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Cardiovascular and Renal Complications in Obesity and Obesity-Related Medical Conditions: Role of Sympathetic Nervous Activity and Insulin Resistance

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1. Introduction

Elevated sympathetic activation, as assessed using a variety of indices, has been observed in lean hypertensive and diabetic patients, and obese individuals [Huggett *et al.* 2006; Masuo *et al.* 2000]. Similarly, many epidemiological studies have shown that hypertensive patients, even those without increased adiposity, display a higher prevalence of insulin resistance, thereby indicating the possible association between sympathetic activation and insulin resistance in the pathogenesis of hypertension [Esler *et al*. 2006; Masuo *et al*. 2002; de Silva *et al*. 2009]. Overweight and obesity is a growing problem across the globe and has reached "epidemic" proportions. The prevalence of diabetes, especially type 2 diabetes, and hypertension are significantly increased with the prevalence of obesity. Obesity, itself, and type 2 diabetes and hypertension associated with obesity are known to be more closely linked with insulin resistance and elevated sympathetic nervous activity. It has been well documented that obesity, hypertension, and diabetes are risk factors for subsequent cardiovascular and renal complications. Many patients are both diabetic and hypertensive while they are obese, but not all diabetic patients have hypertension, indicating that insulin resistance is not the only mechanism for blood pressure elevation in diabetic-hypertensive patients. Several investigators have reported that sympathetic nervous activation plays an important role in cardiovascular complications in patients with hypertension, diabetes, and obesity.

Sympathetic nervous activation accompanying insulin resistance is closely linked with left ventricular hypertrophy in otherwise healthy subjects [Masuo, *et al.* 2008]. In addition,

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sympathetic activation may predict the development of renal injury in healthy normotensive subjects [Masuo, *et al.* 2010]. Weight loss associated suppression of sympathetic nervous activity is associated with improvement of insulin sensitivity and resultant improvement in renal function in obese patients [Masuo, *et al.* 2011b; Straznicky, *et al.* 2009b & 2011]. Furthermore, weight loss improved the prevalence of left ventricular hypertrophy [Masuo, *et al.* 2008], which is one of the predictors for future cardiac complications, renal complications (injury) [Masuo, *et al.* 2007] and hyperuricacidemia [Straznicky, *et al.* 2011].These findings suggest that elevated sympathetic nerve activity associated with insulin resistance may contribute to the onset and maintenance of cardiovascular and renal complications in diabetes, and hypertension in obesity.

Furthermore, genetic polymorphisms of the β2- and β3-adrenoceptor gene have been associated with obesity [Masuo, *et al.* 2005 & 2011a; Kawaguchi, *et al.* 2006], hypertension [Masuo, et al. 2005b & 2010b; Kawaguchi, et al. 2006], type-2 diabetes and insulin resistance [Masuo, et al. 2005 & 2010} in epidemiological studies and may also be implicit in the close relationship between insulin resistance and sympathetic nerve activation. Recently, Masuo *et al*. reported that β2-adrenoceptor polymorphisms (Arg16Gly) accompanying high plasma norepinephrine levels may contribute to the prevalence of left ventricular hypertrophy and renal dysfunction [Masuo, *et al.* 2010a, b & 2011b]. These investigations suggest that β2-adrenoceptor polymorphisms are related to sympathetic activation and insulin resistance and may contribute to cardiovascular- and renal complications in obesity and obesity-related hypertension or type 2 diabetes.

This chapter will provide a synthesis of the current findings on the mechanisms of the onset and maintenance of cardiovascular and renal complications in obesity, hypertension and type 2 diabetes, with a particular focus on sympathetic nervous activity and insulin resistance. A better understanding of the relationships between sympathetic nervous activity and insulin resistance in these important clinical conditions might help with the clinical treatment of diabetes and hypertension in obesity and prevent further cardiovascular and renal complications in this at risk group.

2. Prevalence of type 2 diabetes and hypertension in obesity

The clustering of cardiovascular risk factors associated with obesity, in particular abdominal obesity, is well established [Athyrus, *et al.* 2011]. The prevalence of obesity and overweight increased in the United States between 1978 and 1991 [Mokdad, *et al.* 2001], and recent reports have suggested continuing increases [Ogden, et al. 2004]. The National Health and Nutrition Examination Survey (NHANES) I (1971-1974), NHANES II (1976-1980), and NAHNES III (1988-1994) were conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC). These data from the continuous NHANES studies have showed that the prevalence of obesity and overweight people increased significantly in the United States between 1960 and 2003 [Preis, *et al*. 2009; Ogden, *et al*. 2004; Flegal, *et al.* 2012]. Evidence from several studies indicates that obesity and weight gain are associated with an increased risk of hypertension [Masuo, *et al.* 2000 &

2005a, b, c] and diabetes [Resnick, *et al.* 2000; Ford, *et al*. 1997], and that intentional weight loss reduces the risk that overweight individuals will develop hypertension [Masuo, *et al.* 2001b; Straznicky, *et al.* 2009b] or diabetes [Will, *et al.* 2002].

Recent large cohort studies have showed an increasing prevalence of obesity in children and, importantly, obesity in children is strongly associated with several major health risk factors, including type 2 diabetes mellitus and hypertension [Hedley, *et al.* 2004].

Focusing on the close associations between obesity, hypertension and diabetes, the NHANES and the Behavioural Risk Factor Surveillance System (BRFSS) investigations [Mokdad, *et al.* 2003] showed very close relationships between the prevalence of obesity, hypertension, and diabetes. Further, the Framingham Heart Study [Preis, et al. 2009] showed that diabetic subjects had a 2-fold higher mortality risk consisting of cardiovascular and non-cardiovascular mortality.

3. Sympathetic nervous activity in obesity, hypertension and diabetes

The sympathetic nervous system represents a major pathophysiological hallmark of both hypertension and renal failure, and is an important target of the therapeutic intervention [Grassi, *et al*. 2012; Schlaich, *et al.* 2009]. The sympathetic nervous system participates in regulating the energy balance through thermogenesis. Reduced energy expenditure and resting metabolic rate are predictive of weight gain (obesity). It is also widely recognized that insulin resistance or hyperinsulinemia relates to obesity [Minicardi, *et al.* 1996; Farrannini, *et al.* 1995; Ward, *et al.* 1996]. Many epidemiological and clinical studies have shown a close relationship between sympathetic nervous system activity and insulin levels in obesity [Masuo. *et al.* 2002]. Several studies of longitudinal design have examined the effect of body weight changes (weight loss or weight gain) on sympathetic nervous system activity and insulin sensitivity (fasting plasma insulin levels and the (homeostasis model assessment of insulin resistance,   HOMA-IR). Elevations of sympathetic nervous system activity and insulin levels during weight gain [Masuo, *et al.* 2000; Gentale, *et al.* 2007; Barms, *et al.* 2003], and reductions of sympathetic activity and insulin levels during weight loss [Anderson, *et al.* 1991; Straznicky, et al. 2009], are typically observed. While these longitudinal studies have clearly shown that heightened sympathetic nerve activity and insulin resistance are closely linked to obesity (weight gain), the onset of obesity and the maintenance of obesity, it remains to be elucidated, whether sympathetic hyperactivity or insulin resistance is the prime mover.

The response of the sympathetic nervous system to change in plasma insulin levels after oral glucose loading (oral glucose tolerance test) are different between subjects with and without insulin resistance [Masuo, *et al.* 2005], between nonobese and obese subjects [Straznicky, *et al.* 2009a], and between subjects with and without the metabolic syndrome [Straznicky. 2009b]. Recently, changes in the sympathetic nerve firing pattern were observed with sympatho-inhibition during weight loss [Lambert, *et al*. 2011]. In addition, different regulation by insulin of regional (i.e. hind limb, kidney and brown adipose tissue) sympathetic outflow to peripheral tissue was observed in agouti obese mice compared to lean control mice [Morgani,

et al. 2010]. These observations provide the evidence of a strong linkage between the activity of the sympathetic nervous system and insulin levels. Huggett *et al.* [Huggett, *et al.* 2003] examined muscle sympathetic nerve activity (MSNA) in four groups of subjects, patients with essential hypertension and type 2 diabetes, patients with type 2 diabetes alone, patients with essential hypertension alone, and healthy normotensive controls. They found higher MSNA in the hypertensive-type 2 diabetic patients as compared with hypertensive alone patients or type 2 diabetic alone patients, and higher MSNA in hypertensive alone patients or type 2 diabetic alone patients as compared with healthy normotensive controls. Fasting insulin levels were greater in hypertensive-type 2 diabetic patients and type 2 diabetic patients compared to hypertensive patients or healthy normotensive subjects. These findings, although obtained in patients still under medication, provided evidence that type 2 diabetic patients had elevated sympathetic nerve activity regardless of the prevailing blood pressure levels, and that the combination of hypertension and type 2 diabetes resulted in an augmentation in sympathetic nerve activity and levels of plasma insulin.

Several investigations on the contributions of β2- and β3-adrenoceptor polymorphisms to type 2 diabetes also support a strong relationship between sympathetic nerve hyperactivity and insulin resistance in type 2 diabetes [Masuo, *et al.* 2004 & 2005a, b; Ikarashi, *et al.* 2004].

Figure 1 summarizes the relationships between sympathetic nerve activity and insulin resistance in obesity and type 2 diabetes mellitus (**Figure 1**).
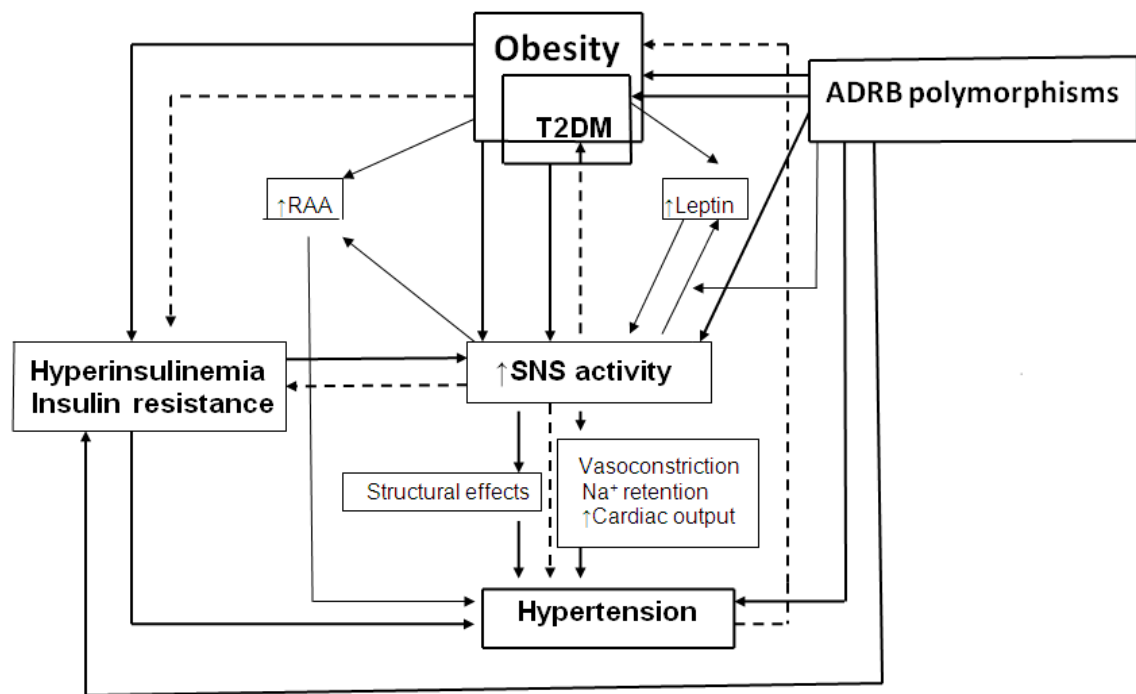
Obesity causes both insulin resistance/hyperinsulinemia and sympathetic nervous activation, and both link closely each other. Many investigations have shown that insulin resistance, sympathetic nervous activation, and adrenoceptor polymorphisms play important roles in the onset and maintenance of obesity, type 2 diabetes and hypertension. T2DM, type 2 diabetes, RAA, renin-angiotensin-aldosterone system; ADRB polymorphisms, adrenoceptor polymorphisms; SNS, sympathetic nervous system.

Figure 1. Potential pathophysiological mechanisms in obesity, hypertension and type2diabetes (T2DM)

4. Insulin resistance in obesity, hypertension and type 2 diabetes

Insulin resistance [Ferrannini, *et al.* 1998] is one of the criteria underpinning the development of the metabolic syndrome. The clinical evaluation of insulin resistance is growing interest because it is a strong predictor and plays an important role in the development of the metabolic syndrome, type 2 diabetes mellitus and hypertension. **Table 1** shows the criteria for metabolic syndrome characterisation, as can be seen insulin resistance is prominent [Alberti, *et al.* 1998; Grundy, *et al.* 2004] (**Table 1**). Measuring insulin sensitivity is important to define insulin resistance. **Table 2** summarizes the methods usually used in clinical and epidemiological studies (**Table 2**). The hyperinsulinemic-euglycemic glucose clamp method is the gold standard and may be suitable for research investigations in specialized laboratories, but the homeostasis model assessment of insulin resistance (HOMA-IR) or fasting plasma insulin concentrations is more practical for epidemiological studies comprising a large number of subjects.

4.1. Hyperinsulinemia as a marker of insulin resistance

Insulin is an exceptional hormone in that its action is regulated not only by changes in concentration but also by changes in the sensitivity of target tissues. Inadequate insulin action can be the consequence of: (*i*) insufficient insulin concentration at the site of action, (*ii*) decreased tissue (effectors) responses to insulin, or (*iii*) a combination of low concentration and a decreased response. Regulation of circulating insulin levels is mainly (but not exclusively) achieved by changes in secretory rates. Nevertheless, the major determinant of insulin secretion, and therefore of plasma insulin concentration, is glucose. Any change in glucose concentration from the narrow normal range results in an insulin response appropriate to restore homeostasis. Thus, changes in insulin sensitivity occur in various physiological states and pathological conditions.

For any amount of insulin secreted by the pancreas, the biological response of a given effector is dependent on its insulin sensitivity. The term insulin resistance customarily refers to glucose metabolism. Any decrease in insulin sensitivity (insulin resistance) is immediately translated into minute increases in blood glucose concentrations that will in turn act on the β-cell to produce a compensatory stimulus of insulin secretion, leading to a degree of hyperinsulinemia that is approximately proportional to the degree of effector resistance. Therefore, hyperinsulinemia may be responsible for insulin resistance. In steady-state conditions, this compensatory hyperinsulinemia prevents a more exaggerated hyperglycaemia. The inability of β-cells to enhance insulin secretion means that blood glucose will keep increasing until the level of hyperglycaemia produces an adequate β-cell stimulus to attain the required insulin response. When the β-cell is unable to compensate for the prevalent insulin resistant state by further augmenting insulin secretion, hyperglycaemia continues to increase, producing impaired fasting glucose, impaired glucose tolerance and diabetes mellitus development.

	WHO (51)	EGIR (52, 53)	NCEP AT III (Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults) (54)	American Heart Association Updated NCEP III (55)
Insulin resistance	Top 25% of population Distribution	Top 25% of population distribution	Not considered	Not considered
Hyperinsulinemia	Not considered	Top 25% of population distribution	Not considered	Not considered
Fasting glucose (mmol/L) hyperglycemia	impaired fasting glucose, or impaired glucose tolerance or diabetes	>6.1, but not diabetic	≥6.1	≥5.6 (100 mg/dL) or medications for
Hypertension (mmHg)	≥160/≥ 90	≥140/≥ 90 or on medications for hypertension	≥130/85	≥130/85 or medications for hypertension
Central obesity	waist/hip ratio >0.9 (men), >0.85 (women) and/or BMI≥30kg/m^2	---	---	---
Waist circumference (cm)	Not considered	≥94 (men), ≥ 80 (women)	>102 (men), >88 (women)	≥102 (men), ≥88 (women)
HDL-cholesterol (mmol/L)	<1.0 or medications for dyslipidemia	<1.0 or medications for dyslipidemia	<1.07 (40 mg/dL, men), <1.25 (50 mg/dL , women)	<1.07 (40 mg/dL, men) <1.25 (50 mg/dL, women)
Triglyceride (mmol/L)	<1.0 or medications for Dyslipidemia	>2.0 or medications for dyslipidemia	≥1.695 (150 mg/dL)	≥1.695 (150 mg/dL)
Micro-albuminemia	Present	Not considered	Not considered	Not considered
Criteria	1 of the first two + 2 of other features	1of the first two + 2 of other features	3 of above	3 of above

BMI, body mass index; EGIR, European Group of the study of Insulin Resistance; NCEP ATPIII, 3rd Recommendations of the Adult Treatment Panel of the National Cholesterol Education Program; HDL-cholesterol, high-density lipoprotein cholesterol. Values in NECP definition and American Heart Association/Updated NCEP are approximations of values in mg/dL.

Table 1. Criteria for Metabolic Syndrome including Insulin Resistance (50)

Methods	Summary/Comments (reference number)
Plasma insulin concentrations	Measurement of insulin concentrations under physiological concentrations (i.e. fasting, postprandial) correlates with IR Useful especially in epidemiological studies including a large number of subjects.
Oral glucose tolerance test (OGTT)	The OGTT contains critical information regarding insulin secretion and sensitivity. (1) The AUC of plasma insulin or C-peptide provides some indication of insulin secretion. The AUCIns/AUCGluc appears to be a good parameter to assess beta-cell function from an OGTT in either diabetic or non-diabetic subjects. (2) ISI provides a reasonable approximation of whole-body insulin sensitivity that represents a composite of hepatic and peripheral tissues and considers insulin sensitivity both in the basal state (fasting glucose · fasting insulin) and after the ingestion of a glucose load (mean glucose · mean insulin). ISIcomp = 10,000/square root of [fasting glucose · fasting insulin] · [mean glucose · mean insulin during OGTT]. (56)
HOMA-IR (homeostasis model assessment of insulin resistance)	Index based on fasting glucose and insulin concentration. Fasting insulin (U/mL) x fasting glucose (mmol/L)/22.5. HOMA-IR correlates strongly with the results of clamping studies. (57, 58)
QUICKI (quantitative insulin sensitivity check index)	QUICKI is said to provide a reproducible and robust estimate of insulin sensitivity that shows excellent linear correlation with the gold standard clamp measurement and has similar variability and discriminative power QUICKI=1/[log (fasting insulin)+log (fasting glucose)], thus QUICKI is the logarithm of the values from one of the HOMA equations. (59)
HOMA-B (homeostasis model assessment of insulin secretion)	HOMA-B allows the beta-cell function (HOMA-B) to be deduced for a given subject from pairs of fasting glucose and insulin (or C-peptide) measurements. HOMA-B=insulin (U/mL) x 20/[glucose (mmol)-3.5].
Minimal model	Estimating IR from results of frequent blood samples during intravenous glucose tolerance test (IVGTT)
Insulin tolerance test	High dose insulin is given intravenously and the decline of glucose concentration measured.
Steady state plasma glucose (SSPG)	A sophisticated method but currently little used. Subjects are infused continuously with an intravenous infusion of somatostatin to suppress endogenous insulin and glucose secretion for 150 min, and determined the steady state plasma glucose levels. Subjects with SSPG>150 mg/dL are considered to be IR. (60) shows the insulin secretary index rather than insulin sensitivity.

Methods	Summary/Comments (reference number)
Clamp methods	
Hyperinsulinemic, euglycemic clamp	The gold standard for investigating and quantifying IR. The amount of glucose necessary to compensate for an increased insulin level without hypoglycemia and to maintain blood glucose level (5.0-5.5 mmol/dL) is determined by continuously glucose infusion. Low dose insulin infusion is more useful for assessing the response of liver, whereas high dose insulin infusion are useful for assessing peripheral (i.e. fat, muscle) insulin action. Required glucose infusion rate ≤4.0 mg/min=insulin resistance, 4.0-7.5 mg/min=impaired glucose tolerance, ≥7.5 mg/min=insulin sensitive.
Hyperglycemic clamp	Sustained hyperglycemia can cause peripheral IR, pancreatic beta-cell dysfunction, and resultant glucose toxicity or glucose desensitization. The amount of insulin necessary to maintain a steady high blood glucose level (220 mg/dL)

IR, insulin resistance; AUS, the area under the curve; ISI, insulin sensitivity index

Table 2. Methods for Measuring Insulin Sensitivity

4.2. Relationships between sympathetic nervous activity and insulin resistance in obesity, hypertension, and type 2 diabetes

It is widely recognized that insulin resistance or hyperinsulinemia relates to obesity [Ferrannini, *et al.* 1991 & 1995; Ward, *et al.* 1996], but the precise relationships linking those factors remain controversial. Many epidemiological and clinical studies have shown a close relationship between sympathetic nervous system activity and insulin levels in obesity [Anderson, *et al.* 1991; Ward, *et al.* 1996; Masuo, *et al.* 2002]. Several studies of longitudinal design have examined the effect of body weight changes (weight loss or weight gain) on sympathetic nervous system activity and insulin sensitivity (fasting plasma insulin levels and HOMA-IR). Elevations of sympathetic nervous system activity and insulin levels during weight gain [Masuo, *et al.* 2000; Bernes, *et al.* 2003; Gentle, et al. 2007} and reductions of sympathetic nerve activity and insulin levels during weight loss [Masuo, *et al.* 2001; Andersson, *et al.* 1991; Straznicky, *et al,* 2010] have been observed. These longitudinal studies have shown that heightened sympathetic nerve activity and insulin resistance are closely linked to obesity (weight gain), the onset of obesity and the maintenance of obesity. In addition, a calorie restricted diet and exercise may have different mechanism on weight loss-induced blood pressure reduction. **Figure 2** shows changes in neurohormonal parameters over a 24-week period weight loss regimens with a mild calorie restricted diet alone, mild exercise alone, or a combination with a mild calorie restricted diet and mild exercise. This study showed that a calorie restricted diet contributed strongly to normalization/suppression of sympathetic activation, and exercise related to insulin resistance. In addition, calorie restricted diet and exercise may have different mechanisms on weight loss-induced blood pressure reduction [Masuo, et al. 2012a].

Reduced energy expenditure and resting metabolic rate are predictive of weight gain and obesity development. The sympathetic nervous system participates in regulating energy balance through thermogenesis **(Figure 1)**. Landsberg and other investigators hypothesized that energy intake stimulates hyperinsulinemia and sympathetic nerve activity resulting in blood pressure elevations in a cycle in order to inhibit thermogenesis. Insulin-mediated sympathetic nerve stimulation in obese subjects is therefore considered part of a compensatory mechanism aimed at restoring the energy balance by increasing the metabolic rate [Landsberg. 2001]. Hyperinsulinemia and insulin resistance in obese subjects are all part of a response to limit further weight gain via stimulating sympathetic nerve activity and thermogenesis [Landsberg, 2001].

On the other hand, Julius and Masuo generated a hypothesis based on data from their longitudinal studies that increased sympathetic nerve activity in skeletal muscle causes neurogenic vasoconstriction, thereby reducing blood flow to muscle and consequently inducing a state of insulin resistance by lowering glucose delivery and uptake in hypertension and obesity. Both blood pressure elevations and weight gain may reflect a primary increase in sympathetic nervous tone. Masuo *et al.* [Masuo, *et al.* 1997, 2000, and 2003] demonstrated that high plasma norepinephrine could predict future blood pressure elevations accompanying deterioration in insulin resistance. This was observed in HOMA-

IR (homeostasis model assessments of insulin resistance) in nonobese, normotensive subjects using longitudinal studies. Rocchini *et al.* [Rocchini, *et al.* 1990] reported that clonidine prevented insulin resistance development in obese dogs over a 6-week period, suggesting that sympathetic nervous activity might play a major role in the development of insulin resistance accompanying blood pressure elevation. The longitudinal studies [Straznicky, *et al.* 2005, 2009b & 2012. Masuo, *et al.* 2000, 2001b, 2003, 2005a, 2012] might provide strong evidence for a close linkage of high sympathetic nervous activity accompanying insulin resistance with the onset of hypertension. Heightened sympathetic nerve activity might play a major role in blood pressure elevations, and insulin resistance might play an ancillary mechanism for blood pressure elevation and genesis of hypertension. In hypertensive patients who already have heightened sympathetic nerve activity and insulin resistance, both heightened sympathetic nerve activity and insulin resistance are related to further blood pressure elevations.
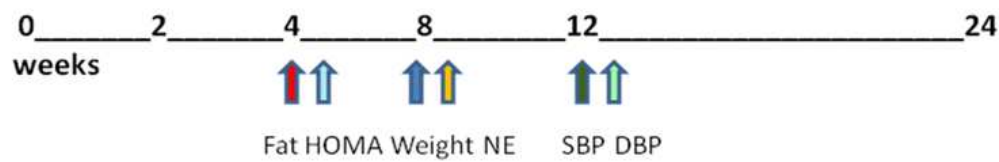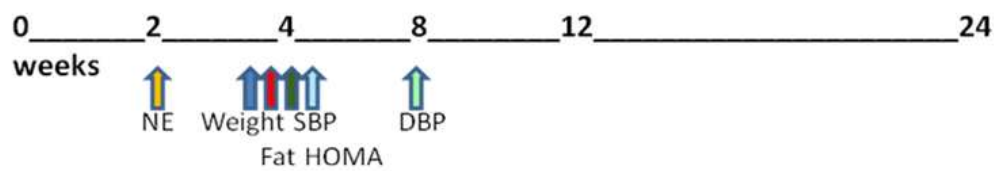

During weight loss with a mild calorie restricted diet, normalization of sympathetic activation measured by plasma norepinephrine was observed following significant weight loss and normalization of insulin resistance (HOMA-IR). On the other hand, in exercise alone group, normalization of insulin resistance was observed, and then weight loss and suppression of sympathetic activation. A low caloric diet and exercise may exert different effects on weight loss. NE, plasma norepinephrine levels; Fat, total body fat-mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA, homeostasis model of assessment of insulin resistance. [Masuo, et al. 2012]

Figure 2. When significant changes were observed comparisons between a calorie restricted diet vs. mild exercise alone vs. combination with diet + exercise over 24 weeks

Very recently, Masuo *et al.* [Masuo, *et al.* 2012} showed the differences in mechanisms of weight loss-induced blood pressure reductions with neurohormonal parameters changes over 24 weeks with loss regimens **(Figure 2)**. A calorie restricted diet caused

suppression/normalization of sympathetic activation measured with plasma norepinephrine levels followed by improvements of insulin resistance, whereas exercise improved insulin resistance followed by normalization of norepinephrine levels. BMI and blood pressure decreased after significant reductions in both plasma norepinephrine and HOMA-IR **(Figure 2)**. Their investigations may help to explain why discordant results have been observed. However, at least their hypotheses showed a strong linkage between sympathetic activation, insulin resistance, obesity and hypertension.

Valentine *et al.* [Valentine, *et al.* 2004] reported attenuation of hemodynamic and energy expenditure responses to isoproterenol infusion in hypertensive patients. Their findings that a generalized decrease of β-adrenergic responsiveness in hypertension supports the hypothesis that heightened sympathetic nerve activity through down-regulation of β-adrenoceptor-mediated thermogenesis, may facilitate the development of obesity in hypertension. Their results suggested that sympathetic nerve activity-induced hypertension may subsequently lead to the development of obesity.

Hoffmann *et al.* [Hoffmann, *et al.* 1999] investigated the effects of the acute induction of hyperglycemia on sympathetic nervous activity and vascular function in eight young normal control subjects. Muscle sympathetic nerve activity (MSNA) and forearm vascular resistance were measured before and during systemic infusion of 20% dextrose with low dose insulin with 60 min of hyperglycemia. Acute hyperglycemia caused sympathetic activation and peripheral vasodilation. Moreover, both acute and chronic hyperglycemia and hyperinsulinemia may enhance adrenergic vasoconstriction and decrease vasodilation in animal models (pithed rats) [Takatori, *et al.* 2006; Zamai, *et al.* 2008]. Insulin causes forearm vasoconstriction in obese, insulin resistant hypertensive humans [Gudbjornsdotti, *et al.* 1998]. On the other hand, van Veen *et al.* [van Veen, *et al.* 1999] found that hyperglycemia induced vasodilation in the forearm, but this vasodilation was not modified by hyperinsulinemia.

4.3. Sympathetic nervous activity and leptin in obesity and the metabolic syndrome

Interactions between the sympathetic nervous system and leptin are widely acknowledged with each being able to influence the other. Indeed, the leptin system mediates some of its action through the sympathetic nervous system [Haynes, et al. 1997; Kuo, et al. 2003]. Trayhurn *et al.* [Trayhurn, *et al.* 1995; Hardie, *et al.* 1996] investigated the effect of acute sympathetic nerve activation caused by exposure to cold on the expression of the leptin gene in white adipose tissue of lean mice, but not in obese mice. In addition, Masuo *et al.* reported the blunted linkage between the sympathetic nervous system and leptin in obese subjects [Masuo, *et al.* 2006; Kawaguchi, *et al.* 2006]. These studies, together with others, indicate that both insulin resistance and leptin may be regulated by the sympathetic nervous system.

Masuo *et al.* [Masuo, *et al.* 2008] showed during oral glucose loading that plasma insulin and plasma norepinephrine increased in both insulin-sensitive and insulin-resistant subjects, but

plasma leptin levels decreased in insulin-sensitive nonobese subjects and increased in insulin- resistant nonobese subjects. Straznicky *et al*. [Straznicky, *et al.* 2005] also reported the blunted responses of whole-body norepinephrine spillover, insulin, and plasma leptin during oral glucose loading in obese subjects with insulin resistance as compared to insulin sensitive subjects. In subjects with the metabolic syndrome, weight loss with a low caloric diet diminished the whole-body and regional sympathetic nerve activity, as indicated by determinants of the whole-body norepinephrine spillover to plasma and muscle sympathetic nerve activity. Of interest, the decrease in norepinephrine spillover to plasma after weight loss was positively and independently associated with the decrease in plasma leptin, but not with insulin sensitivity in overweight insulin resistant subjects, while in overweight subjects without insulin resistance, the decrease in plasma norepinephrine after weight loss correlated with the improvement of insulin sensitivity.

4.4. Sympathetic nervous activity and insulin resistance in the metabolic syndrome

The metabolic syndrome is a cluster of abnormalities with basic characteristics being insulin resistance and visceral obesity. The criteria/definitions of metabolic syndrome are shown in **Table 1**. Importantly, obesity and the metabolic syndrome are associated with significant co-morbidities, such as type 2 diabetes, cardiovascular disease, stroke, and certain types of cancers.

Huggett *et a*l. [Huggett, *et al.* 2003 % 2004] demonstrated in a series of studies using microneurography (muscle sympathetic nerve activity, MSNA) that type 2 diabetic patients had elevated sympathetic nerve activity regardless of the prevailing level of blood pressure, and that the combination of hypertension and type 2 diabetes resulted in an augmentation in sympathetic nerve activity and levels of plasma insulin. They also compared MSNA and insulin levels in 23 non-diabetic offspring of type 2 diabetic patients and 23 normal control individuals [Huggett, *et al.* 2006]. In non-diabetic offspring of type 2 diabetic patients, the fasting plasma levels of insulin and MSNA were greater (p<0.009 and p<0.003) than control subjects. Sympathetic nerve activity was significantly correlated to insulin levels (p<0.0002) and resistance (p<0.0001) in offspring of type 2 diabetic patients, but not in control subjects. Sympathetic activation occurred in not only subjects with the metabolic syndrome, diabetic patients, but also in normotensive non-diabetic offspring of patients with type 2 diabetes with the degree of activation being in proportion to their plasma insulin levels. This series of studies indicates the presence of a mechanistic link between hyperinsulinemia and sympathetic activation, both of which could play a role in the subsequent development of cardiovascular risk factors.

5. Cardiovascular and renal complications in obesity, obesity-related hypertension and diabetes

It has been documented that patients with obesity, hypertension and type 2 diabetes frequently have cardiovascular and renal complications. Obesity was closely associated with

an increase in blood pressure, left ventricular mass, and with early signs of disturbed left ventricular diastolic function [Wikstrand, *et al.* 1993], and changes in left ventricular morphology and diastolic function [Alpert, *et al.* 2012]. It is well known that sudden cardiac death is the most common cause of death in dialysis patients and is usually preceded by sudden cardiac arrest due to ventricular tachycardia or ventricular fibrillation [Alpert, *et al.* 2011]. Left ventricular (LV) mass and loading conditions that may affect LV mass are important determinants of corrected QT intervals (QTc) in normotensive severely obese subjects [Mukergi, *et al.* 2011]. The RICARHD study (Cardiovascular risk in patients with arterial hypertension and type 2 diabetes study), was a multicenter and cross-sectional study, conducted in Spain and included 2,339 patients who were 55 years or more with hypertension and type 2 diabetes of greater than 6 months duration. Left ventricular hypertrophy (LVH) or renal damage (GFR<60 ml/min/1.73 m2 and/or albumin/creatinine ratio ≥0 mg/g or an urinary albumin excretion ≥30 mg/24 hours) were compared between these hypertensive and type 2 diabetes patients and healthy controls. The combined presence of both hypertension and type 2 diabetes were associated with an increased prevalence of established cardiovascular diseases. Similarly, the presence of both cardiac and renal damage was associated to the higher prevalence of cardiovascular diseases [Cea-Calvo, *et al.* 2006].

The Lifestyle Interventions and Independence for Elders (LIFE) study in 8,029 patients with stage II-III hypertension with LVH on ECG showed high prevalence of co-existence of LVH and albuminuria [Wachtell, *et al.* 2002]. In patients with moderately severe hypertension, LVH on two consecutive ECGs is associated with increased prevalence of micro- and macro-albuminuria compared to patients without persistent LVH on ECG. High albumin excretion was related to LVH independent of age, blood pressure, diabetes, race, serum creatinine or smoking, suggesting parallel cardiac damage and albuminuria.

5.1. Hyperglycemia and insulin resistance as risk factors of cardiovascular complications in type 2 diabetes

Hyperglycemia and hyperinsulinemia or insulin resistance that is a characteristic of type 2 diabetes and obesity play major roles in the cardiovascular complications of type 2 diabetes mellitus and obesity. Hyperglycemia is the major risk factor for microvascular complications (retinopathy, neuropathy, and nephropathy) in type 2 diabetes, however 70% or 80% of patients with type 2 diabetes die of macrovascular disease. Atherogenic dyslipidemia (elevated triglyceride levels, low HDL-cholesterol levels, high LDL-cholesterol levels) is the major cause of atherosclerosis in patients with type 2 diabetes [Reasner, *et al.* 2008].

Several investigators have demonstrated that insulin resistance could predict future type 2 diabetes even in nonobese individuals [Morrison, *et al.* 2008], and even in children [Koska, *et al.* 2007; Morrison, *et al.* 2008] Insulin resistance accompanying sympathetic nerve activation may also predict future hypertension development [Masuo, *et al.* 1997, 1998, 2003, & 2005]. Insulin resistance coexisting with inflammation may predict cardiac disease but, interestingly, not stroke in the Japanese diabetic population [Matsumoto, *et al.* 2006].

Hyperglycemia (*i.e.* elevated plasma glucose levels) can also predict hospitalization for congestive heart failure in patients at high cardiovascular risk [Held, *et al*. 2007]. Hyperglycemia and insulin resistance are risk factors of cardiovascular complications.

5.2. Sympathetic nervous activity as a risk factor for cardiovascular complications and renal complications

Heightened sympathetic nerve activity plays an important role in cardiovascular complications and cardiac risk in humans [Esler, *et al*. 2000]. There is consistent evidence that high plasma norepinephrine level, as an index of heightened sympathetic nerve activity, predicts mortality in cardiovascular diseases such as chronic congestive heart failure [Cohn *et al*. 1984; Brum, *et al*. 2006], left ventricular dysfunction [Grassi, *et al*. 2009], remodelling [Abel, et al. 2010], structural changes in obesity {Benedict, 1996}, and end-stage renal disease (ESRD) [Masuo, *et al*. 2007; Grassi, *et al*. 2012; Benedict, *et al*. 1996; Ksiazck, *et al*.

2008]. Renal injury also predicts the development of cardiovascular disease [Masuo, *et al*. 2007; Joles, *et al*. 2009].

Hogarth *et al.* [Hogarth, *et al.* 2001] reported that acute myocardial infarction (AMI) in hypertensive patients resulted in greater sympathetic nervous activity, persisting for at least 6 months longer than in normotensive subjects, indicating that AMI further augmented the sympathetic nerve hyperactivity of hypertension. Sympathetic nerve hyperactivity could be one mechanism involved in the reported worse prognosis in AMI in hypertensive patients [Hogarth, *et al.* 2001]. The sympathetic activation that follows AMI has been associated with increased morbidity and mortality in both anterior-AMI and inferior-AMI, with a similar magnitude of sympathetic nerve hyperactivity [Graham, et al. 2004]. Patients with congenital long-QT syndrome are susceptible to life-threatening arrhythmias, and the sympathetic nervous system may have an important triggering role for cardiovascular events this condition [Shamsuzzaman, *et al.* 2001].

Changes in heart rates during exercise and recovery from exercise are mediated by the balance between sympathetic and vagal activity, and changes in heart rates were evaluated in a total of 5,713 asymptomatic working men cohort (between the ages of 42 and 53 years) in whom there was no evidence of the presence or history of cardiac disease over the preceding 23 years. Baseline heart rates, changes in heart rates during exercise and recovery were strongly related to an increased risk of sudden death from myocardial infarction [Jeuven, *et al.* 2005].

Zoccali *et al.* [Zoccali, *et al*. 2002 & 2004] examined the relationships between sympathetic nerve activity (plasma norepinephrine levels) and mortality and cardiovascular events in 228 patients undergoing chronic hemodialysis originally without heart failure. They found 45% of dialysis subjects had significantly high plasma norepinephrine levels located in the upper limit of the normal range. One-hundred and twenty four (124) fatal and nonfatal cardiovascular events occurred in 85 patients during the follow-up period (34±15 months). Plasma norepinephrine levels proved to be an independent predictor of

fatal and nonfatal cardiovascular events in a multivariate Cox regression model. Recently, Joles *et al.* reported that sympathetic nerve stimulation contributes to the progression of renal disease [Joles, *et al.* 2004]. Masuo *et al.* reported that plasma norepinephrine levels predicted future renal injury in normotensive healthy subjects over a 5-year follow up study in a Japanese cohort [Masuo, *et al.* 2007]. They also found that plasma norepinephrine levels were associated with concentric left ventricular hypertrophy in these patients [Zoccali, *et al.* 2002 a & 2002b].

Petersson *et al.* [Petersson, *et al.* 2002] showed that increased cardiac sympathetic nervous activity in renovascular hypertension might lead to high cardiovascular mortality and morbidity. Prolonged sympathetic nerve stimulation and elevated circulating norepinephrine levels can induce changes in intra-renal blood vessels. Catecholamines can induce proliferation of smooth muscle cells and adventitial fibroblasts in vascular wall.

The association between hypertension, obesity and chronic kidney disease (CKD) is well recognized [White, *et al.* 2005; Hall, *et al.* 2001; Zoccali, *et al.* 2002]. Obesity and hypertension also leads to an increase in the incidence of metabolic diseases such a type 2 diabetes mellitus, which is frequently associated with renal injury (proteinuria/microalbuminuria). In the majority of cases, ESRD occurs as a result of complication of diabetes or hypertension [WHO. 1995]. Obesity, hypertension and type 2 diabetes are characterized as stimulated sympathetic nervous activity and insulin resistance states, indicating renal injury and ESRD are strongly related to sympathetic nervous activity and insulin resistance. Masuo *et al.* reported that significant weight loss resulted in significant amelioration on renal function following suppression on sympathetic activation and hyperinsulinemia (insulin resistance) [Masuo, *et al.* 2012]. The findings suggest that strong linkage between sympathetic nervous activity, insulin resistance and renal function.

Joles *et al.* reported that sympathetic nerve stimulation contributes to the progression of renal disease [Joles, *et al.* 2004]. The 40-minute infusion of NE into the renal artery of dogs produced a reversible ischemic model of acute renal failure [Bulger, et al. 1982]. Another study demonstrated renal protection by β-adrenergic receptor blockade in a nephrectomized rat experiment without any BP changes [Amam, *et al.* 2001]. There is consistent evidence that high plasma norepinephrine levels, as an index of heightened sympathetic nervous activity, predicts mortality in cardiovascular disease, such as chronic congestive heart failure [Cohn, et al. 1984; Brum, et al. 2006], left ventricular dysfunction [Benedict, *et al.* 1996] and end-stage renal disease (ESRD) [Masuo, *et al.* 2007; Ksiazek, *et al.* 2008]. Renal injury also predicts the development of cardiovascular disease [Joles, *et al.* 2004; Masuo, *et al.* 2007].

These investigations have shown strong associations between sympathetic nervous activation, cardiovascular complications and renal complications. Given these observations it may be of importance to aim antihypertensive treatments or anti-diabetic treatment not only at the reduction of raised blood pressure or blood glucose but also at the excessive sympathetic activation and insulin resistance that may underpin these effects.

5.3. Sympathetic nerve hyperactivity in patients with ESRD

Evidence now strongly indicates a role for the sympathetic nervous system in the pathogenesis of hypertension in renal failure (ESRD) [Hausberg, et al. 2002; Schlaich, et al. 2009; Masuo, *et al.* 2010a]. Hypertension occurs commonly and early in renal disease and is paralleled by increases in sympathetic nerve activity, as indicated by increased muscle sympathetic nerve activity and circulating norepinephrine. This appears to be driven by the diseased kidneys, because nephrectomy or denervation has been shown to correct blood pressure and sympathetic nerve activity both in human and animal studies [Jacob, *et al.* 2003].

Masuo *et al.* [Masuo, *et al.* 1995 & 2010] showed that plasma norepinephrine levels were significantly higher in patients with ESRD regardless of hemodialysis compared with those in blood pressure- and body mass index-matched hypertensive patients or healthy normotensive subjects **(Figure 3)**. Further, this was recognized significantly in subjects with a shorter duration of ESRD with hemodialysis compared with those with longer duration, suggesting that sympathetic nerve hyperactivity may be of particular importance in the onset or the early development of ESRD or, alternatively, be influenced by long-term renal replacement therapy (hemodialysis). In the normal state, interactions between the kidney and sympathetic nervous system serve to maintain blood pressure and glomerular filtration rate within tightly controlled levels, but in renal failure, a defect in renal sodium excretory function leads to an abnormal pressure natriuresis relationship and activation of the renin-angiotensin system (RAS), contributing to the development of hypertension and progression of kidney disease [Hall, *et al.* 1997; Lohmeier, *et al.* 2001]. Another mechanism could involve the sympathetic nervous modulation of baroreflex regulation and vasculature tone through the central nervous system and angiotensin II [Burke, *et al.* 2008]. Afferent signals from the kidney, detected by chemoreceptors and mechanoreceptors, feed directly into central nuclei regulating sympathetic nerve activity by circulating and brain-derived angiotensin II [Philips, *et al.* 2005]. Therefore, the pathogenesis of hypertension in renal failure (ESRD) is complex and arises most likely from the interaction of hemodynamic and neuroendocrine factors. Sympathetic nerve activity has strong relationships with regards to increased risk of cardiovascular disease including hypertension [Zoccali, *et al.* 2002a & 2002b] in patients with ESRD and the mortality and morbidity of cardiovascular disease, suggesting that we have to pay much attention to sympathetic nerve activation in our attempts to adequately treat patients with ESRD.

Sympathetic nerve activity is consistently elevated in patients with ESRD, and in obese subjects and hypertensive patients in cross-sectional studies [Masuo, et al. 1995, 2011a & 2011b). The sympathetic nerve hyperactivity is at least in part independent of increased blood pressure levels or obesity. Further, patients with early-ESRD without hemodialysis had already significantly higher plasma norepinephrine levels compared with hypertensive subjects as well as normotensive subjects. Therefore, sympathetic nervous activation in ESRD patients may be independent from obesity or hypertension.
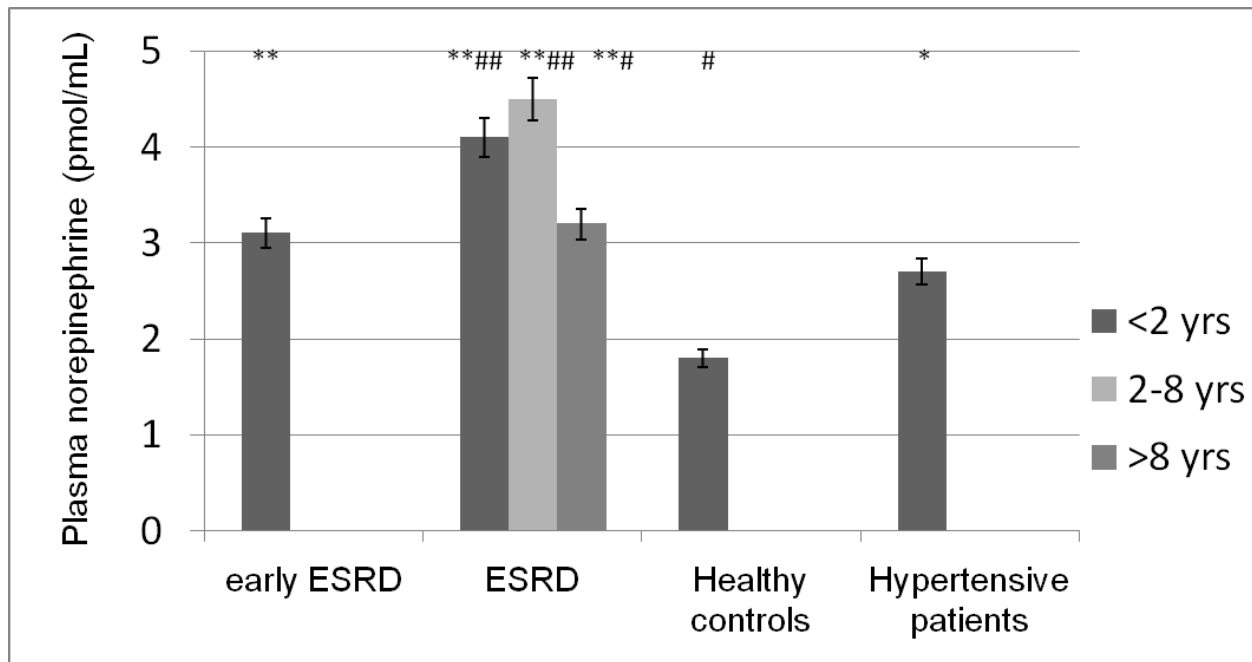
ESRD, end-stage renal disease; *P<0.05 versus healthy controls; **P<0.01 versus healthy controls;
#P<0.05 versus hypertensive patients with normal renal function; ##P<0.01 versus hypertensive patients with normal renal function. [Masuo, *et al.* 2010a]

**Figure 3.** Figure 3. Comparisons of plasma norepinephrine levels between patients with patients with ESRD, hypertensive patients with normal renal function and normal healthy controls.

The amount of norepinephrine in plasma is only a fraction of the amount released into the synaptic cleft, and plasma norepinephrine levels are affected by dialysis therapy, so it is difficult to discount that the elevated plasma norepinephrine levels did not derive in part from reduced plasma norepinephrine clearance rather than solely from elevated sympathetic nerve activity. Grassi *et al.* [Grassi, *et al.* 2009] however, reported similar results using microneurography. In addition, plasma norepinephrine levels did not change between before- and after-hemodialysis therapy (data was not shown), and between after-hemodialysis therapy and before-next hemodialysis therapy. Thus, one could speculate that plasma norepinephrine levels in ESRD patients are reflective of the degree of sympathetic nerve activity.

5.4. β2-adrenoceptor polymorphisms accompanying sympathetic nervous activation may relate to renal injury

Rao *et al.* [Rao, *et al.* 2007] and Masuo *et al.* [Masuo, *et al.* 2007] have shown strong associations between β2-adrenoceptor polymorphisms, elevated plasma norepinephrine levels and elevated HOMA-IR (insulin resistance) or future renal injury, suggesting that stimulated sympathetic nerve activity associated with insulin resistance, may independently play a major role in the onset and development of ESRD without obesity or hypertension. However, the precise mechanisms underlying sympathetic activation in CKD and ESRD have not been clarified.

Furthermore, Masuo *et al.* [Masuo, *et al.* 2011b] measured renal function (creatinine, BUN and creatinine clearance), plasma norepinephrine levels and HOMA-IR (insulin sensitivity) annually over a 5-year period in nonobese, normotensive men with normal renal function. Subjects who had a significant deterioration of renal function (more than 10% increases from baseline of creatinine and BUN or decrease in creatinine clearance) over a 5-year period had higher plasma norepinephrine at the entry period, and greater increases in plasma norepinephrine over 5 years [Masuo, *et al.* 2011b]. In this study, subjects who had significant changes in body weight or blood pressure were excluded, indicating the contributions of obesity or hypertension might be excluded. Further, subjects who had significantly higher levels of plasma norepinephrine had a higher frequency of the Gly16 allele of the β2-adrenoceptor polymorphism [Masuo, *et al.* 2007] (**Figure 4**). The Gly16 allele of the β2-adrenoceptor polymorphism has been shown to be related to obesity [Masuo, *et al.* 2005, 2005a, 2005b], hypertension [Masuo, *et al.* 2005a, 2005b, 2010b, 2011c] and metabolic syndrome development [Masuo, *et al.* 2005b]. Thus, high plasma norepinephrine levels appear to be a predictor that is determined genetically by the β2-adrenoceptor polymorphism (Arg16Gly) for renal injury, obesity, hypertension and metabolic syndrome.
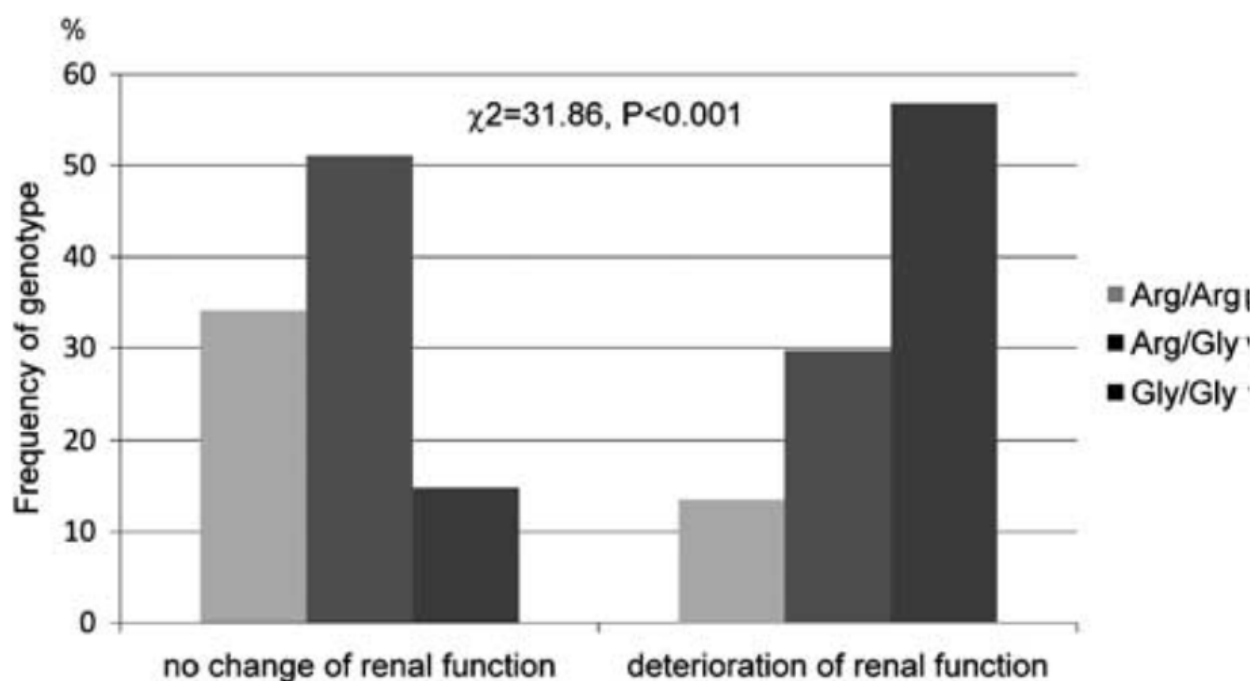
In 154 nonobese, normotensive subjects, renal function (creatinine clearance) was measured over a 5-year period. The deterioration of renal function was defined as >10% decreases in creatinine clearance over a 5-year period. Subjects with deterioration of renal function had higher frequency of Gly allele or Gly homozygous compared to those without changes in renal function. [Masuo, *et al.* 2011b]

Figure 4. Subjects with deteriorations of renal function (creatinine clearance) carried higher frequency of the Gly16 allele of Arg16Gly, the β2-adrenoceptor polymorphisms

These observations show that plasma norepinephrine levels associated with insulin resistance are strongly linked with the onset and development of renal injury.

6. Other medical conditions in obesity

6.1. Obstructive sleep apnea in obesity is a risk factor for cardiovascular diseases

Vozoris [Vozoris. 2012] investigated the relationships between prevalence of obstructive sleep apnea (OSA), obesity, and hypertension, diabetes, congestive heart failure, myocardial infarction, and stroke using a population-based multi-year cross-sectional study design including 12,593 individuals with data from the 2005-2008 United States National Health and Nutrition Examination Surveys (NHANES). They found individuals with OSA had elevated rates of cardiovascular diseases compared to the general population [Vozoris. 2012]. OSA is a common disorder that has been associated with many cardiovascular disease processes, including hypertension and arrhythmias. OSA has also been identified as an independent risk factor for stroke and all-cause mortality. OSA is highly prevalent in patients with transient ischemic attacks and stroke [Das, *et al.* 2012]. Indeed, the majority of patients with OSA suffer from hypertension [Ziegler, *et al.* 2011]. The mechanisms underlying the link between OSA and cardiovascular disease are not completely established. However, there is increasing evidence that autonomic mechanisms are implicated. A number of studies have consistently shown that patients with OSA have high levels of sympathetic nerve traffic [Narkiewicz, *et al.* 2003]. In animal studies, intermittent hypoxia that simulates changes seen in OSA leads to chemoreceptor and chromaffin cell stimulation of sympathetic nerve activity, endothelial damage and impaired blood pressure modulation. Human studies reveal activation of sympathetic nerves, endothelial damage and exaggerated pressor responses to sympathetic neurotransmitters and endothelin [Ziegler, *et al.* 2011]. OSA is also frequently observed in obese individuals [Dos, *et al.* 201].2

6.2. Gout and hyperuricacidemia in obesity

Gout is a growing worldwide health problem, and is associated with increased prevalence of obesity. Gout and hyperuricacidemia are associated with the metabolic syndrome, diabetes mellitus, obesity and hypertension. Masuo *et al.* observed the importance of serum uric acid levels as a predictor for future obesity and hypertension [Masuo, et al. 2003]. Several epidemiological studies have shown the close linkage between hyperuricemia, obesity and hypertension [Robinson, *et al.* 2012]. Recently Robinson, *et al.* [Robinson, *et al.* 2012] reviewed prevalence of hyperuricemia in Australia in 25 articles and 5 reports using a systematic journal search method. From 1968 to 1995/6, the prevalence of gout increased from 0.5% to 1.7% of the population. Especially in the Australian indigenous population a significant rise in the prevalence of gout from 0% in 1965 to 9.7% in 2002 in males, and 0% to 2.9% in females were observed. Those elevations were strongly synchronized with the prevalence of obesity [Chang, *et al.* 2001]. Similar result has been reported in Taiwanese populations that, using a multivariate analysis, showed that BMI (obesity) was an important factor associated with hyperuricemia in both males and females, whereas age was associated with hyperuricemia only in males. In addition, the associations of basic and repeated measures of uric acid level with treatments for uric acid over a 11-year period, and risk of coronary heart disease (CHD) and stroke events were assessed in Taiwanese populations

[Chien, *et al.* 2005]. The study showed that uric acid had significant risk only in hypertension and metabolic syndrome subgroups, but not in their counterparts. They also observed that uric acid, in the baseline and time-dependent variables, could predict cardiovascular events in the community of relatively low CHD but high stroke risk.

Straznicky *et al.* examined the effects of weight loss on serum uric acid levels, and showed that it had ameliorative effects on uric acid levels in the obese subjects with the metabolic syndrome [Straznicky, *et al.* 2011]. Furthermore, they compared these effects between a mild calorie restricted diet alone, combination with a low calorie diet and exercise and control groups. Interestingly, moderate weight loss in obese patients with metabolic syndrome is associated with a reduction in serum uric acid levels, albuminuria and an improvement in eGFR which is augmented by exercise co-intervention [Straznicky, *et al.* 2011]. Improvement of insulin resistance and sympathetic activation were synchronized with a reduction in serum uric acid levels.

7. Conclusion

The role of the sympathetic nervous activity and insulin resistance plays important roles in the etiology of obesity, hypertension, and type 2 diabetes. Several investigations have demonstrated that the sympathetic nervous activation and insulin resistance are strongly related to cardiovascular complication (*i.e.* LVH, congestive heart failure) and the onset and development of ESRD (renal injury). Interestingly, relevant investigations of sympathetic nervous activity and $\beta2$-adrenoceptor polymorphisms indicate their contribution to the onset and maintenance of renal injury and LVH in healthy subjects and in patients with chronic renal failure and cardiovascular events in ESRD patients. Interestingly, the prevalence of OSA and hyperuricemia (gout) are significantly linked with increases in obesity, and both states are connected with the cardiovascular risks associated with sympathetic nervous activation. Serum uric acid, which may be affected strongly by sympathetic nervous activity, may be a predictor for future hypertension and renal injury (ESRD) development.

Recently, it has been demonstrated that renal sympathetic nerve denervation provides promising results in patients with refractory hypertension [Krum, *et al.* 2009; Symplicity HTN-1 Investigators. 2011]. Besides the demonstrable effect on reducing blood pressure, renal denervation significantly and favourably influences LV mass and improves diastolic function, which might have important prognostic implications in patients with resistant hypertension at high cardiovascular risk [Brandt, *et al.* 2012]. Further, renal denervations showed an accompanying improvements in insulin resistance [Mahfoud, *et al.* 2011,: Witkowski, *et al.* 2012] and OSA [Brandt, *et al.* 2011]. Renal sympathetic denervation may conceivably be a potentially useful option for patients with co-morbid refractory hypertension, glucose intolerance, and obstructive sleep apnea.

A better understanding of the relationships between sympathetic nervous activity, insulin resistance, cardiovascular complications, and renal complications, will help to develop

appropriate treatment strategies targeting renal injury or cardiac risk in hypertensive and diabetes patients with and without ESRD or LVH.

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