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FONDAZIONE INTERNAZIONALE MENARINI

# OBESITY AND RELATED DISEASES

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## ABSTRACT BOOK

*CENTRO CONGRESSI TORINO INCONTRA*
*Via Nino Costa n. 8*

## CONTENTS

**Left ventricular hypertrophy and cardiovascular risk**

Enrico Agabiti Rosei
*Clinica Medica, University of Brescia, Italy*

Data from the Framingham Study indicate that the prevalence of LVH, assessed by electrocardiography, is low in the general population (3%). The prevalence of LVH is significantly greater when using of the more sensitive echocardiographic technique, increasing from 5% in subjects younger then 30 years to 50 % in those older than 70 years. The Framingham study has also shown that the prevalence of echocardiographic LVH is 15-20 % in mild hypertensive patients and further increases in patients with more severe hypertension (1). Left ventricular hypertrophy (LVH) in hypertension is initially a useful compensatory process, that represents an adaptation to increased ventricular wall stress; however, it is also the first step toward the development of overt clinical disease.
The increase of LV mass with age might reflect the influence that other risk factors exert with time on the development of LVH. The relationship of echocardiographic LV mass with clinic blood pressure is usually weak. Twenty-four hours blood pressure recordings have shown a much closer correlation between LV mass and average daily blood pressure. Significant non-hemodynamic contributors to the increase in LV mass have been recognized: among them, age, sex, race, body mass index, diabetes, dietary salt intake may strongly contribute to determine who among hypertensive patients develop LVH and to what degree LVM is increased. LVH seems to be associated with an inflammatory state (as indicated by elevated CRP levels), although the relationship appears to be mediated by comorbid conditions. In fact, the coexistence of hypertension with diabetes increases the prevalence of LVH. Moreover, insulin resistance and high insulin levels are associated with the development of LVH in hypertensive patients. Other major cardiometabolic risk factors, notably hypercholesterolemia and hyperglycemia, may also modify the extent of LVM and the prevalence of LVH in the hypertensive population (2). A number of studies have demonstrated that in patients with the metabolic syndrome the prevalence of organ damage, and in particular of LVH, is increased. The increase in LV mass in MS has been reported in various populations, including young individuals, subjects from the general population (2), uncomplicated hypertensives (3), and different ethnic groups.
Several methods are currently available for the assessment of LVH; the techniques differ in cost, availability, sensitivity and specificity. Electrocardiography should be part of all cardiovascular screening

programs; however, despite its good specificity, the sensitivity for LVH detection is low. Nonetheless LVH diagnosed by the Sokolow-Lyon index or the Cornell voltage-duration product has been shown to be an independent predictor of cardiovascular events (4,5).
Echocardiography is a specific, repeatable and far more sensitive measure of LVH in comparison with EKG.
Proper evaluation includes calculation of LV mass according to measurements of LV internal diameter and wall thickness. These methods have been validated with measurements obtained at necroscopic examination.
Although the relationship between LV mass and incidence of cardiovascular events is continuous, ESH/ESC guidelines indicate that the thresholds of 115 g/m2 BSA in men and 95 g/m22in women may be used for conservative estimates of LVH (6).
Geometric adaptation of the left ventricle to increased cardiac load may be different among patients. Concentric hypertrophy is characterized by increased mass and increased relative wall thickness, whereas eccentric hypertrophy is characterized by increased mass and relative wall thickness < 0.42; concentric remodelling occurs when there is increased thickness with respect to radius, in the presence of normal LV mass. These LV geometric patterns are associated with different haemodynamic characteristics, and peripheral resistances are greater in patients with concentric geometry, while cardiac index is increased in those with eccentric hypertrophy.
In addition echocardiography allows the measurement of other parameters (regional and global LV systolic and diastolic function, left atrium dimensions and volume), all associated with an increased incidence of CV events.
LV mass measurement may be obtained by cardiac magnetic resonance (MRI), with a higher reproducibility than echocardiography; the improvement in reproducibility has relevant practical implications, such as more precise detection of serial changes in individual patients in a shorter time interval and smaller sample size design in clinical trials targeting LVH regression during antihypertensive treatment.

**Prognostic value of LVH and its regression by treatment**
A large number of studies have reported on the relationship between LVH at baseline examination, measured either by EKG, echocardiography or MRI, and the risk of subsequent morbid or mortal cardiovascular events in clinical or epidemiological populations. (4,5)
Despite electrocardiography has a low sensitivity for LVH detection, LVH diagnosed by the Sokolow-Lyon index or the Cornell voltage-

duration product is an independent predictor of cardiovascular events (4,5)
The direct measurements of LV mass by echocardiography has proved to be a strong predictor of the risk of cardiovascular morbidity and mortality; subjects with LVH consistently have 2 to 4 or more fold higher rates of cardiovascular complications, independent from other risk factors such as hypercholesterolemia, age, and blood pressure measured in the clinic or by 24 hours blood pressure monitoring (4,5).
The prognostic significance of echocardiographic LVH has also been demonstrated in patients with or without the metabolic syndrome (2,7).
Concentric hypertrophy appears to carry the highest risk and eccentric hypertrophy an intermediate risk.
The prognostic significance of changes in EKG criteria of LVH has been demonstrated in the Framingham population, in high CV risk patients, in hypertensives with isolated systolic hypertension or with EKG-LVH (5).
Other observational, prospective studies have examined the potential clinical benefits of regression of echocardiographic detectable LVH, and have demonstrated that changes in LV mass, during treatment, may imply an important prognostic significance in hypertensive patients (4,5). These studies have clearly shown that subjects who failed to achieve LVH regression or in whom LVH developed during follow-up are much more likely to suffer morbid events than those in whom LVH regressed or never developed.

Further information has been derived from the LIFE echocardiographic substudy: in 930 patients with EKG LVH, a decrease of 25 gr/m$^2$ (i.e.one standard deviation) of LV mass index was associated with a 20% reduction of the primary end-point, adjusting for type of treatment, basal and treatment BP, and basal LV mass index.
Changes in geometric adaptation seem to imply a prognostic value, independent of changes in LV mass. The persistence or the development of a concentric geometry during treatment have been found associated to a greater incidence of cardiovascular events, independent of changes in LV mass (8). The LIFE study has provided results that confirm the prognostic influence of LV geometry, in addition to changes in LV mass.
The better prognosis associated to regression of LVH may be related to the improvement of systolic and diastolic function, to the increase of coronary flow reserve and to the decrease of cardiac arrhythmias.

In conclusion, a large amount of data indicates that assessment of preclinical cardiac damage may represent a useful tool for a better assessment of cardiovascular risk both for research and clinical purposes.

**Reference list:**


1) Kannel WB. *Prevalence and natural history of electrocardiographic left ventricular hypertrophy. Am J Med. 1983;75:4-11.*

2) Mancia G, Bombelli M, Corrao G et al. *Metabolic syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study: daily life blood pressure, cardiac damage, and prognosis. Hypertension. 2007 Jan;49(1):40-7.*

3) Davis CL, Kapuku G, Snieder H et al. *Insulin resistance syndrome and left ventricular mass in healthy young people. Am J Med Sci 2002;324:72e58.*

4) Cuspidi C, Meani S, Fusi V et al. *Metabolic syndrome and target organ damage in untreated essential hypertensives. J Hypertens Oct;22(10):1991-8.*

5) Agabiti Rosei E, de Simone G, Mureddu G et al. – Joint Committee of the Italian Society of Hypertension, Italian Society of Hypertension, Italian Society of Cardiology, Associazione Nazionale Medici Cardiologi Ospedalieri. *Hypertension and Cardiac Damage Diagnostic and Therapeutic Guidelines. High Blood Press Cardiovasc Prev 2008; 15 (3): 141-170.*

6) Agabiti Rosei E, Muiesan ML. *Hypertension and left ventricular hypertrophy. European Society of Hypertension Scientific Newsletters 2011; 12: No. 10R, revised version. www.eshonline.org*

7) Mancia G, Fagard R, Narkiewicz K et al. *2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013 Jul;31(7):1281-357).*

8) de Simone G, Devereux RB, Chinali Met al. *Metabolic syndrome and left ventricular hypertrophy in the prediction of cardiovascular events: the Strong Heart Study. Nutr Metab Cardiovasc Dis. 2009 Feb;19(2):98-10.*

9) Muiesan ML, Salvetti M, Monteduro C, Bonzi B, Paini A, Viola S, Poisa P, Rizzoni D, Castellano M, Agabiti-Rosei E. *Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients. Hypertension 2004; 43:731-738.*

## Chronic kidney disease and cardiovascular risk

Roberto Pontremoli, Francesca Viazzi, Giovanna Leoncini
*Universita` degli Studi e I.R.C.C.S. Azienda Ospedaliera Universitaria San Martino-IST, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy*

A cluster of abnormalities including hypertension, dyslipidemia, abdominal obesity, and insulin resistance indicates the presence of metabolic syndrome (MS). In Western countries MS is a fairly common condition among the general population, and even more so in subgroups at high cardiovascular risk such as obese, hypertensive and diabetic patients, among whom it ranges from 30% to 80% (1-3). The prevalence of MS is expected to rise even further worldwide in the near future, and may well reach epidemic proportions (4).

Another often asymptomatic condition, i.e., chronic kidney disease (CKD), is becoming increasingly prevalent, mostly as a consequence of longer life expectancy and exposure to traditional cardiovascular risk factors (5, 6). When including the earliest stages of disease, which have been clearly shown to entail significant worsening of cardiovascular risk, the prevalence of CKD reaches 8-10% of the general population in Western countries (7).

Both MS and CKD are major, independent forerunners of cardiovascular diseases (8, 9). As a consequence, prevention or prompt identification and aggressive treatment of these conditions is a worldwide health priority. The direct and indirect costs of MS and CKD are already relevant and likely to grow even further over the next years (10). Few data are available on the relationship between MS and renal impairment and they are almost exclusively limited to the general population or to specific ethnic groups, such as Native Americans, Australian Aboriginals, and Oriental populations (11-14), while there are no reports on the relationship between CKD and MS in hypertensive patients under specialist care. Previous studies on this topic have often taken only single components of CKD into consideration, e.g., urinary albumin excretion or glomerular filtration rate (GFR). It is still unclear whether MS per se is related to CKD beyond the contribution of its individual components. MS has been found to be strongly associated with the presence of CKD, defined as reduced GFR or increased urinary albumin excretion, in a large cohort of hypertensive patients in Italy (15). This relationship was independent of several potentially confounding factors, including age and gender as well as individual components of MS. Furthermore, the coexistence of MS and CKD was found to be highly frequent in high-

risk hypertensive patients. Upon assessment of estimated GFR and urinary albumin excretion, approximately one half of the patients with MS do show CKD and two thirds of those with CKD show MS. Furthermore, the prevalence of microalbuminuria and/or low GFR increases as the number of clinical traits of MS increased . Altogether, these findings suggest a common pathophysiological link between MS and renal dysfunction.

**References:**


1) Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. Adults. Diabetes Care. 2004;27:2444-2449.

2) Mancia G, Parati G, Borghi C, et al; SMOOTH investigators. Hypertension prevalence, awareness, control and association with metabolic abnormalities in the San Marino population: the SMOOTH study. J Hypertens. 2006;24:837-843.

3) Alexander CM, Landsman PB, Teutsch SM, Haffner SM; Third National Health and Nutrition Examination Survey (NHANES III); National Cholesterol Education Program (NCEP). NCEPdefined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes. 2003;52:1210-1214.

4) Grundy SM. Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol. 2008;28:629-636.

5) Böhm M, Thoenes M, Danchin N, Bramlage P, La Puerta P, Volpe M. Association of cardiovascular risk factors with microalbuminuria in hypertensive individuals: the i-SEARCH global study. J Hypertens. 2007;25:2317-2324.

6) Hallan SI, Stevens P. Screening for chronic kidney disease: which strategy? J Nephrol. 2010;23:147-155.

7) Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007;298:2038-2047.

8) Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. Diabetes Care. 2005;28:1769-1778.

9) Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296-1305. Erratum in: N Engl J Med 2008; 18:4.

10) Levin A, Chaudhry MR, Djurdjev O, Beaulieu M, Komenda P. Diabetes, kidney disease and cardiovascular disease patients. Assessing care of complex patients using outpatient testing and visits: additional metrics by which to evaluate health care system functioning. Nephrol Dial Transplant. 2009;24:2714-2720.

11) Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. J Am Soc Nephrol. 2005;16:2134-2140.

12) Hoehner CM, Greenlund KJ, Rith-Najarian S, Casper ML, McClellan WM. Association of the insulin resistance syndrome and microalbuminuria among nondiabetic native Americans. The Inter-Tribal Heart Project. J Am Soc Nephrol. 2002;13:1626-1634.

13) Chen J, Muntner P, Hamm LL, et al. The metabolic syndrome and chronic kidney disease in U.S. adults. Ann Intern Med. 2004;140:167-174.

14) Hoy WE, Mathews JD, McCredie DA, et al. The multidimensional nature of renal disease: rates and associations of albuminuria in an Australian Aboriginal community. Kidney Int. 1998;54:1296-1304.

15) Leoncini G, Viazzi F, Agabiti Rosei E, Ambrosioni E, Costa FV, Leonetti G, Pessina AC, Trimarco B, Volpe M, Deferrari G, Pontremoli R. Metabolic syndrome and chronic kidney disease in high-risk Italian hypertensive patients: the I-DEMAND study. J Nephrol. 2012 Jan-Feb;25(1):63-74.

## Non Alcoholic Steatohepatitis and Cardiovascular risk

E. Bugianesi, MD PhD
*Division of Gastro-Hepatology, Department of Medical Sciences, University of Torino (Italy)*

In the last few years several clinical and epidemiological studies have convincingly associated hepatic steatosis with an increased risk of developing the metabolic syndrome and its related complications, i.e., type 2 diabetes (T2DM) and cardiovascular disease (CVD), beyond established predictors. Hepatic steatosis is currently named Non Alcoholic Fatty Liver Disease (NAFLD), a term which encompasses a wide spectrum of histological features, ranging from simple fatty liver (fat infiltration >5% of hepatocytes with or without inflammation) to nonalcoholic steatohepatitis (NASH), which is characterised by the presence of steatosis, necroinflammation and/or fibrosis, and could lead to cirrhosis [1]. Liver biopsy is the only reliable tool to diagnose NAFLD, but non-invasive proxy markers (raised liver enzymes and/or fatty liver at ultrasound (US) in the absence of viral and alcohol-related liver disease) are usually used in clinical practice. Excess liver fat is extremely common; as many as 20% of adults in USA and other Western countries have NAFLD [2,3], while NASH may be present in up to 3% of the general population and in up to two thirds of individuals with morbid obesity or type 2 diabetes [3].

Patients with NAFLD have increased markers of subclinical atherosclerosis (impaired flow-mediated vasodilatation and increased carotid-artery intimal medial thickness) independent of obesity and other established risk factors[4], although this finding has been not universally confirmed. This is not surprising since the liver secretes VLDL, C-reactive protein (CRP), fibrinogen and fatty liver is associated with increased oxidized LDL and reactive oxygen species (ROS), all factors linked to endothelial dysfunction and early atherosclerosis.

Coronary risk factors tend to cluster in patients with NAFLD, who exhibit more advanced carotid atherosclerosis compared with healthy controls [5]. In an Italian study on type 2 diabetic patients, the prevalence of coronary, cerebrovascular, and peripheral vascular disease was remarkably higher among patients with US-fatty liver than among those without, independent of traditional risk factors [6]. In a community-based cohort of 2088 male workers, the presence of US-diagnosed NAFLD was independently associated with an increased prevalence of ischemic heart disease [7]. In patients consecutively referred for elective coronary angiography, NAFLD was associated with more severe coronary artery disease independently of established

risk factors [8]. In a prospective study in 612 patients with clinical indications for coronary angiogram, fatty liver prevalence was 58% and was associated with coronary artery disease (CAD) independently of other metabolic factors [9]. However, presence of fatty liver could not predict cardiovascular mortality and morbidity in patients with established CAD, although the follow up was rather short (87 weeks). Cardiac fat, in particular epicardial, has been also associated with coronary calcification (CAC score) measured by CT [10,11].
Early autoptic studies have recognized the heart as an important site of fat accumulation. Fat accumulates preferentially around the heart, within or deep into the pericardium (i.e., epicardial fat), but mainly on the external surface of the parietal pericardium within the mediastinum [12]. Excess adipose tissue in the mediastinum is increased in rough proportion to BMI, but the strongest association is with visceral adipose tissue (VAT) mass [13]. Recent studies employing magnetic resonance imaging (MRI) have recognized that a consistent amount of triglyceride accumulates also inside myocardial cells [14]. The accumulation of triglyceride in the myocardium and around the heart of subjects with fatty liver is significant and may result from fatty acid overflow to the heart because of a generalized condition of ectopic fat excess. Heart and liver share the peculiarity of first-pass organs into which FFAs drain from visceral fat depots , i.e. epicardial and visceral adipose tissue, respectively. Epicardial and visceral fat show similar biochemical properties, including a higher lipolytic rate. Thus, hepatic fat content may represent an indicator of a generalized condition of ectopic triglyceride deposition, also involving the cardiac wall; in turn, lipids in the heart wall would be directly responsible for myocardial insulin resistance and energy impairment.

**References:**


1) Falck-Ytter Y, Younossi ZM, Marchesini G, McCullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. *Semin Liver Dis.* 2001;21(1):17-26.

2) de Alwis NM, Day CP. Non-alcoholic fatty liver disease: the mist gradually clears. *J Hepatol.* 2008;48 Suppl 1:S104-112.

3) Bellentani S, Saccoccio G, Masutti F, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. *Ann Intern Med.* Jan 18 2000;132(2):112-117.

4) Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med.* Sep 30 2010;363(14):1341-1350.

5) Targher G, Bertolini L, Padovani R, Zenari L, Zoppini G, Falezza G. Relation of nonalcoholic hepatic steatosis to early carotid atherosclerosis in healthy men: role of visceral fat accumulation. *Diabetes Care.* Oct 2004;27(10):2498-2500.

6) Targher G, Bertolini L, Padovani R, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care.* May 2007;30(5):1212-1218.

7) Lin YC, Lo HM, Chen JD. Sonographic fatty liver, overweight and ischemic heart disease. *World J Gastroenterol.* Aug 21 2005;11(31):4838-4842.

8) Mirbagheri SA, Rashidi A, Abdi S, Saedi D, Abouzari M. Liver: an alarm for the heart? *Liver Int.* Sep 2007;27(7):891-894.

9) Wong VW, Wong GL, Yip GW, et al. Coronary artery disease and cardiovascular outcomes in patients with non-alcoholic fatty liver disease. *Gut.* Dec 2011;60(12):1721-1727.

10) Ding J, Kritchevsky SB, Harris TB, et al. The association of pericardial fat with calcified coronary plaque. *Obesity (Silver Spring, Md.* Aug 2008;16(8):1914-1919.

11) Djaberi R, Schuijf JD, van Werkhoven JM, Nucifora G, Jukema JW, Bax JJ. Relation of epicardial adipose tissue to coronary atherosclerosis. *The American journal of cardiology.* Dec 15 2008;102(12):1602-1607.

12) Sironi AM, Petz R, De Marchi D, et al. Impact of increased visceral and cardiac fat on cardiometabolic risk and disease. *Diabet Med.* Oct 24 2011.

13) Sironi AM, Gastaldelli A, Mari A, et al. Visceral fat in hypertension: influence on insulin resistance and beta-cell function. *Hypertension.* Aug 2004;44(2):127-133.

14) Sacks HS, Fain JN. Human epicardial adipose tissue: a review. *Am Heart J.* Jun 2007;153(6):907-917.

**Obesity hypoventilation syndrome: co-morbidities and combined treatment strategies**

Miquel Ferrer
*UVIIR, Servei de Pneumologia, Institut del Tòrax, Hospital Clinic, IDIBAPS, Universitat de Barcelona*, Barcelona, Spain. *CibeRes* (CB06/06/0028). E-mail: miferrer@clinic.ub.es
Website: www.idibapsrespiratoryresearch.org

Excess weight and obesity are becoming a global epidemic that affects millions of people in both developed and developing countries and in all age-groups (1,2). Obese subjects have multiple complications derived from excess weight, particularly affecting the cardiovascular, endocrine and respiratory systems (3). The prevalence of obesity (body mass index (BMI) >30 kg/m$^2$) ranges between 9% and 26% in patients admitted to intensive care units (ICU), whilst that of morbid obesity (BMI >40 kg/m$^2$) ranges between 1.4% and 7% (4,5).

Respiratory involvement of the obese patient is complex (6) and involves pulmonary abnormalities (decreased lung volumes, increased respiratory resistance, decreased chest wall compliance), impairment of central respiratory control and frequent sleep-related breathing disorders. Although obesity is frequent in patients with chronic obstructive pulmonary disease (COPD), asthma and sleep apnoea-hyperpnoea syndrome (SAHS), a minority of obese subjects develop obesity-hypoventilation syndrome (OHS). The OHS is defined as a combination of obesity, daytime hypercapnia ($PaCO_2$ >45 mm Hg) and sleep-disordered breathing after ruling out other disorders that may cause alveolar hypoventilation (7). It is a chronic disease associated with respiratory and cardio-metabolic impairments leading to a decrease in activities of daily life and social involvement, increased health-related costs, and higher risks of hospitalization and death (8,9).

Although not well known, the prevalence of OHS increases as the prevalence of obesity increases (9,10), with an estimated prevalence of 0.3% to 0.4% in the general population, 10% to 20% in patients with sleep-related breathing disorders, and nearly 50% among hospitalized patients with BMI >50 kg/m$^2$. Despite its established severity compared with eucapnic obesity, OHS is largely under-recognized, with only one-third of patients actually diagnosed when hospitalized for acute hypercapnic respiratory failure (AHRF) (7,11-13).

Patients with OHS often present exacerbations of their respiratory symptoms that, like COPD, require hospitalization due to AHRF that may require ventilatory support. There is extensive evidence on the efficacy of non-invasive ventilation (NIV) in patients with severe COPD exacerbations and AHRF with respiratory acidosis (14,15). Several reports have shown that OHS is the second most frequent indication, after COPD, for NIV treatment among hospitalized patients with AHRF (16-18). The forecast increase in the incidence of obesity may lead to an increase in OHS in the coming years, with increased hospital admission required for these patients. However, there are no randomized controlled trials and very few well designed studies addressing the question of efficacy of NIV in AHRF due to OHS. Until recently, available studies were retrospective and/or case studies including a limited numbers of patients (19-21). These studies, aiming to demonstrate the impact of NIV on mortality, included patients for whom NIV was initiated both in acute and chronic settings, which clearly correspond to distinct OHS phenotypes. Nevertheless, NIV is frequently used in patients with OHS, particularly during stable clinical condition (22,23) but also during episodes of AHRF (24), with acceptable rates of success.

We recently described the outcomes of 173 patients treated by NIV for AHRF due to OHS (25). Only 9% of them were chronically treated at home by continuous positive airway pressure (CPAP) or NIV prior to admission, although 65% had already been admitted to an ICU, probably for similar episodes of AHRF. These data emphasize the importance of a better awareness of OHS and systematic screening for hypercapnia in patients with obesity, particularly in primary care settings and obesity clinics. A sensitive and inexpensive marker in obese patients is serum bicarbonate; a level greater than 27 mmol/L is associated with a high prevalence of OHS and should lead to the patient's referral to a respiratory physician (9). Early diagnosis is a crucial issue. Patients in whom NIV is initiated in acute conditions are more likely to have developed cardiovascular complications related to OHS, thus increasing the risk of multiple organ failure and death at the time of acute respiratory failure (7,13). In our study we compared these 173 patients with OHS and 543 COPD patients with AHRF (25). Among patients with COPD included, 34% were obese, and 28% had associated SAHS ("overlap syndrome").

Compared with COPD for whom NIV represents standard care in AHRF (14,15), patients with OHS exhibited less late NIV failure, less readmission to the ICU, and better survival. However, both 1-year survival adjusted for confounding variables and 1-year hospital

readmission following AHRF were similar to that of patients with COPD. Patients with OHS are thus clearly responsive to NIV. The pathophysiology of OHS results from complex interactions between various sleep breathing disorders (i.e., obstructive sleep apnoea [OSA] and REM sleep hypoventilation), increased work of breathing as a result of a decreased thoracoabdominal compliance, and altered ventilatory drive. All these mechanisms are successfully addressed by NIV, and patients with OHS were even more effectively treated for their AHRF than were patients with COPD.

Patients with COPD who have survived an episode of AHRF that required NIV have poor long-term outcome, with mortality rates at 1 year approximately 50% in several published series (26,27); this 1-year mortality rate was 31% in our series (25).The short-term and long-term outcome of patients with OHS treated with NIV is consistently better in published series (13,19,25). The different pathophysiology of COPD and OHS, with marked inflammatory activity in patients with advanced COPD (28) may explain the different long-term outcomes between both types of patients. An exception to this good outcome of patients with OHS was recently reported in patients with "malignant" OHS (21). In this study, patients were extremely obese, with a mean BMI of 48 $kg/m^2$, with a very high frequency of diabetes, metabolic syndrome and cardiac and hepatic co-morbidities.

In our study, only 55% of patients with OHS studied were put on a long-term positive pressure ventilatory support (CPAP or NIV) at home, and a very few, 10%, were treated by NIV (25). Clinical guidelines and consensus statements recommend long-term NIV use in patients with OHS. Open studies show that long-term NIV for OHS suppresses respiratory events during sleep, normalizes sleep structure, and restores daytime vigilance (29,30). Much higher survival rates (1-year survival above 90%) have been reported for patients with OHS treated by NIV (7,12,13,23,31), potentially explained by a decrease in incident cardiovascular events, and when comparative data were available, survival was much higher than for patients with COPD treated by NIV. Survival data from our study (25) were similar to those reported by other authors (12) in untreated patients with OHS. This strongly suggests that long-term NIV should be systematically proposed at home after an episode of AHRF in patients with OHS. Oxygen therapy alone is not appropriate when taking into account the underlying mechanisms for hypoventilation in OHS (32) but remains overused as demonstrated by the 39% of patients with OHS on long-term oxygen therapy before their admission for ARHF in our study (25). After an episode of AHRF, patients with OHS should be re-

evaluated on a regular basis. When normalization of $PaCO_2$ and resetting of the respiratory centres is achieved by NIV, a proportion of OHS could be protected from respiratory failure by the use of simple CPAP therapy. ICU and respiratory physicians should favour the implementation of clinical pathways allowing an easy transition from ICU to home NIV treatment.

In conclusion, patients with OHS can be treated with NIV using a similar protocol to that used in patients with COPD during an episode of AHRF, with high efficacy in both groups of patients. A better screening for patients with OHS is necessary to reduce the delay of NIV initiation and avoid episodes of AHRF. NIV appears at least as effective in acute conditions as in COPD. A step forward would be to improve the link between the acute initiation of NIV and long-term care. OHS requires a multimodal therapeutic approach including home NIV/CPAP, rehabilitation programs with physical training, weight loss, lifestyle changes, and appropriate medication to further control cardiovascular risk factors.

**References:**


1) Doak CM, Wijnhoven TM, Schokker DF, Visscher TL, Seidell JC. Age standardization in mapping adult overweight and obesity trends in the WHO European Region. Obes Rev. 2012;13:174-91.

2) Lobstein T, Baur L, Uauy R. Obesity in children and young people: a crisis in public health. Obes Rev. 2004;5 Suppl 1:4-104.

3) Rabec C, de Lucas RP, Veale D. Respiratory complications of obesity. Arch Bronconeumol. 2011;47:252-61.

4) Akinnusi ME, Pineda LA, El Solh AA. Effect of obesity on intensive care morbidity and mortality: a meta-analysis. Crit Care Med. 2008;36:151-58.

5) Oliveros H, Villamor E. Obesity and mortality in critically ill adults: a systematic review and meta-analysis. Obesity (Silver Spring). 2008;16:515-21.

6) BaHammam A. Acute ventilatory failure complicating obesity hypoventilation: update on a 'critical care syndrome'. Curr Opin Pulm Med. 2010;16:543-51.

7) Priou P, Hamel JF, Person C et al. Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. Chest. 2010;138:84-90.

8) Jennum P, Kjellberg J. Health, social and economical consequences of sleep-disordered breathing: a controlled national study. Thorax. 2011;66:560-566.

9) Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. Respir Care. 2010;55:1347-62.

10) Piper AJ, Grunstein RR. Obesity hypoventilation syndrome: mechanisms and management. Am J Respir Crit Care Med. 2011;183:292-98.

11) BaHammam A, Syed S, Al-Mughairy A. Sleep-related breathing disorders in obese patients presenting with acute respiratory failure. Respir Med. 2005;99:718-25.

12) Nowbar S, Burkart KM, Gonzales R et al. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. Am J Med. 2004;116:1-7.

13) Perez de Llano LA, Golpe R, Ortiz PM et al. Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. Chest. 2005;128:587-94.

14) Keenan SP, Sinuff T, Burns KE et al. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. CMAJ. 2011;183:E195-E214.

15) Lightowler JV, Wedzicha JA, Elliott MW, Ram FS. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ. 2003;326:185-89.

16) Confalonieri M, Gorini M, Ambrosino N, Mollica C, Corrado A, Scientific Group on Respiratory Intensive Care of the Italian Association of Hospital Pneumonologists. Respiratory intensive care units in Italy: a national census and prospective cohort study. Thorax. 2001;56:373-78.

17) Chiner E, Llombart M, Martinez-Garcia MA, Fernandez-Fabrellas E, Navarro R, Cervera A. [Noninvasive mechanical ventilation in Valencia, Spain: from theory to practice]. Arch Bronconeumol. 2009;45:118-22.

18) Ciledag A, Kaya A, Akdogan BB et al. [Early use of noninvasive mechanical ventilation in patients with acute hypercapnic respiratory failure in a respiratory ward: a prospective study]. Arch Bronconeumol. 2010;46:538-42.

19) Gursel G, Aydogdu M, Gulbas G, Ozkaya S, Tasyurek S, Yildirim F. The influence of severe obesity on non-invasive ventilation (NIV) strategies and responses in patients with acute hypercapnic respiratory failure attacks in the ICU. Minerva Anestesiol. 2011;77:17-25.

20) Ortega GA, Peces-Barba RG, Fernandez O, I, Chumbi FR, Cubero de FN, Gonzalez MN. [Evolution of patients with chronic obstructive pulmonary disease, obesity hypoventilation syndrome or congestive heart failure in a respiratory monitoring unit]. Arch Bronconeumol. 2006;42:423-29.

21) Marik PE, Desai H. Characteristics of Patients With the "Malignant Obesity Hypoventilation Syndrome" Admitted to an ICU. J Intensive Care Med. 2012;28:124-30.

22) Janssens JP, Derivaz S, Breitenstein E et al. Changing patterns in long-term noninvasive ventilation: a 7-year prospective study in the Geneva Lake area. Chest. 2003;123:67-79.

23) Budweiser S, Riedl SG, Jorres RA, Heinemann F, Pfeifer M. Mortality and prognostic factors in patients with obesity-hypoventilation syndrome undergoing noninvasive ventilation. J Intern Med. 2007;261:375-83.

24) Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. Lancet. 2009;374:250-259.

25) Carrillo A, Ferrer M, Gonzalez-Diaz G et al. Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;186:1279-85.

26) Chu CM, Chan VL, Lin AW, Wong IW, Leung WS, Lai CK. Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure. Thorax. 2004;59:1020-1025.

27) Corral-Gudino L, Jorge-Sanchez RJ, Garcia-Aparicio J et al. Use of noninvasive ventilation on internal wards for elderly patients with limitations to respiratory care: a cohort study. Eur J Clin Invest. 2011;41:59-69.

28) Cosio MG, Saetta M, Agusti A. Immunologic aspects of chronic obstructive pulmonary disease. N Engl J Med. 2009;360:2445-54.

29) Borel JC, Tamisier R, Gonzalez-Bermejo J et al. Noninvasive ventilation in mild obesity hypoventilation syndrome: a randomized controlled trial. Chest. 2012;141:692-702.

30) Chouri-Pontarollo N, Borel JC, Tamisier R, Wuyam B, Levy P, Pepin JL. Impaired objective daytime vigilance in obesity-hypoventilation syndrome: impact of noninvasive ventilation. Chest. 2007;131:148-55.

31) Borel JC, Burel B, Tamisier R et al. Comorbidities and mortality in hypercapnic obese under domiciliary noninvasive ventilation. PLoS One. 2013;8:e52006.

32) Wijesinghe M, Williams M, Perrin K, Weatherall M, Beasley R. The effect of supplemental oxygen on hypercapnia in subjects with obesity-associated hypoventilation: a randomized, crossover, clinical study. Chest. 2011;139:1018-24.

**Adipokines: a novel link between adiposity and carotid plaque vulnerability**

Nikolaos PE Kadoglou, MD, MSc, PhD
*University of Athens*

Obesity is a risk factor for atherosclerotic complications, such as coronary artery disease (CAD) and stroke. Understanding the mechanism linking obesity to atherosclerosis is critical for its prevention and treatment. Many pro-inflammatory adipose tissue derived factors, known as adipokines, are most likely to play an important role in the atherosclerosis development and progression1. On the other hand, the pharmaceutical modulation of those adipokines, using either statins or insulin sensitizers, has mostly exerted favorable results2. Whether the latter effects are related to beneficial clinical outcomes is under investigation.

Stroke is one of the most common causes of mortality and disability in the Western world. It is well established that carotid atherosclerosis highly predisposes to cerebral ischemic events and mounting evidence correlates carotid plaque texture with its stability3. The latter is characterized by high inflammatory burden, large lipid core, thin fibrous cap. Among predisposing risk factors to plaque rupture or plaque erosion, inflammatory mediators, like cytokines, possess predominant role. Up to now, cytokines have been extensively studied in terms of carotid plaque vulnerability.

Notably, their circulating levels seem to mirror the inflammatory burden and the risk of rupture of the atherosclerotic plaques. For these reasons, numerous studies have proposed several cytokines as causative factors or bystanders of acute ischemic cerebrovascular events. However, the minority of those studies investigated the relationship between circulating cytokines and long-term clinical outcomes.

Stabilization of carotid artery plaques by pharmacologic intervention is a promising strategy for the prevention of ischemic stroke. During the last decade, pharmaceutical agents aiming at inflammation modulation, as well as statins, appeared as potential candidates for the primary and secondary prevention of cerebrovascular ischemic events caused by carotid atherosclerosis. Nevertheless, additional large-scale data are required4.

Despite some controversial results, a growing body of evidence has mostly suggested the underlying link between adipokines, circulating and fat-derivatives levels, and atherosclerosis. Most of adipokines have shown pro-atherogenic properties, while other members seem to be atheroprotective. Among adipokines members, a considerable

relationship between the severity of angiographically-proven coronary atherosclerosis and either low serum apelin levels or high visfatin levels has been previously documented5. A similar link was observed in patients with either early or advanced stage of carotid atherosclerosis implicating the association of adipokines with atherosclerosis progression6.
Most recently, our research team demonstrated for first time that low apelin and high visfatin serum levels were associated with carotid plaque vulnerability in patients with carotid atherosclerosis7. In addition to this, a 2-year atorvastatin treatment considerably ameliorated carotid plaque echogenicity, apelin and visfatin serum levels, providing a novel link between adiposity and carotid plaque vulnerability.
Unambiguously, future studies will examine the prognostic significance of adipokines members as biochemical means of carotid atherosclerosis development and destabilization.

**References:**


1) Kadoglou NP, Avgerinos ED, Liapis CD. An update on markers of carotid atherosclerosis in patients with Type 2 diabetes. Biomark Med. 2010;4:601-609.

2) Kadoglou NP, Tsanikidis H, Kapelouzou A, et al. Effects of rosiglitazone and metformin treatment on apelin, visfatin, and ghrelin levels in patients with type 2 diabetes mellitus. Metabolism. 2010 Mar;59:373-9.

3) Kakkos SK, Stevens JM, Nicolaides AN, Kyriacou E, Pattichis CS, Geroulakos G, et al. Texture analysis of ultrasonic images of symptomatic carotid plaques can identify those plaques associated with ipsilateral embolic brain infarction. Eur J Vasc Endovasc Surg. 2007;33:422-429.

4) Lardizabal JA, Deedwania P. Lipid-lowering therapy with statins for the primary and secondary prevention of cardiovascular disease. Cardiol Clin. 2011;29:87-103.

5) Kadoglou NP, Lampropoulos S, Kapelouzou A, Gkontopoulos A, Theofilogiannakos EK, Fotiadis G, Kottas G. Serum levels of apelin and ghrelin in patients with acute coronary syndromes and established coronary artery disease--KOZANI STUDY. Transl Res. 2010;155:238-46.

6) Kadoglou NP, Avgerinos ED, Liapis CD. An update on markers of carotid atherosclerosis in patients with Type 2 diabetes. Biomark Med. 2010;4:601-9.

7) Kadoglou NP, Sailer N, Moumtzouoglou A, Kapelouzou A, Gerasimidis T, Kostakis A, Liapis CD. Adipokines: a novel link between adiposity and carotid plaque vulnerability. Eur J Clin Invest. 2012;42:1278-86.

**Physical activity and circulating endothelial progenitor cells in obesity**

Gian Franco Gensini, MD*°
**Department of Experimental and Clinical medicine, University of Florence, Florence, Italy; ° Don Carlo Gnocchi Foundation, Florence, Italy*

Overweight, through an increased oxidative stress and inflammation, has been demonstrated to determine a sub-clinical atherosclerosis, so representing a susceptibility factor for the development of cardiovascular events [1]. To date, the precise pathophysiological mechanisms that link obesity with atherosclerosis are not well defined; recently, a role for endothelial (EPC) and circulating progenitor cells (CPC) has been reported. [2-3]. EPC and CPC are released from the bone marrow into the circulation in response to cytokines and other stimuli signalling tissue injury. These cells have been demonstrated to be key player in restoration of injured endothelium, either by integrating in the endothelial cell layer or by secreting angiogenic growth factors [4]
In 2008, Muller-Ehmsen and colleagues demonstrated for the first time that CPC were inversely related to body weight, body mass index and waist circumference in a population of obese subjects, with a higher prevalence of cardiovascular risk factors, such as diabetes, hypercholesterolemia and physical inactivity [5]. Moreover, it has been also reported that, by reducing the caloric intake through a dietary intervention, the reduction of CPC and in particular of the CD34+ subpopulation could be reversible [5]. More recently, in addition, a study conducted in a limited sample of obese subjects examined the effect of a dietary intervention on early outgrowth EPC number and functional properties, by demonstrating that, after a 6 months of intervention, a significant weight reduction was able to restore the functional capacity of EPC [6].
Actually, physical exercise is an important part of obesity treatment concepts, by inducing and supporting fat mobilisation from adipose tissue [7]. Over the past few years, research in the field of the effect of physical activity on stem cells' mobilisation produced some interesting findings. In fact, physical exercise has been reported to augment the number of both CPC and EPC in coronary artery disease patients as well as in athletes, showing a positive effect on stem cells' mobilisation [8-9].
We reported the beneficial effects of a personalized physical activity programme on EPC number as well as on weight reduction and body composition of obese and overweight subjects [10]. Indeed, a 3-month

intervention programme with physical activity was able to decrease total weight and percentage of fat mass, by augmenting the number of circulating EPC. Moreover, a significant correlation between the decrease of percentage of fat mass and the increase of EPC, suggesting a possible link between adipose tissue reduction and EPC mobilization, has been also reported[10].
Our results were confirmed in a population of 29 overweight and obese children who were randomly assigned to a 12-week supervised after school combined exercise or to maintain their usual activities of daily living during the study [11]. An increase in the percentage of CPCs were observed in the after-school exercise group compared with the control group. In addition carotid intima-media thickness decreased after 12 weeks in the after school exercise group; this increase in the number of EPC may be one of the component mediating the beneficial effect of exercise training on cardiovascular health in overweight and obese children [11].
On this basis, exercise interventions that improve endothelial cell function are critical for defining effective approaches to prevent atherosclerotic cardiovascular disease associated with obesity. It is important to note that, intervention based only on physical activity, and not on dietary modification need to be personalized according to subjects' variables in order to obtain a personalized prescription which is able to obtain a moderate weight reduction and an increase of progenitor cells.

**References:**


1) Rossi R, Iaccarino D, Nuzzo A, Chiurlia E, Bacco L, Venturelli A, Modena MG. Influence of body mass index on extent of coronary atherosclerosis and cardiac events in a cohort of patients at risk of coronary artery disease. *Nutr Metab Cardiovasc Dis* 2011; 21: 86-93.

2) Tobler K, Freudenthaler A, Baumgartner-Parzer SM, Wolzt M, Ludvik B, Nansalmaa E, Nowotny PJ, Seidinger D, Steiner S, Luger A, Artwohl M. Reduction of both number and proliferative activity of human endothelial progenitor cells in obesity. *Int J Obes* 2010; 34: 687-700.

3) MacEneaney OJ, Kushner EJ, Van Guilder GP, Greiner JJ, Stauffer BL, DeSouza CA. Endothelial progenitor cell number and colony-forming capacity in overweight and obese adults. *Int J Obes* 2009; 33: 219-225.

4) Asahara T, Kawamoto A. Endothelial progenitor cells for postnatal vasculogenesis. *Am J Physiol* 2004; 97:1119-1128.

5) Muller-Ehmsen J, Braun D, Schneider T, Pfister R, Worm N, Wielckens K, Scheid C, Frommolt P, Flesch M. Decreased number of circulating progenitor cells in obesity: beneficial effects of weight reduction. *Eur Heart J* 2008; 29: 1560-1568.

6) Heida NM, Muller JP, Cheng IF, Leifheit-Nestler M, Faustin V, Riggert J, Hasenfuss G, Konstantinides S, Schäfer K. Effects of obesity and weight loss on the functional properties of early outgrowth endothelial progenitor cells. *J Am Coll Cardiol* 2010; 55: 357-367.

7) Byrne NM, Meerkin JD, Laukkanen R, Ross R, Fogelholm M, Hills AP. Weight loss strategies for obese adults: personalized weight management program vs. standard care. *Obesity* 2006; 14: 1777-1788.

8) Steiner S, Niessner A, Ziegler S, Richter B, Seidinger D, Pleiner J, Penka M, Wolzt M, Huber K, Wojta J, Minar E, Kopp CW. Endurance training increases the number of endothelial progenitor cells in patients with cardiovascular risk and coronary artery disease: *Atherosclerosis* 2005; 181: 305-310.

9) Thijssen DHJ, Vos JB, Verseyden C, van Zonneveld AJ, Smits P, Sweep FC, Hopman MT, de Boer HC. Haematopoietic stem cells and endothelial progenitor cells in healthy men: effect of aging and training. *Aging Cell* 2006; 5: 495-503.

10) Cesari F, Sofi F, Gori AM, Corsani I, Capalbo A, Caporale R, Abbate R, Gensini GF, Casini A. Physical activity and circulating endothelial progenitor cells: an intervention study. *Eur J Clin Invest* 2012; 42:927-932.

11) Park JH, Miyashita M, Kwon YC, Park HT, Kim EH, Park JK, Park KB, Yoon SR, Chung JW, Nakamura Y, Park SK. A 12-week after-school physical activity programme improves endothelial cell function in overweight and obese children: a randomised controlled study. *BMC Pediatrics* 2012; 12:111-119.

## Uric Acid and cardiovascular risk

Claudio Borghi
*Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy*

Cardiovascular diseases are the major cause of death in the Western world as a consequence of the extensive prevalence and the inadequate control of cardiovascular risk factors in the general population. Elevated levels of serum uric acid (SUA) are the ethiological mechanism in the development of gout and is also significantly associated with an increase in the relative risk of CV diseases in addition with the more consolidated CV risk factors (e.g. hypertension, lipid disorders, diabetes, etc). The hypothesis linking uric acid with cardiovascular disease is well grounded in animal models where the development in hyperuricemia is associated with an increase in blood pressure that can be prevented by the use of xantine-oxidase inhibitors leading to a decrease in serum uric acid. Similar data have been published in humans and in partyicular in the adolescent population where the levels of SUA are directly associated with the blood pressure levels or the develoipment of hypertension later in life. Data from observational studies and physiological experiments suggest that there may be a causal relationship between plasma levels of SUA and the incidence of cardiovascular and renal disease. However, definetely convincing evidence remains elusive for many different reasons that complicates the understanding of the relationship between the study of SUA, its determinants and its confounders. In particular among the confounders a prominent role is played by statistical and methodological issues as well as by the counfonding role of co-variates that might be also mediators of biological pathways (e.g kidney) or might variably interact with additional cardiovascular risk factors. In particular there is a possibility that the levels of SUA must be considered only as the marker of the oxidative stress associated with the activation of xantino oxidase that is involved in its production. Thiw hypothesis might open an interesting interpretation of the role of SUA in CV disease that should involve a functional difference among patients whose plasma levels of SUA ar due to an excessive production when compared to subjects whose hyperuricemia is the consequence of a reduced renal excretion or an exaggerated tubular re-absorption who would be more prone to tissue deposion of urate and gout. However despite these limitations in the methodological approach, the possible association between s.uric acid and cardiovascular disease is well supported by several epidemiological observation, can be reasonably explaind by a

mechanicistc approach and might be favorably modified by appropriate treatment strategies involving both a biochemical and a structural approach addressing the protection of target organ.

**References:**


1) Borghi C, Reggi A, Pavesi A, Cicero AFG. Arrigo F. G. Cicero Increased Serum Uric Acid as a Risk Factor for Cardiovascular Diseases.Curr Obes Rep 2013; DOI 10.1007/s13679-013-0067-6.

2) Syamala S, Li J, Shankar A: Association between serum uric acid and prehypertension among US adults. J Hypertens, 2007; 25: 1583-89.

3) Grayson PC, Kim SY, LaValley M, M, Choi HK: Hyperuricemia and incident hypertension: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2011 Jan;63(1):102-10.

4) Feig DI, Johnson RJ: Hyperuricemia in childhood primary hypertension. Hypertension. 2003;42:247-252.

5) Fang J, Alderman MH: Serum uric acid and cardiovascular mortality: the NHANES I epidemiologic follow up study, 1971-1992. *JAMA*. 2000;283:2404 –2410.

6) Feig DI, Soletsky B, Johnson RJ: Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. JAMA. 2008;300:924-932.

## Hyperuricemia: Pharmacologic Intervention

Giovambattista Desideri[1], Antonella Ventresca[1], Raffaella Bocale[2]
[1]*Geriatric Division, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy*
[2]*Complesso Integrato Columbus, Rome, Italy*

Gout prevalence has been increasing in recent years and it is currently one of the most common causes of inflammatory arthritis in most industrialized countries (1). Gout is brought on by an abnormally high concentration of uric acid in the blood (hyperuricemia), which provokes deposition of sodium urate in the joints, either through increased synthesis of uric acid, or through decreased capacity of the kidneys to excrete such acid (1). If the crystals are dissolved completely and no new crystals can form, then the condition is controlled and signs and symptoms disappear, cured, although increase of uric acid can recur if the urate lowering treatment is discontinued with a risk of reacutizations (2). The cornerstone of effective gout management is longterm serum urate lowering below saturation concentrations (3,4). This has been recognized in recent evidence-based recommendations from the European League Against Rheumatism (EULAR) Task Force for Gout (5) and American College of Rheumatology (6) which recommend that serum uric acid should be reduced to at the minimum target of 6 mg/dl (360 mmol/l). The management of gout includes not only pharmacological approaches, but also lifestyle and dietary changes that could affect the course of the disease (4,5,6). The guidelines recommend a number of nonpharmacologic interventions aimed at lessening attack risk, lowering uric acid levels, and promoting general health while preventing the development of comorbidities (4,5,6). Lifestyle recommendations include restriction of purin-rich food (i.e. organ meats), foods containing high-fructose corn syrup and excessive alcohol use, weight loss in those who are overweight, smoking cessation, and regular physical activity (4,5,6). The guidelines recommend xantine oxidase inhibitor therapy with either allopurinol or febuxostat as the first line pharmacologic approach (3,6). Allopurinol has been widely used to reduce circulating levels of serum uric over the past four decades and is effective in the wide majority of patients. However, toxicity, in particular to the skin, may limit the use of allopurinol. In addition, the risk of renal failure contraindicates increases of the dosage, frequently leading to poor efficacy (3). The currently recommended starting dose of allopurinol is 100 mg/d (or 50 mg/d in patients with severe kidney dysfunction). When given at the usual dosage of 300 mg/d, allopurinol presently enables the target

uricemia of 6 mg/dl to be reached in only a minority of gouty patients (7). However, raising the dose may lead to an increased risk of toxicities, although further evidence on this issue is required. After almost 50 years of dormancy, a new therapeutic agent for the management of gout, febuxostat, have entered the market providing to the clinicians a new pharmacological tool to safely reduce serum uric acid. Febuxostat is a nonpurine analogue uricostatic agent structurally different from allopurinol (3). There is no recommendation for dose reduction with febuxostat in mild to moderate renal impairment, which is a valuable advantage over allopurinol in patients with renal impairment (8). Phase III trials that have documented the efficacy of febuxostat when compared with allopurinol. The Febuxostat versus Allopurinol Control Trial (FACT) compared patients who received febuxostat (80 mg or 120 mg) with patients who received allopurinol 300 mg (9). At the end the study the use of febuxostat at either 80 mg or 120 mg doses was more effective than allopurinol 300 mg in lowering serum urate levels (9). In the CONFIRMS trial, 40 mg of febuxostat was similar to 300 mg of allopurinol in effectiveness, but 80 mg of febuxostat outperformed allopurinol (10). In the European phase 3 data from the study known as Allopurinol and Placebo-Controlled Efficacy Study of Febuxostat (APEX), male subjects were randomized to a once-daily fixed dose of placebo; febuxostat 80 mg, 120 mg, or 240 mg; or allopurinol. The 240 mg dose of febuxostat (double the recommended highest dose) was used as a safety-evaluation dose (11). The primary end point for the trial was the proportion of subjects with serum urate levels of <6.0 mg/dL at each of the last three visits. Patients with moderate renal impairment achieved the end point in 44% of the febuxostat 80 mg group, 45% of the 120 mg group, and 60% of the 240 mg group compared with 0% of allopurinol and placebo groups (11).

Even if gout is often considered as a middle-age disease, it really represents the most common inflammatory arthritis seen in the elderly (12). Prevalence of gout increases with advancing age in men, peaking at 75–84 years of age, with a more equal gender distribution. The effective management of gout in the elderly is challenging as global clinical condition of people in this demographic segment can be frequently complicated by substantial comorbidities: up to 58% of patients with gout have comorbid hypertension, 45% have a comorbid lipid disorder, 33% have both hypertension and a lipid disorder and 20% have comorbid diabetes mellitus (3). Although the guidelines of gout treatment are the same in the elderly as in the general population, recognition of the physiological changes that affect medication metabolism, drug interactions, and medical comorbities in older individuals is paramount (3). In this regards, data obtained from the

374 elderly subjects enrolled in CONFIRMS study demonstrated that febuxostat 80 mg and 40 mg is superior to commonly prescribed fixed doses of allopurinol (200/300 mg) in subjects ≥65 years of age with high rates of renal dysfunction and is well tollerated (13). Thus, for the elderly patients febuxostat would represent a good treatment choice.

Despite an increased understanding of the disease etiology and risk factors, evidence is accumulating that part of the patient population is not optimally managed and continues to experience clinical manifestations of gout (14,15,16). There are widespread misconceptions and lack of knowledge among both patients and health professionals concerning the nature of gout and its recommended management, which leads to suboptimal care. This represents a relevant topic since success of lifelong treatment is dependent on the patient's commitment to treatment, which is a function of the patient's understanding of the illness and treatment. Urate lowing therapy is at the core of an effective long-term management scheme to reduce the underlying metabolic cause of gout. Furthermore, the growing body of evidence indicating an unfavorable impact of increased serum uric levels on cardiovascular and renal diseases suggests the opportunity to pay attention to uric acid levels independently on the diagnosis of gout. Continuation of the urate lowering treatment should be emphasized in subjects with elevated serum uric acid levels as being critical to success.

**References:**


1) Richette P, Bardin T. Gout. Lancet 2010;375:318-28.

2) Perez-Ruiz F. Treating to target: a strategy to cure gout. Rheumatology 2009;48(Suppl 2):ii9-14.

3) Bardin T, Desideri G. How to manage patients with gout. Curr Med Res Opin. 2013;29(3):17-24.

4) Manara M, Bortoluzzi A, Favero M, et al. Italian Society of Rheumatology recommendations for the management of gout. Reumatismo. 2013 Mar 28;65(1):4-21.

5) Zhang W, Doherty M, Bardin T, et al. EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies

Including Therapeutics (ESCISIT). Ann Rheum Dis. 2006;65(10):1312-24.

6) Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012;64:1431-46.

7) Hamburger M, Baraf HS, Adamson TC et al. 2011 recommendations for the diagnosis and management of gout and hyperuricemia. Phys Sportsmed. 2011;39(4):98-123.

8) Garcia-Valladares I, Khan T, Espinoza LR. Efficacy and safety of febuxostat in patients with hyperuricemia and gout. Ther Adv Musculoskel Dis 2011;3:245-53.

9) Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005;353(23):2450-2461.

10) Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the COMFIRMS trial. Arthritis Res Ther 2010;12:R63.

11) Schumacher HR Jr, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum. 2008;59(11):1540-8.

12) Fam AG. Gout in the elderly. Clinical presentation and treatment. Drugs Aging 1998;13:229-43.

13) Jackson RL, Hunt B, MacDOnald PA. The efficacy and safety of febuxostat for urate lowering in gout patients ≥65 years of age. BMC Geriatrics 2012:12:11. Published online march 2012.

14) Fels E, Sundy JS. Refractory gout: what is it and what to do about it? Curr Opin Rheumatol 2008;20:198-202.

15) Pascual E, Sivera F. Why is gout so poorly managed? Ann Rheum Dis 2007;66:1269-70.

16) Roddy E. Hyperuricemia, gout, and lifestyle factors. J Rheumatol 2008;35: 1689-91.

**Metabolic syndrome and target organ damage: role of blood pressure**

Veglio F, Losano I, Buffolo F, Sabia L. Di Monaco S.
*Department of Medical Sciences, Internal and Hypertension Division, University of Turin, Italy*

Metabolic syndrome is a cluster of metabolic symptoms, that are strongly associated with type II diabetes mellitus. It is defined by three or more of the following characteristics: abdominal obesity, hyperglycemia, hypertension, hypertrigyceridemia and hypo-high-density lipoprotein cholesterolemia. An important role is played by insulin resistance, with secondary hyperinsulinemia, which are associated with hypertension, dyslipidemias, atherosclerosis and obesity. There are many conditions, which leads to the development of hypertension in patients with metabolic syndrome. Insulin resistance is the common etiological factor of a group of disorders, such as high blood pressure, hyperinsulinemia, high levels of low density lipoproteins (LDL), tryglicerides, cholesterol, low levels of high density lipoproteins (HDL) and central adiposity, that are part of the so called metabolic syndrome. Insulin resistance is defined as the inability of a known quantity of insulin to increase glucose uptake and utilization. It is epidemiologically linked to hypertension. Insulin resistance is associated with endothelial disfunction. Endothelial cell membrane has insulin receptors (IRS-1). Insulin has indeed a hemodynamic component, albeit small compared to the metabolic one. Insulin-signaling pathways in vascular endothelium lead to the activation of endothelial NO syntase. In particular, Akt directly phosphorylates eNOS, resulting in NO production. NO is involved in the insulin-elicited increase in blood flow and recruitment of capillaries, which are part of the metabolic effects of insulin on tissues. The insulin-induced increase of microvascular endothelium-dependent vasodilatation is abolished in insulin resistance condition, such as obesity. The inhibition of NO synthesis leads to a vasoconstrictor effect of insulin on isolated arterioles. On the other hand, insulin is able to stimulate endothelin-1 (ET-1) gene expression in endothelial cells, with a vasoconstriction effect. Insulin can modulate circulating ET-1 levels and they are increased in patients affected by diabetes mellitus type II. Insulin induces endothelin-mediated vasoconstriction only when NO-syntase is inhibited. MAPK activation by IRS-1 causes the release of ET-1, which promotes insulin resistance, increase oxidative stress, reduces the bioavailability of NO and promotes a proatherogenic state. An imbalance between the release of both NO and ET-1 may be involved in pathophysiology

of hypertension and atherosclerosis in insulin-resistance states associated with endothelial dysfunction. Glucose favours vasoconstriction and impairs vasodilatation. It has been demonstrated that in the arteries of diabetic rats hyperglycaemia reduces the tonic release of NO and impairs endothelium-dependent vasodilatation in both the microcirculation and the macrocirculation. The vasodilatory effect of insulin disappears when hyperglycaemia exists, because it is blunted by the vasoconstrictive effects of glucose. Furthermore, compensatory hyperinsulinemia, that occurs with insulin resistance, increases sodium reabsorption and sympathetic activity , which lead to an increase in blood pressure. These observations lead to the so called insulin hypothesis of hypertension. *Ferrannini et al*. has affirmed that essential hypertension is "per se" an insulin resistance state. This insulin resistance involves glucose metabolism, is located in peripheral tissues and is directly correlated with the severity of hypertension. Furthermore, insulin has multiple actions on the sympathetic nervous system, the kidney and the vasculatures, that lead to hypertension. It has been observed that drugs which improves insulin resistance and decrease hyperinsulinemia can also reduce blood pressure. For instance, oral administration of metformin to insulin-resistant , hypertensive patients increased insulin sensitivity and decreased arterial pressure and metabolic risk factors [*Landin et al.*]. Insulin sensitizers glitazones can also lower blood pressure[*Ogihara et al.*]. Finally, some anthypertensive drugs, such as angiotensin II converting enzymes inhibitors or agiotensin II receptor antagonists increase insulin sensitivity[*Sanchez et al.*]. In the metabolic syndrome there is an increase in sympathetic tone, which leads to an increase in circulating levels of noradrenaline, accompanied by an increase in blood pressure. Hyperinsulinemia, hyperleptinaemia and high levels of free fatty acids leads to exacerbation of sympathetic tone. Independently of changes in glycemia, insulin has a sympathoexcitatory effect centrally-mediated. In addition, high levels of insulin increase sodium reabsorption, favouring expansion of extracellular volume, which may predispose to hypertension. There is a clear association between arterial pressure and body mass index. Obesity impairs renal-pressure natriuresis and leads to sodium retention. In obese subjects an increase arterial pressure is required to maintain sodium balance. Leptin, an adipokine, in another link between obesity and increased sympathetic activity. Leptin acts in the ventromedial and dorsomedial hypothalamus, and leads to increase of blood pressure through the activation of the sympathetic nervous system. High levels of free fatty acids in visceral obese individuals may lead to the activation of the sympathetic nervous system. Adipose tissue is not only an energy reservoir, but it's

indeed an endocrine tissue. Its product are named adipokines. Dysregulation of the production and secretion of adypokines is involved in the development of metabolic and cardiovascular diseases and can explain the development of hypertension in metabolic syndrome. Intra-abdominal visceral fat accumulation plays a key role in the development of a variety of metabolic and circulatory disorders, such as hypertension. Almost all the systemic arteries are surrounded by a layer of perivascular adipose tissue (PVAT), which has a modulator action on vascular contractility. In particular, several works supposed a prorelaxing role of PVAT, due to the uptake and elimination of the catecholamines by adipose tissue. PVAT exhibits a proinflammatory phenotype compared to other depots such as subcutaneous one. PVAT is very sensitive to the effects of excess dietary fat. It has been demonstrated in obese rats that PVAT causes endothelial dysfunction via proinflammatory cytokines, such as TNF- , monocyte chemotactic protein-1 and oxidative stress. PVAT can produce NO and in non-obese subjects PVAT would have a vascular protective and beneficial role. During the onset of obesity, several adaptive mechanisms within the vessel wall and within PVAT itself are activated to preserve vascular function [*Gil-Ortega et al.*]. At some time point during obesity development, PVAT switches from a vascular protective influence to a deleterious one. Endothelium cells have leptin receptors. The concentration of plasma leptin is correlated with adiposity and hyperleptinemia is indeed considered an independent cardiovascular disease risk factor. Leptin is a NO-dependent vasodilator but also increases peripheral vascular resistance and sympathetic nerve activity. Its very presence impairs endothelium-dependent relaxation, producing endothelial dysfunction. Adiponectin is an adipokine, which plasma levels are negatively correlated with body mass index and visceral adiposity. There is a closer relationship between low concentrations of adiponectin in the blood, insulin resistance and hyperinsulinemia. Adiponectin improves NO-dependent vasodilatation by opening voltage-dependent potassium-channels. High adiponectin levels should protect from the deterioration of glucose metabolism. Thus, hypoadiponectinemia could be a significant background of vascular changes and metabolic disorders, including insulin resistance and a background or hypertension. Indeed, *Mallamaci et al.* have found that essential hypertensive patients had high plasma levels of adiponectin, maybe a counter-regulatory response aimed endothelial damage and cardiovascular risk associated with high arterial pressure. Tumor necrosis factor- (TNF- )has been recognized as one of the most important adipokine. It is the molecule linking inflammation with obesity. TNF- triggers ET-1 and Ang II-induced vasoconstriction

and impairs endothelium-dependent vasodilatation due to increased ROS production or decreased NO production. Adipocytes can produce vasoactive substances, such as prostaglandins, angiotensin II and andothelin-1. Adipocytes produce vasodilators PGE2 and PGI2 in response to sympathetic stimulation. Lypolitic hormones, such as adrenaline, target membrane adipocyte receptors and activate hormone sensitive lipase. Prostaglandins production results from the cooperation between adipocytes, which are the source of the original fatty acid component of prostaglandins, and endothelial cells, which convert fatty acids in prostaglandins. Insulin decreases the production of these vasodilators. Hypertension associated with insulin resistance and hyperinsulinemia would be due partly caused by the lack of proper PGE2 and PGI2 release. PVAT has been recognized as a source of angiotensin II. Furthermore, it has been discovered that adipocytes also produce aldosterone in response to ang II. In this regard, adipocytes can be considered a miniature renin-angiotensin-aldosterone system. Adipocytes derived ang II favours vasoconstriction. Plasma renin activity and thus the production of ang II are high in obese individuals. In particular, angiotensinogen gene expression is higher in intra-abdominal fat than in other fat depots or nonadipose tissue. Aldosterone levels are elevated in some obese hypertensives, especially patients with visceral obesity. The prevalence of the metabolic syndrome was higher in primary aldosteronism than in essential hypertension (41.1% vs 29.6%, $P< 0.05$) ( Fallo et al.).Furthermore, adipose cells also produce mineralcorticoid-releasing factors, named adipogensis or aldosterone-releasing factors (ARF), with important effects on aldosterone release from adrenocortical cells. There is a close relationship between release of aldosterone and insulin resistance. In particular, aldosterone promotes insulin resistance through mineralcorticoid receptors activation and, on the other hand, hyperinsulinemia induces increase in aldosterone levels. Endothelin-1 has been qualified as adipokine and its levels increase in obesity and type II diabetes. It effect is vasoconstriction and, furthermore, it generates insulin resistance specifically in visceral adipose tissue. The presence of coexisting hypertension and metabolic syndrome can lead to modifications in central hemodynamic parameters, such as brachial central pulse pressure (PP), PP amplification, aortic stiffness and wave reflections. *Safar et al.* compared Data were compared a population of patients with essential hypertension without metabolic syndrome with patients affected by hypertension and metabolic syndrome. Patients with diabetes mellitus have, for the same age, sex and MAP, significantly higher mean values of hearth rate, aortic stiffness and PP amplification, but lower mean values of AIx (augmentation

pressure/pulse pressure). Aix is the increase in SBP and PP produced by the reflected wave and expressed as a percentage of the PP. In metabolic syndrome, PWV, a surrogate of aortic stiffness, increases in proportion to the number of metabolic syndrome criteria and increases with age more rapidly in these patients. PWV is associated with increased values of carotid wall thickness and subcutaneous trunk fat. Small vessels and arterioles are the principal sites of wave reflections from the incident wave and the reflected waves return from the periphery to the larger thoracic aorta. Insulin has effects on resistive vessels and precapillary arterioles, but also on large arterial vessels through the mechanism of wave reflections, causing a reduction in amplitude and timing of the carotid pulse. In metabolic syndrome this mechanism in disrupted and may contribute to the development of systolic hypertension. Management of hypertension may differ markedly in the presence or absence of associated diabetes mellitus and/or metabolic syndrome. These differences are due to changes in central hemodynamic, influenced by age, sex, hearth rate, MAP and several glucose-related factors too. All these factors, such as waist circumference, play a consistent role in blood pressure control when hypertension and diabetes are associated. The choice of medications causing aortic destiffening should be discussed, such as those involving angiotensin blockade, calcium inhibition and diuretics. Lifestyle modifications might be recommended, mainly in the field of nutrition. Finally, the link of hypoglycemic agents and insulin with arterial stiffness should be investigated. In the context of the combination of hypertension and diabetes, the presence of increased arterial stiffness requires the reduction of the systolic blood pressure, but also the need to maintain and/or even increase diastolic blood pressure. Low DBP is alone a significant risk factor for cardiac complications, particularly in the elderly.

**References:**


1) Nava, Eduardo. "Hypertension in Metabolic Syndrome: Vascular Pathophysiology. "*International journal of hypertension* 2013 (2013).

2) Ferrannini, Eleuterio, et al. "Insulin resistance in essential hypertension. "*New England Journal of Medicine* 317.6 (1987): 350-357.

3) Landin, K., L. Tengborn, and U. Smith. "Treating insulin resistance in hypertension with metformin reduces both blood

pressure and metabolic risk factors. "*Journal of internal medicine* 229.2 (1991): 181-187.

4) Ogihara, Toshio, et al. "Enhancement of insulin sensitivity by troglitazone lowers blood pressure in diabetic hypertensives. "*American journal of hypertension* 8.3 (1995): 316-320.

5) Sanchez, Ramiro A., et al. "Telmisartan improves insulin resistance in high renin nonmodulating salt-sensitive hypertensives. "*Journal of hypertension* 26.12 (2008): 2393-2398.

6) Fallo F, Veglio F, Bertello C, et al.: Prevalence and characteristics of the metabolic syndrome in primary aldosteronism. *J Clin Endocrinol Metab* 2006, 91:454–459.

7) Gil-Ortega, Marta, et al. "Adaptative nitric oxide overproduction in perivascular adipose tissue during early diet-induced obesity. "*Endocrinology* 151.7 (2010): 3299-3306.

8) Mallamaci, Francesca, et al. "Adiponectin in essential hypertension. "*Journal of nephrology* 15.5 (2002): 507.

9) Safar, Michel E., et al. "Hypertension and vascular dynamics in men and women with metabolic syndrome. "*Journal of the American College of Cardiology* 61.1 (2013): 12-19.

**Angiotenisn type 2 receptor in hypertensive cardiovascular disease**

Carmine Savoia. MD, FAHA
*Clinical and Molecular Medicine Department, Sapienza University of Rome, Cardiology Unit and Chair, Sant'Andrea Hospital, Rome (Italy)*

Angiotensin II exerts its effects by acting on two receptors, the angiotensin type 1 receptor (AT1R) and the angiotensin type 2 receptor (AT2R). Whereas AT1R seems to mediate most of the recognized actions of angiotenisn II, it appears that AT2R opposes in part the actions mediated by AT1R. AT2R may have the homeostatic role of exerting a countervailing influence on excess stimulation of AT1R. Since the AT2R is expressed in adult tissues in smaller numbers than AT1R, the actions and cell signaling of AT2R have been less well characterized than those of AT1R. It is generally accepted that $AT_2R$ mediate vasodilation as demonstrated in large and small vessels including the mesenteric, uterine, renal, coronary, and cerebral vascular beds. It has been reported that Ang II may evoke flow-mediated dilation of perfused rat mesenteric arteries in an $AT_2R$/NO-dependent manner. In vitro and in vivo studies show that AT2R mediates also antigrowth and proapoptotic effects, and may modulates the progression of atherosclerosis.
Several lines of evidence derived mainly from in vitro and in vivo studies in experimental animals as well as in humans have indicated that AT2R may exert a protective role in the cardiovascular system, mainly during chronic AT1R inhibition. In presence of an $AT_1R$ blocker, Ang II induced approximately a 30% increase in vasorelaxation in rat aorta as well as in mesenteric arteries. Thus, in presence of $AT_1R$ blockade, $AT_2R$ stimulation may reduce vascular tone and have beneficial effects on the control of blood pressure in hypertension. This is relevant to the potential contribution of unblocked $AT_2R$ in the antihypertensive effect of ARBs. Evidence from studies performed in humans has confirmed the data from animal studies. Angiotensin II induced vasodilation through $AT_2R$ in human coronary microarteries from non-diseased hearts of subjects with a wide age range. $AT_2R$ reduced tone of isolated resistance arteries from hypertensive diabetic patients chronically treated with an ARB, suggesting that in these subjects the unblocked $AT_2R$ stimulated by the increased angiotensin II could participate in blood pressure reduction induced by $AT_1R$ blockers. Moreover, $AT_2R$ may participate in the improvement of vascular remodeling observed in these high cardiovascular risk patients after treatment with ARBs.

Although *in vitro* studies have clearly demonstrated that $AT_2R$ have antigrowth properties, contradictory results have been reported on the role of $AT_2R$ in cardiac hypertrophy. In $AT_2R$ knock-out mice $AT_2R$ may promote or inhibit cardiac hypertrophy. These opposing results may be explained by the fact that the strain of the mice and the experimental conditions of these studies were different. Therefore, $AT_2R$ may play a context-specific role, and that they are not intrinsically "good" or "bad" players in cardiovascular control.
Cardiac $AT_2R$ overexpression in transgenic mice improved left ventricular systolic function at baseline and preserved function during post-myocardial infarction remodeling, via NO-dependent pathway. Moreover, Chronic loss of $AT_2R$ by gene targeting in knock-out mice prevented collagen deposition, leading to cardiac rupture.
$AT_2R$ may possibly play a role in vascular inflammation and atherosclerotic plaque stability and evolution, although the evidences are in part contradictory and inconclusive. $AT_2R$ function as major antinflammatory mediators in animal models of vascular injury. Genetic polymorphism A1675G on AT2R gene reduces cardiovascular risk and the severity of atherosclerosis by modifying systemic inflammation, especially in hypertensive males. On the other hand, in isolated human monocytes, $AT_2R$ stimulation enhanced $PGE_2$-mediated increase in MMP-1 that has been associated to atherosclerotic plaque instability.

## Effects of treatment strategy on endothelial function

Stefano Taddei
*Department of Clinical and Experimental Medicine, University of Pisa*

Essential hypertension is associated with endothelial dysfunction, which is caused mainly by production of oxygen free radicals that can destroy NO and impair its beneficial and protective effects on the vessel wall. In prospective studies endothelial dysfunction is associated with increased incidence of cardiovascular events (1).
Awareness that mere blood pressure normalization is not sufficient to normalize endothelial alterations in essential hypertensive patients is of crucial importance (2). It implies that antihypertensive drugs must be endowed with the ability to restore endothelial function, a specific property which goes far beyond blood pressure reduction.
Antihypertensive drugs must therefore be reconsidered in terms of specific efficacy on endothelial function. Experimental studies indicate that the majority of available compounds have the potential to improve endothelium-dependent relaxations (3). Drugs can act by different mechanisms including activation of NO-synthase, a scavenger activity on oxidative stress or by decreasing the production of oxygen free radicals (3). However, when the same compounds have been tested in a clinical setting, positive animal evidence has not always been confirmed and antihypertensive drugs show contrasting effects in terms of improvement or restoration of endothelial function.
Concerning ß-adrenoceptor antagonists, while treatment with atenolol is negative in peripheral subcutaneous and muscle microcirculation, compounds such as nebivolol, which activates the L-Arginine-NO pathway (4,5), and carvedilol, which has strong antioxidant activity, can improve endothelial function in hypertensive patients. Calcium antagonists and particularly the dihydropyridine-like, can reverse impaired endothelium-dependent vasodilation in different vascular districts, including the subcutaneous, epicardial, renal and forearm circulation (3). In the forearm circulation nifedipine and lacidipine can improve endothelial dysfunction by restoring NO availability through a mechanism probably related to an antioxidant effect (6,7). In contrast, conflicting results are found in the brachial artery (8). ACE-inhibitors, on the other hand, seem to improve endothelial function in subcutaneous, epicardial, brachial and renal circulation (3), whereas they are ineffective in potentiating the blunted response to acetylcholine in the forearm of essential hypertensive patients (9). They can also selectively improve endothelium-dependent vasodilation to bradykinin, an effect not mediated by restoring NO

availability, but probably related to hyperpolarization (10). Finally, recent evidence suggests angiotensin II receptor antagonists can restore endothelium-dependent vasodilation to acetylcholine in subcutaneous microcirculation (11), but not in that of the forearm muscle (12). Evidence concerning the effect of these drugs on the brachial artery in patients with atherosclerosis is in conclusive (3). However treatment with an angiotensin II receptor antagonist can improve basal NO release and decrease the vasoconstrictor effect of endogenous endothelin-1 (12).
Finally, it is worth noting that the renin inhibitor aliskiren, while sharing with ACE-inhibitors the ability of improving conduit artery endothelial function, is also able to increase vasodilation to acetylcholine and restore NO availability in the forearm of hypertensive patients (13).
In conclusion, despite the considerable evidence that impaired endothelium-dependent vasodilation can be improved by appropriate antihypertensive treatment, no clinical data exist demonstrating that the reversal of endothelial dysfunction is associated with a reduction in cardiovascular events. In the near future large scale clinical trials are required to demonstrate that treatment of endothelial dysfunction can lead to better prognosis in essential hypertensive patients.

**References:**


1) Flammer AJ, Anderson T, Celermajer DS, Creager MA, Deanfield J, Ganz P, Hamburg NM, Lüscher TF, Shechter M, Taddei S, Vita JA, Lerman A. The assessment of endothelial function: from research into clinical practice. Circulation. 2012;126:753-67.

2) Panza JA, Quyyumi AA, Callahan TS, Epstein SE. Effect of antihypertensive treatment on endothelium-dependent vascular relaxation in patients with essential hypertension. J Am Coll Cardiol 1993;21:1145-1151.

3) Ghiadoni L, Taddei S, Virdis A. Hypertension and endothelial dysfunction: therapeutic approach. Curr Vasc Pharmacol. 2012;10:42-60.

4) Cockcroft JR, Chowienczyk PJ, Brett SE, Chen C PL-H, Dupont AG, Van Nueten L, Wooding SJ, Ritter JM. Nebivolol vasodilates human forearm vasculature: evidence for an L-Arginine/NO-dependent mechanism. J Pharmacol Exp Ther 1995;274:1067-1071.

5) Dawes M, Brett SE, Chowienczyk PJ, Mant TG, Ritter JM. The vasodilator action of nebivolol in forearm vasculature of subjects with essential hypertension. Br J Clin Pharmacol 1999; 48: 460-463.

6) Taddei S, Virdis A, Ghiadoni L, Uleri S, Magagna A, Salvetti A: Lacidipine restores endothelium-dependent vasodilation in essential hypertensive patients. Hypertension 1997, 30 ; 1606-1612.

7) Taddei S, Virdis A, Ghiadoni L, Magagna A, Favilla S, Pompella A, Salvetti A. Restoration of nitric oxide availability after calcium antagonist treatment in essential hypertension. Hypertension 2001;37:943-948.

8) Ghiadoni L, Magagna A, Versari D, Kardasz I, Huang Y, Taddei S, Salvetti A. Different effect of antihypertensive drugs on conduit artery endothelial function. Hypertension 2003; 41:1281-1286.

9) Creager MA, Roddy MA. Effect of captopril and enalapril on endothelial function in hypertensive patients. Hypertension 1994;24:499-505.

10) Taddei S, Ghiadoni L, Virdis A, Buralli S, Salvetti A. Vasodilation to bradykinin is mediated by an ouabain-sensitive pathway as a compensatory mechanism for impaired NO availability in essential hypertensive patients. Circulation 1999;100:1400-1405.

11) Schiffrin EL, Park JB, Intengan HD, Touyz RM: Correction of arterial structure and endothelial dysfunction in human essential hypertension by the angiotensin receptor antagonist losartan. Circulation 2000;101 (14): 1653-1659.

12) Ghiadoni L, Virdis A, Magagna A, Taddei S, Salvetti A: Effect of the angiotensin II type 1 receptor blocker candesartan on endothelial function in patients with essential hypertension. Hypertension 2000; 35 (part 2): 501-506.

13) Virdis A, Ghiadoni L, Qasem AA, Lorenzini G, Duranti E, Cartoni G, Bruno RM, Bernini G, Taddei S. Effect of aliskiren treatment on endothelium-dependent vasodilation and aortic stiffness in essential hypertensive patients. Eur Heart J. 2012;33:1530-8.

**Blood pressure variability, adrenergic overdrive and cardiovascular risk in hypertension**

Guido Grassi
*Clinica Medica, Dipartimento di Scienze della Salute, Ospedale San Gerardo dei Tintori, Monza, Università Milano Bicocca, Milan (Italy)*

The importance of hypertension as a cardiovascular risk factor is widely acknowledged. It is also well established that the hypertensive state frequently clusters together with dysmetabolic conditions, such as dyslipidemia, obesity, diabetes mellitus, and/or with subclinical organ damage at the level of the brain, heart, kidney and arteries. This led the recent European Guidelines on hypertension (1) to emphasize the relevance of hypertension as a risk factor in relation not only to the magnitude of the blood pressure elevation, but also in terms of the so-called total cardiovascular risk resulting from the coexistence of high blood pressure with different risk factors, organ damage and disease which all together exert an adverse impact on patients prognosis. In the past few years, however, new studies have provided evidence in favour of the potential importance of some variables or conditions that, although at present cannot be regarded as established risk factors, can be considered as intermediate endpoints with evidence of prognostic importance. This is the case for inflammatory markers, procoagulant factors, endothelial dysfunction, small arteries structural alterations, increased arterial stiffness and myocardial and/ or vascular fibrosis. This may also be the case for new factors, i.e. short- and long-term blood pressure variability (2-4) and sympathetic activity (5), which, in essential hypertension, both display remarkable abnormalities with potential adverse impact on cardiovascular risk profile and, probably, prognosis .

This presentation will discuss in depth the relationships between cardiovascular risk and the increase in blood pressure variability, and in sympathetic cardiovascular drive characterizing the hypertensive state. This will be done by analysing the possible mechanisms of these alterations, the strengths and limitations of the findings linking the two above mentioned factors to cardiovascular risk and their clinical implications.

**References:**

1) Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the

European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013 ;31:1281-357.

2) Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet. 2010;375:895.

3) Mancia G. Short- and long-term blood pressure variability: present and future. Hypertension 2012;60:512-17.

4) Mancia G, Facchetti R, Parati G, et al. Visit-to-visit blood pressure variability, carotid atherosclerosis and cardiovascular events in the European Lacidipine Study on Atherosclerosis. Circulation. 2012;126:569-78.

5) Grassi G. Sympathetic neural activity in hypertension and related disease. Am J Hypertens. 2010;23:1052-60.

**Alzheimer Disease and Arterial Hypertension**

Giuseppe Lembo
*Department of Molecular Medicine, "Sapienza" University of Rome, IRCCS Neuromed, Pozzilli (Isernia, Italy)*

Genetic Alzheimer's disease (AD) accounts for only few AD cases and is almost exclusively associated to increased amyloid production in the brain. Instead, the majority of patients is affected with the AD sporadic form and typically has an alteration of clearance mechanisms. The identification of factors that influence the onset and progression of sporadic AD is a key step toward understanding its mechanism(s) and developing successful therapies. Increasing epidemiological studies describe a strong association between AD and cardiovascular risk factors, particularly hypertension, that exerts detrimental effects on the cerebral circulation, favouring chronic brain hypoperfusion. However, a clear demonstration of a pathophysiological link between cardiovascular risk factors and AD aetiology is still missing. To deepen our knowledge of the mechanisms involved in brain response to hypertension and their possible role in promoting amyloid deposition in the brain, we have deeply investigated murine models of hypertension, leading in the long time to plaque formation in the brain parenchyma and around blood vessels and cognitive deficits of learning and memory tasks. During the seminar I will go through our major findings, obtained in this particular experimental setting that allow us to suggest that this appears to be a unique possibility to study the pathogenetic mechanisms of sporadic AD triggered by vascular risk factors.

**Selected publications on topic:**

1) Carnevale D, Mascio G, D'Andrea I, Fardella V, Bell RD, Branchi I, Pallante F, Zlokovic B, Yan SS, Lembo G. Hypertension induces brain -amyloid accumulation, cognitive impairment, and memory deterioration through activation of receptor for advanced glycation end products in brain vasculature. Hypertension. 2012 Jul;60(1):188-97.

2) Carnevale D, Lembo G. 'Alzheimer-like' pathology in a murine model of arterial hypertension. Biochem Soc Trans. 2011 Aug;39(4):939-44.

3) Carnevale D, Mascio G, Ajmone-Cat MA, D'Andrea I, Cifelli G, Madonna M, Cocozza G, Frati A, Carullo P, Carnevale L,

Alleva E, Branchi I, Lembo G, Minghetti L. Role of neuroinflammation in hypertension-induced brain amyloid pathology. Neurobiol Aging. 2012 Jan;33(1):205.e19-29.

4) Gentile MT, Poulet R, Di Pardo A, Cifelli G, Maffei A, Vecchione C, Passarelli F, Landolfi A, Carullo P, Lembo G. Beta-amyloid deposition in brain is enhanced in mouse models of arterial hypertension. Neurobiol Aging. 2009 Feb;30(2):222-8.

5) Poulet R, Gentile MT, Vecchione C, Distaso M, Aretini A, Fratta L, Russo G, Echart C, Maffei A, De Simoni MG, Lembo G. Acute hypertension induces oxidative stress in brain tissues. J Cereb Blood Flow Metab. 2006 Feb;26(2):253-62.

## Cardiovascular consequences of poor compliance to antihypertensive therapy

Claudio Ferri
*University of L'Aquila, San Salvatore Hospital, Italy*

As it has been recently pointed out by the Guidelines for the management of arterial hypertension elaborated by the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) (1) and is generally recognized by either local scientific societies or national surveys (2,3) awareness and control of hypertension is still largely not satisfactory in the majority of hypertensive patients. Similar findings have been described for the control of risk factors other than hypertension in known essential hypertensive patients (4).

In this context, a truly tailored antihypertensive therapy is the combined result of a non-pharmacologic + a pharmacologic approach to hypertension. Thus, at least in recognized antihypertensive patients the main reasons leading to insufficient hypertension control worldwide is related either to physician inertia or to poor adherence to prescribed antihypertensive medication, or both (5).

In this regard, previous findings from Finland indicated that efforts to implement the recommended non-pharmacological and pharmacological principles for the control of cardiovascular risk factors including arterial hypertension, stroke and coronary heart disease have been accompanied by an approximately 10 mmHg fall in the population average of diastolic blood pressure, and about 60% decrease in deaths from both stroke and ischaemic heart disease among 30-59-year-old men and women (6). Adherence to antihypertensive drug therapy was substantially good and accounted for 5-6% of the observed fall of blood pressure, and 10-15% of the decrease in deaths from strokes and coronary heart disease. In contrast, there was a poor adherence to several non-pharmacological recommendations. As a consequence, increments in the intake of alcohol, obesity (in males), and smoking (in women) were also observed. In contrast, adherence to recommendations to decrease the intakes of sodium and saturated fats, and to reduce the sodium-to-potassium ratio as well as the saturated-to-unsaturated fat ratio, was substantially good. Concordantly, dietary changes appeared to account for a consistent part of the fall of blood pressure and the decrease in the cardiovascular diseases.

In Italy, there are no data on adherence to non-pharmacologic recommendations. In contrast, data obtained from 400 Italian primary

care physicians and 18.806 hypertensive patients ≥35 years of age during the years 2000 to 2001 (7) indicated that 51.4% of patients manifested with a low adherence level to prescribed antihypertensive drugs. Multiple drug treatment (odds ratio, 1.62; 95% CI, 1.43 to 1.83), dyslipidemia (odds ratio, 1.52; 95% CI, 1.24 to 1.87), diabetes mellitus (odds ratio, 1.40; 95% CI, 1.15 to 1.71), obesity (odds ratio, 1.50; 95% CI, 1.26 to 1.78), and antihypertensive combination therapy (odds ratio, 1.29; 95% CI, 1.15 to 1.45) were significantly ($P<0.001$) associated with high adherence to antihypertensive treatment. Compared with their low-adherence counterparts, high adherers (only 8.1% of the whole hypertensive population) reported a significantly decreased risk of acute cardiovascular events (hazard ratio, 0.62; 95% CI, 0.40 to 0.96; $P=0.032$).

In summary, long-term reduction of acute cardiovascular events is associated with high adherence to antihypertensive treatment. The combination of two drugs in a single pill seem to be relevant in favouring adherence to the prescribed antihypertensive medication. Simultaneous adherence to prescribed lifestyle changes is also important in daily clinical practice and demonstrated to be effective in further reducing cardiovascular events in the long run.

**References:**


1) Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. 2013 ESH/ESC Guidelines for the management of arterial hypertension - The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). European Heart Journal doi:10.1093/eurheartj/eht151.

2) Tocci G, Rosei EA, Ambrosioni E, Borghi C, Ferri C, Ferrucci A, Mancia G, Morganti A, Pontremoli R, Trimarco B, Zanchetti A, Volpe M. Blood pressure control in Italy: analysis of clinical data from 2005-2011 surveys on hypertension. J Hypertens. 2012 Jun;30(6):1065-74.

3) Olives C, Myerson R, Mokdad AH, Murray CJ, Lim SS. Prevalence, awareness, treatment, and control of hypertension in United States counties, 2001-2009. PLoS One. 2013;8(4):e60308.

4) Cortez-Dias N, Martins SR, Belo A, Fiuza M. Association of metabolic risk factors with uncontrolled hypertension: comparison of the several definitions of metabolic syndrome. J Hypertens. 2013 Jun 27. [Epub ahead of print]

5) Redon J, Erdine S, Böhm M, Ferri C, Kolloch R, Kreutz R, Laurent S, Persu A, Schmieder RE; SHARE Steering Committee. Physician attitudes to blood pressure control: findings from the Supporting Hypertension Awareness and Research Europe-wide survey. J Hypertens. 2011;29(8):1633-40.

6) Karppanen H, Mervaala E. Adherence to and population impact of non-pharmacological and pharmacological antihypertensive therapy.J Hum Hypertens. 1996;10 Suppl 1:S57-61.

## Hypertension in women

Bruno Trimarco
*Department of Advanced Biomedical Sciences, Federico II University of Naples, Italy*

Clinical differences between men and women with essential hypertension have been described as early as 1913 by Janeway [1] and later by Pickering [2] in 1955, however, despite its high prevalence in the population hypertension in women has received less attention than hypertension in men [3].
Two unique hypertension- inducing mechanisms, pregnancy and the use of oral contraceptives, are primary causes of hypertension that occur only in women, but the pathophysiology of hypertension in women differs in other ways from that in men: women tend to have more labile blood pressures and higher prevalence of the white-coat phenomenon [4], and are more likely to have low rennin, high volume hypertension than men [5].
Gender differences in blood pressure emerge during adolescence and persist through adulthood [6]. Hypertension becomes more prevalent among women than men after age 59. The influence of menopause on blood pressure in women is a matter of controversy, although there is convincing evidence that at least a portion of the rise in blood pressure seen later in life in women is due to menopause and its effect on the female hormone milieu [7]. Finally, the Framingham Heart Study [8] and the National Health and Nutrition Examination Survey [9] uniformly demonstrated a higher prevalence of hypertension and a lower blood pressure control rate in elderly women than in men. Specifically, only 23 to 28% of hypertensive women over the age of 60 years achieved blood pressure goals on treatment, whereas 36 to 38% of hypertensive men of the same age reached the target blood pressure. It has been recognized that the pathophysiology of hypertension in the elderly is largely attributed to an age-related elastin fragmentation and collagen accumulation in the arterial tree, with a substantial increase in the intrinsic rigidity of the arterial wall, which occurs more rapidly in women than in men [10]. In addition, one recent study demonstrated that aging was accompanied by a greater increase in sympathetic traffic in women than in men [11], an observation which may allow the speculation that also a sympathetic neural mechanism may be responsible for the high prevalence and poor blood pressure control rate in women.
Finally, although some studies have shown that the treatment of hypertension among women conferred less benefit against cardiac events compared to antihypertensive treatment in men [12-14] large

long-term clinical trials of antihypertensive treatment include both men and women have not demonstrated clinical significant gender differences in blood pressure response and outcomes [15, 16], and the international guidelines recommend the same approach for treating hypertensive men and women [17].

**References:**


1) Janeway, T.C., *A clinical study of hypertensive cardiovascular disease.* Archives of Internal Medicine, 1913. **XII**(6): p. 755-798.

2) Pickering, G.W.S., *High Blood Pressure, etc. [With plates and a bibliography.]*. 1955, London: J. & A. Churchill.

3) Calhoun, D.A. and S. Oparil, *The Sexual Dimorphism of High Blood Pressure.* Cardiol Rev, 1998. **6**(6): p. 356-363.

4) Pickering, T.G., *The ninth Sir George Pickering memorial lecture. Ambulatory monitoring and the definition of hypertension.* J Hypertens, 1992. **10**(5): p. 401-9.

5) Hanes, D.S., *Strategies for the Treatment of Hypertension in Postmenopausal Women.* J Clin Hypertens (Greenwich), 1999. **1**(1): p. 62-71.

6) Yong, L.C., et al., *Longitudinal study of blood pressure: changes and determinants from adolescence to middle age. The Dormont High School follow-up study, 1957-1963 to 1989-1990.* Am J Epidemiol, 1993. **138**(11): p. 973-83.

7) Calhoun DA, Oparil S. Gender and blood pressure. In: Izzo JL Jr and Black HR (eds). *Hypertension Primer*. American Heart Association, 1998, pp 229–232.

8) Lloyd-Jones, D.M., J.C. Evans, and D. Levy, *Hypertension in adults across the age spectrum: current outcomes and control in the community.* JAMA, 2005. **294**(4): p. 466-72.

9) Wassertheil-Smoller, S., et al., *Hypertension and its treatment in postmenopausal women: baseline data from the Women's Health Initiative.* Hypertension, 2000. **36**(5): p. 780-9.

10) Smulyan, H., et al., *Comparative effects of aging in men and women on the properties of the arterial tree.* J Am Coll Cardiol, 2001. **37**(5): p. 1374-80.

11) Narkiewicz, K., et al., *Gender-selective interaction between aging, blood pressure, and sympathetic nerve activity.* Hypertension, 2005. **45**(4): p. 522-5.

12) Kaplan, N.M., *The treatment of hypertension in women.* Arch Intern Med, 1995. **155**(6): p. 563-7.

13) Reynolds, E. and R.B. Baron, *Hypertension in women and the elderly. Some puzzling and some expected findings of treatment studies.* Postgrad Med, 1996. **100**(4): p. 58-63, 67-70.

14) Safar, M.E. and H. Smulyan, *Hypertension in women.* Am J Hypertens, 2004. **17**(1): p. 82-7.

15) Gueyffier, F., et al., *Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men. A meta-analysis of individual patient data from randomized, controlled trials. The INDANA Investigators.* Ann Intern Med, 1997. **126**(10): p. 761-7.

16) Oparil, S. and A.P. Miller, *Gender and blood pressure.* J Clin Hypertens (Greenwich), 2005. **7**(5): p. 300-9.

17) Mancia, G., et al., *2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC).* Eur Heart J, 2013. **34**(28): p. 2159-219.

## Preeclampsia and cardiovascular risk

Alves E.[1,2]
[1] *Institute of Public Health – University of Porto (ISPUP), Porto, Portugal;*
[2] *Department of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto Medical School, Porto, Portugal*

Cardiovascular diseases (CVD) result from a complex interplay of genetic, developmental, environmental and behavioural factors (1, 2). CVD mortality rates increase with the number of risk factors to which an individual is exposed (3, 4), supporting that the risk for CVD depends on the interaction among those factors to complete a sufficient causal mechanism (5). Pregnancy induces profound alterations in maternal haemodynamics and metabolism (6, 7), which may reveal previous background risk and/or induce long-term metabolic and vascular abnormalities that increase the propensity to develop cardiovascular diseases (8-10).

The aim of this study was to assess the impact of age, education, family history of cardiovascular disease, prepregnancy overweight/obesity and weight gain during pregnancy on hypertensive disorders, and to which extent gestational hypertensive disorders lead to higher blood pressure in women and their offspring 4 years after birth.

The birth cohort Geração XXI was assembled between 2005 and 2006 at all 5 public maternity units covering the metropolitan area of Porto, Portugal (11). A total of 8647 infants, corresponding to 8495 mothers, were enrolled in the cohort. At 4 years of the child's age, between 2009 and 2011, all the mothers with their children were invited to attend the re-evaluation of the cohort, and 86.2% of the children and 84.2% of the mothers were re-evaluated.

Overall, hypertensive disorders, including chronic hypertension, gestational hypertension, preeclampsia and eclampsia, affected 4.6% of single pregnancies, and were associated with older age, lower education, family history of cardiovascular disease and excessive weight before and during pregnancy, similarly in primiparae and multiparae. Approximately 50% of hypertensive disorders among primiparae and 70% among multiparae were attributable to the joint effect of pregnancies after 34 years of age, education below 12 years, family history of cardiovascular disease, overweight/obesity before pregnancy and excessive weight gain during pregnancy. Four years after delivery, gestational hypertensive disorders were associated with significant increases of systolic and diastolic blood pressure of the mother. The risk of hypertension in women affected by gestational

hypertensive disorders was almost 6 times higher among mothers who delivered a girl, and 3 times higher among those who delivered a boy. Additionally, systolic and diastolic blood pressure at 4 years were significantly higher in boys born of mothers with hypertensive disorders of pregnancy, while no effect was detected among girls.

In conclusion, prepregnancy risk factors explained a high proportion of hypertensive disorders during pregnancy, with excessive weight before and during pregnancy, having a very large contribution, particularly among primiparae. Additionally, 4 years after a single pregnancy complicated by gestational hypertensive disorders in primiparae, the impact on mothers' blood pressure and incident hypertension was large, and this effect was stronger when the foetus was female. Regarding the children, a differential effect by child's sex was observed, supporting the hypothesis of heterogeneous causes of hypertension in pregnancy and that boys live dangerously in the womb.

In the last decades, a stronger emphasis on women's health status and risk behaviour patterns before pregnancy is advocated (12) in order to increase the awareness and the potential for prevention at younger ages. The short-term outcomes described in the present study reinforce the importance of effective preventive strategies to control cardiovascular risk from preconceptional to post-partum care.

**References:**


1) Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation 2001;104(22):2746-53.

2) Delles C, McBride MW, Padmanabhan S, Dominiczak AF. The genetics of cardiovascular disease. Trends Endocrinol Metab 2008;19(9):309-16.

3) Stamler J, Stamler R, Neaton JD, Wentworth D, Daviglus ML, Garside D, et al. Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy: findings for 5 large cohorts of young adult and middle-aged men and women. Jama 1999;282(21):2012-8.

4) Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation 2006;113(6):791-8.

5) Rothman K. Causes. Am J Epidemiol 1995;141(2):90-5.

6) Weissgerber TL, Wolfe LA. Physiological adaptation in early human pregnancy: adaptation to balance maternal-fetal demands. Appl Physiol Nutr Metab 2006;31(1):1-11.

7) Hunter S, Robson SC. Adaptation of the maternal heart in pregnancy. Br Heart J 1992;68(6):540-3.

8) Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 2005;330(7491):565.

9) Forman JP, Stampfer MJ, Curhan GC. Diet and lifestyle risk factors associated with incident hypertension in women. Jama 2009;302(4):401-11.

10) Agatisa PK, Ness RB, Roberts JM, Costantino JP, Kuller LH, McLaughlin MK. Impairment of endothelial function in women with a history of preeclampsia: an indicator of cardiovascular risk. Am J Physiol Heart Circ Physiol 2004;286(4):H1389-93.

11) Alves E, Correia S, Barros H, Azevedo A. Prevalence of self-reported cardiovascular risk factors in Portuguese women: a survey after delivery. Int J Public Health 2012;57(5):837-47.

12) Moos MK. Preconceptional health promotion: progress in changing a prevention paradigm. J Perinat Neonatal Nurs 2004;18(1):2-13.

## Hypertension in the elderly

Tomasz Grodzicki
*Department of Internal Medicine and Gerontology, Jagiellonian University Medical College, Cracow, Poland*

Populations worldwide, especially those in Western and westernized countries, are undergoing a profound demographic change as they age. As recently shown, 50% of people who were born in recent years in countries such as the UK, USA, France, Denmark or Japan will live to celebrate their hundredth birthday. Populationwise, blood pressure (BP) raises with advancing age, resulting in an age-related increase in the prevalence of hypertension. The pathophysiology of hypertension in the elderly differs from that implicated in the disease at younger age. The major factor in the pathogenesis of hypertension in the elderly is the progressive stiffening of large conduit arteries with subsequent increase in pulse-wave velocity, resulting in an increase of systolic (SBP) and a decrease of diastolic (DBP) blood pressure. Increased SBP has been associated with increased rates of complications, some of which tend to be closely related to pulse pressure. A higher SBP has been shown to be associated with a substantial increase of risk of major complications such as all-cause mortality (14%), cardiovascular mortality (12%), fatal and nonfatal cardiovascular events (8%) and stroke (12%) [6]. This risk has been shown to be reversible upon effective antihypertensive treatment.
Treatment of hypertension in elderly patients is, largely, beneficial. It reduces health burden to the society while decreasing the suffering of affected individuals and their families. However, the evidence we have at present does not apply equally to all our elderly hypertensive patients. It is widely accepted that the relationship between level of blood pressure and cardiovascular risk is linear and universal across age groups.. On the other hand, some data point to the possibility that in older individuals the SBP cut-off value for increase in cardiovascular risk is 160 mmHg rather than 140 mmHg. Similarly, no trial in elderly hypertensives has included patients with mild ISH with SBP in the range of 140 -- 150 mmHg, marking a lack of trial evidence for the guideline recommendation to lower SBP in such individuals to < 140 mmHg -- an issue recently appreciated in the guideline reappraisal document. The only trial so far that has tested the hypothesis that more stringent (goal SBP < 140 mmHg) blood pressure control in elderly patients would be beneficial, the JATOS (Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients) trial, yielded negative results [38]; and some data point to the possibility of a J-shaped relation between blood

pressure and cardiovascular complications, especially in older patients with clinically more advanced atherosclerosis or with diabetes mellitus. Both issues can and should be resolved to avoid unnecessary treatment or to avoid unnecessary cerebrovascular and cardiovascular morbidity and mortality. We clearly need a placebo-controlled clinical trial to guide us in what seems to be one of the last terrae incognitae of antihypertensive therapy in the elderly.

**References:**


1) Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet 2009;374:1196-208.

2) Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988 -- 1991. Hypertension 1995;25:305-13.

3) Chaudhry KN, Chavez P, Gasowski J, Grodzicki T, Messerli FH. Hypertension in the elderly: Some practical considerations. Clevel. Clin. J. Med. 2012; 79: 697-704.

4) G sowski J, Tikhonoff V, Stolarz-Skrzypek K, Thijs L, Grodzicki T, Kawecka-Jaszcz K, Staessen JA.: Treatment of hypertension in the elderly in 2010 - a brief review. Expert Opin. Pharmacother. 2010; 11 :2609-2617.

5) Laurent S, Boutouyrie P, Benetos A. Pathophysiology of hypertension in the elderly. Am J Geriatr Cardiol 2002;11:34-9.

6) Zanchetti A, Grassi G, Mancia G. When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. J Hypertens 2009;27:923-34.

7) JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). Hypertens Res 2008;31:2115-27

## Epidemiology of diabetes and cardiovascular risk

Roberto Miccoli, MD PhD
*Department of Clinical and Experimental Medicine, Diabetes Unit, University of Pisa*

Type 2 diabetes (T2D) affects 366 million people worldwide, and that number is expected to reach 552 million by the year 2030, with 80% of all diabetes cases live in low- and middle-income countries (1). This epidemic is primarily driven by rapid urbanization, nutrition transition, and increasingly sedentary lifestyles, changes that predispose to obesity which is considered to be the most important risk factor for T2D (2). In Italy the prevalence of disease is 5.8%, with an increasing gradient from northern to southern areas. Nearly two third of cases were aged over 64, with one third being over 80. The prevalence of diabetes increased steadily from 2.8% in 1997 to 5.8% in 2011, particularly in men with an annual incidence of 7 cases per 1000 persons-year. Its increasing prevalence and associated health complications are responsible of the high costs of disease (3). Population-based diabetes studies consistently show that a substantial proportion of those found to have diabetes had not been previously diagnosed. Half of peolple with diabetes don't know they have it largely because there are few symptoms during the early years of T2D. Moreover, it is currently estimated that more than 300 million people have impaired glucose tolerance putting them at increased risk for T2D and its adverse consequences (1). Screening for risk should include both blood glucose testing in high-risk populations and prescreening (e.g. by questionnaire, waist circumference measurement) to identify high-risk individuals in overall low-risk populations. The identification, through genetic analysis, of genes implicated in disease development represents a powerful tool for revealing the key pathways that are involved in predisposition and progression. Recent development in the field of multifactorial T2D genetics has been the identification of TCF7L2 as the most important T2D-susceptibility gene to date (4).
Excess global mortality attributable to T2D has been estimated to be 2.9 million deaths, i.e 5.2% of all deaths (5). Type 2 diabetes is associated with a marked increase in the risk of cardiovascular disease (CVD). The overall risk of CVD for people with diabetes is two- to threefold higher in men, and three- to fivefold higher in women when compared to people without diabetes (6) and the rate at which diabetic patients develop CV events is the same at an age 15 years earlier compared to their non-diabetic gender comparators (7). During the last years despite diabetic patients experienced similar reductions in case-

fatality rates related to acute myocardial infarction and stroke than those without diabetes, the number of diabetes cases increased. Thus, the number of events occurring in this population rose substantially.
The etiology of this excess cardiovascular morbidity and mortality is not completely clear. There is convincing evidence that hyperglycaemia is closely and independently related to CVmorbidity and mortality. However, the results of recent large-scale intervention trials suggest that there are few opportunities to influence the development and/or progression of CV complications in individuals with long-standing diabetes. Conversely, an early strict glycaemic control generates a legacy that may confer protection against, or delay, long-term CV complications (8). In addition to hypertension and hyperlipidemia some emerging risk factors predispose patients with diabetes to develop CVD.
For people with diabetes, meeting the recommended guidelines for blood pressure and cholesterol is even more important than meeting the guidelines for glucose control in reducing the risk. However, the best way to prevent or delay the development of CVD is to prevent diabetes itself.

**References:**


1) International Diabetes Federation. Available at: http://www.idf.org/home.

2) Kelly T,Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond) 2008;32:1431–1437.

3) Bruno G, Bonora E, Miccoli R, Vaccaro O, Rossi E, Bernardi D, De Rosa M, Marchesini G; SID-CINECA ARNO Working Group. Quality of diabetes care in Italy: information from a large population-based multiregional observatory (ARNO diabetes). Diabetes Care. 2012 Sep;35(9):e64.

4) Bianchi C, Miccoli R, Pulizzi N, Bonadonna R, Trombetta M, Cavallo G, Faloia E, Leonetti F, Marchesini G, Groop L, Del Prato S. The concurrent presence of risk alleles for TCF7L2 and HHEX/IDE potentiates the insulin secretory difect in subjects at high risk of diabetes. The GENFIEV Study. Diabetologia 2008, S 134.

5) Roglic G, Unwin N, Bennett PH, Mathers C, Tuomilehto J, Nag S, Connolly V, King H. The burden of mortality attributable to diabetes: realistic estimates for the year 2000. Diabetes Care. 2005; 28: 2130-5.

6) Juutilainen A, Lehto S, Ronnemaa T, Pyörälä K, Laakso M. Similarity of the impact of type 1 and type 2 diabetes on cardiovascular mortality in middle-aged subjects. Diabetes Care 2008; 31: 714–719.

7) Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet 2006; 368: 29–36.

8) Miccoli, Roberto, Bianchi, Cristina, Del Prato, Stefano. Hyperglycemia and vascular metabolic memory: truth or fiction? Curr Diab Rep. 2013;13: 403-10.

## Cardiovascular risk in subjects at high risk for type 2 diabetes

Massimo Federici
*Department of Systems Medicine, University of Rome Tor Vergata, Italy. E-mail: federicm@uniroma2.it*

Diabetes Mellitus (DM) is a disease characterized by high blood glucose due to either insulin absence, or insulin resistance causing a relative insulin deficiency. The hallmark of type II DM being an impaired biological response at a cellular level[1]. Especially type II DM has become a growing medical concern currently affecting over 285 million people in the world (6,4% of the total adult population)[2]. This number is expected to double by the year 2030 [3] making it the most common non-communicable disease worldwide. In Europe alone 52.8 million patients (8.1% percent of the adult population) with an estimated further 66 million people (9.1% of the general population) being classified as pre-diabetic with impaired glucose tolerance[2]. Diabetes is now the 9th leading cause of death in the whole world, with higher rates in the higher income countries. In Europe alone diabetes accounts for 1 in 10 death every year. Only in low income countries does it not figure under the top-10 causes of death[4]. However, with ever increasing urbanization and the associated sedentary lifestyle the incidence is strongly rising with some countries easily surpassing Europe and North Africa regarding the diabetes incidence.[2]
The most common cause of death of diabetics in Europe is Coronary artery disease (CAD) with several studies having shown that the risk of macrovascular complications (stroke and myocardial infarction) is 2-4 times higher in people with diabetes than in non-diabetics [5].

While many theories have been put forward over the years, the exact molecular mechanism of this obvious link between diabetes and atherosclerosis remain obscure. Two main reasons for the unclear situation appear as obvious. One being that atherosclerosis is a multifactorial disease involving a wide range of responses of different tissues and cell types to metabolic and environmental stimuli [6]. The other reason appears to be that the cellular response to insulin depends on it binding to a cell surface insulin receptor with an ability to elucidate a different response depending on the cells expressing this receptor. The main action of insulin is to promote glucose uptake mainly in skeletal muscle and adipose tissue[7]. However, it has also been proven that insulin exerts actions completely unrelated to the glucose metabolism including vessel dilatation and contraction[8] and endothelial dysfunction [9].

Another part of the metabolism that is strongly regulated by insulin is lipid metabolism. Indeed diabetics show increased deposition of triglycerides in muscles, liver and pancreas. Indeed diabetics tend to exhibit a tendency towards central adiposity with the enlarged visceral adipocytes responding poorly to insulin and thereby resulting in inappropriate timing of FFA release which the exposes non adipose tissue to them[10]. On top of this it has been shown that insulin is able to directly affect monocyte to macrophage differentiation [11].
With inflammation being pivotal to the development of atherosclerosis[12] and the monocyte macrophage axis being involved at every step of the formation of a mature plaque from the fatty streak it appears that the actions of insulin are both directly and indirectly able to manipulate this and therefore may explain the increased occurrence of atherosclerosis in diabetics. In this talk we will attempt to summarize the effects of insulin and insulin resistance on the development of atherosclerosis.For some time it has now been known that diabetes and atherosclerosis are chronic inflammatory diseases that are closely associated to one another and often develop together. In both there is an increase in the general setting of inflammation which is exhibited by the infiltration of immune cells into the adipose tissue and the vascular walls respectively.
The monocytes/macrophage populations that are recruited in these settings also display a high similarity by exhibiting similar phenotypes. In the insulin resistant and atherosclerotic setting there is a distinct switch in the macrophage populations present from an anti-inflammatory (M2) population to an inflammatory (M1) population which releases cytokines and chemotactic factors which worsen the local environment and thus aggravate the situation by creating a vicious circle.
However, while some discoveries suggest that preventing the development of M1 macrophages reduces inflammation and thereby aggravation of these diseases, there are currently no clear-cut opinions on how to achieve a switch from M2 to M1. Here we will briefly discuss novel pathways regulating inflammatory risk factors and their effects on metabolic disorders (13-16).

**References:**


1) Eckel, R. H., Alberti, K. G., Grundy, S. M. and Zimmet, P. Z. (2010). The metabolic syndrome. Lancet. 375, 181-183.

2) Federation, I. D. (2011) IDF Diabetes Atlas. ed.)^eds.)

3) Wild, S., Roglic, G., Green, A., Sicree, R. and King, H. (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 27, 1047-1053.

4) WHO. (2011) The top 10 causes of death. ed.)^eds.), WHO.

5) Petersen, K. F. and Shulman, G. I. (2006) Etiology of insulin resistance. Am J Med. 119, S10-16.

6) Ross, R. (1995) Cell biology of atherosclerosis. Annu Rev Physiol. 57, 791-804.

7) DeFronzo, R. A. (1992) Pathogenesis of type 2 (non-insulin dependent) diabetes mellitus: a balanced overview. Diabetologia. 35, 389-397.

8) Feener, E. P. and King, G. L. (1997) Vascular dysfunction in diabetes mellitus. Lancet. 350 Suppl 1, SI9-13.

9) Hsueh, W. A., Lyon, C. J. and Quinones, M. J. (2004) Insulin resistance and the endothelium. Am J Med. 117, 109-117.

10) Raz, I., Eldor, R., Cernea, S. and Shafrir, E. (2005) Diabetes: insulin resistance and derangements in lipid metabolism. Cure through intervention in fat transport and storage. Diabetes Metab Res Rev. 21, 3-14.

11) Malide, D., Davies-Hill, T. M., Levine, M. and Simpson, I. A. (1998) Distinct localization of GLUT-1, -3, and -5 in human monocyte-derived macrophages: effects of cell activation. Am J Physiol. 274, E516-526.

12) Libby, P., Okamoto, Y., Rocha, V. Z. and Folco, E. (2010) Inflammation in atherosclerosis: transition from theory to practice. Circ J. 74, 213-220.

13) Avogaro A, de Kreutzenberg SV, Federici M, Fadini GP. The endothelium abridges insulin resistance to premature aging. J Am Heart Assoc. 2013 Jun 21;2(3):e000262. doi: 10.1161/JAHA.113.000262.

14) Stöhr R, Federici M. Insulin resistance and atherosclerosis: convergence between metabolic pathways and inflammatory nodes. Biochem J. 2013 Aug 15;454(1):1-11.

15) Menghini R, Casagrande V, Federici M. MicroRNAs in Endothelial Senescence and Atherosclerosis. J Cardiovasc Transl Res. 2013 Jun 29.

16) Menghini R, Fiorentino L, Casagrande V, Lauro R, Federici M. The role of ADAM17 in metabolic inflammation. Atherosclerosis. 2013 May;228(1):12-7.

## Lifestyle interventions for the prevention or delay of type 2 diabetes

Gabriele Riccardi
*Naples, Italy*

Type 2 diabetes is a predominantly lifestyle disorder associated with affluence: advancing age, lack of exercise, being overweight, and a high energy fat-rich diet increase the risk in genetically predisposed individuals. Many studies have demonstrated that a modest reduction in body weight is effective in slowing the progress of glucose tolerance to type 2 diabetes in individuals at-risk; in this respect, of special importance is the control of abdominal adiposity. The results obtained by the Finnish Diabetes Prevention study in Finland and the Diabetes Prevention Program in the United States indicate that a reduction of 5-7% of body weight, combined with regular physical activity of 2-3 hours per week and changes in diet composition aiming at a reduction of fat intake and an increased consumption of fiber rich foods, is able to reduce the incidence of type 2 diabetes by as much as 60%.

Taking a more detailed look at the relationship between diet and diabetes, it is immediately clear that there are some macronutrients which are particularly important. The available evidence (derived almost exclusively from observational studies) indicates that shifting from a diet predominantly based on fat from animal sources to a diet in which vegetable fat is more often employed might be beneficial in relation to the prevention of type 2 diabetes. The mechanism by which dietary fat consumption could influence the development of diabetes is strictly linked with insulin sensitivity. Excessive fat consumption, irrespectively of its source, has a negative impact on insulin sensitivity and, possibly, on the risk of type 2 diabetes; however only when it exceeds a threshold level of 35–40% total energy intake this effect seems to be of clinical relevance.

In relation to dietary fat composition, the consistent finding from epidemiological studies is the association between saturated fat intake and impaired insulin sensitivity. A specific fatty acid profile in cell membranes could influence insulin action through several potential mechanisms, including altered insulin receptor binding or affinity, and by influencing ion permeability and cell signalling. More information on the issue of dietary fat quality and insulin sensitivity in view of a reduction of the risk to develop type 2 diabetes has emerged from the KANWU Study, which is the first intervention study on this topic performed using adequate methodologies and a sufficiently large sample size. This study involved 162 healthy individuals from five

different countries, randomly assigned to consume diets high in saturated fat or monounsaturated fat without any change in other dietary constituents; insulin sensitivity (assessed by the frequent sampling intravenous tolerance test) was significantly impaired with the diet high in saturated fat (-21 %, $p<0{\cdot}05$) but remained unchanged with the diet high in monounsaturated fat.

As for carbohydrate rich foods, diets that are high in fibre with foods of a low Glycemic Index are associated with reduced postprandial levels of glucose and insulin, improved lipid levels and possibly reduced insulin sensitivity. In the long term this type of diet would be expected to confer a lower risk of type 2 diabetes and several major prospective studies have found this to be the case. In addition, it should be considered that high intakes of sucrose or fructose, particularly if present in soft drinks, have shown a detrimental impact not only on body weight, particularly in children, but also on insulin sensitivity and blood glucose regulation. The relationship between alcohol intake and the incidence of type 2 diabetes has a J shape, with the lowest rate of diabetes associated with 1 or 2 alcoholic drinks /day.

In conclusion, there is very suggestive evidence that weight reduction and increased physical exercise should be combined with a diet rich in carbohydrate and fibre, with a low glycaemic index and a high vegetable/animal fat ratio, in order to achieve the most powerful effect on type 2 diabetes prevention; therefore. legumes, oats, pasta, parboiled rice, fruits, vegetables, wholegrain bread should replace, whenever possible, refined foods with a high glycaemic index, while unsaturated fat (olive oil) should be a preferential source of dietary fat instead of butter or cheese or fatty meat. In this context, sweetend beverages should be limited while alchohlic beverages could be permitted if used with moderation.

**References:**


1) Riccardi G, Giacco R, Rivellese AA Dietary fat, insulin sensitivity and the metabolic syndrome..Clin Nutr. 2004 23(4):447-56.

2) M. Parillo, G. Riccardi. Diet composition and the risk of type 2 diabetes: epidemiological and clinical evidence. Br J Nutr 2004; 92(1):7-19.

3) G. Riccardi, P. Aggett, F. Brighenti, N. Delzenne, K. Frayn, A. Nieuwenhuizen, D. Pannemans, S. Theis, S. Tuijtelaars, B.Vessby. PASSCLAIM--body weight regulation, insulin

sensitivity and diabetes risk. Eur J Nutr 2004;43 Suppl 2: II7-II46.

4) Tuomilehto J, Undstrom J, Eriksson JG, Valle TI, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaannie.mi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa MftFDPSG (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. New Engl J Med 344:1343-1350.

5) Diabetes Prevention Program Research Group (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. New England Journal of Medicine. New Engl J Med 346:393-403.

6) R. Giacco, G. Della Pepa, D. Luongo, G. Riccardi (2011) Whole grain intake in relation to body weight: From epidemiological evidence to clinical trials. Nutrition, Metabolism and Cardiovascular Diseases 21:901-908.

## Type 2 diabetes and cardiovascular risk in children and adolescents

Francesco Chiarelli, M. Loredana Marcovecchio
*University Department of Paediatrics, Chieti, Italy*

Type 2 diabetes (T2D) is caused by a combination of insulin resistance and decrease insulin secretion (1). For a long time T2D has been considered as a disease almost exclusive of the adult obese population. However, over the last decades there has been an alarming increase of youth-onset T2D concomitant with the rise of obesity in this age group (2). Whereas until 10 years ago T2D accounted for less than 3% of all cases of new-onset diabetes in adolescents, T2D now accounts for 8-45% of all new cases of diabetes in the USA (2). An increase in cases of T2D has been reported also in Europe, Japan and other countries, although the rates are lower than in the US (2).
Much of the health burden of T2D in youth is due to the development of chronic complications, including microvascular diseases and cardiovascular disease (CVD).
It is well known that in adults T2D is a key risk factor for an early occurrence of cardiovascular events (3). Alarmingly, in adults CVD appears to be more aggressive in those with an onset of T2D at an earlier age (18-44 years) compared to those with a later-onset of the disease (4).
Data on CVD in youth with T2D are scant, mainly due to the recent emergence of T2D in this age group (5, 6). However, recent studies have shown that youth with T2D have a higher prevalence of many CVD risk factors, such as central obesity, high blood pressure, dyslipidaemia, increased albumin excretion, when compared to youth of similar age without diabetes. Both adiposity and glycemia seem to be independent predictors of the above CVD risk factors (7).
Although hard-endpoints, such as heart attacks or strokes, are uncommon events among youth with T2D, subclinical vascular abnormalities have been reported in this age group. In particular, youth with T2D shows early signs of atherosclerosis, represented by increased arterial stiffness and carotid intima-media thickness (8, 9).
The available data so far on CVD in youth with T2D highlight the importance of preventing this disease in order to reduce the associated CVD health burden. Therefore, identifying obese children at risk for T2D is of primary importance in order to prevent its development and the diabetes-related cardiovascular complications in this age group.

**References:**


1) Rosenbloom AL, Silverstein JH, Amemiya S, Zeitler P, Klingensmith GJ. Type 2 diabetes in children and adolescents. PediatrYouth with obesity and obesity-related type 2 diabetes mellitus demonstrate abnormalities in carotid structure and function. Diabetes 2009;10(Suppl. 12):17-32.

2) D'Adamo E, Caprio S Type 2 Diabetes in Youth: Epidemiology and Pathophysiology. Diabetes Care 2011;34:S161-S165.

3) Milicevic Z, Raz I, Beattie SD, Campaigne BN, Sarwat S, Gromniak E, Kowalska I, Galic E, Tan M, Hanefeld M: Natural history of cardiovascular disease in patients with diabetes: role of hyperglycemia. Diabetes Care 2008;31:S155–S160.

4) Hillier TA, Pedula KL: Complications in young adults with early-onset type 2 diabetes: losing the relative protection of youth. Diabetes Care 2003;26:2999–3005.

5) Pinhas-Hamiel O, Zeitler P. Acute and chronic complications of type 2 diabetes mellitus in children and adolescents. Lancet 2007;369:1823–1831.

6) Marcovecchio ML, Chiarelli F. Microvascular disease in children and adolescents with type 1 diabetes and obesity. Pediatr Nephrol. 2011;26(3):365-75.

7) West NA, Hamman RF, Mayer-Davis EJ, D'Agostino RB Jr, Marcovina SM, Liese AD, Zeitler PS, Daniels SR, Dabelea D. Cardiovascular risk factors among youth with and without type 2 diabetes: differences and possible mechanisms. Diabetes Care 2009;32:175-180.

8) Wadwa RP, Urbina EM, Anderson AM, Hamman RF, Dolan LM, Rodriguez BL, Daniels SR, Dabelea D; SEARCH Study Group. Measures of arterial stiffness in youth with type 1 and type 2 diabetes: the SEARCH for diabetes in youth study. Diabetes Care 2010;33:881-886.

9) Urbina EM, Kimball TR, McCoy CE, Khoury PR, Daniels SR, Dolan LM. Circulation 2009;119:2913-2919.

## The effect of GLP1-based therapies on cardiovascular risk

Edoardo Mannucci
*Diabetes Agency, Careggi Teaching Hospital, Florence, Italy*

The efficacy of the intensification of glucose control in prevention of cardiovascular disease in type 2 diabetes has always been controversial (1). Although the long-term extension of the UK Prospective Diabetes Study has shown a significant reduction in the incidence of major cardiovascular events in the intensively treated group (2), the results of other studies have been inconclusive (3, 4); in one trial, a more aggressive treatment of diabetes was even associated with an increase in cardiovascular mortality (5). If all available studies on the long-term effects of improved glycemic control on cardiovascular disease are considered together, some benefit can be observed (6, 7), although hypoglycemia could represent a major limiting factor (7).

GLP-1-based therapies (i.e., GLP-1 receptor agonists and DPP4 inhibitors), which are capable of reducing hyperglycemia with a minimal risk of hypoglycemia (unless associated with insulin or sulfonylureas), seem to be particularly suited for the prevention of cardiovascular disease through the improvement of glycemic control. In addition, they also show favorable effects on several extra-glycemic risk factors: GLP-1 receptor agonists induce weight loss and a small reduction of blood pressure (8, 9), whereas DPP4 inhibitors could have some (marginal) favorable effects on lipid profile (10). Furthermore, a wide body of experimental evidence shows that GLP-1 has direct myocardial effects, including augmented adaptation to ischemia and improved systolic function (11, 12). Such actions have also been demonstrated in humans in pilot studies with short-term GLP-1 infusions (13, 14).

Preliminary data on major cardiovascular events reported in phase III and early phase IV studies fuelled further enthusiasm about the potential cardiovascular benefits of GLP-1-based therapy, showing a trend toward a reduced risk both for GLP-1 receptor agonists and DPP4 inhibitors (8, 15). However, when the first two large cardiovascular outcome trials were published in September, 2013, no significant benefit of either alogliptin or saxagliptin (two DPP4 inhibitors) could be observed (16, 17). This result, which was below the expectations of many experts, is in apparent contrast with observations from earlier studies. This difference could be due to several reasons: early studies were designed for metabolic, and not cardiovascular, endpoints; on the other hand, cardiovascular outcome studies were designed to assess safety, and not efficacy, of newer

agents. In addition, the characteristics of patients enrolled in SAVOR and EXAMINE are very different from those of patients enrolled in earlier trials with DPP4 inhibitors. Post-hoc analyses of results of the first cardiovascular outcome trials could shed some light on the reasons underlying the discordance of results. Further large scale trials are currently ongoing, both for GLP-1 receptor agonists and DPP4 inhibitors; considering the differences in design across studies, in the next few years a wider body of evidence will allow a clearer picture of cardiovascular effects of incretin-based therapies. For the moment, current evidence confirms the cardiovascular safety of GLP-1 based therapies, without excluding the possibility of some glucose-independent protective effect on the cardiovascular system.

**References:**


1) Mannucci E, Dicembrini I, Lauria A, Pozzilli P. Is glucose control important for prevention of cardiovascular disease in diabetes? Diabetes Care 2013;36 Suppl 2:S259-263.

2) Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589.

3) Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572.

4) Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139.

5) Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559.

6) Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. BMJ 2011;343:d6898.

7) Mannucci E, Monami M, Lamanna C, Gori F, Marchionni N. Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a metaanalysis of randomized clinical trials. Nutr Metab Cardiovasc Dis 2009;19:604–612.

8) Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2013 (ePub).

9) Sun F, Yu K, Wu S, Zhang Y, et al. Cardiovascular safety and glycemic control of glucagon-like peptide-1 receptor agonists for type 2 diabetes mellitus: a pairwise and network meta-analysis. Diabetes Res Clin Pract 2012;98:386-395.

10) Monami M, Vitale V, Ambrosio ML, et al. Effects on lipid profile of dipeptidyl peptidase 4 inhibitors, pioglitazone, acarbose, and sulfonylureas: meta-analysis of placebo-controlled trials. Adv Ther 2012;29:736-746.

11) Burgmaier M, Heinrich C, Marx N. Cardiovascular effects of GLP-1 and GLP-1-based therapies: implications for the cardiovascular continuum in diabetes? Diabet Med 2013;30:289-299.

12) Mannucci E, Dicembrini I. Incretin-based therapies and cardiovascular risk. Curr Med Res Opin 2012;28:715-721.

13) Nikolaidis LA, Mankad S, Sokos GG, et al. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. Circulation 2004;109:962-965.

14) Sokos GG, Nikolaidis LA, Mankad S, Elahi D, Shannon RP. Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. J Card Fail 2006;12:694-699.

15) Monami M, Ahrén B, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2013;15:112-120.

16) Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013 (ePub).

17) White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013 (ePub).

**Achieving glycemic control in patients with type 2 diabetes and renal impairment**

Roberto Trevisan
*Direttore USC Malattie Endocrine – Diabetologia, AO Papa Giovanni XXIII, Bergamo, Italy*

Approximately 40% of Type 2 diabetic patients (T2DM) have chronic renal disease (CKD). Screening for and assessment of renal dysfunction should occur as soon as a diagnosis of T2DM has been made. It is important to detect early CKD so treatment can be initiated to delay any decline in renal function, reduce cardiovascular risk, and improve outcomes. Serum creatinine and albuminuria should be measured and these tests repeated annually. The Modification of Diet in Renal Disease (MDRD) equation can be used to estimate eGFR. A more accurate equation for estimation of eGFR has been proposed (Chronic Kidney Disease Epidemiology Collaboration), which reflects the actual measured GFR more accurately (1). javascript:pop_layer('references_layer'); T2DM patients with renal impairment are at greater risk of experiencing a hypoglycemic event compared with T2DM patients without renal impairment.[12] Patients with T2DM and CKD frequently have lower insulin requirements because less insulin excretion and metabolism occurs. Hypoglycemia has important safety implications, and the risk for death is increased (2).
Adequate glycemic control is central to the management of CKD and the preservation of kidney function in patients with T2DM. A good metabolic control was associated with a significant decrease in the development of new microalbuminuria and macroalbuminuria in the ACCORD, ADVANCE and VADT study (3, 4). The ADA/EASD has recently published a position statement on the management of hyperglycemia in patients with T2DM who may or may not have CKD (5). The position statement recommends an HbA1c goal of less than 7.0% in most patients to reduce the incidence of microvascular disease, but this target should be individualized, taking into account hypoglycemic episodes, cardiovascular complications, renal insufficiency, and any other comorbid conditions (5).
Metformin is the first-line treatment for glycemic control in patients with T2DM. It is weight neutral, inexpensive, and inhibits the generation of glucose in the liver; it does not affect insulin levels and is associated with a low risk for hypoglycemia. Because metformin is excreted unchanged by the kidney, there is a theoretical risk for lactic acidosis in patients with CKD. Thus, prescribing guidelines

contraindicate metformin in patients with moderate (<60 mL/min/1.73 $m^2$) renal insufficiency. However, there is ongoing debate, and a recent critical review of the literature supports the safe use of appropriate doses of metformin in patients with chronic stable renal impairment (6, 7). The recommendation from the ADA/EASD position paper, is that metformin can be used down to an eGFR of 30 mL/min/1.73 $m^2$, but the dose of metformin should be reduced when eGFR is less than 45 mL/min/1.73 $m^2$. Kidney function should be checked regularly (every 6 months) and metformin should be discontinued if eGFR falls below 30 mL/min/1.73 $m^2$.

Although Sulfonylureas have been used extensively in patients with T2DM (8), Sulfonylureas are associated with a high risk for hypoglycemia, which is especially problematic in patients with CKD who are at an increased risk of experiencing a hypoglycemic episode. Sulfonylureas should be avoided, when possible, in diabetes patients with renal impairment, especially the longer-acting first-generation sulfonylureas. Thiazolidinediones are insulin sensitizers, but safety concerns limit their use. Pioglitazone does not require any dose adjustment in patients with CKD, but is not recommended for use in patients on dialysis. Acarbose is not recommended for use in patients with severe CKD (9).

The DPP-4 inhibitors sitagliptin, saxagliptin, vildagliptin, linagliptin, and alogliptin have low propensity to cause hypoglycemia unless administered in combination with an agent associated with a hypoglycemic high risk, such as sulfonylureas. These agents are generally well tolerated, are weight neutral, and provide clinically important reductions in HbA1c. While all DPP-4 inhibitors provide effective glycemic control in patients with T2DM, dose reductions are required for all DPP-4 inhibitors, except linagliptin, in T2DM patients with moderate-to-severe CKD (10).

At the present moment, GLP-1 receptor agonists are not recommended for moderate or severe CKD due to lack of clinical experience, although trials are ongoing.

Insulin can be administered by injection at any stage of CKD, but hypoglycemic events are an obvious risk along with weight gain. Daily self-monitoring of blood glucose is necessary initially but can be reviewed once the insulin dose is stabilized.

In conclusion, a good metabolic control is crucial to the management of CKD and to the preservation of renal function in patients with Type 2 diabetes. The majority of oral agents have several limitations in diabetic patients with renal disease. The DPP-4 inhibitors offer a new opportunity to get a good control with no hypoglycemia and little adverse effects.

**References:**


1) Bakris GL. Recognition, pathogenesis, and treatment of different stages of nephropathy in patients with type 2 diabetes mellitus. *Mayo Clin Proc*. 2011;86(5):444-456.

2) Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. *Clin J Am Soc Nephrol*. 2009;4(6):1121-1127.

3) Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet*. 2010;376(9739):419-430.

4) Jun M, Perkovic V, Cass A. Intensive glycemic control and renal outcome. *Contrib Nephrol*. 2011;170:196-208.

5) Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2012;55(6):1577-1596.

6) Nye HJ, Herrington WG. Metformin: the safest hypoglycaemic agent in chronic kidney disease? *Nephron Clin Pract*. 2011;118(4):c380-c383.

7) Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. *Diabetes Care*. 2011;34(6):1431-1437.

8) Aquilante CL. Sulfonylurea pharmacogenomics in type 2 diabetes: the influence of drug target and diabetes risk polymorphisms. *Expert Rev Cardiovasc Ther*. 2010;8(3):359-372.

9) Bain S, Kalra P, Frankel A, et al. Practical guidance: addressing kidney health in type 2 diabetes. *Diabetes Prim Care*. 2012;14(4 Supplement):1-12.

10) Golightly LK, Drayna CC, McDermott MT. Comparative clinical pharmacokinetics of dipeptidyl peptidase-4 inhibitors. *Clin Pharmacokinet*. 2012;51(8): 501-514.

**Very-low-calorie diet: a quick therapeutic tool to improve, cell function in morbidly obese patients with 2 diabetes**

Simona Frontoni
*Department of Medicine, University of Rome Tor Vergata, Ospedale Fatebenefratelli, Rome (Italy)*

Caloric restriction in obese diabetic patients significantly impacts on several parameters (1, 2, 3). However weight loss, which is invariably associated to caloric restriction, is a confounding factor for its own effects on the same parameters. Therefore, we were interested in evaluating the early effects of caloric restriction, when weight loss is still trivial, on various aspects.
In particular, the early effects of a very-low-calorie diet (VLCD) on insulin sensitivity and insulin secretion in morbidly obese patients with type 2 diabetes are still unclear.
Since obesity seems to play a causal role in both Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS) and type 2 diabetes, the question arises whether caloric restriction is equally efficacious in type 2 diabetic patients with and without OSAHS.
Finally, data on the impact of caloric restriction on renal function are still lacking.
Our aims were to investigate the effects of 1 week VLCD, in severely obese diabetic patients, on:

- the relative contributions of insulin sensitivity, insulin secretion, or both in improving glucose metabolism.
- oxygen desaturation index (ODI) and on glucose regulation in OSAHS *vs.* non-OSAHS patients.
- renal function, measured as glomerular filtration rate

We found a marked improvement in metabolic profile, in severely obese patients with type 2 diabetes after a 7-d VLCD, primarily due to the amelioration of cell function, whereas no contribution of insulin sensitivity was shown.
Morbidly obese patients with type 2 diabetes and OSAHS appeared to be specifically resistant to the acute beneficial effects of VLCD on metabolic parameters.
Finally, we observed an improved renal function, following acute caloric restriction, when weight loss is still irrelevant, suggesting that caloric restriction *per se* is able to influence renal function.
Our preliminary observation deserves further investigation to clarify the pathogenic mechanisms involved.

**References:**


1) Wing RR, Blair EH, Bononi P, Marcus MD,Watanabe R, Bergman RN. Caloric restriction per se is a significant factor in improvements in glycemic control and insulin sensitivity during weight loss in obese NIDDM patients. Diabetes Care 1994;17:30–6.

2) Foster GD, Borradaile KE, Sanders MH et al. for the Sleep AHEAD Research Group of the Look AHEAD Research Group: The Sleep AHEAD Study A Randomized Study on the Effect of Weight Loss on Obstructive Sleep Apnea Among Obese Patients With Type 2 Diabetes. Arch Intern Med 2009; 169(17): 1619-26.

3) Praga M. and Morales E. Obesity-related renal damage: changing diet to avoid progression Kidney International 2010;78(7):633-5.

## Metabolic surgery for diabetes and metabolic syndrome

Antonio E. Pontiroli
*Clinica Medica, Dipartimento di Scienze della Salute, Università degli Studi di Milano, Ospedale San Paolo, Milan, Italy*

Use of bariatric surgery has been increasing in parallel with the expanding epidemics of obesity. Bariatric surgery includes progressively invasive techniques going from intragastric balloon (BIB), to laparoscopic gastric banding (LAGB), to gastric bypass (RYGB), to biliopancreatic diversion (BPD). Newer techniques include sleeve-gastrectomy (LSG), duodenal-jejunal bypass, and ileal interposition. Mechanisms of action of bariatric surgery are several, and include reduced stomach volume with early satiety, reduced caloric intake, malabsorption of nutrients, weight loss and in particular visceral fat loss; additional mechanisms to explain metabolic effects are likely represented by involvement of gastrointestinal hormones, while gastric emptying and change of intestinal microbiota are also probably involved.
The effectiveness of bariatric surgery in terms of excessive weight loss (EWL) and rate of disappearance of (type 2) diabetes varies according to techniques, going from 46.2% and 56.7% for LAGB, respectively, to 59.7% and 80.7% for RYGB, to 63.6% and 95.1% for BPD (1). All techniques have been shown, in randomized studies, to be more effective than intensive medical treatment, in leading to resolution of diabetes (2). Aside from a different effect on weight loss, a recent study has emphasized the different mechanism of action between malabsorptive and restrictive surgery as to cholesterol; with malabsorptive surgery, but not with restrictive surgery, intestinal absorption of cholesterol is decreased, while endogenous synthesis is increased, coupled with enhanced catabolism (3), indicating malabsorptive surgery as the kind of surgery more indicated for hyperlipidemia. Bariatric surgery is also effective in preventing progression of impaired glucose tolerance to diabetes, be it LAGB or RYGB (4-7). The International Diabetes Federation has endorsed bariatric surgery as treatment of choice for obese diabetic patients not achieving treatment targets with medical therapies.
Bariatric surgery does not affect only diabetes; several actions are evident after weight loss/bariatric surgery, namely reduction of the sympathetic drive, of hypertension, and of left ventricular hypertrophy, disappearance of Obstructive Apnea Syndrome (OSA); metabolic events include decrease of insulin resistance, leptin, oxidized LDL-lipoproteins, PAI-1, white blood cells, adhesion molecules (8-16). Consistent with thsese findings, clinical changes

observed after bariatric surgery include decreased prevalence of liver steatosis (17-19), decreased prevalence of kidney disease (20-22), decreased intima media thickness (IMT), and increased flow mediated vasodilation (FMD, 23), so that the CV score is improved together with the Framingham Score (24). Also consistent with these data is the fact that bariatric surgery prevents long term mortality as compared with traditional medical treatment (25). Of interest is the fact that decreased cardiovascular morbidity and mortality are improved whatever the surgical technique employed (26).
In conclusion, bariatric surgery has shown of value in the prevention and treatment of type 2 diabetes, in prevention of death, not only in diabetes , being of value for hypertension, CV diseases, liver steatosis, kidney diseases. Open questions still remain: for instance, and this is likely to be possible only through large collaborative studies, which is the value of bariatric surgery for patients with BMI<35 $kg/m^2$; at what stage and duration of type 2 diabetes bariatric surgery is more effective; in addition, there should be clear criteria for resolution of diabetes, and more data should be available on the rate or recurrence of diabetes after resolution; finally, we need studies on long term prevention of complications in type 2 diabetes, and on long term prevention of mortality in type 2 diabetes.

**References:**


1) Buchwald. Amer J Med 2009; 122: 248-256.

2) Pontiroli. Nutr Metab Cardiovasc Dis. 2012;22:e24-5.

3) Benetti. Diabetes Care. 2013;36:1443-7.

4) Long. Diabetes Care 1994; 17: 372.

5) Sjostrom. New Engl J Med 2004; 351: 2683.

6) Pontiroli. Diabetes Care 2005: 28, 2703.

7) SOS. N Engl J Med 2012; 367: 695.

8) Pontiroli. Circulation 2002; 106: e42.

9) Uzun. Obes surg 2004; 14: 659.

10) Adami. Int J Obes 2004; 28: 671.

11) Pontiroli. Eur J Endocrinol 2004; 150: 194.

12) Veronelli. Diabetes Care 2004; 27: 2501.

13) Perego. J Clin Endocrinol Metab. 2005; 90: 4087.

14) Pontiroli. Diabetes Care 2006; 29: 2735.

15) García de la torre. JCE&M 2008; 93: 4276.

16) Pontiroli. Cardiovasc Diabetol 2009; 8: 37.

17) Dixon. Obes Surg 2006; 16: 1278.

18) Furuya. J Gastroent Pathol 2007; 22: 1510.

19) Weiner. Dig Dis 2010; 28: 274.

20) Schuster. Surgery for Obesity and Related Diseases 2011; 7: 459.

21) Agrawal. Surgery for Obesity and Related Diseases 2009; 5: 20.

22) Iaconelli. Diabetes Care 2011; 34: 561.

23) Sturm. Eur Heart J 2009; 30: 2038.

24) Heneghan. Am J Cardiol 2011; 108: 1499.

25) Pontiroli. Ann Surg 2011; 253: 484-7.

26) Sjostrom. JAMA. 2012; 307: 56.

## Quality of diabetes care

Graziella Bruno
*Associate Professor, Department of Medical Sciences, University of Turin, Italy*

Prevalence of diabetes is increasing worldwide, due to both population aging and modifications in lifestyle habits, and significantly impacts on National Health Systems (NHS). In Italy, direct costs are 4-fold higher in persons with diabetes compared to persons without diabetes of similar age and sex, and the amount of national health care resources invested in diabetes is over 10%. Strict control of classical cardiovascular risk factors can reduce the excess mortality of diabetic people. However, a marked variability has been documented in preventive and therapeutic approaches over countries, thus suggesting that the level of diabetes care currently delivered may not produce the expected health-related gains. Over the past 5-10 years, there have been substantial improvements in many processes of medical care of diabetic people suggested by international guidelines (frequencies of tests to be performed and cut-off values defining optimal control of the disease), but less dramatic improvements in intermediate outcomes. In this context, monitoring quality of care is crucial to reduce the survival gap between subjects with and without diabetes and to reduce the health-related costs of complications, but few population-based studies have been performed on this issue. Although clinical practice guidelines have the potential to improve the care received by patients promoting interventions of proven benefit and discouraging ineffective interventions, the potential effect of their translation at community level has seldom been assessed. The two Italian scientific diabetes societies (AMD and SID), provided specific recommendations for the diagnosis and treatment of diabetes and its complications in 2008, which were disseminated and discussed at the local level with diabetologists and general practitioners. The second edition of Standards of Care for Diabetes was published and further implemented in 2010 with a pocket version for general practitioners (GPs). Therefore, Italy is the ideal setting for assessing adherence to quality of diabetes care provided by both diabetologists and GPs after the implementation of national guidelines. Administrative data linking independent data sources have increasingly been used for epidemiological purposes. The ARNO Observatory covers 29 administrative areas of 8 different Italian Regions allowing to explore different aspects of the epidemiology of diabetes, including process and outcome indicators at the community level. We investigated the quality of care indicators in a large and representative population-

based cohort of Italian diabetic people; in particular, we focused on adherence to national guidelines regarding monitoring and treatment of diabetes and its complications, and on frequencies over the last year of laser photocoagulation, dialysis and hospital admissions for macrovascular complications as outcome indicators. This large multiregional population-based study, covering almost 1 over 20 diabetic people resident in Italy, provides evidence of a large widespread inadequacy of care provided in the community under the coverage of universalistic NHS The report, with a population-based multiregional study design including a great number of patients cared for by both diabetes clinics and GPs, is to our knowledge the firsts European experience linking primary care performance to outcomes of care and allowing to indicate that quality of care is far from being satisfactory. Noteworthy, our data were recorded two years after the publication of the first edition of Italian Standard of Care for diabetes and during the implementation of its second edition, which included a pocket version for GPs. This finding is particularly disappointing, providing evidence that other strategies need to be applied to improve care provided to the diabetic population. In spite of the evidence that good glucose control soon after the diagnosis of diabetes is mandatory to lower the risk of macrovascular disease, the ARNO Observatory shows that as many as 42% of diabetic people had no HbA1c measurement over the previous year. Even considering only insulin-treated diabetic people, this frequency remains disappointingly high (35%). We can hypothesize that a subgroup of subjects with diabetes might rely on self-blood glucose monitoring rather than on HbA1c measurement; however, its usefulness in non insulin-treated diabetic people is questionable and anyway does not eliminate the need of measuring HbA1c. Another disappointing finding is the very low proportion of subjects in whom microalbuminuria was tested, in spite of the evidence of its role as strong predictor of cardiovascular diseases and dyalisis. It is remarkable also that less than one over two diabetic persons discharged for acute myocardial infarction was treated with statins. Therefore, our findings of a ten-fold increased risk for laser photocoagulation and amputations and two-fold increased risk for dialysis and macrovascular diseases might be largely driven by inadequacy of care in the community, in spite of universal coverage from NHS. A greater adherence to guidelines by all knots of diabetes healthcare system is mandatory to reduce the burden of diabetes complications.

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