 2006, Mukamal et al, 2005, NRID, 2006) while a drink is considered to be 12 oz beer, 5 oz wine, 1.5 oz 80 proof spirits, or 1 oz 100-proof spirits, all of which is equivalent to approximately 13 g to 15 g ethanol (O'keefe et al, 2007)

3 OBJECTIVES

The objectives of this study are;

i. To find correlation between insulin resistance and coronary heart disease mortality in middle aged men in Kuopio, Eastern Finland
ii. To find the correlation between alcohol consumption and coronary heart disease mortality
iii. Assess the relationship between alcohol consumption, insulin resistance and coronary heart disease mortality in this population.

4 SUBJECTS AND METHODS

4.1 Study population

The study sample consisted of participants of an on-going prospective population-based cohort study, designed to investigate the risks factors for cardiovascular diseases and other related outcomes in Eastern Finland; the Kuopio Ishaemic Heart Disease Risk Factor Study. Ethical approval was obtained from the Research Ethics Committee of the University of Kuopio and the participants gave their written informed consent. Of 3235 eligible men, 2682 (82.9%) participated and were recruited into two cohorts. The first cohort had 1166 54-year old men recruited between March 1984 and August 1986 and the second cohort had 1516 42-60-year old men recruited between August 1986 and December 1989.

The following factors had missing data from some of the men: systolic blood pressure, 10 men; body mass index (BMI), 6 men; alcohol consumption, 3 men and plasma fibrinogen, 99 men. The mean value for all men is used as substitute for a value missing.

The present analysis, excluded men with existing coronary heart disease/ other cardiovascular diseases, diabetes mellitus and cerebrovascular disease at baseline.

4.2 Laboratory methods

Subjects gave blood specimens between 8 and 10AM. In addition to fasting, they were instructed to abstain from drinking alcohol for at least days prior and from smoking for at least 12 hours. A 30-minute rest period was allowed in the supine position before blood collection using vacuum tubes (Terumo Venoject; Terumo, Tokyo, Japan). No tourniquet was used.

Serum insulin level was determined using a radioimmunoassay kit (Novo Biolabs; Novo Nordisk, Bagsvaerd, Denmark (Jorgensen and Larsen 1980)). The serum samples were stored frozen at -80^{o}C for 0.2-2.5 years. The between batch coefficient of variation was 8.9% for 65pmol/L and 17.5% at 222pmol/L (n=10). The values obtained were immunoreactive insulin as the assay has cross reactivity with proinsulin. A glucose dehydrogenase method (Merck,

Darmstadt, Germany) was used to assess the blood glucose after precipitation of proteins by trichloroacetic acid. Insulin resistance was assessed using the fasting serum insulin as well as the homeostasis model assessment for insulin resistance (HOMA-IR). The HOMA-IR is a technique used for assessing insulin resistance and B cell function from fasting plasma glucose, serum insulin as well as C-peptide levels. It is both reliable and appropriate for an epidemiological study as opposed to the gold-standard and expensive euglycemic-hyperinsulinemic clamp method. It, not only compares the B-cell function and insulin sensitivity in subjects with abnormal glucose tolerance but also, compares the collection of longitudinal data on subjects who go on to develop abnormal glucose tolerance (Wallace 2004).

The cholesterol contents of lipoprotein fractions and serum triglycerides were measured enzymatically (Boehringer Mannheim, Mannheim Germany) on the day after the High density lipoprotein was separated from fresh samples by ultracentrifugation and precipitation. Plasma fibrinogen level was determined on the basis of clotting of diluting plasma with excess thrombin (Coagulometer KC4; Heinrich Amelung, Lemgo, Germany) while the blood leucocytes was assessed by a cell counter (Coulter Counter Electronics, Luton, England).

4.3 Alcohol consumption

A structured quantity and frequency method using the Nordic alcohol consumption inventory was used to assess alcohol consumption (Hauge et al 1981 & Kauhanen 1992). A structured response form was used to obtain information on the usual frequency of intake and usual quantity (in glasses and bottles) for each type of alcoholic drink (beer, wine, strong wine, spirits) and the total alcohol intake, timing or pattern of drinking (usual number of drinks per session were assessed. On the basis of the known alcohol content of each type of drink and reported quantity and frequencies of drinking sessions, the measures of average weekly intake of alcoholic beverages were calculated. In Finland, a third of a litre bottle of ordinary beer (class iii) contains 12g of ethanol; strong beer (class IV) contains 14g of ethanol, equivalent to one (1) portion of hard liquor. At baseline, blood samples for serum gamma-glutamyl

transpeptidase (GGT) and Mean Corpuscular Volume (MCV) were obtained as biomarkers for excessive alcohol intake.

4.4 Coronary deaths

Coronary heart disease deaths that occurred between the study entry (March 1984 to December 1989) and December 2008 were included. Deaths coded coronary heart disease (CHD), *International Classification of Diseases; Ninth Revision (ICD-9)* codes 410-414 and was validated according to the international criteria adopted by the World Health Organization (WHO) Monitoring of Trends and Determinants of Cardiovascular Disease (MONICA) project (Tuomilehto et al, 1992, Tuomilehto, Arstila et al, 1992, WHO MONICA, 2002). Between 1982 and 1992, the province of Kuopio participated in the multinational MONICA project during which the CHD deaths were determined by the coronary register group of the Finnish MONICA (FINMONICA) center (Tuomilehto, Arstila et al, 1992). Fatal coronary event data from January 1993 and December 2008 were obtained through computer linkage to national hospital discharge registry and diagnostic information and classification were collected from hospitals by an internist using identical diagnostic criteria (Lakka et al, 2002)

5 RESULTS

5.1 Baseline characteristics of participants

At baseline the fasting serum insulin concentration (mean and standard deviation) was 11.7mU/L and 7.35mU/L and it ranged from 1 to 77mU/L. Also, the mean alcohol consumption and standard deviation were 75.36g/week and 136.72g/week respectively, ranging from 0 to 2853g/week. The baseline characteristics of the study population in median of alcohol consumption are shown in table 1.

TABLE 1: BASELINE CHARACTERISTICS IN MEDIAN OF ALCOHOL CONSUMPTION

Variable	alcohol consumption (0-31g alcohol/week) (Mean) S.D	alcohol consumption (>31g alcohol/week) (Mean) S.D
Follow-up years	(20.08) 5.77	(18.96) 6.36
Age, years	(53.69) 4.78	(52.46) 5.32
Alcohol/week, g/week	(8.69) 9.03	(141.98) 168.70
Smoking (%)	22	42
Symptomatic IHD or IHD history (%)	26	24
Mean systolic blood pressure, mmHg	(133.48) 16.69	(135.10) 17.30
Body mass index, kg/m^2	(26.63) 3.45	(27.18) 3.63
Serum fasting insulin, mU/L	(11.59) 7.04	(11.82) 7.65
HOMA-IR	(2.85) 2.39	(2.91) 2.40
LDL-cholesterol, mmol/L	(4.03) 1.02	(4.06) 1.01
Plasma fibrinogen, g/L	(2.98) 0.55	(3.06) 0.54
Blood leukocyte count, $x10^9/L$	(5.60) 1.53	(5.81) 1.67

IHD- Ischaemic heart disease, HOMA-IR; homeostasis model assessment for insulin resistance, LDL; low density lipoproteins, S.D; standard deviation

The alcohol consumption level was directly associated with serum fasting insulin levels, HOMA-IR, mean systolic blood pressure, and blood leukocyte count. However, it was

inversely associated with the Body Mass Index (BMI) and the plasma fibrinogen with little or no difference in the low density lipoprotein (LDL) levels.

5.2 Important risk factors for coronary heart disease (CHD) deaths

Of 2588 cases read, 294 events occurred during the follow up period. Serum fasting insulin divided into quartiles using -25% as reference value (table 2), gave a significant (p=.003) hazard ratio (HR) of 1.771 (95% CI, 1.07-2.59) for the upper quartile (75-%) for coronary heart disease deaths. Conversely, the upper quartile (75-%) of the HOMA-IR was also significant (p<.001) with a HR of 1.92 (95% CI, 1.31-2.82).

TABLE 2: IMPORTANT RISK FACTORS FOR CORONARY HEART DISEASE DEATHS

Variable	Covariate Mean	HR (95%CI)	*P*
Serum fasting insulin 75-%	25.83	1.771 (1.07-2.59)	0.003
HOMA-IR 75-%	25.01	1.92 (1.31-2.823)	<0.001
Age, years	53.08	1.097 (1.065-1.131)	<0.001
Alcohol/week, g/week	75.36	1.001 (1.0-1.0015)	0.057
Smoking (%)	31.90	1.64 (1.25-2.13)	<0.001
Symptomatic IHD or IHD history (%)	25.12	2.31 (1.82-2.92)	<0.001
Mean systolic blood pressure, mmHg	134.28	1.016 (1.0054-1.018)	<0.001
LDL-cholesterol, mmol/L	4.042	1.16 (1.0-1.294)	0.009
Plasma fibrinogen, g/L	3.023	1.34 (1.082-1.651)	0.0072
Blood leukocyte count, $x10^9$/L	5.702	1.12 (1.04-1.21)	0.003

IHD; Ischaemic heart disease, HOMA-IR; homeostasis model assessment for insulin resistance, LDL; low density lipoproteins, HR; hazard ratio, 95%CI; 95% confidence interval

Other factors associated with increased risk of a CHD HR (95%CI, p-value) were: age; 1.097 (1.065-1.131, <0.001), smoking; 1.64 (1.25-2.13, <0.001), symptomatic or IHD history; 2.31

(1.82-2.92, <0.001), mean systolic blood pressure; 1.016 (1.0054-1.018, <0.001), LDL cholesterol levels; 1.16 (1.04-1.294, 0.009), plasma fibrinogen; 1.34 (1.082-1.65, 0.0072), blood leukocyte count; 1.12 (1.04-1.21, 0.003) and alcohol consumption; 1.001 (1.0-1.0015, 0.057).

5.3 Alcohol consumption, insulin resistance and risk of CHD deaths

Of 1158 cases read for the lower median of alcohol consumption, 130 events occurred while of 1129 cases read for the upper median of alcohol consumption, 164 events occurred. After adjusting for age, smoking, symptomatic and IHD history, cigarette smoking, body mass index (BMI), systolic blood pressure (SBP), LDL cholesterol levels, plasma fibrinogen, blood leucocyte; the risk for CHD mortality in the lower median of alcohol consumption (table 3)

TABLE 3: LOWER MEDIAN OF ALCOHOL CONSUMPTION (0-31g alcohol/week), INSULIN RESISTANCE AND RISK OF CORONARY HEART DISEASE DEATHS

Variables	(Mean) S.D	HR (95% CI)	*P*
Serum fasting insulin -25%	(5.89) 1.18		
Serum fasting insulin 25-50%	(8.66) 0.73	0.62 (0.33-1.15)	0.127
Serum fasting insulin 50-75%	(11.47) 1.02	1.12 (0.66-1.92)	0.675
Serum fasting insulin 75-%	(20.69) 9.38	1.59 (0.91-2.77)	<0.001
HOMA-IR -25%	(1.30) 0.26		
HOMA-IR 25-50%	(1.95) 0.17	0.94 (0.52-1.72)	0.85
HOMA-IR 50-75%	(2.68) 0.28	1.18 (0.66-2.13)	0.57
HOMA-IR 75-%	(5.59) 3.45	2.13 (1.19-3.79)	0.011

S.D; standard deviation, N; number of participants, HOMA-IR; homeostasis model assessment for insulin resistance, LDL; low density lipoproteins, HR; hazard ratio, 95%CI; 95% confidence interval
 # adjusted for age, symptomatic/ IHD history, cigarette smoking, BMI, SBP, LDL cholesterol, plasma fibrinogen, blood leucocyte

was 1.59 fold (95% CI 0.91-2.77, p<0.001) for the upper quartile of serum fasting insulin and 2.13 fold (95% CI 1.19-3.379, p=0.011) for the upper quartile of HOMA-IR.

Conversely, the risk for CHD mortality in the upper median of alcohol consumption after adjusting for the confounders (Table 4) was 1.99 fold (95% CI 1.18-3.35, p-0.0094) for the upper quartile of serum fasting insulin and 1.79 folds (95% CI 1.063-3.01, p-0.029) for the upper quartile of HOMA-IR.

TABLE 4: UPPER MEDIAN OF ALCOHOL CONSUMPTION (> 31g alcohol/week), INSULIN RESISTANCE AND RISK OF CORONARY HEART DISEASE DEATHS

Variables	**(Mean) S.D**	**HR (95% CI)**	***P***
Serum fasting insulin -25%	(5.89) 1.18		
Serum fasting insulin 25-50%	(8.66) 0.73	1.28 (0.78-2.102)	0.33
Serum fasting insulin 50-75%	(11.47) 1.02	0.93 (0.55-1.57)	0.79
Serum fasting insulin 75-%	(20.69) 9.38	1.99 (1.18-3.35)	0.0094
HOMA-IR -25%	(1.30) 0.26		
HOMA-IR 25-50%	(1.95) 0.17	1.12 (0.67-1.87)	0.67
HOMA-IR 50-75%	(2.68) 0.28	0.98 (0.59-1.62)	0.94
HOMA-IR 75-%	(5.59) 3.45	1.79 (1.063-3.01)	0.029

S.D; standard deviation, N; number of participants, HOMA-IR; homeostasis model assessment for insulin resistance, LDL; low density lipoproteins, HR; hazard ratio, 95%CI; 95% confidence interval
 # adjusted for age, symptomatic/ IHD history, cigarette smoking, BMI, SBP, LDL cholesterol, plasma fibrinogen, blood leucocyte

6 DICUSSION

In this population based sample of middle aged men in a prospective study, who at baseline had no diabetes, cancer, cerebrovascular and cardiovascular diseases; insulin resistance, alcohol consumption, age, smoking, symptomatic or ischaemic heart disease (IHD) history, mean systolic blood pressure, cholesterol levels, plasma fibrinogen, blood leucocyte count were shown to be risk factors of coronary heart disease (CHD) mortality. Insulin resistance and its risk for CHD were shown to be higher in those with higher alcohol intake. However, in the lower median of alcohol consumption; men in the highest quartile of fasting insulin levels and HOMA-IR had 1.59 fold and 2.13 fold CHD mortality respectively, as compared to those in the lowest quartile. Likewise, in the upper median of alcohol consumption; men in the highest quartile of fasting insulin levels and HOMA-IR had 1.99 fold and 1.79 fold CHD mortality as compared to those in the lowest quartile. It is obvious that the serum fasting insulin levels and HOMA-IR are comparative measures of insulin resistance. The expected increase in risk of CHD mortality in the upper median of alcohol consumption as compared to the lower median of alcohol consumption was seen in fasting serum insulin levels but not in the HOMA-IR; of which we cannot explain but may be attributable to the population in question. Insulin resistance was associated with increased CHD mortality which was further enhanced by excessive alcohol consumption.

In the studies by Lazarus et al (1997), Renate et al (2003), Mayer et al (1993) and Flanagan et al (2000), they found that moderate regular alcohol use may be associated with lower levels of insulin resistance which is consistent with our study. Bell et al (2000) suggested that the enhanced insulin sensitivity with light-to-moderate alcohol consumption may be a function solely of a body mass index (BMI) and central adiposity profile more favorable to higher insulin sensitivity. Amongst non-diabetic adults in Malmo, Sweden, insulin resistance estimated by HOMA-IR was associated with coronary events and all-cause mortality (Hedblad et al 2002). Similarly, non-diabetic persons with normal BMI in the United States had HOMA-IR associated with all-cause mortality (Ausk et al 2010). High fasting insulin concentrations were shown to be independent predictors of coronary heart disease (CAD) in a study by Despre's et al (1996).

The biological mechanisms underlying the association between alcohol consumption and insulin resistance are not known, however, suggested mechanisms indicate alterations in hepatic glucose metabolism with decreased gluconeogenesis (Krebs 1968, Flanagan et al 2002), alteration of the counter regulatory hormones actions (Lecavalier et al 1989, Kirkman and Nelson 1988, Jenjins and Connolly 1968, Eisenhofer et al 1983), a direct effect on beta cells of the pancreas (Flanagan et al 2000), or through a reduction in the sympathetic activity (Flanagan et al 2002). However, the differential effect of low as opposed to high doses of ethanol was suggested to be attributable to the ability of low doses of alcohol to increase the antioxidant activity, lower insulin resistance and reduce advanced glycation end products (AGEs) thereby preventing hypertension and atherosclerosis, whereas, the reverse is the case for high doses (Vasdev et al 2006). Furthermore, low dose alcohol exerts its beneficial effect on the cardiovascular system through the release of NO (Puddey et al, 2001) which explains the vasodilator effect of alcohol.

The pathogenic mechanism by which insulin resistance is thought to induce CHD is said to be through its direct atherogenic action on vessel wall cells and indirectly through upper body obesity, lipids and homeostasis (Janku 1994); and it has been associated with higher levels of triglycerides, lower levels of HDL-C, elevated blood pressure, non-insulin dependent diabetes mellitus (NIDDM) (Mayer et al 1993). One of the key vascular actions of insulin is to stimulate production of the potent vasodilator nitric oxide (NO) from the endothelium via the phosphatidyl inositol 3 kinase (PI3K) pathway which in turn, enhances glucose uptake in skeletal muscles while simultaneously, stimulating the production of endothelin-1 (ET-1), a potent vasoconstrictor that opposes the actions of NO and via the mitogen activated protein kinase (MAPK) pathway (Muniyappa and Quon, 2007). The MAPK signaling pathway control the prohypertensive effects of insulin promoting the secretion of ET-1, activate cation pumps, increase expression of vascular cell adhesion molecules-1 (VCAM-1) and other adhesion molecules.

The key feature of insulin resistance is that it is characterized by specific impairment of PI3K-dependent signaling pathway while other insulin-signaling pathways including the Ras/MAPK-dependent pathways are unaffected (Jiang et al 1999, Cusi et al 2000).

Pathophysiologically, the implication is that compensatory hyperinsulinemia which often accompanies metabolic insulin resistance to maintain euglycemia in the vasculature and elsewhere overdrives the unaffected MAPK-dependent pathways resulting in an imbalance between the PI3K and MAPK-dependent functions of insulin (Kim et al 2006). This preferential signaling contribute to the progression of atherosclerosis by promoting the secretion of ET-1, activate cation pumps, increase vascular smooth muscle cell (VSMC) migration in the expression of cell adhesion molecules (VCAM-1, E-selectin) and cell interactions between vascular cells and macrophage/ monocytes (Montagnani et al 2002, Kim et al 2006); subsequently, stimulated VSMC increase the production of plasminogen activator inhibitor type 1 (PAI-1) resulting in reduced fibrinolysis and increased vascular occlusion (Nigro et al 2006). In as much as hyperinsulinaemia compensates for resistance to some biological actions of insulin, it results in overexpression of actions of insulin in tissues that retain normal or minimal impairment in insulin sensitivity thereby, contributing to the maintenance of the insulin resistance (Wheatcroft et al 2003). Thus, under conditions of insulin resistance, the antihypertensive effects of insulin to produce vasodilator, NO are reduced.

Our study which is a population-based study had no loss to follow-up, and we are confident these are strong points even though the population has one of the highest CHD risks in the world; impacts of other risk factors were evaluated thoroughly. However, we did have some limitations which stem from the fact that our population is an aging population and this could have affected the outcome; information on alcohol which was self-reported and insulin resistance were obtained at baseline; and our classification of alcohol into median of consumption did not allow for differentiation of no-drinkers from low to moderate drinkers. This study constituted of only middle-aged men, therefore caution is needed in interpretation and inference of our results on women.

7 CONCLUSION

Insulin resistance is directly associated with CHD mortality and this was further enhanced by excessive alcohol consumption. The presence of alcohol in the equation resulted in a U-shaped relationship between insulin resistance and CHD. We, therefore conclude that even though insulin resistance is an independent risk factor for CHD mortality, alcohol consumption modifies this relationship.

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